frontiers | Research Topics

Women in Cardiovascular epidemiology and prevention

Edited by
Liesl Joanna Zühlke, Amanda Henry and Stefania Triunfo

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Women in cardiovascular epidemiology and prevention

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STUDY PROTOCOL
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Rationale and Design of a Pharmacist-led Intervention for the Risk-Based Prevention of Heart Failure: The FIT-HF Pilot Study

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Background: Given rising morbidity, mortality, and costs due to heart failure (HF), new approaches for prevention are needed. A quantitative risk-based strategy, in line with established guidelines for atherosclerotic cardiovascular disease prevention, may efficiently select patients most likely to benefit from intensification of preventive care, but a risk-based strategy has not yet been applied to HF prevention.

Methods and Results: The Feasibility of the Implementation of Tools for Heart Failure Risk Prediction (FIT-HF) pilot study will enroll 100 participants free of cardiovascular disease who receive primary care at a single integrated health system and have a 10-year predicted risk of HF of ≥5% based on the previously validated Pooled Cohort equations to Prevent Heart Failure. All participants will complete a health and lifestyle questionnaire and undergo cardiac biomarker (B-type natriuretic peptide [BNP] and high-sensitivity cardiac troponin I [hs-cTn]) and echocardiography screening at baseline and 1-year follow-up. Participants will be randomized 1:1 to either a pharmacist-led intervention or usual care for 1 year. Participants in the intervention arm will undergo consultation with a pharmacist operating under a collaborative practice agreement with a supervising cardiologist. The pharmacist will perform lifestyle counseling and recommend initiation or intensification of therapies to optimize risk factor (hypertension, diabetes, and cholesterol) management according to the most recent clinical practice guidelines. The primary outcome is change in BNP at 1-year, and secondary and exploratory outcomes include changes in hs-cTn, risk factor levels, and cardiac mechanics at follow-up. Feasibility will be examined by monitoring retention rates.

Conclusions: The FIT-HF pilot study will offer insight into the feasibility of a strategy of quantitative risk-based enrollment into a pharmacist-led prevention program to reduce heart failure risk.

Clinical Trial Registration: https://clinicaltrials.gov/ct2/show/NCT04684264

Keywords: heart failure, primary prevention, pharmacist, risk prediction, natriuretic peptides

BACKGROUND

Although overall cardiovascular disease mortality has declined 3-fold over the past five decades (1), this has been largely driven by improvement in ischemic heart disease mortality rates (2). Advances in the prevention of ischemic heart disease have now been offset by increasing mortality related to heart failure (HF), resulting in stagnation in overall cardiovascular disease mortality rates since 2011 (3). HF affects an estimated six million American adults, a prevalence which is expected to increase nearly 50% by 2030, and is responsible for ∼1 million hospitalizations and two million physician office visits annually (4).

Given the large and rising morbidity, mortality, and costs of HF, evidence-based and generalizable prevention strategies, which currently exist for atherosclerotic cardiovascular disease (ASCVD) (5) but not HF, are needed. Two important questions in the design of a potential HF prevention strategy include (1) how to assess patients' individual risk for HF and (2) how to intensify prevention efforts in patients identified as high risk.

Heart Failure Risk Assessment

The 2017 focused update of the American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of HF highlights the potential role of natriuretic peptide biomarker screening, followed by team-based care, in those at risk for HF (6). This guideline recommendation was informed by two randomized controlled trials, the STOP-HF trial and the PONTIAC trial, which demonstrated that referral to collaborative cardiology care based on natriuretic peptide value cutoffs in patients at high cardiovascular risk may prevent HF (7, 8). However, in STOP-HF, only 27% of patients had a BNP > 50 pg/mL, the threshold for referral to cardiology. In addition, a risk factor-based approach that treats all risk factors equally (as in STOP-HF) or requires the presence of a particular risk factor such as diabetes (as in PONTIAC) may miss some patients at high risk due to elevations below treatment thresholds in multiple risk factors and may over-sample some patients at low risk, such as younger adults with a single risk factor. In contrast, multivariable risk prediction equations for HF, such as the Pooled Cohort equations to Prevent HF (PCP-HF) (9), that incorporate clinical measures readily available in primary care settings may improve identification of those at risk for HF who may merit more intensive prevention strategies.

Pharmacist-led Intensification of Preventive Care

Efforts to intensify preventive care have been implemented with a variety of healthcare and non-healthcare team members such as pharmacists (10, 11), nurses (12, 13), and community healthcare workers (14), and through leveraging digital tools such as web-based portals (15) and remote monitoring (16). Several prior reports suggest a potential benefit of involvement of these team members in strategies for hypertension or diabetes control (11, 13–16); for example, a trial of a nurse-led clinic for patients with diabetes showed that, at 1 year, 37.2% of patients in the intervention met their cholesterol and/or blood pressure target compared with 30.7% of patients receiving usual care (OR 1.37 [95% CI: 1.11, 1.69]) (13). Pharmacist-led interventions have unique advantages, as pharmacists are experts in the medications that achieve core targets of primary prevention, including blood pressure, glucose, and lipid lowering; pharmacists are well-positioned to counsel patients about sodium-glucose cotransporter-2 (SGLT-2) inhibitors, one of the most promising recent medications for the prevention of heart failure (17); and pharmacists may, under collaborative practice agreements with supervising physicians, directly prescribe and titrate medications for patients. In addition, pharmacists may be deployed in communities and have a potent effect on preventive care for underserved populations, as was recently demonstrated in a trial of a pharmacist-led intervention for blood pressure reduction in barbershops in predominantly Black communities (18).

Rationale of Risk-Based Heart Failure Prevention

It would be neither feasible nor cost-effective to perform biomarker screening or intensify preventive efforts in the entire population. Risk-based prevention strategies, in which the intensity of prevention efforts are tailored to the predicted risk of disease based on a comprehensive risk factor profile, maximize the potential benefits of preventive strategies and are well-established in atherosclerotic cardiovascular disease (ASCVD) (19–21). However, a quantitative risk-based approach has not yet been applied to the primary prevention of heart failure and requires further investigation with regard to the feasibility and efficacy of such an approach. Therefore, in this report we describe the design of a pilot study of a pharmacist-led intervention program for risk-based prevention of HF, the Feasibility of the Implementation of Tools for Heart Failure Risk Prediction (FIT-HF) Study. The FIT-HF Study will enroll 100 patients free of any type of cardiovascular disease with a predicted 10-year risk of developing heart failure, based upon the PCP-HF, (9) of 5% or higher. Patients will undergo BNP, hs-cTn, and echocardiogram testing at baseline and will be randomized to a pharmacist-led intervention or usual care. Successful completion of this pilot study will demonstrate feasibility of the proposed strategy and generate preliminary data to support the design of a subsequent, well-powered trial evaluating clinical event outcomes.

STUDY DESIGN

Eligible Study Population

The FIT-HF study will enroll 100 participants who receive primary care at a single integrated academic healthcare center, Northwestern Medicine. Eligible participants will be aged 30–79 years and have at least one internal medicine visit in the past year, at least two such visits in the past 5 years, and cholesterol and glucose levels measured within the past 5 years. In addition, using the most recently available data in the electronic health record (EHR), participants will have a predicted 10-year risk of developing HF of at least 5% based on the PCP-HF model (9). The variables in the PCP-HF model are age, sex, race, smoking, body mass index, systolic blood pressure, hypertension treatment, fasting glucose, diabetes treatment, total cholesterol,

high density lipoprotein cholesterol, and QRS duration. Because real-world glucose measurements are often non-fasting, and QRS duration is not routinely clinically available, a version of the PCP-HF equations calibrated to random glucose values and excluding QRS duration will be used (22). The 5% cutoff of 10-year predicted HF risk represents approximately the top quintile of risk among US adults (23). Participants are ineligible if they have a history of cardiovascular disease (by EHR diagnosis code or self-report), signs or symptoms of HF, a current pregnancy, an estimated glomerular filtration rate < 45 mL/min/1.73 m^2 using the CKD-EPI (2009) formula either prior to or during the baseline exam, or stage three or four cancer. Detailed inclusion and exclusion criteria are available in the **Supplementary Methods**.

Study Recruitment

Recruitment will be accomplished leveraging the robust Northwestern Medicine Enterprise Data Warehouse (NMEDW), which is a comprehensive and integrated repository of all clinical, administrative, and research data sources on the campus. Briefly, the NMEDW currently stores observations on more than 7.1 million distinct patients and is updated in real time with data elements from 142 separate sources, including electronic health records, pathology data from the hospital and research laboratories, biomarker data from research databases and research transactional data from the Northwestern Institutional Review Board and other institutional systems. The NMEDW-based algorithm has been customized to identify all patients meeting study eligibility criteria based on existing data in their electronic health record and automatically excludes patients who opted out of being contacted for research studies, thus allowing for targeted and highly efficient recruitment of patients. The baseline characteristics of patients in the recruitment report are listed in **Table 1**, which identified 13,059 potentially eligible patients with a mean (standard deviation) age of 66.6 (8.5) years. The time frame for full enrollment is 1 year, with the final participant expected to complete the protocol 2 years after the beginning of the study.

TABLE 1 | Baseline characteristics of patients potentially eligible for recruitment.

N	13,059
Age (years), mean (SD)	66.6 (8.5)
Gender, *N* (%)	
Female	6,040 (46.3%)
Male	7,019 (53.7%)
Self-reported race, *N* (%)	
White	8,832 (67.6%)
Black or African American	2,210 (16.9%)
Asian	450 (3.4%)
Other or Declined	1,567 (12.0%)
Body mass index (kg/m^2), median (IQR)	29.7 (26.1, 34.6)
Systolic blood pressure (mmHg), mean (SD)	136.1 (17.2)
Diastolic blood pressure (mmHg), mean (SD)	78.3 (10.0)
Glucose (mg/dL), mean (SD)	116.3 (42.4)
Total cholesterol (mg/dL), mean (SD)	181.3 (40.5)
HDL cholesterol (mg/dL), mean (SD)	53.8 (15.7)
LDL cholesterol (mg/dL), mean (SD)	101.6 (36.3)
Medication use, *N* (%)	
Antihypertensive	10,594 (81.1%)
Antidiabetic	2,919 (22.4%)
Statin	8,132 (62.3%)
Current smoking, *N* (%)	1,180 (9.0%)
Estimated 10-year heart failure risk, median (IQR)	8.0% (6.2, 11.2)

Study Protocol

A research coordinator will call patients listed in the recruitment report to confirm eligibility, describe the study, and ask if they are interested in participating. If so, the research coordinator will review study procedures over the phone and schedule a visit in the research clinic. Participants will be emailed a link to sign electronic consent (e-Consent) and complete a baseline health and lifestyle questionnaire. The e-Consent option will offer flexibility and minimize in-person time to decrease participant burden during and after the COVID-19 pandemic. The questionnaire is composed of previously validated questions from the World Health Organization, Multi-Ethnic Study of Atherosclerosis (MESA), and EuroQol. Participants who are unwilling or unable to complete these procedures online will be instructed to arrive 30 min before their scheduled visit in order to sign written consent and complete the questionnaire in person. After consent is obtained, participants will then be randomized in 1:1 fashion to intervention vs. usual care (**Figure 1**). The randomization table will be generated using random permuted blocks of sizes four and six by a statistician with no other involvement in the study.

All participants will undergo phlebotomy for measurement of BNP, hs-cTn, basic metabolic panel, lipid panel, and biorepository storage, and baseline echocardiography with Doppler measurements. All participants will also undergo measurement of vital signs and receive an educational packet of information from the Centers for Disease Control and Prevention and American Heart Association on signs and symptoms of HF and heart-healthy lifestyle.

Participants who are randomized to the intervention arm will receive a referral to the pharmacist-led intervention (supervised by an attending cardiologist), and have their first visit on the same day as the baseline testing. Two pharmacy residents will deliver the intervention under the supervision of an attending pharmacist. Residents have received standardized training on lifestyle modification and risk factor management through the residency program. Pharmacists will review participants' medications and may make adjustments according to a medication protocol (**Figure 2**) for blood pressure, glucose, and lipid control according to the latest evidence-based practice guidelines. Specifically, the medication protocol specifies blood pressure control according to the protocol employed by Kaiser Permanente Health (24), consideration of SGLT-2 inhibitor initiation in patients with diabetes per ACC/AHA and American Diabetes Association (ADA) guidelines (5, 25), and statin initiation or intensification per

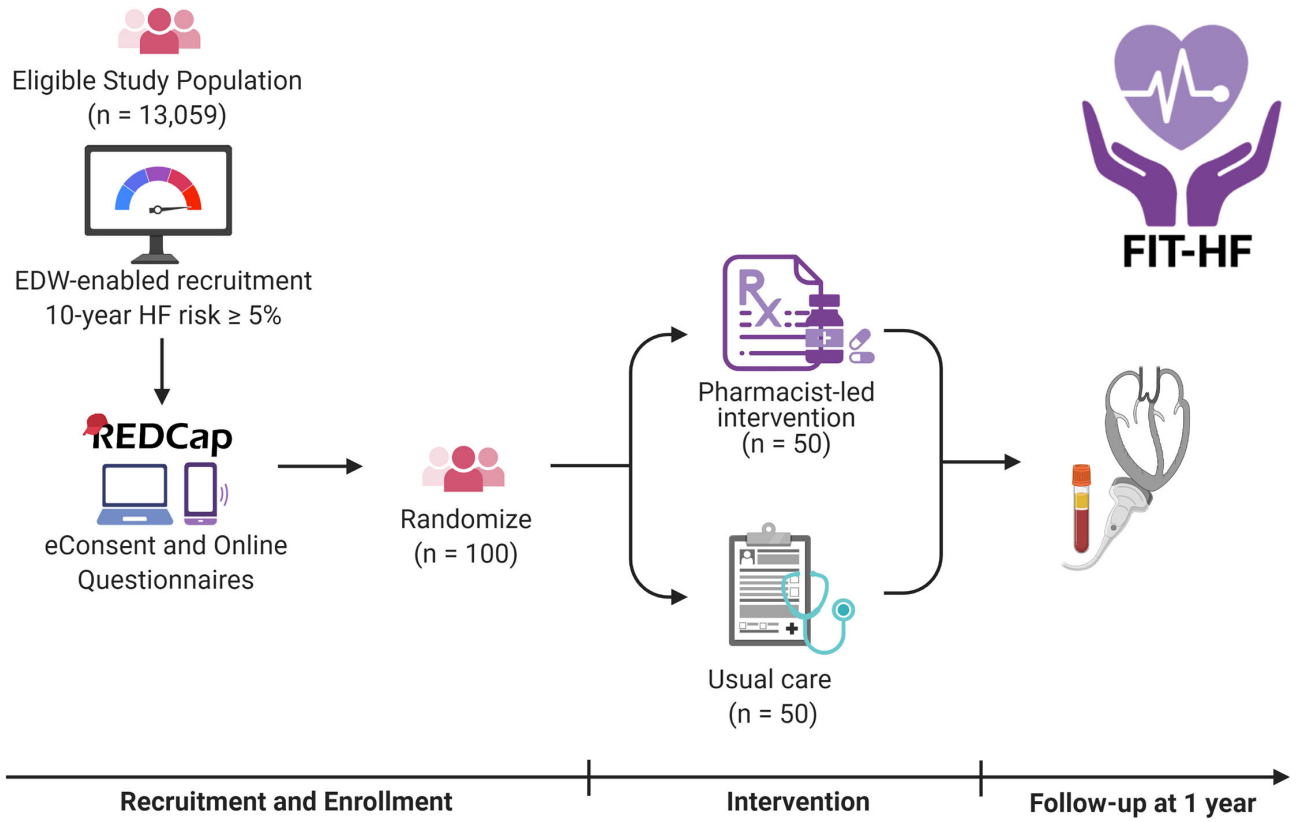

FIGURE 1 | Overview of the FIT-HF study. Participants will be recruited by invitation from the eligible study population using an electronic health record-based report. They will complete eConsent and questionnaires online and have biomarkers measured and echocardiograms performed at baseline and 1 year. In the interim, they will be randomized 1:1 to a pharmacist-led intervention or to usual care. HF represents heart failure; EDW Enterprise Data Warehouse. Created with BioRender.com.

the 2018 ACC/AHA cholesterol guideline (20). Pharmacists will additionally counsel patients regarding heart-healthy lifestyles and may order laboratory tests when medications are added to follow potassium levels, kidney function, or other relevant laboratory parameters according to the standard of care. Adherence to follow-up lab tests is monitored by the pharmacists, with reminders sent at their discretion according to their typical clinical practice. The study population comprises patients who receive their usual care on the same medical campus as the study site, mitigating access to care limitations for the purposes of this pilot study. The pharmacist visits are provided at no cost to participants; medications are e-prescribed to participants' preferred pharmacies according to the standard of care and are billed through participants' insurance. The results from participants' BNP, hs-cTn, and echocardiography will be provided to them and their primary care physicians as well as the pharmacist and cardiologist team members. Participants in the intervention arm will receive follow-up from the pharmacist team approximately every 3 months for a period of 1 year. Follow-ups will be clinical telephone visits structured similarly to the baseline visit, with interim review of laboratory values, if applicable, for medication monitoring and titration. The pharmacist team will provide a detailed note in the electronic medical record to the primary care doctor after every clinical encounter.

The participants (and their primary care physicians) who are randomized to usual care will be blinded to their 10-year heart failure risk estimates as well as biomarker and echocardiography results, unless there are critical or alert values from the hs-cTn (i.e. >500 pg/mL) or echocardiography (see **Supplementary Methods**), in which case their primary care physician will be informed. All patients will be requested to repeat the health and lifestyle questionnaire and schedule an in-person visit at 1-year follow-up. At this visit, all participants will undergo repeat measurement of vital signs and anthropometrics, phlebotomy, and echocardiography. The 1-year follow-up time was selected based on a limited duration by which a significant change in risk factor control would be expected based on prior studies (11, 13, 18). Participants receive free parking for all study-related visits and are paid $25 at the end of the study for their time spent participating.

Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Northwestern University (26, 27). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive

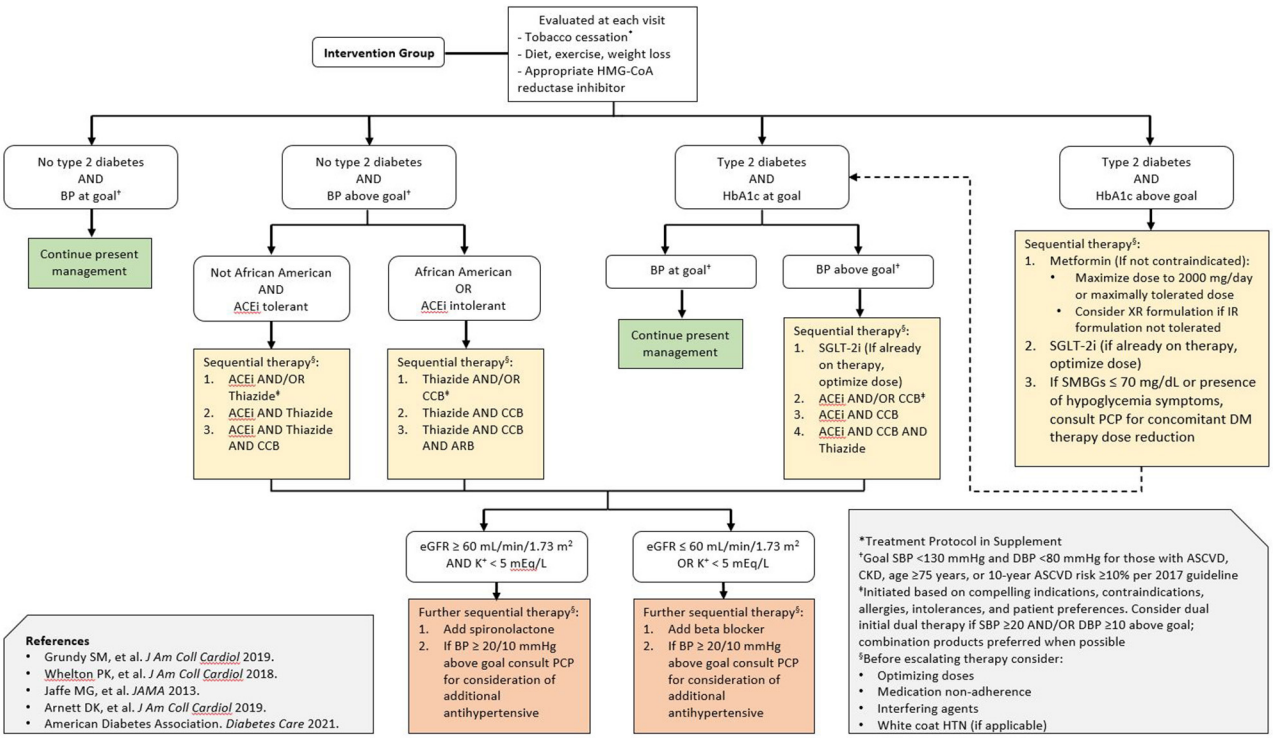

FIGURE 2 | Pharmacist-directed intervention treatment algorithm. The treatment algorithm was derived from professional society guidelines for the primary prevention of cardiovascular disease as well as blood pressure, glucose, and lipid lowering. Special consideration is given to the early initiation of SGLT-2 inhibitors in patients with diabetes, given the evidence supporting their efficacy in heart failure prevention and current guideline recommendations. BP represents blood pressure; ACEi angiotensin converting enzyme inhibitor; ARB angiotensin receptor blocker; CCB calcium channel blocker; SMBG self-monitored blood glucose; eGFR estimated glomerular filtration rate; PCP primary care physician; DM diabetes mellitus; SBP systolic blood pressure; DBP diastolic blood pressure; HTN hypertension.

interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Outcomes

The primary outcome is change in BNP at 1 year. Secondary outcomes include change in hs-cTn, systolic and diastolic blood pressure, weight and body mass index, serum glucose and low density lipoprotein cholesterol, estimated glomerular filtration rate and creatinine, and current smoking at 1 year. Exploratory outcomes include medication adherence and changes in echocardiographic parameters such as left ventricular mass index, diet and physical activity, and health utility at 1 year. Adherence to medications is measured using the same questionnaire as the Atherosclerosis Risk in Communities (ARIC) study: the four-item Morisky Green Levine Scale, frequency of non-adherence in the past 4 weeks, and direct measure of adherence in the past 4 weeks (28). Feasibility will also be examined by monitoring participant retention rates. Retention will be defined as completion of the 1-year study protocol and measured as the proportion of enrolled participants in each arm who successfully complete the study. All demographics (e.g., sex, race, ethnicity, education), health behaviors (e.g., smoking, diet, physical activity), and patient-centered outcomes (e.g., health-related quality of life) are self-reported.

The following serious adverse events will be reported: echocardiogram or troponin alert (at baseline or 1-year follow-up), death, hospitalization, or ER visit (all at 1-year follow-up, or sooner if the study team becomes aware of the adverse event). All adverse events will be determined by chart review and personally adjudicated by the principal investigator. As a process of care intervention using guideline-directed medical therapy (rather than a trial of a novel therapy), drug-related adverse events will not be reported for this study.

Statistical Analysis

Baseline characteristics will be reported by group assignment in the form of means (standard deviations) and medians (interquartile ranges) for continuous variables, as appropriate, and proportions for categorical variables. The analysis will use two-sample t-tests to compare continuous variables and χ^2-tests to compare categorical variables between the pharmacist-directed intervention and usual care groups. All participants will be included according to the intention-to-treat principle for all endpoints. A per protocol analysis will be reported as a secondary analysis to evaluate whether study dropout significantly influenced the outcome of the trial. Because the total study population is 100, subgroup analyses are not planned for this study due to insufficient power. Since this is a pilot and

feasibility study, no formal power analysis has been performed to inform the sample size. However, given $N = 50$ in each study arm and under the assumption of similar BNP changes as in STOP-HF (7), the study would have 80% power to detect a 12 pg/mL mean difference in the change in BNP between the two study arms.

DISCUSSION

This report describes, to our knowledge, the first clinical study of a quantitative risk-based screening and pharmacist-led intervention for the primary prevention of heart failure. BNP-based risk assessment has shown potential to identify patients at higher risk of developing heart failure, and other biomarkers such as hs-cTn and imaging modalities such as echocardiogram have a potential role in sequential testing strategies. However, such adjunctive risk stratification methods are unlikely to be cost-effective if applied to the general population (29), and an important gap remains to understand which subpopulations of patients may be best to target for screening and intensification of preventive care. Successful completion of the FIT-HF pilot trial, leveraging the multivariable risk prediction tool, PCP-HF, is anticipated to offer insight into the feasibility, safety, and potential efficacy of a risk-based strategy to reduce the risk of incident HF events. Examination of the distributions of predicted risk, biomarkers, clinical data, and echocardiographic parameters, and how these measures respond to a pharmacist-led intervention, will support refinement of the risk-based protocol for a future well-powered, multi-center clinical outcomes trial.

Prior studies of pharmacist-led interventions for individual risk factors or chronic conditions, such as blood pressure and diabetes, have shown that pharmacist management is often superior, if not equal, to usual care (30–35). However, neither pharmacist-based intervention nor other non-physician team-based care has been tested specifically in HF prevention, in particular using the risk factor-agnostic strategy of FIT-HF. Thus, a feasibility study is warranted, and the study outcomes align with two of the eight general areas of feasibility studies as described by Bowen et al. (36): limited efficacy (evaluated using the primary outcome of change in BNP as a key intermediate variable) and practicality (evaluated with successful enrollment of 100 participants and high retention through the end of the study). As this process of care trial will test a new concept of HF prevention, usual care rather than another non-physician role has been selected as the comparator. The usual care group is selected as individuals with a primary care physician in the health system and, therefore, have access to routine care. However, an important limitation to note if there is a significant difference between the two groups is that the intervention group likely has more interactions with the healthcare system during the study period.

The ultimate goal of this research is to develop a paradigm for HF prevention that is analogous to established practice guidelines for risk-based ASCVD prevention. Even in the context of ASCVD prevention, prospective randomized trial data of quantitative risk-based interventions are limited; most prior trials have used inclusion criteria based on the presence of one or more risk factors, and quantitative risk, if used, is added as an additional inclusion criterion (37). Thus, the benefit of a pure quantitative risk-based prevention strategy is largely extrapolated from such trials and observational data. A large trial of quantitative ASCVD risk modification, the Centers for Medicare and Medicaid Services-sponsored Million Hearts Model evaluation, is underway; a pre-specified interim analysis showed improvements in the use of statins and antihypertensives (38). In this context, FIT-HF and subsequent studies may also inform the design of risk-based interventions in the primary prevention of cardiovascular diseases more generally. A key consideration to strengthen these studies to be generalizable and promote health equity is the representative recruitment of participants. Given practical constraints on the scope of a pilot study, FIT-HF will recruit from a convenience sample of patients of a large urban medical center. Although the representation of Black patients in our recruitment report is 17%, we recognize that due to socioeconomic and structural factors such as competing demands of work and residential segregation, the final recruitment of Black patients into FIT-HF may not be as high. However, we have assembled a diverse study team with expertise in recruiting populations traditionally underrepresented in clinical research. In larger, multi-centered trials that may follow, we propose partnerships with community organizations and study sites in under-resourced communities with lower access to care to ensure that the population studied represent those at greatest risk of HF, as well as use of the RE-AIM framework during a wider implementation phase to evaluate whether the intervention has the intended public health impact (39).

Of particular relevance to potential strategies for HF prevention are the SGLT-2 inhibitors. Large outcome trials have already supported the use of SGLT-2 inhibitors not only to decrease major adverse cardiovascular events in patients with HF with reduced ejection fraction (40, 41), but also to prevent HF in patients at high risk based on established risk factors of diabetes (42) and chronic kidney disease (43). In response, multiple professional societies have recommended the use of SGLT-2 inhibitors in patients with type two diabetes (5, 25), and these guideline recommendations were incorporated into the medication protocol of the FIT-HF intervention. As ongoing trials validate the efficacy of SGLT-2 inhibitors for HF prevention in other subgroups, such as those with chronic kidney disease, future guidelines may be able to broaden the patient populations in which SGLT-2 inhibitors are recommended; SGLT-2 inhibitors could potentially take a place in heart failure prevention akin to statins for atherosclerotic cardiovascular disease prevention (44). In this context, pharmacists are uniquely positioned to collaborate with physicians in identifying appropriate patients for SGLT-2 inhibitor initiation, counseling patients on their risks and benefits, and prescribing and titrating the medication. Future studies may be able to incorporate pharmacist-led intensification of preventive care in the context of expanded indications for SGLT-2 inhibitors to primary prevention patients without diabetes, given the low risk of

hypoglycemia with these agents owing to their mechanisms of action (45).

CONCLUSION

The FIT-HF pilot study will test a strategy of quantitative risk-based enrollment into a screening and pharmacist-led intervention program for the primary prevention of heart failure. FIT-HF is designed to be an initial step toward developing a robust, generalizable, and efficacious prevention strategy to disrupt the increasing burden of heart failure in the general population.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Northwestern University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MW, BD, LV, NM, AW, KH, AL, SS, CY, DL, and SK: conception and design. All authors: acquisition, analysis, or interpretation of data and revision of manuscript for important intellectual content. MW: drafting of manuscript. SS, CY, DL, and SK: supervision.

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The authors take responsibility for decision to submit the manuscript for publication. Dr. Khan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.785109/full#supplementary-material

REFERENCES

1. Ma J, Ward EM, Siegel RL, Jemal A. Temporal trends in mortality in the United States, 1969-2013. *JAMA*. (2015) 314:1731–9. doi: 10.1001/jama.2015.12319
2. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, et al. Explaining the decrease in U.S. Deaths from coronary disease, 1980–2000. *N Engl J Med*. (2007) 356:2388–98. doi: 10.1056/NEJMsa053935
3. Shah NS, Molsberry R, Rana JS, Sidney S, Capewell S, O'Flaherty M, et al. Heterogeneous trends in burden of heart disease mortality by subtypes in the United States, 1999-2018: observational analysis of vital statistics. *BMJ*. (2020) 370:m2688. doi: 10.1136/bmj.m2688
4. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics—2021 update: a report from the American Heart Association. *Circulation*. (2021) 143:e254–743. doi: 10.1161/CIR.0000000000000950
5. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *J Am Coll Cardiol*. (2019) 74:e177–232. doi: 10.1016/j.jacc.2019.03.009
6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the american college of cardiology/american heart association task force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. (2017) 136:e137–61. doi: 10.1161/CIR.0000000000000509
7. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, et al. Natriuretic peptide–based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA*. (2013) 310:66–74. doi: 10.1001/jama.2013.7588
8. Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, et al. PONTIAC (NT-proBNP Selected Prevention of cardiac events in a population of dIabetic patients without a history of Cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol*. (2013) 62:1365–72. doi: 10.1016/j.jacc.2013.05.069
9. Khan SS, Ning H, Shah SJ, Yancy CW, Carnethon M, Berry JD, et al. 10-year risk equations for incident heart failure in the general population. *J Am Coll Cardiol*. (2019) 73:2388–97. doi: 10.1016/j.jacc.2019.02.057
10. Santschi V, Chiolero A, Colosimo AL, Platt RW, Taffé P, Burnier M, et al. Improving blood pressure control through pharmacist interventions: a meta-analysis of randomized controlled trials. *J Am Heart Assoc*. (2014) 3:e000718. doi: 10.1161/JAHA.113.000718
11. Mehuys E, Van Bortel L, De Bolle L, Van Tongelen I, Annemans L, Remon JP, et al. Effectiveness of a community pharmacist intervention in diabetes care: a randomized controlled trial. *J Clin Pharm Ther*. (2011) 36:602–13. doi: 10.1111/j.1365-2710.2010.01218.x
12. Clark CE, Smith LF, Taylor RS, Campbell JL. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. *BMJ*. (2010) 341:c3995. doi: 10.1136/bmj.c3995
13. New JP, Mason JM, Freemantle N, Teasdale S, Wong LM, Bruce NJ, et al. Specialist nurse-led intervention to treat and control hypertension and hyperlipidemia in diabetes (SPLINT): a randomized controlled trial. *Diabetes Care*. (2003) 26:2250–5. doi: 10.2337/diacare.26.8.2250
14. Spencer MS, Rosland AM, Kieffer EC, Sinco BR, Valerio M, Palmisano G, et al. Effectiveness of a community health worker intervention among African American and Latino adults with type 2 diabetes: a randomized controlled trial. *Am J Public Health*. (2011) 101:2253–60. doi: 10.2105/AJPH.2010.300106
15. Thomas KL, Shah BR, Elliot-Bynum S, Thomas KD, Damon K, Allen LaPointe NM, et al. Check it, change it: a community-based, multifaceted intervention to improve blood pressure control. *Circ Cardiovasc Qual Outcomes*. (2014) 7:828–34. doi: 10.1161/CIRCOUTCOMES.114.001039
16. Scirica BM, Cannon CP, Fisher ND, Gaziano TA, Zelle D, Chaney K, et al. Digital care transformation: interim report from the first 5000 patients enrolled in a Remote Algorithm-Based Cardiovascular Risk Management Program to improve lipid and hypertension control. *Circulation*. (2021) 143:507–9. doi: 10.1161/CIRCULATIONAHA.120.051913
17. Vardeny O. The sweet spot: heart failure prevention with SGLT2 inhibitors. *Am J Med*. (2020) 133:182–5. doi: 10.1016/j.amjmed.2019.08.013

18. Victor RG, Lynch K, Li N, Blyler C, Muhammad E, Handler J, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. *N Engl J Med*. (2018) 378:1291–301. doi: 10.1056/NEJMoa1717250
19. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. (2014) 63:2935–59. doi: 10.1161/01.cir.0000437741.48606.98
20. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol. a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. (2019) 73:e285–350. doi: 10.1016/j.jacc.2018.11.003
21. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. (2018) 71:e127–248. doi: 10.1016/j.jacc.2017.11.006
22. Bavishi A, Bruce M, Ning H, Freaney PM, Glynn P, Ahmad FS, et al. Predictive accuracy of heart failure-specific risk equations in an electronic health record-based cohort. *Circ Heart Fail*. (2020) 13:e007462. doi: 10.1161/CIRCHEARTFAILURE.120.007462
23. Glynn PA, Ning H, Bavishi A, Freaney PM, Shah S, Yancy CW, et al. Heart failure risk distribution and trends in the United States Population, NHANES 1999-2016. *Am J Med*. (2021) 134:e153–64. doi: 10.1016/j.amjmed.2020.07.025
24. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. *JAMA*. (2013) 310:699–705. doi: 10.1001/jama.2013.108769
25. American Diabetes Association. Standards of medical care in diabetes-—2021: pharmacologic approaches to glycemic treatment. *Diabetes Care*. (2021) 44(Suppl. 1):S111–24. doi: 10.2337/dc21-S009
26. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. (2019) 95:103208. doi: 10.1016/j.jbi.2019.103208
27. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. (2009) 42:377–81. doi: 10.1016/j.jbi.2008.08.010
28. Beyhaghi H, Reeve BB, Rodgers JE, Stearns SC. Psychometric properties of the four-item morisky green levine medication adherence scale among Atherosclerosis Risk in Communities (ARIC) study participants. *Value Health*. (2016) 19:996–1001. doi: 10.1016/j.jval.2016.07.001
29. Wang TJ, Levy D, Benjamin EJ, Vasan RS. The epidemiology of asymptomatic left ventricular systolic dysfunction: implications for screening. *Ann Intern Med*. (2003) 138:907–16. doi: 10.7326/0003-4819-138-11-200306030-00012
30. Omboni S, Caserini M. Effectiveness of pharmacist's intervention in the management of cardiovascular diseases. *Open Heart*. (2018) 5:e000687. doi: 10.1136/openhrt-2017-000687
31. Abdulrhim S, Sankaralingam S, Ibrahim MIM, Awaisu A. The impact of pharmacist care on diabetes outcomes in primary care settings: an umbrella review of published systematic reviews. *Prim Care Diabetes*. (2020) 14:393–400. doi: 10.1016/j.pcd.2019.12.007
32. Fazel MT, Bagalagel A, Lee JK, Martin JR, Slack MK. Impact of Diabetes Care by Pharmacists as Part of Health Care Team in ambulatory settings: a systematic review and meta-analysis. *Ann Pharmacother*. (2017) 51:890–907. doi: 10.1177/1060028017711454
33. Mills KT, Obst KM, Shen W, Molina S, Zhang HJ, He H, et al. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: a systematic review and meta-analysis. *Ann Intern Med*. (2018) 168:110–20. doi: 10.7326/M17-1805
34. Hou K, Yang H, Ye Z, Wang Y, Liu L, Cui X. Effectiveness of pharmacist-led anticoagulation management on clinical outcomes: a systematic review and meta-analysis. *J Pharm Pharm Sci*. (2018) 20:378–96. doi: 10.18433/J3SQ0B
35. McKay C, Park C, Chang J, Brackbill M, Choi JY, Lee JH, et al. Systematic review and meta-analysis of pharmacist-led transitions of care services on the 30-day all-cause readmission rate of patients with congestive heart failure. *Clin Drug Investig*. (2019) 39:703–12. doi: 10.1007/s40261-019-00797-2
36. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. *Am J Prev Med*. (2009) 36:452–7. doi: 10.1016/j.amepre.2009.02.002
37. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med*. (2015) 373:2103-16. doi: 10.1056/NEJMoa1511939
38. Peterson GG, Pu J, Magid DJ, Barterian L, Kranker K, Barna M, et al. Effect of the million hearts cardiovascular disease risk reduction model on initiating and intensifying medications: a prespecified secondary analysis of a randomized clinical trial. *JAMA Cardiol*. (2021) 6:1050–9. doi: 10.1001/jamacardio.2021.1565
39. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health*. (1999) 89:1322–7. doi: 10.2105/ajph.89.9.1322
40. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. (2019) 381:1995–2008. doi: 10.1056/NEJMoa1911303
41. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. (2020) 383:1413–24. doi: 10.1056/NEJMoa2022190
42. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. (2015) 373:2117–28. doi: 10.1056/NEJMoa1504720
43. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. (2020) 383:1436–46. doi: 10.1056/NEJMoa2024816
44. Freaney PM, Lloyd-Jones DM, Khan SS. Could flozins be the statins for risk-based primary prevention of heart failure? *JAMA Cardiol*. (2021) 6:741–2. doi: 10.1001/jamacardio.2021.1133
45. Vallon V, Thomson SC. Targeting renal glucose reabsorption to treat hyperglycaemia: the pleiotropic effects of SGLT2 inhibition. *Diabetologia*. (2017) 60:215–25. doi: 10.1007/s00125-016-4157-3

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Favorable Cardiovascular Health Is Associated With Lower Hepatocyte Growth Factor Levels in the Multi-Ethnic Study of Atherosclerosis

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Introduction: Hepatocyte growth factor (HGF) is a cytokine released in response to endothelial injury and a potential biomarker of cardiovascular disease (CVD) risk. We examined the association between cardiovascular health (CVH) and HGF in a multi-ethnic cohort of adults free from CVD at baseline.

Methods: This cross-sectional study conducted between 2020 and 2021 used MESA baseline examination data (2000–2002) from 6,490 US adults aged 45–84 years. The independent variable was CVH measured by the CVH score and number of ideal metrics. The score was derived from seven metrics: smoking, body mass index, physical activity, diet, total cholesterol, blood pressure and blood glucose. Each metric was scored 0 points (poor), 1 point (intermediate) and 2 points (ideal). The total CVH score ranged from 0 to 14. An inadequate score was 0–8, average, 9–10 and optimal, 11–14. The dependent variable was logarithmically transformed HGF. We used regression analyses to estimate associations between CVH and HGF adjusting for sociodemographic factors.

Results: Participants' mean (SD) age was 62 (10) years. Fifty-three percent were female. A one-unit increment in the CVH score was significantly associated with 3% lower HGF levels. Average and optimal CVH scores were significantly associated with 8% and 12% lower HGF levels, respectively, compared to inadequate scores. Additionally, a greater number of ideal metrics was associated with lower HGF levels.

Conclusion: Favorable CVH was significantly associated with lower HGF levels in this ethnically diverse cohort. Interventions aimed at promoting and preserving favorable CVH may reduce the risk of endothelial injury as indicated by lower serum HGF levels.

Keywords: biomarker, cardiovascular disease, hepatocyte growth factor, ideal cardiovascular health metrics, life's simple 7, risk factors

INTRODUCTION

Hepatocyte growth factor (HGF) is a mesenchyme-derived cytokine released in response to endothelial injury and may be elevated due to insufficient compensatory mechanisms (1–4). However, HGF has cardioprotective effects in cardiac tissue through the activation of several biological pathways such as angiogenesis, anti-apoptosis, anti-inflammation and anti-fibrosis (1–4). Several studies have provided evidence that HGF is an independent predictor of coronary heart disease, heart failure, stroke and progression of atherosclerosis (5–8). Likewise, higher serum levels of HGF have been found in individuals with cardiovascular disease (CVD) risk factors e.g., smoking, obesity, hypertension and diabetes (9–13).

The American Heart Association (AHA) introduced the concept of "ideal cardiovascular health (CVH)" defined as meeting specific criteria for seven metrics. These modifiable health behaviors and factors include smoking, physical activity, body mass index (BMI), diet, blood pressure, total cholesterol and fasting plasma glucose (14, 15). The goal of the concept is to use the CVH metrics to measure and monitor CVH along with the incidence, mortality and outcomes of CVD globally (14–17). With prior studies showing that favorable CVH is associated with better endothelial function (18), lower risk of incident CVD (19) and lower levels of CVD biomarkers such as GlycA, homocysteine and cardiac troponin (20, 21), it is expected that individuals with favorable CVH would also be at lower risk of endothelial injury.

However, as little is known about the association between favorable CVH and HGF, our study aimed to analyze data from the Multi-Ethnic Study of Atherosclerosis (MESA) to examine whether participants with favorable CVH have lower levels of HGF and if the association is modified by age, sex or race/ethnicity.

MATERIALS AND METHODS

Study Population

The methodology of the MESA study has been described elsewhere (22). In brief, the MESA study was initiated to investigate the characteristics of subclinical CVD along with the risk factors that may predict progression to clinical CVD. Between July 2000 and August 2002, MESA study personnel recruited 6,814 men and women between 45 and 84 years with no history of clinical CVD at the time of enrollment. The six recruitment centers in the U.S. were Los Angeles, CA; Chicago, IL; Baltimore, MD; St Paul, MN; Forsyth County, NC and New York, NY. The study enrolled 38% non-Hispanic White American, 12% Chinese American, 28% non-Hispanic Black American and 22% Hispanic American participants. Baseline data were collected using standardized questionnaires, physical examinations, and fasting laboratory blood tests. In this study, we included 6,490 participants from the baseline examination after the exclusion of participants with missing information for the CVH score and HGF ($n = 324$).

Independent Variable: Cardiovascular Health

According to the AHA, a person meets the criteria for "ideal CVH" if they have ideal levels for seven modifiable health behaviors and factors which is defined as follows: (1). non-smoking; (2). BMI $<25 kg/m^2$; (3). weekly physical activity of 75 min of vigorous exercise or 150 min of moderate exercise; (4). a healthy diet consistent with recommended guidelines; (5). untreated total cholesterol <200 mg/dL; (6). untreated blood pressure $<120/<80$ mmHg and (7). untreated fasting blood glucose <100 mg/dL (14). Information on smoking status was obtained from a self-report questionnaire and defined as non-smokers (participants who had never smoked or stopped smoking >12 months), former smokers (participants who stopped smoking within the last 12 months) and current smokers. Using the measured weights and heights of participants, BMI was calculated and reported in kg/m^2. A self-report survey instrument adapted from the Cross-Cultural Activity Participation Study (23) was used to assess physical activity. The survey contained 28 questions on time and frequency of activities during a week in the previous month. The total sum of minutes for moderate and vigorous exercise were calculated in metabolic equivalent of task (MET/min) (24). MESA study personnel used a 120-item validated food frequency questionnaire adapted from the Insulin Resistance Atherosclerosis Study instrument (25, 26) to collect data on dietary habits. Based on recommended dietary guidelines, a healthy diet comprised of fruits and vegetables, fish, whole grains, intake of sodium $<1,500$ mg/day and sugar-sweetened beverages ≤ 450 kcal (36 oz.)/week 14. Fasting blood samples were collected after a 12-h fast to measure total cholesterol (mg/dL) and blood glucose (mg/dL) levels. MESA study personnel used the cholesterol oxidase method to measure total cholesterol in ethylenediaminetetraacetic (EDTA) plasma using a centrifugal analyzer (Roche). While blood glucose was measured by the glucose oxidase method on a Vitros analyzer (Johnson & Johnson). Three blood pressure readings were taken from participants after 5 minutes was of rest in a seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon) and the mean of the last two blood pressure readings was used in the analysis.

Dependent Variable: Hepatocyte Growth Factor

MESA study personnel obtained peripheral blood samples from participants for the measurement of HGF at baseline. The samples were stored at $-70^{\circ}C$ in serum separated by centrifugation within 30 minutes of collection (8). Serum HGF was measured by quantitative sandwich enzyme-linked immunosorbent assay using the Human soluble HGF/CD62P Immunoassay kit (R&D Systems, Minneapolis, MN) with a lower limit of detection of 40 pg/mL (5, 8). For lyophilized manufacturer's controls, the inter-assay laboratory coefficients of variation (CV) were 12.0, 8.0 and 7.4% at mean concentrations of 687, 2,039 and 4,080 pg/mL, respectively (5, 8). For in-house pooled serum control, the inter-assay laboratory CV was 10.4% at a mean concentration of 688 pg/mL (5, 8). HGF

TABLE 1 | Characteristics of study participants at the MESA baseline exam (2000–2002) by cardiovascular health score.

	Total $N = 6,490$	Inadequate $n = 3,069$	Average $n = 2,115$	Optimal $n = 1,306$	*P*-value
HGF, pg/mL	903 (755–1,085)	969 (821–1,159)	870 (740–1,036)	807 (678–962)	–
Age, years	62 (10)	63 (10)	62 (11)	60 (10)	
<65 years	3,703 (57%)	1,682 (55%)	1,202 (57%)	819 (63%)	<0.001
≥65 years	2,787 (43%)	1,387 (45%)	913 (43%)	487 (37%)	
Sex					
Male	3,067 (47%)	1,460 (48%)	1,000 (47%)	607 (46%)	0.80
Female	3,423 (53%)	1,609 (52%)	1,115 (53%)	699 (54%)	
Race/ethnicity					
Non-Hispanic White	2,534 (39%)	977 (32%)	905 (43%)	652 (50%)	<0.001
Chinese-American	796 (12%)	216 (7%)	319 (15%)	261 (20%)	
Non-Hispanic Black	1,706 (26%)	1,035 (34%)	472 (22%)	199 (15%)	
Hispanic	1,454 (22%)	841 (27%)	419 (20%)	194 (15%)	
Education					
≥ Bachelor's degree	2,329 (36%)	795 (26%)	833 (39%)	701 (54%)	<0.001
<Bachelor's degree	4,161 (64%)	2,274 (74%)	1,282 (61%)	605 (46%)	
Income					
≥$40,000	3,206 (49%)	1,267 (41%)	1,122 (53%)	817 (63%)	<0.001
<$40,000	3,284 (51%)	1,802 (59%)	993 (47%)	489 (37%)	
Health insurance					
Yes	5,909 (91%)	2,781 (91%)	1,940 (92%)	1,188 (91%)	0.39
No	581 (9%)	288 (9%)	175 (8%)	118 (9%)	

HGF, hepatocyte growth factor; MESA, multi-ethnic study of atherosclerosis. Data were presented as mean (SD), median (IQR) or n (%). Percentages were rounded up to whole numbers. P-values indicate differences across the CVH score categories.

was logarithmically transformed for this analysis because of the skewness of the data.

Covariates

Baseline sociodemographic factors included as covariates were age, sex, race/ethnicity, education, income, health insurance status and study site. Age was assessed as a continuous variable while sex was categorized into male and female. Study participants self-classified themselves as either non-Hispanic White, Chinese, non-Hispanic Black, or Hispanic American. Education and income were grouped into 9 and 13 categories, respectively for analysis but both variables were dichotomized in the descriptive statistics reported in **Table 1**. We categorized health insurance status as participants with or without health insurance.

Statistical Analysis

All analyses were conducted with version 15.0 of STATA (StataCorp LP, College Station, TX) between 2020 and 2021 and a two-sided p value < 0.05 was considered statistically significant. We reported the characteristics of participants for the total study population and by the CVH score. In **Supplementary Material**, we also presented the baseline characteristics of study participants by HGF tertiles. For categorical variables, we reported frequencies with percentages while for continuous variables we reported medians with interquartile range (IQR) or means with standard deviation (SD). We used the chi-square and ANOVA tests to compare baseline characteristics by the CVH score for categorical and continuous variables, respectively. The individual CVH metrics were categorized into poor, intermediate and ideal as shown in the **Supplementary Table S1** (14). We assigned points to the categories as follows: 0 points for poor, 1 point for intermediate and 2 points for ideal with a total CVH score of 0 to 14 (27). The CVH score was further categorized as inadequate (0–8), average (9–10) and optimal (11–14) based on prior studies (28, 29).

We estimated the associations between CVH and log (HGF) using multiple linear regression. We fitted two separate models. Model 1 was unadjusted while model 2 was adjusted for sociodemographic factors [age, sex, race/ethnicity, education (9 categories), income (13 categories), health insurance status and study site]. We analyzed CVH using three measures: the continuous CVH score, the categorical CVH score and the number of ideal metrics. Of note, the number of ideal metrics was derived by counting the number of individual CVH metrics in the ideal category. We reported the percentage difference of the geometric mean of log (HGF) and the corresponding 95% confidence intervals (CI) for each measure of CVH. The percentage difference was calculated from the exponentiated beta coefficient minus 1 multiplied by 100 ([Exp (β) – 1]*100). For the CVH score and the number of ideal metrics, the reference groups were the "inadequate score" and "zero ideal metrics," respectively. We assessed effect modification by age (<65 vs. ≥65 years), sex and race/ethnicity by inserting interaction terms in

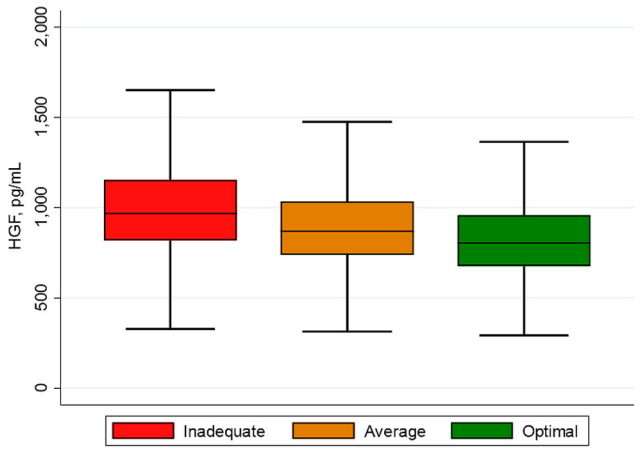

FIGURE 1 | Box plot of HGF by CVH scores. The lower and upper boundaries of the rectangles denote the 25th and 75th percentiles while the horizontal line within the rectangles is the median. Lines extend from the rectangles to the smallest and largest values within 1.5 × interquartile range.

model 2. Furthermore, we examined the associations between the individual CVH metrics and log (HGF) using multiple linear regression. The models were adjusted as previously described. We reported the percentage difference of the geometric mean of log (HGF) and the corresponding 95% CI for the intermediate and ideal categories of each CVH metric compared to the poor category.

RESULTS

Most of the baseline characteristics of study participants (N = 6,490) varied by the categories of the CVH score and HGF tertiles as reported in **Table 1** and in the **Supplementary Table S2**. The mean age (SD) of participants was 62 (10) years and 53% were female. As illustrated in **Figure 1**, participants with inadequate CVH scores had higher HGF levels compared to those with optimal CVH scores. Additionally, the mean (SD) of CVH scores declined across tertiles of HGF [9.4 (2.0), 8.6 (2.1) and 7.8 (2.2) for tertiles 1–3, respectively] as shown in the **Supplementary Table S2**.

Table 2 shows the associations between CVH and HGF. A one-unit increment in the continuous measure of the CVH score was significantly associated with 3% lower HGF levels after adjusting for sociodemographic factors. For the categorical measure of the CVH score, the average and optimal scores were significantly associated with 8% and 12% lower HGF levels, respectively, compared to inadequate scores. In addition, a greater number of ideal metrics was associated with lower HGF levels. For example, study participants with 5 and 6–7 ideal metrics had 18% and 23% lower HGF levels, respectively. These associations were slightly attenuated when compared to the unadjusted model. The tests for effect modification by age, sex and race/ethnicity were not statistically significant ($p > 0.05$).

TABLE 2 | Associations between cardiovascular health and hepatocyte growth factor in MESA (2000–2002), N = 6,490.

	Model 1 % difference (95% CI)	Model 2 % difference (95% CI)
CVH score, continuous	**−4 (−4, −3)***	**−3 (−3, −3)***
CVH score, categorical		
Inadequate	Reference	Reference
Average	**−10 (−11, −9)***	**−8 (−9, −6)***
Optimal	**−17 (−18, −16)***	**−12 (−14, −11)***
Number of ideal metrics		
0	Reference	Reference
1	−3 (−12, 7)	−4 (−13, −5)
2	−6 (−15, 3)	−6 (−14, 3)
3	**−13 (−21, −5)****	**−12 (−20, −4)****
4	**−18 (−25, −10)***	**−15 (−23, −7)***
5	**−22 (−29, −15)***	**−18 (−25, −10)***
6–7	**−29 (−36, −22)***	**−23 (−30, −16)***

CI, confidence interval; CVH, cardiovascular health; MESA, multi-ethnic study of atherosclerosis.

CVH score ranges from 0 to 14. Inadequate score, 0–8; average, 9–10; optimal, 11–14.

*% difference is the % difference of the geometric mean of HGF calculated from [Exp (β) − 1]*100.*

*Statistically significant results are in bold font: *P < 0.001; **P < 0.01.*

Model 1: Unadjusted.

Model 2: Adjusted for age, sex, race/ethnicity, education, income, health insurance and study site.

Interpretation: A one-unit increment in the CVH score was significantly associated with 3% lower HGF levels in model 2 [−3 (−3, −3)]. No significant interaction by age, sex or race/ethnicity.

Table 3 shows the associations between the individual CVH metrics and HGF. Participants in the ideal category for smoking had 11% lower HGF levels in the adjusted model compared to those in the poor category of smoking which was a stronger association in comparison to the unadjusted model. Although slightly attenuated, ideal BMI and physical activity were associated with an adjusted 12% and 4% lower HGF levels, respectively. Participants who reported eating an ideal diet had 7% lower HGF levels with no appreciable change from the unadjusted model. However, those who met the ideal criteria for total cholesterol had an adjusted 3% higher HGF levels. Ideal blood pressure and blood glucose were associated with 7% and 11% lower HGF levels, respectively, although the estimates were slightly attenuated in comparison to the estimates from the unadjusted model.

DISCUSSION

In this cross-sectional analysis of 6,490 adults free of clinical CVD at baseline, we found that participants with higher CVH scores or greater number of ideal metrics had lower levels of HGF. Similarly, we found that participants who met the ideal criteria for the individual CVH metrics had lower levels of HGF except for total cholesterol where ideal levels were associated with higher levels of HGF.

TABLE 3 | Associations between the cardiovascular health metrics and hepatocyte growth factor in MESA (2000–2002), $N = 6{,}490$.

	Model 1 % difference (95% CI)		Model 2 % difference (95% CI)	
	Intermediate vs Poor	Ideal vs Poor	Intermediate vs Poor	Ideal vs Poor
Smoking	**−10 (−15, −4)****	**−9 (−11, −7)***	**−11 (−16, −5)***	**−11 (−12, −9)***
Body mass index	**−9 (−10, −7)***	**−14 (−16, −13)***	**−8 (−10, −7)***	**−12 (−14, −11)***
Physical activity	**−3 (−5, −1)****	**−7 (−8, −5)***	−1 (−3, 1)	**−4 (−6, −3)***
Diet	**−2 (−3, −1)****	**−7 (−13, −1)****	**−2 (−3, −1)****	**−7 (−13, −1)****
Total cholesterol	1 (−2, 3)	0 (−3, 2)	**2 (0.1, 4)****	**3 (1, 5)****
Blood pressure	**−5 (−7, −3)***	**−12 (−13, −11)***	**−2 (−4, −1)****	**−7 (−9, −6)***
Blood glucose	**−5 (−7, −2)***	**−15 (−17, −13)***	**−3 (−5, −1)****	**−11 (−13, −9)***

CI, confidence interval; MESA, multi-ethnic study of atherosclerosis.
*% difference is the % difference of the geometric mean of HGF calculated from [Exp (β) − 1]*100.*
*Statistically significant results are in bold font: *P < 0.001; **P < 0.01.*
Model 1: unadjusted.
Model 2: adjusted for age, sex, race/ethnicity, education, income, health insurance and study site.
Interpretation: Ideal smoking was significantly associated with 11% lower HGF levels in model 2 [−11 (−12, −9)].

Prior studies in the MESA cohort have examined the association between HGF and CVD. One of these studies found that the risk of incident stroke was 17% greater with every standard deviation increase in circulating HGF independent of sociodemographic and CVD risk factors (7). Another study from the same cohort found that every standard deviation increase in circulating HGF was associated with 12% greater odds of having any coronary artery calcium and 20% increased risk of coronary heart disease after adjusting for traditional CVD risk factors (30). Furthermore, in another analysis from the MESA cohort, the risk of heart failure and heart failure with preserved ejection fraction was 59% and 90% higher, respectively, for participants with HGF levels in the 3rd tertile compared to those in the 1st tertile, independent of sociodemographic and CVD risk factors (31). These studies support our findings of an association between favorable CVH and lower levels of HGF since HGF is elevated in CVD as a response to endothelial damage (7). Factors that lead to HGF release may mediate the association between poorer CVH and incident CVD events.

In addition, our results showing that ideal CVH metrics (excluding total cholesterol) were associated with lower levels of HGF are supported by the findings from prior research. For example, Chen et al. (32) demonstrated that a history of current or previous smoking increases HGF expression in non-tumor lung tissue. The authors postulated that smoking increases HGF levels by activating HGF gene expression, however, the mechanism by which this process occurs is yet to be determined (32). Rehman et al. (10) showed that obesity was associated with more than three times increase in HGF levels and this finding was correlated linearly with BMI. The presence of excess adipose tissue may explain the association between poor BMI and elevated HGF (10). The explanation for the association between ideal physical activity and lower HGF levels is still under investigation.

In contrast to the inverse association for the other CVH metrics, we found that ideal cholesterol was paradoxically associated with higher HGF. This finding has also been observed in another study by Hiratsuka et al. (13) where participants with higher HGF levels in the fourth quartile had lower total cholesterol levels compared to those in the first quartile. However, the biological pathway responsible for the association between higher HGF levels and lower cholesterol levels is still unknown. Nakamura et al. (11) reported HGF levels in participants with hypertension was significantly higher than in participants without hypertension. In addition, Bancks et al. (12) observed that higher levels of circulating HGF was significantly associated with incident type 2 diabetes in the MESA cohort. These findings are not surprising given that hypertension and diabetes are associated with endothelial damage and dysfunction which may lead to elevated HGF levels (11, 12).

Our study revealed that poorer CVH was associated with higher HGF levels, therefore measuring HGF levels may be of utility in identifying people in poorer CVH because prior research has provided insight into the clinical significance of HGF as a risk marker for subclinical and clinical CVD (7, 8, 30). With the increasing burden and cost of managing CVD, effective interventions that promote favorable CVH are needed (33). These public health intervention programs should encourage lifestyle modification which will reduce the risk of developing CVD through several potential mechanisms including the reduction of endothelial injury as indicated by lower HGF levels (33).

Strengths and Limitations

Although this study was conducted in a large multi-ethnic population using standardized methods for data collection, our study findings should be interpreted with the consideration of some limitations. First, because this study is cross-sectional, we cannot determine temporality or make causal inferences for the association between CVH and HGF. Second, information collected from study participants for the individual CVH metrics such as smoking, diet and physical activity was from self-report questionnaires and may be subject to recall bias. Third, MESA study personnel assessed circulating HGF and not tissue-specific HGF, however, prior studies have shown that both measurements are correlated (8, 34). Fourth, selection of our study population was non-randomized. In addition, the participants were free of CVD at the time of study enrollment and may have been healthier compared to the general population, therefore limiting the generalizability of our findings. Finally, CVH was measured only at baseline and may not reflect the future CVH status of study participants.

CONCLUSION

In this multicenter cross-sectional study of adults free of CVD at baseline, we found that favorable CVH was associated with lower levels of HGF. Interventions aimed at promoting and preserving favorable CVH may reduce endothelial injury and decrease CVD

risk as indicated by lower serum HGF levels. However, there is need for prospective studies to examine the relationship between CVH and HGF to determine whether HGF levels can be modified by improvements in the CVH metrics. More research is needed to provide further understanding of the underlying mechanisms driving the associations.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because there are restrictions on sharing the actual MESA database because it has patient identifiers and protected health information and thus is subject to IRB approval. We have signed a data use agreement (DUA) with the MESA Coordinating Center that we cannot directly share data and that anyone with access to the data has to follow MESA policies and procedures for data use. We are not allowed to personally share the datasets and have to keep them stored securely in a Cloud using encrypted software for protection. However, other researchers may obtain the minimal dataset required to replicate our study's findings by submitting a proposal through the NIH BioLINCC (https://biolincc.nhlbi.nih.gov/studies/mesa/). Additionally, one can apply to the MESA Coordinating Center to become a new investigator after signing a DUA. The findings of this study should be easily reproducible through the methods described in this paper. Requests to access the datasets should be directed to Craig Johnson (wcraigj@uw.edu) at the Coordinating Center or at https://www.mesa-nhlbi.org/.

ETHICS STATEMENT

The MESA study protocol was approved by the Institutional Review Boards (IRB) at each recruitment center and informed consent was given by all participants. At Johns Hopkins University, this study was approved by the Johns Hopkins School of Medicine IRB applicant number NA_00030361. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

OOs, OOg, and EM: study conception and design and drafting of manuscript. OOs and OOg: acquisition of data and analysis. OOs, OOg, RF, CN, GB, NL, SB, and EM: interpretation of data and critical revision and approval of final version submitted. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.760281/full#supplementary-material

REFERENCES

1. Morishita R, Aoki M, Yo Y, Ogihara T. Hepatocyte growth factor as cardiovascular hormone: role of HGF in the pathogenesis of cardiovascular disease. *Endocr J.* (2002) 49:273–84. doi: 10.1507/endocrj.49.273
2. Shintani Y, Aoki H, Nishihara M, Ohno S, Furusho A, Hiromatsu S, et al. Hepatocyte growth factor promotes an anti-inflammatory cytokine profile in human abdominal aortic aneurysm tissue. *Atherosclerosis.* (2011) 216:307–12. doi: 10.1016/j.atherosclerosis.2011.02.025
3. Boros P, Miller CM. Hepatocyte growth factor: a multifunctional cytokine. *Lancet.* (1995) 345:293–5. doi: 10.1016/S0140-6736(95)90279-1
4. Forte G, Minieri M, Cossa P, Antenucci D, Sala M, Gnocchi V, et al. Hepatocyte growth factor effects on mesenchymal stem cells: proliferation, migration, and differentiation. *Stem Cells.* (2006) 24:23–33. doi: 10.1634/stemcells.2004-0176
5. Decker PA, Larson NB, Bell EJ, Pankow JS, Hanson NQ, Wassel CL, et al. Increased hepatocyte growth factor levels over 2 years are associated with coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J.* (2019) 213:30–4. doi: 10.1016/j.ahj.2019.03.018
6. Lamblin N, Susen S, Dagorn J, Mouquet F, Jude B, Van Belle E, et al. Prognostic significance of circulating levels of angiogenic cytokines in patients with congestive heart failure. *Am Heart J.* (2005) 150:137–43. doi: 10.1016/j.ahj.2005.03.047
7. Bell EJ, Larson NB, Decker PA, Pankow JS, Tsai MY, Hanson NQ, et al. Hepatocyte growth factor is positively associated with risk of stroke: the MESA (multi-ethnic study of atherosclerosis). *Stroke.* (2016) 47:2689–94. doi: 10.1161/STROKEAHA.116.014172
8. Bell EJ, Decker PA, Tsai MY, Pankow JS, Hanson NQ, Wassel CL, et al. Hepatocyte growth factor is associated with progression of atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis.* (2018) 272:162–7. doi: 10.1016/j.atherosclerosis.2018.03.040
9. Yamamoto Y, Kohara K, Tabara Y, Miki T. Association between carotid arterial remodeling and plasma concentration of circulating hepatocyte growth factor. *J Hypertens.* (2001) 19:1975–9. doi: 10.1097/00004872-200111000-00007
10. Rehman J, Considine RV, Bovenkerk JE Li J, Slavens CA, Jones RM, et al. Obesity is associated with increased levels of circulating

hepatocyte growth factor. *J Am Coll Cardiol.* (2003) 41:1408–13. doi: 10.1016/S0735-1097(03)00231-6
11. Nakamura Y, Morishita R, Nakamura S, Aoki M, Moriguchi A, Matsumoto K, et al. A vascular modulator, hepatocyte growth factor, is associated with systolic pressure. *Hypertension.* (1996) 28:409–13. doi: 10.1161/01.HYP.28.3.409
12. Bancks MP, Bielinski SJ, Decker PA, Hanson NQ, Larson NB, Sicotte H, et al. Circulating level of hepatocyte growth factor predicts incidence of type 2 diabetes mellitus: The Multi-Ethnic Study of Atherosclerosis (MESA). *Metabolism.* (2016) 65:64–72. doi: 10.1016/j.metabol.2015.10.023
13. Hiratsuka A, Adachi H, Fujiura Y, Yamagishi S, Hirai Y, Enomoto M, et al. Strong association between serum hepatocyte growth factor and metabolic syndrome. *J Clin Endocrinol Metab.* (2005) 90:2927–31. doi: 10.1210/jc.2004-1588
14. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* (2010) 121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703
15. Labarthe DR. From cardiovascular disease to cardiovascular health: a quiet revolution? *Circ Cardiovasc Qual Outcomes.* (2012) 5:e86–92. doi: 10.1161/CIRCOUTCOMES.111.964726
16. Angell SY, McConnell MV, Anderson CAM, Bibbins-Domingo K, Boyle DS, Capewell S, et al. The American Heart Association 2030 Impact Goal: A Presidential Advisory From the American Heart Association. *Circulation.* (2020) 141:e120–38. doi: 10.1161/CIR.0000000000000758
17. Roger VL, Sidney S, Fairchild AL, Howard VJ, Labarthe DR, Shay CM, et al. Recommendations for cardiovascular health and disease surveillance for 2030 and beyond: a policy statement from the American Heart Association. *Circulation.* (2020) 141:e104–19. doi: 10.1161/CIR.0000000000000756
18. Lane-Cordova AD, Kershaw K, Liu K, Herrington D, Lloyd-Jones DM. Association between cardiovascular health and endothelial function with future erectile dysfunction: the multi-ethnic study of atherosclerosis. *Am J Hypertens.* (2017) 30:815–21. doi: 10.1093/ajh/hpx060
19. Ogunmoroti O, Michos ED, Aronis KN, Salami JA, Blankstein R, Virani SS, et al. Life's simple 7 and the risk of atrial fibrillation: The Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis.* (2018) 275:174–81. doi: 10.1016/j.atherosclerosis.2018.05.050
20. Benson EA, Tibuakuu M, Zhao D, Akinkuolie AO, Otvos JD, Duprez DA, et al. Associations of ideal cardiovascular health with GlycA, a novel inflammatory marker: The Multi-Ethnic Study of Atherosclerosis. *Clin Cardiol.* (2018) 41:1439–45. doi: 10.1002/clc.23069
21. Osibogun O, Ogunmoroti O, Tibuakuu M, Benson EM, Michos ED. Sex differences in the association between ideal cardiovascular health and biomarkers of cardiovascular disease among adults in the United States: a cross-sectional analysis from the multiethnic study of atherosclerosis. *BMJ Open.* (2019) 9:e031414. doi: 10.1136/bmjopen-2019-031414
22. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol.* (2002) 156:871–81. doi: 10.1093/aje/kwf113
23. Ainsworth BE, Irwin ML, Addy CL, Whitt MC, Stolarczyk LM. Moderate physical activity patterns of minority women: the cross-cultural activity participation study. *J Womens Health Gend Based Med.* (1999) 8:805–13. doi: 10.1089/152460999319129
24. Unger E, Diez-Roux AV, Lloyd-Jones DM, Mujahid MS, Nettleton JA, Bertoni A, et al. Association of neighborhood characteristics with cardiovascular health in the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Qual Outcomes.* (2014) 7:524–31. doi: 10.1161/CIRCOUTCOMES.113.000698
25. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. *J Clin Epidemiol.* (1990) 43:1327–35. doi: 10.1016/0895-4356(90)90099-B
26. Mayer-Davis EJ, Vitolins MZ, Carmichael SL, Hemphill S, Tsaroucha G, Rushing J, et al. Validity and reproducibility of a food frequency interview in a multi-cultural epidemiology study. *Ann Epidemiol.* (1999) 9:314–24. doi: 10.1016/S1047-2797(98)00070-2
27. Lloyd-Jones DM. Improving the cardiovascular health of the US population. *JAMA.* (2012) 307:1314–6. doi: 10.1001/jama.2012.361
28. Osibogun O, Ogunmoroti O, Spatz ES, Fashanu OE, Michos ED. Ideal cardiovascular health and resting heart rate in the multi-ethnic study of atherosclerosis. *Prev Med.* (2020) 130:105890. doi: 10.1016/j.ypmed.2019.105890
29. Osibogun O, Ogunmoroti O, Spatz ES, Burke GL, Michos ED. Is self-rated health associated with ideal cardiovascular health? The multi-ethnic study of atherosclerosis. *Clin Cardiol.* (2018) 41:1154–63. doi: 10.1002/clc.22995
30. Bielinski SJ, Berardi C, Decker PA, Larson NB, Bell EJ, Pankow JS, et al. Hepatocyte growth factor demonstrates racial heterogeneity as a biomarker for coronary heart disease. *Heart.* (2017)103:1185–93. doi: 10.1136/heartjnl-2016-310450
31. Ferraro RA, Ogunmoroti O, Zhao D, Ndumele CE, Rao V, Pandey A, et al. Hepatocyte growth factor and incident heart failure subtypes: the multi-ethnic study of atherosclerosis (MESA). *J Card Fail.* (2021) 27:981–90. doi: 10.1016/j.cardfail.2021.04.022
32. Chen JT, Lin TS, Chow KC, Huang HH, Chiou SH, Chiang SF, et al. Cigarette smoking induces overexpression of hepatocyte growth factor in type II pneumocytes and lung cancer cells. *Am J Respir Cell Mol Biol.* (2006) 34:264–73. doi: 10.1165/rcmb.2005-0117OC
33. Labarthe DR, Dunbar SB. Global cardiovascular health promotion and disease prevention: 2011 and beyond. *Circulation.* (2012) 125:2667–76. doi: 10.1161/CIRCULATIONAHA.111.087726
34. Zhu Y, Hojo Y, Ikeda U, Shimada K. Production of hepatocyte growth factor during acute myocardial infarction. *Heart.* (2000) 83:450–5. doi: 10.1136/heart.83.4.450

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Prevalence of Metabolic Syndrome in Women After Maternal Complications of Pregnancy: An Observational Cohort Analysis

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Introduction: Certain complications of pregnancy, including hypertensive disorders of pregnancy, gestational diabetes mellitus, intrauterine growth restriction, spontaneous preterm birth, and placental abruption, are established independent risk factors for premature cardiovascular disease in women. Metabolic syndrome, which is associated with an increased risk of cardiovascular disease, may be a suitable alternative to traditional cardiovascular risk calculators that underestimate risk in young women. This study aimed to investigate the prevalence of metabolic syndrome in women who experienced a complicated pregnancy 6 months earlier.

Methods: This observational study investigated the prevalence of metabolic syndrome as defined by the International Diabetes Federation in all eligible participants ($n = 247$) attending a postpartum lifestyle intervention clinic from August 2018 to June 2021 at the Lyell McEwin Hospital in Adelaide, South Australia.

Results: A total of 89 (36%) participants met the criteria for metabolic syndrome at a mean follow up time of 7 months postpartum. Almost 90% of the cohort were abdominally obese, and over two thirds of the total cohort met at least two of the criteria for metabolic syndrome.

Conclusions: Women with a prior history of one of the common major pregnancy complications are at high risk of future cardiovascular and metabolic disease, with many showing either metabolic syndrome or multiple risk factors at only 7 months postpartum. The results indicate that follow-up within 1 year postpartum is an appropriate time to commence preventative strategies, as many women are already showing early signs of disease.

Keywords: metabolic syndrome, pregnancy complications, cardiovascular disease, cardiovascular disease prevention, women

INTRODUCTION

Cardiovascular disease (CVD) continues to be the leading cause of death for women worldwide, and rates of CVD and stroke are increasing in women aged <45 years (1, 2). Certain complications of pregnancy, including hypertensive disorders of pregnancy, gestational diabetes mellitus, intrauterine growth restriction, spontaneous preterm birth, and placental abruption, are established independent risk factors for premature cardiovascular disease in women (3–9). Despite this, awareness of the increased risk of CVD for women who have experienced at least one of these complications of pregnancy remains low (10, 11).

In 2011, the American Heart Association and the European Society of Cardiology updated their guidelines to include recommendations for monitoring women with a previous history of any of these complications (12, 13), an important step in recognizing the risk posed to this specific population of high-risk women. The Maternal Health Clinic in Ontario, Canada, was introduced in 2011 and is the first postpartum intervention for women with a recent history of complicated pregnancies, inviting eligible women to attend lifestyle education at 6 months postpartum (14). This model has been adopted across a number of sites worldwide in the last decade, and in recent years, a number of research-based postpartum interventions have also been developed. However, these research-based interventions are often opt-in research studies rather than routine outpatient care, tend to focus on specific complications of pregnancy, such as preeclampsia (15–18), and the effectiveness of these interventions at reducing cardiovascular and metabolic disease risk has not been rigorously assessed in a real-world clinic setting. The first nurse-led postpartum clinic in Australia was introduced in 2018 at the Lyell McEwin Hospital and aims to provide structured lifestyle and risk education (19). To our knowledge, this is the only published and freely available nurse-led model of care in Australia of standardized, routine, ongoing outpatient care for all eligible women who have experienced a serious complication of pregnancy. In most areas of Australia and the world, there remains little to no attention paid to women in this cohort, despite the recommendations for follow-up in national and international guidelines.

In the minority of women who do receive follow up after a complicated pregnancy, there remains the difficulty of effectively communicating risks to women. The currently available cardiovascular risk scores have been developed using acute coronary syndrome thresholds found in predominantly male populations, reducing their reliability for use in women (20). The vast majority also fail to consider early changes in cardiovascular measures as well as the young age of the study population, which conceals the high-risk, long-term impact of a complication of pregnancy (21). The Absolute Cardiovascular Disease Risk Calculator, for example, is commonly used by general practitioners in Australia for calculating cardiovascular risk in adults, and is recommended by the Australian Heart Foundation. However, there is minimal evidence supporting its use in people aged less than 30 years old, and limited strong evidence for people aged 30–45 years (22). Current cardiovascular risk calculators are therefore not appropriate tools for detecting subclinical disease in and communicating risk to young women. A lack of a clear and effective way to explain risk to women may reduce the impact of preventative strategies.

Metabolic syndrome is defined as a 'cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure' (23, 24). Metabolic syndrome is associated with a 4-fold higher risk of developing cardiovascular disease in women and 2-fold higher risk in men (25). Considering the lack of availability of appropriate cardiovascular risk scores for younger women, metabolic syndrome may be an appropriate alternative for assessing and communicating the high long-term risk to women who are at low short-term risk of CVD. However, the prevalence of metabolic syndrome in young women is not well-documented, especially in socioeconomically disadvantaged cohorts where it may be higher (26). Therefore, investigating the prevalence of metabolic syndrome is the first step in understanding the risk of future cardiovascular disease in these populations.

The primary objective of this research is to investigate the prevalence of metabolic syndrome in a cohort of women who experienced a severe maternal complication of pregnancy 6 months earlier. The secondary objectives were to explore the presence of socioeconomic, metabolic, and cardiovascular risk factors in this cohort.

METHODS

Study Design

This was an observational study of women attending the postpartum lifestyle intervention clinic from 7th August 2018 to 30th June 2021 at the Lyell McEwin Hospital, located within the Northern Adelaide Local Health Network (NALHN), South Australia (19). The Central Adelaide Local Health Network Human Research Ethics Committee approved the study [HREC/16/TQEH/258].

Study Participants

To be eligible for referral to the postpartum intervention clinic, patients must have experienced at least one of the following complications in their index pregnancy:

- Hypertensive disorders of pregnancy (including gestational hypertension, preeclampsia, eclampsia and HELLP syndrome), requiring medical therapy or resulting in birth <37 weeks' gestation. Hypertensive disorders were diagnosed according to criteria defined by the International Society for the Study of Hypertension in Pregnancy (27).
- Gestational diabetes mellitus, diagnosed according to HAPO criteria (28, 29) requiring metformin or insulin therapy.
- Spontaneous preterm birth <34 weeks' gestation.
- Intrauterine growth restriction indicated by serial ultrasound measurements, estimated fetal weight, and umbilical artery doppler, or delivery of a small for gestational age infant at <5th customized birth centile, as per South Australian Perinatal Practice Guidelines (30, 31).
- Placental abruption.

Study Setting

The Lyell McEwin Hospital is a public tertiary acute-care facility providing obstetric care, adult cardiac and intensive care services, and neonatal care for infants for ≥32 weeks' gestation. Located within the NALHN catchment area, the Lyell McEwin Hospital services a population of approximately 400,000 people in the northern and north-eastern suburbs of Adelaide, South Australia. The NALHN area is characterized by a population with low socioeconomic status with high rates of CVD morbidity and mortality, and is among Australia's most disadvantaged suburban communities (32).

Study Procedures

The postpartum intervention is a hospital-based outpatient clinical service with an associated quality assurance registry, the methods of both have been previously described (19). Briefly, eligible patients are offered appointments at approximately 6 and 18 months postpartum to undergo a thorough health assessment and receive individualized health counseling from an expert nurse practitioner. Variables are collected from a combination of patient self-report and abstraction from the hospital medical record. Information collated and included in the registry includes patient demographics, medical history, family history, current medications, alcohol, drug and smoking practices, obstetric history, cardiovascular and metabolic screening pathology results, peripheral and central blood pressure, augmentation index, pulse rate, height, weight, and waist circumference. Blood pressure, augmentation index, and pulse rate were measured using an oscillometric pulse wave analysis device, the USCOM BP+ [USCOM, Sydney, Australia]. This device has been previously validated against aneroid blood pressure measurements (33).

Outcomes

The primary outcome of interest for this study was prevalence of metabolic syndrome at approximately 6-months postpartum.

Metabolic syndrome was defined as the presence of any three of the following five risk factors (24):

- Elevated waist circumference with ethnicity specific values defined by the International Diabetes Federation (23), which for women is ≥80 cm for all ethnicities.
- Elevated triglycerides of ≥1.7 mmol/L, or drug treatment for this lipid abnormality.
- Reduced HDL cholesterol of <1.3 mmol/L, or drug treatment for this lipid abnormality.
- Elevated systolic blood pressure of ≥130 mmHg and/or diastolic blood pressure of ≥85 mmHg, or antihypertensive drug treatment.
- Elevated fasting glucose of ≥5.6 mmol/L, or drug treatment of elevated glucose.

Secondary outcomes were individual cardiovascular and metabolic risk factors and included current smoking, waist circumference, BMI, peripheral and central systolic blood pressure, peripheral and central diastolic blood pressure, pulse rate, augmentation index, triglycerides, HDL cholesterol, fasting plasma glucose, and fasting insulin. Demographic outcomes recorded included ethnicity, country of birth, preferred language, level of education, employment status, marital status, and combined household income. Area-level socioeconomic status was recorded using the Socio-Economic Indexes for Areas (SEIFA), specifically the Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD).

Analysis

Continuous variables are presented as mean and standard deviation for normally distributed variables, and median and interquartile range for non-normally distributed variables. Categorical data are presented as count and percentage. Participants with metabolic syndrome at 6 months postpartum were compared to the reference group, which was comprised of participants without metabolic syndrome. As this study presented purely descriptive data and no inferences could be made, no statistical tests were performed. All descriptive analyses were conducted using IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY: IBM Corp).

Participants were only included in this study if their metabolic syndrome status could be confirmed. Therefore, those with abdominal obesity who did not complete biochemistry were excluded, as metabolic syndrome status could not be confirmed. Participants who were pregnant again at the time of their appointment were also excluded due to the inability to accurately determine abdominal obesity and the influence of the pregnancy on blood pressure, maternal lipids, and glucose.

COVID-19 Considerations

During the study period, the postpartum intervention clinic was required to close for two separate periods, firstly between 1st April 2020 and 20th May 2020, and then again between 20th and 27th of July 2021, due to COVID-19 lockdowns. During these periods, appointments were unable to take place and patients with scheduled appointments were planned to be rescheduled upon the clinic reopening. Online and telehealth consults were not offered due to the impossibility of obtaining accurate anthropometric measurements (including blood pressure, height, weight, and waist circumference) and performing physical assessments.

RESULTS

A total of 517 eligible women were offered appointments at the postpartum intervention clinic during the study timeframe. A total of 261 participants (50.4%) attended appointments and were included in the registry. Ten participants were excluded from the present analysis as they had not completed their biochemistry testing and metabolic syndrome status was unable to be determined. Another four participants were excluded due to being pregnant at their first postpartum appointment. This resulted in a final cohort of 247 for analysis in the present study.

Descriptive statistics for metabolic measures and socioeconomic factors at time of appointment are presented in

TABLE 1 | Maternal characteristics according to maternal metabolic syndrome status at first postpartum appointment.

Variable	Value, mean ± SD or n (%)					
	Total cohort	**Total, *n***	**MetS *n* = 89 (36%)**	**Total, *n***	**No MetS *n* = 158 (64%)**	**Total, *n***
Time to follow-up, months	7.13 ± 2.2	247	7.4 ± 2.1	89	7.0 ± 2.3	158
Age, years	32.8 ± 5.2	247	33.3 ± 5.2	89	32.6 ± 5.2	158
Gravidity at time of referral, n	2.8 ± 1.7	247	3 ± 2.0	89	2.7 ± 1.6	158
Pregnancy booking BMI, kg/m^2	30.6 ± 8.0	242	33.8 ± 7.7	88	28.7 ± 7.7	154
Cardiovascular and metabolic risk factors						
BMI, kg/m^2	31.62 ± 7.9	247	35.8 ± 7.9	89	29.3 ± 6.9	158
Waist circumference, cm	98.30 ± 17.7	246	107.8 ± 16.6	89	92.9 ± 15.9	157
Peripheral SBP, mmHg	123 ± 13	245	127 ± 13	88	120 ± 12	157
Peripheral DBP, mmHg	74 ± 10	245	78 ± 10	88	72 ± 10	157
Central SBP, mmHg	116.0 ± 13.5	238	120.6 ± 13.0	86	113.4 ± 13.1	152
Central DBP, mmHg	76.6 ± 10.5	238	80.4 ± 10.0	86	74.36 ± 10.1	152
Pulse rate, bpm	74.6 ± 11.0	245	77.1 ± 12.2	88	73.2 ± 10.0	157
Augmentation index, %	76.4 ± 28.9	238	77.5 ± 28.5	86	75.8 ± 28.5	152
Triglycerides, mmol/L	1.33 ± 0.8	242	1.9 ± 0.8	88	1.0 ± 0.6	154
HDL cholesterol, mmol/L	1.37 ± 1.0	241	1.1 ± 0.2	88	1.5 ± 1.2	153
Glucose, mmol/L	5.24 ± 1.34	240	5.7 ± 1.5	86	5.0 ± 1.2	154
Insulin, μ/L	15.60 ± 13.7	237	23.4 ± 1.7	86	11.2 ± 10.1	151
Current smoking	23 (9.3)	247	10 (11.2)	89	13 (8.2)	158
T2DM	11 (4.5)	247	8 (9.0)	89	3 (1.9)	158
T1DM	4 (1.6)	247	0 (0)	89	4 (2.5)	158
Hypertension	16 (6.5)	247	13 (14.6)	89	3 (1.9)	158
Demographics						
Born in Australia	133 (53.8)	247	48 (53.9)	89	85 (53.8)	158
Interpreter required	43 (17.4)	247	16 (18.0)	89	27 (17.1)	158
Ethnicity		247		89		158
Caucasian	135 (54.7)		49 (55.1)		86 (54.4)	
Chinese & other Asian	50 (20.2)		20 (22.5)		30 (19.0)	
Middle eastern	22 (8.9)		9 (10.1)		13 (8.2)	
Indian subcontinent	20 (8.1)		7 (7.9)		13 (8.2)	
African	14 (5.7)		2 (2.2)		12 (7.6)	
Hispanic	2 (0.8)		1 (1.1)		1 (0.6)	
Aboriginal	4 (1.6)		1 (1.1)		3 (1.9)	
Marital status		247		89		158
Married	174 (70.4)		61 (68.5)		113 (71.5)	
De facto	49 (19.8)		17 (19.1)		32 (20.3)	
Single	19 (7.7)		10 (11.2)		9 (5.7)	
Relationship, not living together	4 (1.6)		1 (1.1)		3 (1.9)	
Separated	1 (0.4)		0 (0)		1 (0.6)	
Level of education		247		89		158
Unknown	27 (10.9)		13 (14.6)		14 (8.9)	
<= Year 10	15 (6.1)		6 (6.7)		9 (5.7)	
Year 11	12 (4.9)		2 (2.2)		10 (6.3)	
Year 12	33 (13.4)		14 (15.7)		19 (12.0)	
TAFE certificate/diploma	96 (38.9)		36 (40.4)		60 (38.0)	
Bachelor	48 (19.4)		14 (15.7)		34 (21.5)	
Higher degree	16 (6.5)		4 (4.5)		12 (7.6)	
Currently employed	130 (53.8)	247	37 (41.6)	89	93 (58.9)	158
Type of employment		247		89		158
Maternity leave	73 (29.6)		21 (23.6)		52 (32.9)	
Full-time	8 (3.2)		5 (5.6)		3 (1.9)	
Part-time	25 (10.1)		4 (4.5)		21 (13.3)	
Casual	22 (8.9)		6 (6.7)		16 (10.1)	
Student	2 (0.8) 117		1 (1.1)		1 (0.6)	
None	(47.4)		52 (58.4)		65 (41.1)	

(Continued)

TABLE 1 | Continued

Variable	Value, mean ± SD or n (%)					
	Total cohort	**Total, *n***	**MetS *n* = 89 (36%)**	**Total, *n***	**No MetS *n* = 158 (64%)**	**Total, *n***
Annual household income		247		89		158
$205,000	2 (0.8)		0 (0)		2 (1.3)	
$105–205,000	39 (15.8)		9 (10.1)		30 (19.0)	
$70–100,000	54 (21.9)		21 (23.6)		33 (20.9)	
$40–70,000	43 (17.4)		16 (18.0)		27 (17.1)	
$20–40,000	15 (6.1)		4 (4.5)		11 (7.0)	
<= $20,000	9 (3.6)		4 (4.5)		5 (3.2)	
Unknown or declined to answer	85 (34.4)		35 (39.3)		50 (31.6)	
SEIFA - IRSAD	920.5 ± 65.4	247	916.2 ± 69.9	89	922.9 ± 62.7	158

SD, standard deviation; MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; TAFE, technical and further education; SEIFA, socioeconomic index for area; IRSD, index of relative socioeconomic disadvantage; IRSAD, index of relative socioeconomic advantage and disadvantage; IEO, index of education and occupation; IER, index of economic resources.

Table 1. The mean time to follow up was 7 months postpartum, with a range of 4–21 months. Delayed appointments were caused by numerous factors, including: clinic closure due to COVID-19, multiple rescheduled appointments due to maternal request/illness, missed or late referrals to the service, and administrative issues.

Overall, 89 (36%) of the participants met the criteria for metabolic syndrome. The mean age of women seen in the postpartum intervention clinic was 32.8 years, with a BMI of 31.62 kg/m^2. Sixteen and eleven women had been diagnosed with hypertension and type 2 diabetes prior to their first postpartum appointment, respectively. Half of the cohort was Caucasian and born in Australia, and most were married or in de facto relationships.

When comparing those women with and without metabolic syndrome, there were differences in all metabolic measures, as expected. There was also a higher number of participants with previously diagnosed type 2 diabetes and hypertension in the metabolic syndrome group. There were no differences in socioeconomic measures between groups, excepting employment status. Employment rates were higher in participants that did not have metabolic syndrome (58.9%) vs. those with metabolic syndrome (41.6%).

Table 2 presents metabolic and cardiovascular risk factors for the total cohort and comparing between metabolic syndrome status groups. Overall, 89.5% of the cohort had abdominal obesity at the time of their appointment, and over 90% of the cohort fulfilled at least one criterion for metabolic syndrome (including, but not necessarily meeting the abdominal obesity requirement).

The breakdown of referring pregnancy complications is presented in **Table 3**. There were no differences between the metabolic syndrome group and the group without metabolic syndrome, although there was a slightly higher percentage of gestational diabetes in the metabolic syndrome group. Gestational diabetes was the most frequent reason for referral to the clinic (71.7%), followed by hypertensive disorders of pregnancy (32.4%).

DISCUSSION

In this prospective cohort of 247 participants with a major prior pregnancy complication, over one-third (36%) of the cohort met the criteria for metabolic syndrome 6months after pregnancy. This indicates that these young women are at detectably high risk of future cardiovascular disease. Worryingly, two-thirds (67.5%) of the whole cohort met at least two of the metabolic syndrome criteria, and 89.5% had abdominal obesity with a BMI >30 kg/m^2 and/or waist circumference ≥80 cm, irrespective of metabolic syndrome. In the group without metabolic syndrome, 89.6% met at least one of the metabolic syndrome criteria. This suggests that, even in those without metabolic syndrome, the vast majority of women in this cohort are at least obese and therefore on a trajectory to additional cardiovascular and metabolic disease risk. Although metabolic syndrome status prior to pregnancy was not able to be determined, pregnancy booking BMI, taken at the time of the antenatal triage appointment in the first trimester, was significantly higher in the group of participants who had metabolic syndrome postpartum (33.8 kg/m^2) vs. those without (28.7 kg/m^2), suggesting that metabolic syndrome was likely already present in a number of the cohort prior to conception.

Previous studies have found that women with a history of pregnancy complications show increased risk and subclinical signs of chronic disease early after pregnancy. The prevalence of metabolic syndrome in this study was more than twice that found in a Canadian study by Cusimano and colleagues, which reported that 17.4% of women had metabolic syndrome at 6 months postpartum following a complicated pregnancy (34). Their cohort included women of any gravidity with the same complications of pregnancy who were included in our study, and therefore their results are directly comparable to those presented in this analysis. The disparity in prevalence of metabolic syndrome between cohorts demonstrate how risk and health status may vary greatly between populations, emphasizing the need for analyzing and understanding the risk profile of local cohorts when introducing preventative strategies.

TABLE 2 | Metabolic syndrome and cardiovascular risk factors present in total cohort.

Variable	Value, n (%)					
	Whole cohort	Total, *n*	MetS	Total, *n*	No MetS	Total, *n*
Abdominal obesity: add BMI + WC	221 (89.5)	247	89 (100)	89	132 (83.5)	158
Reduced HDL cholesterol: <1.29 mmol/L or treatment for this lipid abnormality	113 (46.8)	241	76 (86.4)	88	37 (24.2)	153
Raised triglycerides: ≥1.7 mmol/L or treatment for this lipid abnormality	62 (25.6)	242	54 (61.4)	88	8 (5.2)	154
Raised fasting plasma glucose: ≥5.6 mmol/L or treatment for T2DM	48 (19.8)	242	39 (44.3)	88	9 (5.8)	154
Additional risk factors						
Raised fasting plasma glucose: ≥5.6 mmol/L, treatment for T2DM or raised fasting insulin: ≥12 μ/L	132 (55.5)	238	77 (88.5)	87	55 (36.4)	151
Treated hypertension, SBP ≥135mmHg or DBP ≥85mmHg	75 (30.6)	245	48 (54.5)	88	27 (17.2)	157
Current smoking	23 (9.3)	247	10 (11.2)	89	13 (8.2)	158
Number of MetS risk factors present*		243		89		154
0	16 (6.6)		0 (0)		16 (10.4)	
1	63 (25.9)		0 (0)		63 (40.9)	
2	76 (31.3)		1 (1.1)		75 (48.7)	
3	54 (22.2)		54 (60.7)		0 (0)	
4	27 (11.1)		27 (30.3)		0 (0)	
5	7 (2.9)		7 (7.9)		0 (0)	

** Includes any one criterion for metabolic syndrome, whether or not abdominal obesity is present.*
MetS, metabolic syndrome; HDL, high-density lipoprotein; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure.

There are some previous studies exploring metabolic syndrome both in pregnancy and after pregnancy complications. A study of the Screening for Pregnancy Endpoints (SCOPE) cohort found that 29.4% of nulliparous women recruited from the Adelaide, South Australia, site had metabolic syndrome at 15 weeks' gestation (35). These participants were recruited in 2005–2008 from the same hospital as the cohort in the present study. Although the study included healthy nulliparous women without pre-existing hypertension and/or diabetes, most of whom went on to have an uncomplicated pregnancy, the lower percentage of metabolic syndrome reported in a very similar population could suggest that rates may have increased over the last 15 years. The higher prevalence of metabolic syndrome in our cohort also suggests that we are referring the right individuals for further follow up and education.

Another study found 34% of women with a history of hypertensive disorders of pregnancy had metabolic syndrome 2.5 years after the index pregnancy, compared to only 5% of those who had had a normotensive pregnancy (36). This is a similar percentage to our cohort (36%) but our women were followed up much earlier in the postpartum period. It is possible that, especially without intervention, we would see an increase in the rate of metabolic syndrome in our cohort over time. However, Smith and colleagues followed women with a history of preeclampsia and found that the prevalence of metabolic syndrome did not change from 1 to 3 years postpartum (37). Further research should explore the progression of metabolic syndrome over time, especially in women with a history of the complications not characterized by hypertension. Although the current study was not able to address progression of metabolic syndrome without intervention, the results indicate that due to a high prevalence of metabolic syndrome at 6 months postpartum, commencing follow-up and education strategies within 1 year postpartum is appropriate.

TABLE 3 | Index pregnancy complications of cohort* ($n = 247$).

Variable	Value, *n* (%)		
	Total cohort *N* = 247	MetS *N* = 89	No MetS *N* = 158
Hypertensive disorder of pregnancy	80 (32.4)	33 (37.1)	47 (29.7)
Gestational diabetes	177 (71.7)	70 (78.7)	107 (67.7)
Placental abruption	4 (1.6)	1 (1.1)	3 (1.9)
Intrauterine growth restriction	17 (6.9)	4 (4.5)	13 (8.2)
Spontaneous preterm birth	5 (2.0)	2 (2.2)	3 (1.9)

** Participants may have experienced more than one complication; the pregnancy complication categories are not mutually exclusive. These complications include only those listed on the referral, which is made at time of discharge from delivery of infant. Only complications experienced in the index pregnancy were considered during the referral process.*
MetS, metabolic syndrome.

In the existing literature, less attention has been paid to the rarer complications of pregnancy, including intrauterine growth restriction, spontaneous preterm birth, and placental abruption. Underweight women are at higher risk of having a growth restricted infant (38), and would therefore not meet the essential abdominal obesity criterion of metabolic syndrome. However, one study exploring women with previous delivery of a small for gestational age infant reported 7.6% had metabolic syndrome (as defined by the World Health Organization) after pregnancy (39). Another small study found that women with metabolic syndrome early in pregnancy were almost three times more likely to deliver preterm compared to those without metabolic syndrome (40). Our study was unable to show any differences in metabolic syndrome prevalence between complications of pregnancy due to small numbers, but further research in these groups should be conducted.

This study also explored differences in individual- and area-level socioeconomic factors between those with metabolic syndrome and those without, although there were no noticeable differences in any of these except for employment status. Although women with metabolic syndrome were less likely to be employed (41.6) compared to those without metabolic syndrome (58.9), the data may not capture an accurate reflection of employment history, as some women may have been previously employed but recently ceased working due to caring responsibilities for their new infant. We did not collect data on future employment plans or recent employment history. There were also missing data in education (10.9%) and income variables, with 34.4% of the cohort either declining to answer or reporting not knowing their household income. Previous literature has reported a relationship between low socioeconomic status (determined using one or a combination of level of education, income, and employment) and higher incidence of metabolic syndrome, especially for women (41–45). The lack of differences in the present analysis may be due to the small sample size or the heterogeneity of the participants. Further socioeconomic analyses of this cohort will be conducted as more women are included in the quality assurance registry.

The high prevalence of metabolic syndrome, and the high percentage of modifiable metabolic and cardiovascular disease risk factors, in our cohort provide justification for the need for early postpartum intervention with ongoing follow up for women who experience complicated pregnancies. In the literature, it is evident that many women remain unaware of the risk posed to them after having a complicated pregnancy. Follow up for cardiovascular risk screening after hypertensive disorders of pregnancy remains minimal (46), with most women reporting low personal awareness of cardiovascular disease risk (11). Even after being informed of their increased risk, most women attending the Maternal Health Clinic in Canada continued to underestimate their risk (10). Furthermore, women with gestational diabetes also underestimate their risk of developing type 2 diabetes (47), generally tend to not adopt healthy lifestyles postpartum (48), and report a number of barriers to making healthy lifestyle changes (49). It is therefore vital to provide structured follow up care for these patients to encourage positive lifestyle modifications as soon as possible.

The attendance rate to the intervention clinic was only just over 50% during the study timeframe, and the current analysis did not capture data from women who did not attend their appointment, so inclusion bias in the present study is highly likely. Although not explored in this analysis, previous research from the Maternal Health Clinic in Canada found that women choosing not to attend had more adverse metabolic and social risk profiles than those who did attend (50). This could indicate that the women in our population most in need of intervention are not engaging with preventative health services. Future research into how to improve engagement is required. Introduction of positive health messages during pregnancy and ideally prior to conception may be of additional benefit. A previous systematic review found that dietary and lifestyle interventions introduced during pregnancy have the potential for reducing the risk of developing preeclampsia (51).

Another factor that may have influenced the attendance rate is the COVID-19 pandemic. COVID-19 lockdowns resulted in the postpartum intervention clinic closing for two separate periods during the study. Although women were re-offered appointments upon reopening, we expect that attendance was at least in part influenced by general concerns about attending healthcare facilities during the pandemic, when the general population were strongly encouraged to avoid leaving their homes unless absolutely necessary. Since 2022, online consultations have been offered by the postpartum clinic due to ongoing pandemic restrictions on outpatient services, however online or telehealth consults introduce further difficulties as measurements and physical assessments cannot be performed. Remote consults are also impractical for non-English speaking patients who require an interpreter.

There are several limitations of the present study that warrant discussion. The postpartum clinic's eligibility criteria are currently limited to the most severe examples of complications of pregnancy and do not include women with unmedicated hypertensive disorders of pregnancy or gestational diabetes. If unmedicated participants were also included, the overall prevalence of metabolic syndrome may have been reduced. Furthermore, there are no data available on the prevalence of metabolic syndrome in women with healthy pregnancies or in the wider population of young women from which our cohort was recruited, and so the prevalence reported in this study may be reflective of the broader profile of our population. Only prospective data were recorded at the time of the postpartum appointment, so no historical socioeconomic information (for example, the socioeconomic status the women were raised in) were available. Finally, the data in this study were collected from a unique outpatient service in a highly disadvantaged community, and therefore the prevalence of metabolic syndrome may not reflect that of other settings.

A strength of this study included using complete metabolic syndrome diagnostic criteria instead of traditional cardiovascular risk calculators to provide a more accurate reflection of risk. We were also able to collect a comprehensive dataset for inclusion in the registry, which will continue to collect data for future in-depth analyses as this cohort grows.

CONCLUSION

The results of this study highlight the need for ongoing follow-up services for women who have had a complication of pregnancy, as they are at high risk of future metabolic and cardiovascular disease. Pregnancy and the early postpartum period are opportune times to engage with high-risk women about their increased risk due to increased contact with the healthcare system. Future research should focus on improving engagement with postpartum interventions, exploring the effectiveness of preventative services in the reduction of metabolic syndrome, and development of other methods of calculating cardiovascular risk in this disadvantaged population.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available as the authors are not permitted to share datasets due to ethical requirements. Requests to access the datasets should be directed to Emily Aldridge, emily.aldridge@adelaide.edu.au.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by Central Adelaide Local Health Network Human Research Ethics Committee (CALHN HREC). The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

EA designed the study, collected the data, performed data analysis, and prepared the manuscript. MP and SS assisted with data collection. SYL provided statistical analysis support. CTR, GAD, and MAA supervised the study. All authors edited the draft manuscript, provided critical feedback, and approved the final manuscript.

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REFERENCES

1. Khan SU, Yedlapati SH, Lone AN, Khan MS, Wenger NK, Watson KE, et al. A comparative analysis of premature heart disease- and cancer-related mortality in women in the USA, 1999–2018. *Eur Hear J - Qual Care Clin Outcomes.* (2021). doi: 10.1093/ehjqcco/qcaa099
2. Australian Institute of Health and Welfare. Cardiovascular disease in Australian women - a snapshot of national statistics. *Canberra*. (2019).
3. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C Zaman A Fryer AA Kadam U Chew-Graham CA, et al. Preeclampsia and future cardiovascular health: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. (2017) 10:347. doi: 10.1161/CIRCOUTCOMES.116.003497
4. Wu P, Gulati M, Kwok CS, Wong CW, Narain A, O'Brien S, Chew-Graham CA, Verma G, Kadam UT, Mamas MA. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc.* (2018) 7:7809. doi: 10.1161/JAHA.117.007809
5. Andraweera PH, Dekker GA, Arstall M, Bianco-Miotto T, Roberts CT. Complications of pregnancy and future cardiovascular risk. In: Vasan R, Sawyer D, editors. Encyclopedia of Cardiovascular Research and Medicine, Vol. 1. Oxford: *Elsevier Inc.* (2018) p. 643–50. doi: 10.1016/b978-0-12-809657-4.99726-6
6. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. (2005) 366:1797–803. doi: 10.1016/S0140-6736(05)67726-4
7. Ngo AD, Roberts CL, Chen JS, Figtree G. Delivery of a small-for-gestational-age infant and risk of maternal cardiovascular disease - a population-based record linkage study. *Hear Lung Circ.* (2015) 24:696–704. doi: 10.1016/j.hlc.2015.01.004
8. Neiger R. Long-term effects of pregnancy complications on maternal health: a review. *J Clin Med.* (2017) 6:76. doi: 10.3390/jcm6080076
9. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia*. (2019) 62:480. doi: 10.1007/s00125-019-4840-2
10. Chan SE, Nowik CM, Pudwell J, Smith GN. Standardized postpartum follow-up for women with pregnancy complications: barriers to access and perceptions of maternal cardiovascular risk. *J Obstet Gynaecol Can.* (2021) 43:746–55. doi: 10.1016/j.jogc.2021.03.006
11. Hutchesson M, Shrewsbury V, Park F, Callister R, Collins C. Are women with a recent diagnosis of pre-eclampsia aware of their cardiovascular disease risk? A cross-sectional survey. *Aust New Zeal J Obstet Gynaecol.* (2018) 58:E27–8. doi: 10.1111/ajo.12900
12. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update a guideline from the american heart association. *J Am Coll Cardiol.* (2011) 57:1404–23. doi: 10.1016/j.jacc.2011.02.005
13. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J.* (2011) 32:3147–97. doi: 10.1093/eurheartj/ehr218
14. Smith GN, Pudwell J, Roddy M. The maternal health clinic: a new window of opportunity for early heart disease risk screening and intervention for women with pregnancy complications. *J Obs Gynaecol Can.* (2013) 35:831–839. Available online at: http://www.ncbi.nlm.nih.gov/pubmed/24099450
15. Henry A, Arnott C, Makris A, Davis G, Hennessy A, Beech A, et al. Blood pressure postpartum (BP2) RCT protocol: follow-up and lifestyle behaviour change strategies in the first 12 months after hypertensive pregnancy. *Pregnancy Hypertens.* (2020) 22:1–6. doi: 10.1016/j.preghy.2020.07.001
16. Taylor R, Shrewsbury VA, Vincze L, Campbell L, Callister R, Park F, et al. Be Healthe for your heart: protocol for a pilot randomized controlled trial evaluating a web-based behavioral intervention to improve the cardiovascular health of women with a history of preeclampsia. *Front Cardiovasc Med.* (2019) 6:144. doi: 10.3389/FCVM.2019.00144
17. Kamravamanesh M, Kohan S, Rezavand N, Farajzadegan Z. A comprehensive postpartum follow-up health care program for women with history of preeclampsia: protocol for a mixed methods research. *Reprod Heal.* (2018) 15:1–8. doi: 10.1186/S12978-018-0521-8
18. Haugdahl HS, Sandsæter HL, Lysne M, Bjerkeset O, Uhrenfeldt L, Horn J. Postpartum lifestyle interventions among women with pre-eclampsia: a scoping review protocol. *BMJ Open.* (2020) 10:e035507. doi: 10.1136/BMJOPEN-2019-035507
19. Aldridge E, Verburg PE, Sierp S, Andraweera P, Dekker GA, Roberts CT, et al. A protocol for nurse-practitioner led cardiovascular follow-up after pregnancy complications in a socioeconomically disadvantaged population. *Front Cardiovasc Med.* (2020) 6:184. doi: 10.3389/fcvm.2019.00184
20. Garcia M, Mulvagh SL, Merz CNB, Buring JE, Manson JAE. Cardiovascular disease in women: clinical perspectives. *Circ Res.* (2016) 118:1273–93. doi: 10.1161/CIRCRESAHA.116.307547

21. Arnott C, Patel S, Hyett J, Jennings G, Woodward M, Celermajer DS. Women and cardiovascular disease: pregnancy, the forgotten risk factor. *Hear Lung Circ.* (2020) 29:662–7. doi: 10.1016/j.hlc.2019.09.011
22. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. (2012). Available online at: https://www.heartfoundation.org.au/getmedia/6db03c7d-3092-4f3b-949d-ce3bdd94a6ee/Absolute-CVD-Risk-Full-Guidelines_1.pdf
23. International Diabetes Federation. *The IDF Consensus Worldwide Definition of the Metabolic Syndrome*. Brussels (2006).
24. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International. *Circulation.* (2009) 120:1640–5. doi: 10.1161/CIRCULATIONAHA.109.192644
25. Bonora E. The metabolic syndrome and cardiovascular disease. *Ann Med.* (2006) 38:64–80. doi: 10.1080/07853890500401234
26. Blanquet M, Legrand A, Pélissier A, Mourgues C. Socio-economics status and metabolic syndrome: a meta-analysis. *Diabetes Metab Syndr Clin Res Rev.* (2019) 13:1805–12. doi: 10.1016/j.dsx.2019.04.003
27. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertension.* (2018) 72:24–43. doi: 10.1161/HYPERTENSIONAHA.117.10803
28. HAPO Study Cooperative Research Group. Hyperglycemiaand adverse pregnancy outcomes. *N Engl J Med.* (2008) 358:1991–2002. doi: 10.1056/NEJMoa0707943.
29. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a world health organization guideline. *Diabetes Res Clin Pract.* (2014) 103:341–363. doi: 10.1016/j.diabres.2013.10.012
30. Department of Health Government of South Australia. South Australia Perinatal Practice Guidelines: Fetal Growth (Restricted) (2011). Available online at: https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs+and+practice+guidelines/womens+and+babies+health/perinatal/perinatal+practice+guidelines/perinatal+practice+guidelines
31. Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. *Am J Obstet Gynecol.* (2011) 204:288–300. doi: 10.1016/J.AJOG.2010.08.055
32. Heart Foundation Australia. Cardiovascular disease map by South Australian local health network. Available online at: https://www.heartfoundation.org.au/assets/HeartMaps/SouthAust/lhn-map/StatPlanet.html
33. Aldridge E, Mollen J, Verburg PE, Wittwer M, Dekker G, Roberts CT, et al. Agreement of aneroid and oscillometric blood pressure devices used in pregnancy. *Pregnancy Hypertens.* (2019) 17:43–8. doi: 10.1016/j.preghy.2019.05.005
34. Cusimano MC, Pudwell J, Roddy M, Cho CK, Smith GN. The maternal health clinic: an initiative for cardiovascular risk identification in women with pregnancy-related complications. *Am J Obs Gynecol.* (2014) 210:438. doi: 10.1016/j.ajog.2013.12.001
35. Grieger JA, Bianco-Miotto T, Grzeskowiak LE, Leemaqz SY, Poston L, McCowan LM, et al. Metabolic syndrome in pregnancy and risk for adverse pregnancy outcomes: a prospective cohort of nulliparous women. *PLoS Med.* (2018) 15:e1002710. doi: 10.1371/journal.pmed.1002710
36. Hermes W, Franx A, Van Pampus MG, Bloemenkamp KWM, Bots ML, Van Der Post JA, et al. Cardiovascular risk factors in women who had hypertensive disorders late in pregnancy: a cohort study. *Am J Obstet Gynecol.* (2013) 208:474. doi: 10.1016/j.ajog.2013.02.016
37. Smith GN, Pudwell J, Walker M, Wen SW. Risk estimation of metabolic syndrome at 1 and 3 years after a pregnancy complicated by preeclampsia. *J Obstet Gynaecol Canada.* (2012) 34:836–41. doi: 10.1016/S1701-2163(16)35382-8
38. Verma A, Shrimali L. Maternal body mass index and pregnancy outcome. *J Clin Diagnostic Res.* (2012) 6:1531–3. doi: 10.7860/JCDR/2012/4508.2551
39. Al-Nasiry S, Ghossein-Doha C, Polman SEJ, Lemmens S, Scholten RR, Heidema WM, et al. Metabolic syndrome after pregnancies complicated by pre-eclampsia or small-for-gestational-age: a retrospective cohort. *BJOG An Int J Obstet Gynaecol.* (2015) 122:1818–23. doi: 10.1111/1471-0528.13117
40. Chatzi L, Plana E, Daraki V, Karakosta P, Alegkakis D, Tsatsanis C, et al. Metabolic syndrome in early pregnancy and risk of preterm birth. *Am J Epidemiol.* (2009) 170:829–36. doi: 10.1093/aje/kwp211
41. Matthews KA, Räikkönen K, Gallo L, Kuller LH. Association between socioeconomic status and metabolic syndrome in women: testing the reserve capacity model. *Health Psychol.* (2008) 27:576. doi: 10.1037/0278-6133.27.5.576
42. Zhan Y, Yu J, Chen R, Gao J, Ding R, Fu Y, et al. Socioeconomic status and metabolic syndrome in the general population of China: a cross-sectional study. *BMC Public Heal.* (2012) 12:1–7. doi: 10.1186/1471-2458-12-921
43. Montez JK, Bromberger JT, Harlow SD, Kravitz HM, Matthews KA. Life-course socioeconomic status and metabolic syndrome among midlife women. *J Gerontol Ser B.* (2016) 71:1097–107. doi: 10.1093/GERONB/GBW014
44. Cho KI, Kim BH, Je HG, Jang JS, Park YH. Gender-specific associations between socioeconomic status and psychological factors and metabolic syndrome in the Korean population: findings from the 2013 Korean national health and nutrition examination survey. *Biomed Res Int.* (2016) 2016:3197. doi: 10.1155/2016/3973197
45. Kim JY, Kim SH, Cho YJ. Socioeconomic status in association with metabolic syndrome and coronary heart disease risk. *Korean J Fam Med.* (2013) 34:131. doi: 10.4082/KJFM.2013.34.2.131
46. Lewey J, Levine LD, Yang L, Triebwasser JE, Groeneveld PW. Patterns of postpartum ambulatory care follow-up care among women with hypertensive disorders of pregnancy. *J Am Heart Assoc.* (2020) 9:16357. doi: 10.1161/JAHA.120.016357
47. Sharma M, Purewal TS, Fallows S, Kennedy L. The low-risk perception of developing type 2 diabetes among women with a previous history of gestational diabetes: a qualitative study. *Pract Diabetes.* (2019) 36:15–19. doi: 10.1002/PDI.2204
48. Stage E, Ronneby H, Damm P. Lifestyle change after gestational diabetes. *Diabetes Res Clin Pract.* (2004) 63:67–72. doi: 10.1016/J.DIABRES.2003.08.009
49. Dennison RA, Ward RJ, Griffin SJ, Usher-Smith JA. Women's views on lifestyle changes to reduce the risk of developing Type 2 diabetes after gestational diabetes: a systematic review, qualitative synthesis and recommendations for practice. *Diabet Med.* (2019) 36:702–17. doi: 10.1111/DME.13926
50. Nowik CM, Pudwell J, Smith GN. Evaluating the postpartum maternal health clinic: how patient characteristics predict follow-up. *J Obstet Gynaecol Canada.* (2016) 38:930–5. doi: 10.1016/j.jogc.2016.05.005
51. Allen R, Rogozinska E, Sivarajasingam P, Khan KS, Thangaratinam S. Effect of diet- And lifestyle-based metabolic risk-modifying interventions on preeclampsia: a meta-analysis. *Acta Obstet Gynecol Scand.* (2014) 93:973–85. doi: 10.1111/aogs.12467

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Methodological Quality and Risk of Bias Assessment of Cardiovascular Disease Research: Analysis of Randomized Controlled Trials Published in 2017

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Background: All randomized-controlled trials (RCTs) are required to follow high methodological standards. In this study, we aimed to assess the methodological quality of published cardiovascular clinical research trials in a representative sample of RCTs published in 2017.

Methods: Cochrane Central Register of Controlled Trials was used to identify cardiovascular clinical research trials with adult participants published in 2017. Overall, 250 (10%) RCTs were randomly selected from a total of 2,419 studies. Data on general trial characteristics were extracted and the risk of bias (RoB) was determined.

Results: Overall, 86% of RCTs have reported at least one statistically significant result, with the primary outcome significant in 69%, treatment favored in 55%, and adverse events reported in 68%. Less than one-third (29%) of trials were overall low RoB, while the other two-thirds were rated unclear (40%) or with high RoB (31%). Sequence generation, allocation concealment, and selective reporting were the domains most often rated with high RoB. Drug trials were more likely to have low RoB than non-drug trials. Significant differences were found in RoB for the allocation concealment and blinding of participants and personnel between industry-funded and non-industry-funded trials, with industry-funded trials more often rated at low RoB.

Conclusion: Almost two-thirds of RCTs in the field of cardiovascular disease (CVD) research, were at high or unclear RoB, indicating a need for more rigorous trial planning and conduct. Prospective trial registration is a factor predicting a lower risk of bias.

Keywords: randomized controlled trials, risk of bias, cardiovascular diseases, funding source, data monitoring committee, trial registration

Abbreviations: RCT, randomized-controlled trials; RoB, risk of bias; CVD, cardiovascular disease.

INTRODUCTION

Randomized controlled trials (RCTs) are widely recognized as the most optimal methodology for causal inference, where humans are prospectively included and randomly allocated to groups to evaluate the efficacy and safety of an intervention (1). The strength of the RCTs comes from the randomization procedure, which ensures that all participants have the same chance of being assigned to each of the study groups (1) and guarantees that the characteristics of the participant are similar through the different groups at the baseline (2). However, the extent to which we can draw final conclusions based on RCTs strongly depends on how rigorous study methodology is; methodological inaccuracies during trial planning and conduct will subsequently reduce the reliability of results and their usability in medical practice (3). Biased results can finally lead to the underestimation or overestimation of the true intervention effect (3).

In cardiovascular disease (CVD) research, RCTs have been widely used to provide reliable knowledge on the best treatment strategies, such as therapies which are able to improve patient's symptoms, correct disease markers, and improve clinical outcomes (4, 5). However, the risk of bias (RoB) has not been assessed in these studies.

The risk of bias (RoB) reflects the degree to which the results of a trial should be believed (6, 7). To reduce the possibility of RoB in RCT's, the Cochrane Collaboration introduced a tool designed to appraise RoB (8, 9), involving six domains related to the internal validity of a trial: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other" potential threats to validity (6, 7). The risk of bias assessment enables the assessment of flaws in the trial design, conduct, and analysis that may affect study results (10).

In this study, we aimed to describe the reliability of evidence of cardiovascular diseases from a representative sample of cardiovascular RCTs published in 2017. Specific objectives were to examine: (1) the reliability of published cardiovascular trials using the RoB tool; (2) specific trial characteristics which increase the likelihood of unclear/high RoB; and (3) any potential differences in methodological issues between studies funded by the industry or the academy.

MATERIALS AND METHODS

Sample Selection

We used the Cochrane CENTRAL Register of Controlled Trials to search for RCTs published in 2017 using subject headings and keywords related to adults (aged $\geq$ 18 years) and CVDs (such as, atherosclerosis, arrhythmia, cardiomyopathy, heart failure, hypertension, ischemic heart disease, heart attack, angina, sudden death, cardiac arrest, hypercholesterolemia, high blood pressure, CVD, ejection fraction, echocardiography, pericarditis, coronary artery disease, angioplasty, and angiography). The search and the screening of identified studies for eligibility were conducted by the first author (OB). Our search yielded a total of 2,556 studies (**Supplementary File 1**). Following deduplication, 2,419 studies underwent further analysis. Cochrane CENTRAL was the priority search source as it is the most comprehensive resource available of RCTs, containing publications from MEDLINE and EMBASE, as well as hand-search results, and gray literature (6, 11). Results of the search were randomly ordered in Excel, by the following method: after exporting the search result as an Excel file from Cochrane CENTRAL, we assigned a random number between 0 and 1 to each record using Excel's random number generator, then reordered them from the smallest to the highest number (12). As a next step, we screened studies consecutively for eligibility, and the first 250 (∼10%) RCTs matching our pre-specified inclusion criteria were selected (**Supplementary File 2**). Trials were eligible for inclusion if they were published in the year 2017, were written in English, the described results of an RCT in the field of cardiovascular medicine, and included participants aged $\geq$ 18 years. Decision on the inclusion of a study was made after a careful consideration of the methodology in the full text.

Data Extraction

For data extraction, we used a data extraction sheet already tested and described in a previous study (11), data extracting guide available here: https://doi.org/10.1016/j.jpeds.2017.09.014 (12). The following data were extracted: journal type (e.g., specialty cardiovascular, or general medical), the publication details and characteristics of the published trials (such as study design, intervention, trial conduct, study sample, sample size, presence of a data monitoring committee, research outcomes, and conclusions). Further, we collected information about trial registration. Data extraction was completed by two reviewers (OB, OF): the first reviewer extracted the data and then, the second reviewer double-checked the sample. Conflicts were resolved through discussion and by reaching a consensus. Trial registration and protocol availability were investigated by retrieving information from the publications and *via* additional Internet searches (in Google and Google scholar). For the internet searches, we used the trial register number, the investigators' names, and keywords describing the intervention or the condition.

Assessment of Methodological Quality and Reporting

We used the Cochrane RoB assessment tool (13) to evaluate the methodological quality of included RCTs. This tool assesses seven domains: (1) random sequence generation (whether the method used to generate the allocation sequence is described in sufficient detail to allow an assessment of whether it should produce comparable groups); (2) allocation concealment (whether the method used to conceal the allocation sequence is described in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrollment); (3) the blinding of participants and personnel; (4) the blinding of outcome assessors; (5) incomplete outcome data (whether attrition and exclusions were reported, whether missing data were balanced across groups or were related to the outcomes); (6) selective reporting (whether pre-specified outcomes were reported in a pre-specified way); and (7) other bias.

We used the Cochrane RoB tool to assess RoB for the primary outcome. When the primary outcome was not clearly defined, we presumed it was the outcome either (1) described

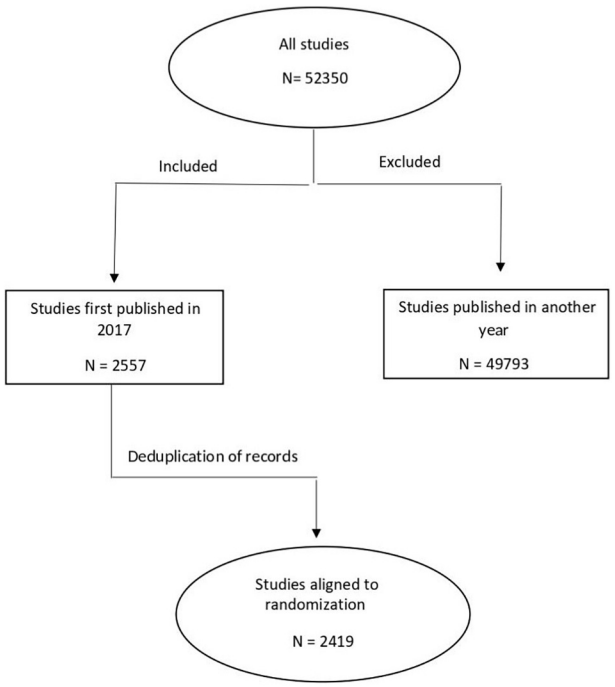

FIGURE 1 | Flowchart of study selection.

under aims/objectives of the study, (2) the outcome used to determine the sample size, or (3) the first outcome reported in the publication (the first applicable was used). One researcher performed a RoB assessment, while a second researcher was assigned to ensure the correctness of the assessments for each study.

Following Cochrane procedures (7), we classified each domain as low, unclear, or high risk. Then, the overall RoB was determined as follows: low when all domains were assessed as low RoB; unclear when at least 1 domain was assessed as unclear and no domains were assessed as high RoB; and high if any domain was assessed as high RoB (7).

Statistical Analysis

Statistical analyses were conducted by the statistical software R version 4.1.2 (14). The data were analyzed descriptively, using means and standard deviations (SDs) or medians and ranges for continuous variables and proportions for categorical variables. A multivariable logistic regression analysis was conducted to investigate the association between pre-specified study characteristics and the odds of high/unclear RoB. The value of $p < 0.05$ was considered as a significant result.

RESULTS

Study Design and Reporting Characteristics of the Study Sample

Out of the 2,419 studies identified *via* search, we included the first 250 randomly selected trials, which met our search inclusion criteria as shown in **Figure 1**. The publication and trial

TABLE 1 | Publication and trial characteristics (*N* = 250).

Study characteristics	*N* (%)
The geographical location of the corresponding author	
Asia	65 (26.0%)
North America	69 (27.6%)
Europe (Excluding United Kingdom)	93 (37.2%)
South America	13 (5.2%)
Australia	2 (0.8%)
United Kingdom	8 (3.2%)
Type of journal	
Specialty cardiovascular journal	100 (40.0%)
General cardiovascular journal	46 (18.4%)
Specialty medical journal	49 (19.6%)
General medical journal	41 (16.4%)
Non-medical journal	14 (5.6%)
Study design	
Parallel	231 (92.4%)
Crossover	15 (6.0%)
Factorial	4 (1.6%)
Study type	
Efficacy/Superiority	237 (94.8%)
Equivalence	3 (1.2%)
Non-inferiority	4 (1.6%)
None of the above	6 (2.4%)
Intervention	
Drug	139 (55.6%)
Prevention or screening	20 (8.0%)
Device	23 (9.2%)
Other	68 (27.2%)
Placebo-controlled	
Yes	68 (27.2%)
No	182 (72.8%)
Number of centers	
Multicenter	157 (62.8%)
Single center	93 (37.2%)
Data Monitoring Committee	
Yes	105 (42.0%)
No	94 (37.6%)
Unclear	51 (20.4%)
Funding source	
Academic or Research institute	94 (37.6%)
Pharmaceutical	48 (19.2%)
Government	24 (9.6%)
Industry for device	10 (4.0%)
No external funding	4 (1.6%)
Private	50 (20.0%)
Unclear	21 (8.4%)
Primary outcome explicitly specified	
Yes	157 (62.8%)
No	93 (37.2%)
Intervention favored	
Treatment	139 (55.6%)
Control	9 (3.6%)
Non	104 (41.6%)

(Continued)

TABLE 1 | (Continued)

Study characteristics	*N* (%)
Sample size calculation reported	
Yes	151 (60.4%)
No	99 (39.6%)
Was there at least one statistically significant outcome?	
Yes	215 (86.0%)
No	35 (14.0%)
Was the primary outcome statistically significant?	
Yes	173 (69.2%)
No	77 (30.8%)
Overall authors conclusion	
Positive	170 (68.0%)
Negative	34 (13.6%)
Neutral	46 (18.4%)
Adverse events	
Reported	170 (68.0%)
Non-reported	82 (32.8%)
Trial registered	
Yes	209
No	41

characteristics of our sample are shown in **Table 1**. Most of the included trials had a parallel design (92.4%) and were efficacy trials (94.8%). Overall, 20.8% were placebo-controlled trials. An important part of the results of the trial was published in specialty cardiovascular journals (40.0%). In 139 studies (55.6%), the main goal was to evaluate the effects of pharmacological interventions. All geographic areas were represented; the majority of authors were from Europe (37.4%) and North America (26.0%).

The funding source was specified in 91.6% of the included trials: most of the trials were funded by an academic grant or a research institute (37.6%), while industrial and pharmaceuticals funding were reported in 23.2% of the trials.

When analyzing the main results of trials, we observed that at least one statistically significant result was reported in 86.0% of the studies; in these studies, the primary outcome was reported to be statistically significant in 69.2% of the cases. The treatment was favored in 55.6% and control in 3.6%. At least one adverse event was reported in 68% of the trials. A data monitoring committee was reported in 42% and sample size calculation in 60.4%. A total of 83.6% of the studies were registered in one of the clinical trials registries out of the 77.5% were registered in clinicaltrials.gov.

Risk of Bias Assessment

Table 2 shows the RoB assessment results. Overall, 29.2% of the studies were deemed as low RoB, while the remaining studies were at either unclear (39.6%) or high risk (31.2%). We rated the domains sequence generation, allocation concealment, and selective reporting to be the domains most often at high RoB (13.2, 9.6, and 10.4%, respectively).

We investigated whether the RoB was associated with the following variables: type of the intervention (drug vs. non-drug); single or multiple study centers; sample size; the presence of a Data Monitoring Committee; statistical significance of the primary outcome and trial registration (**Table 3**). Of these variables, trial registration influenced overall RoB to the greatest extent (odds ratio [OR] 0.06, 95% CI 0.03–0.31). Drug trials were more likely to have a low RoB than non-drug trials (OR 0.53, 95% CI 0.29–0.97), and multicenter trials more likely than single-center trials (OR 0.39, 95% CI 0.18–0.80). Other investigated variables did not have a significant influence on the RoB.

TABLE 2 | Risk of bias (RoB) assessments by domain (*N* = 250).

Domain	Risk of bias assessment N (%)		
	High	Unclear	Low
Sequence generation	33 (13.2%)	68 (27.2%)	149 (59.6%)
Allocation concealment	24 (9.6%)	51 (20.4%)	175 (70.0%)
Blinding: participant and personnel	11 (4.4%)	112 (44.8%)	127 (50.8%)
Blinding: outcome assessor	11 (4.4%)	33 (13.2%)	206 (82.4%)
Incomplete outcome data	8 (3.2%)	57 (22.8%)	185 (74.0%)
Selective reporting	26 (10.4%)	67 (26.8%)	157 (62.8%)
Other bias	36 (14.4%)	106 (42.4%)	108 (42.8%)
Overall RoB	78 (31.2%)	99 (39.6%)	73 (29.2%)

We observed the following results after investigating individual RoB intems separately: drug trials (OR 0.39, 95% CI 0.22–0.66) and registered trials (OR 0.39, 95% CI 0.18–0.83) were more likely to have low RoB for random sequence generation. Drug trials (OR 0.51, 95% CI 0.28–0.93), registered trials (OR 0.49, 95% CI 0.26–0.91), and multicenter trials (OR 0.49, 95% CI 0.26–0.91) were more likely to have low RoB for allocation concealment, while trials with a statistically significant result were more likely to have unclear or high RoB (OR 2.59, 95% CI 1.34–5.31). Registered trials (OR 0.18, 95% CI 0.06–0.43), trials larger than 500 participants (OR 0.47, 95% CI 0.24–0.92), and trials with a Data Monitoring Committee (OR 0.50, 95% CI 0.28–0.87) had more often low RoB for the blinding of participants and personnel while the blinding of outcome assessors was more often low RoB in multicenter trials (OR 0.42, 95% CI 0.19–0.89) and registered trials (OR 0.27, 95% CI 0.12–0.63). There were no factors that increased the likelihood of low RoB for incomplete outcome data; however, trials with statistically significant results decreased the likelihood of low RoB for incomplete outcome data (OR 2.40, 95% CI 1.18–5.21). Larger trials with more than 500 participants were more likely to have low RoB for selective reporting (OR 0.44, 95% CI 0.19–0.95). Registered trials (OR 0.23, 95% CI 0.08–0.56) and multicenter trials (OR 0.31, 95% CI 0.16–0.59) were more likely to have low RoB for other biases.

Risk of Bias According to a Funding Source

When funding source was added as an additional independent variable to the multivariable regression model, funding did not seem to influence the likelihood of overall low RoB (industry funding: OR 0.76, 95% CI 0.40–1.45).

In the sub-group of industry-funded trials, multicenter trial and Data Monitoring Committee were factors that increased the likelihood of overall low RoB. None of the investigated factors influenced the overall RoB within the sub-group of trials with non-industry funding (**Table 3**).

TABLE 3 | Multivariable regression analyses for all included trials, and trials with and without stated funding from the industry*.

	All trials (*N* = 250)		Industry-funded trials (*N* = 106)		Non-industry funded trials (*N* = 119)	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Drug trial (vs. non-drug trial)	0.53 (0.29 – 0.97)	0.04	0.49 (0.18 – 1.27)	0.15	0.50 (0.20 – 1.20)	0.12
Multicentre (vs. single center)	0.39 (0.18 – 0.80)	0.01	0.13 (0.02 – 0.61)	0.02	0.80 (0.32 – 2.00)	0.64
Sample size (>500 vs. smaller)	0.67 (0.34 – 1.31)	0.24	0.60 (0.23 – 1.56)	0.29	1.72 (0.52 – 6.86)	0.40
Data Monitoring Committee (yes vs. no)	0.59 (0.32 – 1.09)	0.09	0.36 (0.13 – 0.96)	0.045	0.91 (0.37 – 2.27)	0.84
Primary outcome statistically significant (vs. not)	0.92 (0.48 – 1.74)	0.80	0.52 (0.81 – 1.11)	0.49	1.36 (0.54 – 3.38)	0.51
Trial registration reported (vs. not reported)	0.06 (0.003 – 0.31)	<0.01	0.19 (0.01 – 1.28)	0.15	1.13 (0.01 – 0.75)	0.06

**Funding was not reported in N = 25 studies.*

TABLE 4 | Risk of bias assessments by domain in studies funded by the industry or non-industry (*N* = 250).

RoB domain	Funding source (industrial vs. non-industrial)				
	Industrial	*N* (%)	Non-industrial	*N* (%)	*p*-value
Random sequence generation	Low Unclear High	66 (62.3) 32 (30.2) 8 (7.5)	Low Unclear High	71 (59.7) 33 (27.7) 15 (12.6)	0.4533
Allocation concealment	Low Unclear High	90 (84.9) 13 (12.3) 3 (2.8)	Low Unclear High	76 (63.9) 32 (26.9) 11 (9.2)	0.0014*
Blinding: participant and personnel	Low Unclear High	70 (66.0) 35 (33.0) 1 (0.94)	Low Unclear High	51 (42.9) 61 (51.3) 7 (5.9)	0.0001*
Blinding: outcome assessor	Low Unclear High	95 (89.6) 8 (7.5) 3 (2.8)	Low Unclear High	95 (79.8) 19 (16.0) 5 (4.2)	0.1198
Incomplete outcome data	Low Unclear High	86 (81.1) 14 (13.2) 6 (5.7)	Low Unclear High	91 (76.5) 25 (21.0) 3 (2.5)	0.1734
Selective reporting	Low Unclear High	80 (75.5) 23 (21.7) 3 (2.8)	Low Unclear High	86 (72.3) 29 (24.4) 4 (3.4)	0.8598
Other bias	Low Unclear High	55 (51.9) 41 (38.7) 10 (9.4)	Low Unclear High	47 (39.5) 56 (47.1) 16 (13.4)	0.1659
Overall RoB	Low Unclear High	42 (39.6) 41 (38.7) 23 (21.7)	Low Unclear High	30 (25.2) 53 (44.5) 36 (30.3)	0.0587

*Statistical analysis was made by regression analysis. *Statistically significant results ($p < 0.001$).*

Compared with non-industry funded studies more industry funded studies were rated as low RoB (84.9 vs. 63.9%) and less were rated as unclear (12.3 vs. 26.9%) or high RoB (2.8 vs. 9.2%) for allocation concealment ($p < 0.001$) (**Table 4**). More industry funded studies were rated low (66.0 vs. 42.9%) and fewer were rated as unclear (33.0 vs. 51.3%) or high risk (0.94 vs. 5.9%) for the blinding of participants and personnel ($p < 0.001$).

DISCUSSION

Summary of Main Findings

To our knowledge, this is the first research evaluating the RoB and its association with specific trial characteristics in a randomly selected sample of recently published clinical trials in adult cardiovascular disease. Included trials were mainly parallel RCTs investigating the efficacy of an intervention, with a very diverse trial scope and published in a variety of cardiovascular and general medical journals.

Of the 250 studies included, more than 85% have reported at least one statistically significant result, with the primary outcome significant in 69%. Treatment was favored in 55% of the studies, and adverse events were reported in 68%.

Less than one-third of our samples were overall low RoB, while the other two-thirds were unclear or high RoB. Sequence generation, allocation concealment, and selective reporting were the RoB domains most frequently rated at high risk. Trial registration influenced overall RoB to the greatest extent. Drug trials were more likely to be at low RoB than non-drug trials, and multicenter trials were more likely at a low risk RoB than single-center trials.

In the subgroup of industry-funded trials, multicenter trial and Data Monitoring Committee were factors that increased the likelihood of overall low RoB, while none of the investigated factors influenced the overall RoB within the subgroup of non-industry-funded trials. Significant differences were found in the RoB for the domains allocation concealment and the blinding of participants and personnel between industry-funded and non-industry-funded trials, with industry-funded trials more often rated at low risk.

Strengths and Weaknesses of the Study

We aimed to select a sample of studies representative for all randomized controlled trials published in 2017; we did not exclude published trials based on the country, type of journal, type of participants, or type of intervention. Included trials were randomly selected from all eligible trials. We used the most well-recognized tool for methodological assessment and the results indicated several areas of methodological weaknesses. To increase the reliability of findings, both data extraction and RoB assessment were conducted by two independent researchers.

This study was not pre-registered. Our study is limited by the included trials published in the English language only; conclusions cannot be generalized to trials published in other languages. We could not identify register entries or trial protocols for a subsample of trials, and it was difficult to properly evaluate the selective outcome reporting in these trials. We have not contacted the authors to get additional information about their

trials, therefore the assessments are solely based on published information. Additionally, our study focused on the internal validity of trials, but have not assessed factors that may impact the external validity.

Discussion of Findings Considering Other Studies

Of the 250 analyzed trials, more than two-thirds (70.8%) were at high or unclear RoB, which is consistent with previous study results (15, 16). The RoB domains sequence generation, allocation concealment, and selective reporting were rated most often to be at high risk in our study.

Trial registration had the most beneficial effect on RoB in our study. In previous studies, random sequence generation, allocation concealment, and selective reporting were shown to differ between registered and unregistered gynecology and fertility trials (17). Registration was shown to be a factor influencing all RoB domains except selective outcome reporting in a sample of pediatric research trials (6). Trial registration is a factor that has the potential to facilitate higher methodological quality (18).

We found that drug trials were more likely at a low RoB than non-drug trials. This might be in connection with the strict regulations surrounding drug trials. Differences in protocol quality (19) registration and publication tendencies were described already in previous publications (20, 21), between trials with regulated and non-regulated interventions.

In our study, multi-center trials have demonstrated lower RoB compared with single-center trials. This is consistent with the conclusions of Landoni et al., who underlined bias issues characteristic for single-center trials (e.g., local effect bias, selection and performance bias, detection and reporting bias, analysis and attrition bias, concomitant therapy bias, low fragility index, and publication bias). Caution is advised for the results of single-center RCTs (22).

The source of funding may have an important impact on trial planning, conduct, and reporting (23–25). In our study, we investigated the role of funding sources on RoB by comparing trials both funded or not by the industry. In our study, industry-funded studies were rated more often low for the allocation concealment and the blinding of participants and personnel, as non-industry-funded studies. Our findigs on the higher probability of industry-funded trials to have adequate blinding are supported by the results of a similar study conducted in pediatric RCTs (6, 25). The blinding of participants and personnel may not always be feasible, however, studies should attempt blinding wherever possible.

Implications for Practice and Future Research

Our results underline the need of further improvement in the process of planning and performing a clinical trial in the field of CVD research. Trial registration was associated with a larger likelihood of low RoB, therefore mandatory trial registration should be endorsed and enforced by ethic committees, funders, and journal editors. Further favorable trial features associated with the lower RoB were multicenter trials, larger trials with more than 500 participants, and trials with a Data monitoring Committee. Trials not funded by the industry were more often at a high RoB for the allocation concealment and the blinding of participants and personnel, indicating, that studies without industry involvement need to pay greater attention to following certain methodological recommendations. The same is applicable for cardiovascular research trials investigating the effects of a non-drug intervention. In the present study, we focused on the methodological quality of CVD research trials but did not assess reporting issues in detail. This may need further assessed in the future.

CONCLUSION

Almost two-thirds of RCTs published in 2017 in the field of CVD research were at high or unclear RoB. This indicates a need for more rigorous trial planning and conduct. Prospective trial registration is a factor that predicts the lower RoB.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

SL conceptualized the research, supervised the research, and reviewed and edited the manuscript. OB and OF performed the research. OB led data extraction and assessment, responsible for data curation, and wrote the first draft of the manuscript. DN conducted statistical analyses. All authors critically revised and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.830070/full#supplementary-material

REFERENCES

1. Altman D. *Practical Statistics for Medical Research*. London: Chapman and Hall (1991).
2. Stolberg HO, Norman G, Trop I. Fundamentals of clinical research for radiologists. *Am J Roentgenol.* (2004) 183:1539–44. doi: 10.2214/ajr.180.4.1800917
3. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S editors. London: The Cochrane Collaboration (2011).
4. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *J Am Med Assoc.* (2006) 296:1377–84. doi: 10.1001/jama.296.11.1377
5. Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA.* (2009) 302:977–84. doi: 10.1001/jama.2009.1242
6. Hamm MP, Hartling L, Milne A, Tjosvold L, Vandermeer B, Thomson D, et al. A descriptive analysis of a representative sample of pediatric randomized controlled trials published in 2007. *BMC Pediatr.* (2010) 10:96. doi: 10.1186/1471-2431-10-96
7. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Ssystematic Rreviews of Iinterventions* 2nd ed. Chichester: John Wiley & Sons (2019).
8. Jadad AR. Randomised controlled trials: a user's guide. *BMJ.* (1998) 317:1258. doi: 10.1136/bmj.317.7167.1258
9. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA.* (1995) 273:408–12. doi: 10.1001/jama.1995.03520290060030
10. Furuya-Kanamori L, Xu C, Hasan SS, Doi SA. Quality versus risk-of-bias assessment in clinical research. *J Clin Epidemiol.* (2021) 129:172–5. doi: 10.1016/j.jclinepi.2020.09.044
11. Thomson D, Hartling L, Cohen E, Vandermeer B, Tjosvold L, Klassen TP. Controlled trials in children: quantity, methodological quality and descriptive characteristics of pediatric controlled trials published 1948-2006. *PLoS One.* (2010) 5:e13106. doi: 10.1371/journal.pone.0013106
12. Gates A, Hartling L, Vandermeer B, Caldwell P, Contopoulos-Ioannidis DG, Curtis S. The conduct and reporting of child health research: an analysis of randomized controlled trials published in 2012 and evaluation of change over 5 years. *J Pediatr.* (2018) 193:237–244.e37. doi: 10.1016/j.jpeds.2017.09.014
13. Higgins JPT, Savoviæ J, Page MJ, Elbers RG, Sterne JAC. Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Hoboken, NJ: Wiley-Blackwell (2019). p. 205–28. doi: 10.1002/9781119536604.ch8
14. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2021).
15. Pildal J, Hrobjartsson A, Jørgensen KJ, Hilden J, Altman DG, Gøtzsche PC. Impact of allocation concealment on conclusions drawn from meta–analyses of randomized trials. *Int J Epidemiol.* (2007) 36:847–57. doi: 10.1093/ije/dym087
16. Viswanathan M, Ansari MT, Berkman ND, Chang S, Hartling L, McPheeters M, et al. *Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Quide for Comparative Effectiveness Reviews*. Rockville, MD: AHRQ Publication (2012).
17. Farquhar CM, Showell MG, Showell EAE, Beetham P, Baak N, Mourad S, et al. Clinical trial registration was not an indicator for low risk of bias. *J Clin Epidemiol.* (2017) 84:47–53. doi: 10.1016/j.jclinepi.2016.11.011
18. Roberts I, Ker K, Edwards P, Beecher D, Manno D, Sydenham E. The knowledge system underpinning healthcare is not fit for purpose and must change. *BMJ.* (2015) 350:h2463. doi: 10.1136/bmj.h2463
19. Lohner S, Gryaznov D, von Niederhäusern B, Speich B, Kasenda B, Ojeda-Ruiz E, et al. Reporting quality of trial protocols improved for non–regulated interventions but not regulated interventions: a repeated cross–sectional study. *J Clin Epidemiol.* (2021) 139:340–9. doi: 10.1016/j.jclinepi.2021.05.011
20. Rokhsefat S, Morra DE, Offringa M, Askie LM, Kelly LE. Trial registration in pediatric surgery trials. *J Pediatr Surg.* (2018) 53:1273–9. doi: 10.1016/j.jpedsurg.2017.10.049
21. Dal-Ré R, Bracken MB, Ioannidis JPA. Call to improve transparency of trials of non–regulated interventions. *BMJ.* (2015) 350:h1323. doi: 10.1136/bmj.h1323
22. Landoni G, Pieri M, Young PJ, Bellomo R. Why do multicenter randomized controlled trials not confirm the positive findings of single center randomized controlled trials in acute care? *Minerva Anestesiol.* (2019) 85:194–200. doi: 10.23736/S0375-9393.18.13070-7
23. Blümle A, Wollmann K, Bischoff K, Kapp P, Lohner S, Nury E, et al. Investigator initiated trials versus industry sponsored trials – translation of randomized controlled trials into clinical practice (IMPACT). *BMC Med Res Methodol.* (2021) 21:182. doi: 10.1186/s12874-021-01359-x
24. Fundytus A, Wells JC, Sharma S, Hopman WM, Del Paggio JC, Gyawali B. Industry funding of oncology randomised controlled trials: implications for design, results and interpretation. *Clin Oncol.* (2021) 34:28–35. doi: 10.1016/j.clon.2021.08.003
25. Sismondo S. Pharmaceutical company funding and its consequences: a qualitative systematic review. *Contemp Clin Trials.* (2008) 29:109–13. doi: 10.1016/j.cct.2007.08.001

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Hypertensive Disorders in Pregnancy Are Associated With Congenital Heart Defects in Offspring: A Systematic Review and Meta-Analysis

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Zhang S, Qiu X, Wang T, Chen L, Li J, Diao J, Li Y, Qin J, Chen L and Jiang Y (2022) Hypertensive Disorders in Pregnancy Are Associated With Congenital Heart Defects in Offspring: A Systematic Review and Meta-Analysis. Front. Cardiovasc. Med. 9:842878. doi: 10.3389/fcvm.2022.842878

Background: Although research indicates an association between hypertensive disorders of pregnancy (HDP) and congenital heart defects (CHDs) in offspring, consistency is still lacking. Therefore, we aimed to synthesize the updated published epidemiologic evidence to estimate the association of maternal HDP with the risk of total CHDs and its phenotypes in offspring.

Methods: A systematic search of Web of Science Database, PubMed, and Embase were searched from inception through April 30, 2021 based on a preprepared protocol, and the reference lists were also manually searched. The combined risk estimates were calculated using either the fixed-effect models or random-effect models. Possible heterogeneity moderators were detected by subgroup, sensitivity analyses, and Galbraith plot.

Results: Twenty-four studies involving 477,839 CHDs cases among 40,394,699 participants were included in our meta-analysis. Mothers who had HDP exposure were significantly associated with an increased risk of total CHDs compared with non-exposure. When maternal HDP exposure was further subdivided into pre-eclampsia (*OR* = 1.79, 95% CI: 1.50–2.13), gestational hypertension (*OR* = 1.16, 95% CI: 1.02–1.31), and chronic hypertension (*OR* = 1.68, 95% CI: 1.49–1.89), a significantly increased risk of total CHDs were still presented. Furthermore, a statistically significant increased association was found between maternal HDP exposure and most CHD phenotypes. Besides, relevant heterogeneity moderators have been identified by subgroup and sensitivity analyses.

Conclusion: Our study suggested that maternal HDP exposure may be associated with an increase in the risk of CHDs in offspring. These findings highlight the need for greater surveillance of pregnant women with HDP exposure to allow early prevention that may be good for reducing the risk of CHDs in offspring.

Clinical Trial Registration: [www.ClinicalTrials.gov], identifier [CRD42021268093].

Keywords: congenital heart defects, pre-eclampsia, gestational hypertension, chronic hypertension, meta-analysis, hypertensive disorders of pregnancy

INTRODUCTION

Congenital heart defects (CHDs), defined as gross structural malformation of the heart or large blood vessels during the fetal period, are the most frequent congenital anomalies in newborns, affecting 8.6–10.3 per 1,000 live births (1–3). Heart defects are a major cause of infant non-infectious morbidity and mortality, which can lead to about 6.0% neonatal and 46% congenital deaths (4, 5). Evidence showed that more than one million children with CHDs are born every year in the world, and more than half of them need surgical intervention within 1-year-old (6, 7). Although the surgical repair of CHD has achieved remarkable success, many interventions are palliative rather than curative (8). Survivors with CHDs are usually at significant risk of cardiovascular complications and neurodevelopmental disorders in the long term (8, 9). At present, the cause of CHDs is largely unknown.

Hypertensive disorders in pregnancy (HDP) are a group of maternal disorders characterized by increased blood pressure during pregnancy, which include gestational hypertension, pre-eclampsia or eclampsia, chronic hypertension, and preeclampsia superimposed on chronic hypertension (10). It was estimated that approximately 5–8% of all pregnant women worldwide were affected by HDP (11). Previous studies suggested that HDP produces an adverse *in utero* environment, which may increase the risk of adverse pregnancy outcomes (for example, low birth weight, neonatal death, intrauterine growth restriction, congenital malformations, and so on) (12, 13). These indicated that mothers with HDP may increase the risk for heart defects in offspring. Despite some published original studies that have evaluated the relationship between HDP and CHDs risk, the findings were still inconsistent (14–18).

Until now, one meta-analysis has been published to discuss this question (19). This study reported a significant association between maternal hypertension and the risk of CHDs in offspring (19). However, this review did insufficient consider the heterogeneity of results when exploring the association of maternal hypertension with CHDs (19), so the risk estimates are not entirely precise and robust. Meanwhile, the association between hypertension and specific CHD phenotypes was limited in terms of sample size, which may cause the bias of results due to the lack of statistical power. Additionally, of note, the previous review did not focus on the associated different types of HDP with the risk of CHDs. Furthermore, given the increasing prevalence of HDP, and partially after the publication of that meta-analysis, several large-scale cohort studies with inconsistent outcomes have been reported, collating the existing evidence of the association of HDP with CHDs is required (14–18).

Therefore, based on the above-mentioned situation, we synthesized the available published studies on the association between maternal HDP and the risk of CHDs in offspring in a systematic review and meta-analysis. The objective of this study is as follows: (i) to review and summarize the epidemiologic evidence on the association of maternal HDP on total CHDs and specific CHD phenotypes in offspring; (ii) to estimate the association of different types of HDP with total CHDs in offspring; and (iii) to identify potential sources of heterogeneity by subgroup, sensitivity analyses, and Galbraith plot.

MATERIALS AND METHODS

Literature Search Strategy

We conducted and reported this study by following the protocol of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (20). Web of Science Database, PubMed, and Embase was searched from inception through April 30, 2021. Search terms associated with HDP and CHDs were combined according to the principles of Boolean logic (using AND, OR, or NOT). For example, (hypertensive disorders in pregnancy OR gestational hypertension OR preeclampsia) AND (congenital heart disease OR congenital heart defect OR congenital heart malformation). The full search strategy is included in **Supplementary Table 1**. Additionally, the reference lists of relevant studies and reviews were also manually searched. The protocol for this systematic review and meta-analysis was registered on PROSPERO, the international prospective register of systematic reviews (CRD42021268093), and subsequently published.

Exposure and Outcomes

The exposures of interest were HDP, which was defined as a group of characteristic diseases that occur during the gestational period. HDP was usually divided into four categories: gestational hypertension, preeclampsia/eclampsia, chronic hypertension, and preeclampsia superimposed on chronic hypertension. The definitions of HDP of individual studies were guided by guidelines in place at the time of each study in our study. Traditionally, gestational hypertension was defined as new-onset elevated blood pressure ($\geq$140/90 mmHg) after 20 weeks of gestation, and recovery before 12 weeks of delivery (21, 22). Preeclampsia was defined as hypertension ($\geq$140/90 mmHg) and

proteinuria (≥300 mg protein per day) developing after 20 weeks of gestation in women who were previously normotensive (21, 22). Chronic hypertension was defined as increased blood pressure (≥140/90 mmHg) before 20 weeks gestation, but not associated with additional systemic features of preeclampsia (21, 22). Chronic hypertension with superimposed preeclampsia was defined when ≥1 of the systemic features of preeclampsia develops in women with chronic hypertension (21, 22). Additionally, considering the possibility that CHDs could be more strongly associated with some variants of preeclampsia, preeclampsia was further classified as mild or severe preeclampsia according to the disease severity, and early onset preeclampsia (less than 34 weeks of gestation) or late-onset preeclampsia (greater than or equal to 34 weeks) based on the disease onset (23).

The outcomes of interest were CHDs or specific CHD phenotypes including conotruncal defects (CTD), atrial septal defects (ASD), ventricular septal defects (VSD), atrioventricular septal defect (AVSD), tetralogy of fallot (TOF), transposition of the great vessels (TGA), coarctation of the aorta (COA), right ventricular outflow tract obstruction (RVOTO), left ventricular outflow tract obstruction (LVOTO), hypoplastic left heart syndrome (HLHS), and heterotaxia, which were confirmed by surgery and/or diagnosed by ultrasonography.

Study Selection

Two authors (SMZ and TTW) independently initial screened titles and abstracts of all studies, and then reviewed full texts of relevant studies when necessary. Eligibility criteria for fulfilling in our meta-analysis included the following: (i) cohort or case-control studies; (ii) HDP were the exposure of interest including gestational hypertension, pre-eclampsia or eclampsia, chronic hypertension, and preeclampsia superimposed on chronic hypertension; (iii) CHDs or specific CHD phenotypes (e.g., ASD, VSD, TOF, etc.) were the outcomes of interest; (iv) the association between HDP and CHDs or specific CHD phenotypes were part of the main objective of the study (including studies that investigated other perinatal risk factors in addition to HDP); (v) reported odds ratios (ORs) or relative risks (RRs), with corresponding 95% confidence intervals (CIs) (or provided sufficient information to calculate effect value, such as β coefficient and standard error (se), or complete four grid table data (2 × 2 tables) which is sufficient to calculate their OR value or RR value); (vi) published in English-language. On the contrary, exclusion criteria of studies were as follows: (i) reviews, meta-analysis, case reports, letters, and conference abstracts; (ii) without sufficient or clear data; (iii) duplicate publications (If the same population was studied in more than one study, we included the study with the longest follow-up time or the most information). Additionally, we also excluded some studies that focused on the treatment of HDP or special populations (e.g., very low birth weight preterm infants).

Data Extraction and Quality Assessment

Two authors (SM.Z and TT.W) independently extracted data and assessed study quality for each included literature using a standardized data collection form. All discrepancies were resolved through discussion with third authors (X.Q) until consensus could be reached. Information extracted included the first author's, year of publication, recruitment period, geographic region, study design, sample sources, sample sizes, the exposure of interest, the outcome of interest, whether confounding factors were adjusted, and quality assessment. Quality assessment of all included studies was conducted by using the Newcastle-Ottawa Scale (24). With this tool, each study is evaluated from three dimensions: the selection of study groups, the comparability of groups, and the ascertainment of the interest of exposure or outcome for case-control or cohort studies. The Stars awarded for each quality item (a total of 9 items) can be used as a quick visual assessment. A study that received greater than or equal to 7 stars was considered of high methodological quality.

Statistical Analysis

OR and their corresponding 95% CIs were used as the common measure of association of maternal HDP exposure with the risk of CHDs in offspring. Since CHDs were rare (the prevalence was 8.6–10.3 per 1,000 live births), we considered OR as RRs. Random-effect models were used to calculate the combined risk estimates when there is heterogeneity across studies, otherwise, the fixed-effect model was used (25). The Q statistics (significance level at $P < 0.10$) and I^2 statistic (significance level at $I^2 > 50\%$) were identified as a quantitative measurement index for detecting the heterogeneity between studies (26).

Subgroup analyses were performed according to the following factors: geographic region, sample sources, study design, sample sizes, publication years, types of HDP, whether the confounding factors were adjusted, and quality assessment. Sensitivity analyses were conducted to estimate the effect of removing one or more studies at a time on the overall risk estimate. Meanwhile, a Galbraith plot was also conducted to detect the heterogeneity due to individual studies. Besides, funnel plots and Egger's test was used to evaluate the publication bias (significance level at $P < 0.10$) (27). Data were analyzed using Review Manager Version 5.3 and Stata version 12.0. Each effect size was weighted by the inverse of its variance. Statistical analyses were performed using two-sided *P*-values, and $P < 0.05$ was viewed as statistically significant unless otherwise specified.

RESULTS

Literature Search

We initially searched 4,140 possibly relevant literature from three databases. The original search engendered 3,187 unique results after excluding duplicate literature. Meanwhile, most articles (n = 3,135) were further eliminated after screening titles and abstracts. Then 52 potential articles were carefully reviewed by full-text. Of these, 28 articles were further removed because they did not meet the inclusion criteria. Finally, a total of 24 articles (14–18, 28–46) were included in our meta-analysis. The detailed process is summarized in **Figure 1**.

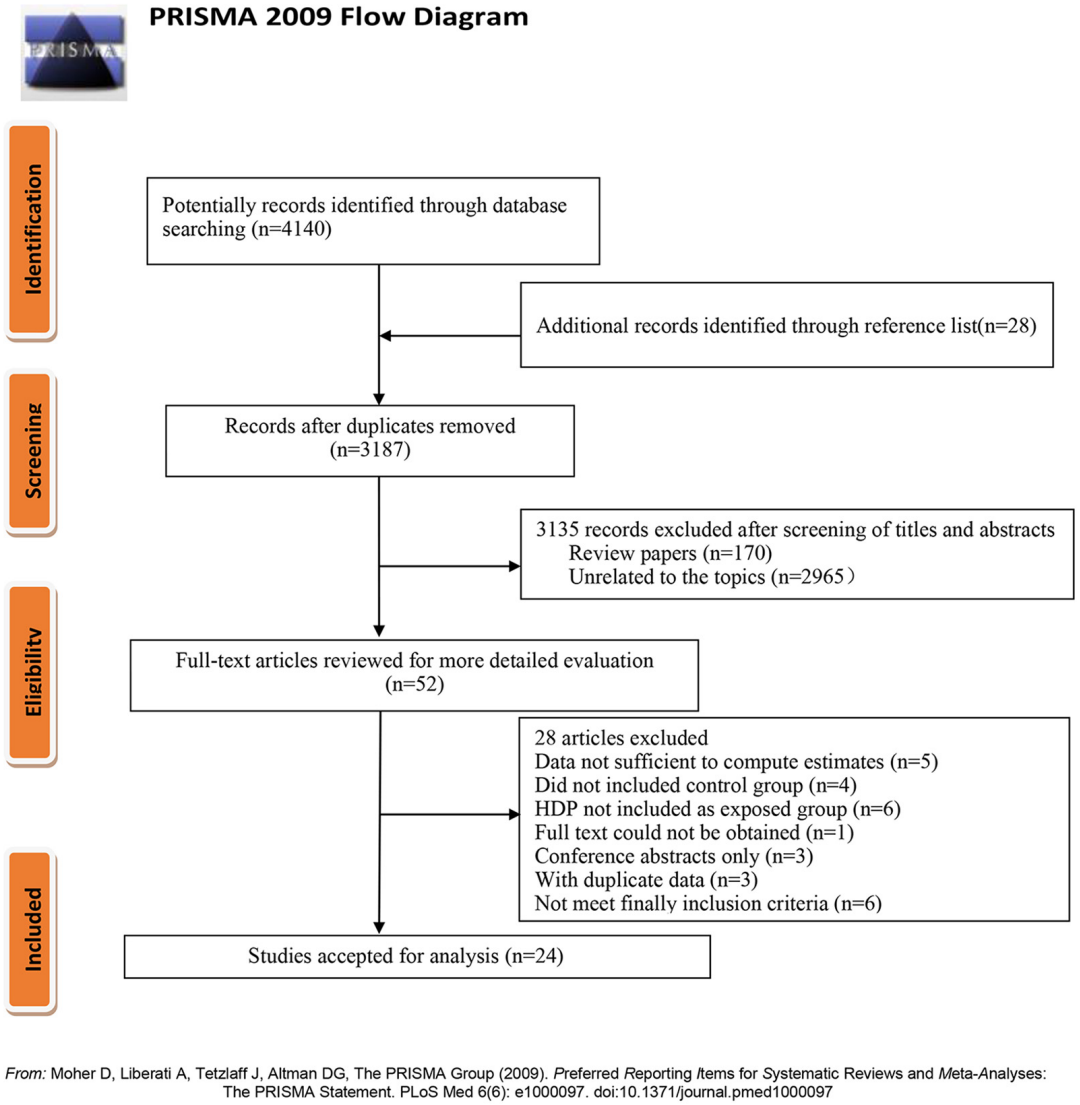

FIGURE 1 | Flow chart of literature selection.

Characteristics of Study

All included literature that was published from 1989 to 2021, with a summary of 477,839 CHDs cases among 40,394,699 participants, are provided in **Table 1**. Of them, five studies were conducted in Asia, eight in Europe, eight in North America, and the remaining three studies were from South America, Oceania, and Africa. Thirteen studies were based on community populations, while the remaining studies were hospital populations. Seventeen studies belonged to cohort design and seven studies were case-control studies. Among them, most studies (n = 15) controlled for possible confounding factors when evaluating the association of maternal HDP with CHDs risk. Fifteen studies had a higher methodological quality; these studies devote most research participants. Additionally, based on the types of HDP, pre-eclampsia was reported in ten studies, gestational hypertension in six studies, chronic hypertension in twelve studies, and preeclampsia superimposed on chronic hypertension in one study.

Maternal Hypertensive Disorders of Pregnancy and Risk of Congenital Heart Defects in Offspring

Figure 2 displays the pooled risk estimates between maternal HDP and the development risk of total CHDs in offspring according to random-effect models Overall, mothers who had HDP exposure had a significantly increased risk of total CHDs (OR = 1.70, 95% CI: 1.46–1.98; $P < 0.001$) compared with those without HDP exposure. However, substantial heterogeneity was found in the present study ($P < 0.001$; I^2 = 94.0%).

The results of pooled estimates between maternal HDP and risk of CHD phenotypes are summarized in **Figure 3** and

TABLE 1 | Characteristic of studies of maternal HDP exposure and risk of congenital heart defects in offspring.

References	Geographic region	Study design	Sample source	Recruitment period	No. of Cases/Controls*	Types of exposure	Outcomes	Whether the confounding factors were adjusted or matched	Quality scores
Stoll et al. (28)	France (European)	Case-control	Hospital	1979–1986	801/801	CH	CHDs/VSD/ASD	Crude	5
Tikkanen and Heinonen (29)	Finland (European)	Case-control	Hospital	1982–1984	573/1055	CH	CHDs	Adjusted	6
Strobino et al. (30)	America (North America)	Case-control	Hospital	1985–1995	796/704	CH	CHDs	Crude	5
Cedergren and Kallen (31)	Sweden (Europe)	Cohort	Population	1992–2001	6346/770355	PE	CHDs	Adjusted	7
Zen et al. (32)	Brazil (South America)	Case-control	Hospital	2005–2006	250/330	CH	CHDs	Crude	5
Mateja et al. (33)	America (North America)	Case-control	Hospital	1996–2005	234/934	CH	CHDs	Adjusted	6
Csáky-Szunyogh et al. (36)	Hungary (Europe)	Case-control	Population	1980–1996	598/38151	CH	CTD	Matched	7
Liu et al. (35)	Canada (North America)	Cohort	Population	2002–2010	23200/2278838	CH	CHDs/CTD/VSD/ASD/AVSD/LVOTO/RVOTO/Heterotaxia	Adjusted	9
Tabib et al. (34)	Iran (Asia)	Case-control	Hospital	2008–2012	14/155	CH	CHDs	Crude	6
Demirpence et al. (37)	Turkey (Asia)	Cohort	Hospital	2010–2012	66/337	GH	CHD	Adjusted	6
Auger et al. (38)	Canada (North America)	Cohort	Population	1989–2012	1219/1942072	PE	CHD/VSD/ASD/TGA/TOF/COA/Heterotaxia	Adjusted	9
Bateman et al. (40)	American (North America)	Cohort	Population	2000–2007	NA/878126	CH	CHDs/CTD/VSD/ASD/LVOTO/RVOTO	Adjusted	8
Liu et al. (39)	China (Asia)	Cohort	Population	2009–2011	1817/90796	GH	CHDs	Adjusted	8
Brodwall et al. (42)	Norway (Europe)	Cohort	Population	1994–2009	10691/914703	GH/PE	CHDs/AVSD/TGA/TOF/COA/HLHS/Heterotaxia	Adjusted	8
Chou et al. (14)	China (Asia)	Cohort	Population	2004–2010	23483/1387650	CH	CHDs	Adjusted	8
Ruiz et al. (41)	Spain (Europe)	Cohort	Population	2003–2014	279/6314	PE	CHDs	Crude	6
Boyd et al. (15)	Denmark (Europe)	Cohort	Population	1978–2011	17035/1972857	GH/PE	CHDs/CTD/VSD/ASD/AVSD/LVOTO/RVOTO/Heterotaxia	Adjusted	9
Steurer et al. (43)	American (North America)	Cohort	Population	2007–2012	6903/2989925	CH/GH/PE	CHDs	Crude	7
Weber et al. (44)	American (North America)	Cohort	Population	2007–2011	2041/2209691	CH/GH/PE/PE superimposed on CH	CHDs/TGA/TOF/COA	Adjusted	8
Fantasia et al. (16)	England (Europe)	Cohort	Hospital	2006–2017	206/91407	PE	CHDs	Crude	7

(Continued)

TABLE 1 | (Continued)

References	Geographic region	Study design	Sample source	Recruitment period	No. of Cases/Controls*	Types of exposure	Outcomes	Whether the confounding factors were adjusted or matched	Quality scores
Liu et al. (45)	Australia (Oceania)	Cohort	Hospital	2010–2017	342/73030	HDP	CHDs/TGA/HLHS	Crude	7
Liu et al. (17)	China (Asia)	Cohort	Population	2004–2017	1289/201987	PE	CHDs/VSD/ASD /TGA/TOF/COA/	Adjusted	8
Sanapo et al. (18)	American (North America)	Cohort	Hospital	1997–2012	363116/ 24525889	HDP	CHDs/CTD	Adjusted	7
Yilgwan et al. (46)	Nigeria (Africa)	Cohort	Hospital	2017–2018	45/90	PE	CHDs	Adjusted	6

CHDs, congenital heart defects; CTD, conotruncal defects; ASD, atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; TOF, tetralogy of fallout; TGA, D-transposition of the great; COA, coarctation of the aorta; RVOTO, right ventricular outflow tract obstruction; LVOTO, left ventricular outflow tract obstruction; HLHS, hypoplastic left heart syndrome; HPD, hypertensive disorders of pregnancy; PE, pre-eclampsia; GH, gestational hypertension; CH, chronic hypertension; NA, not available.

**Number of participants with heart defects/total participants are listed when the study was not a case–control study.*

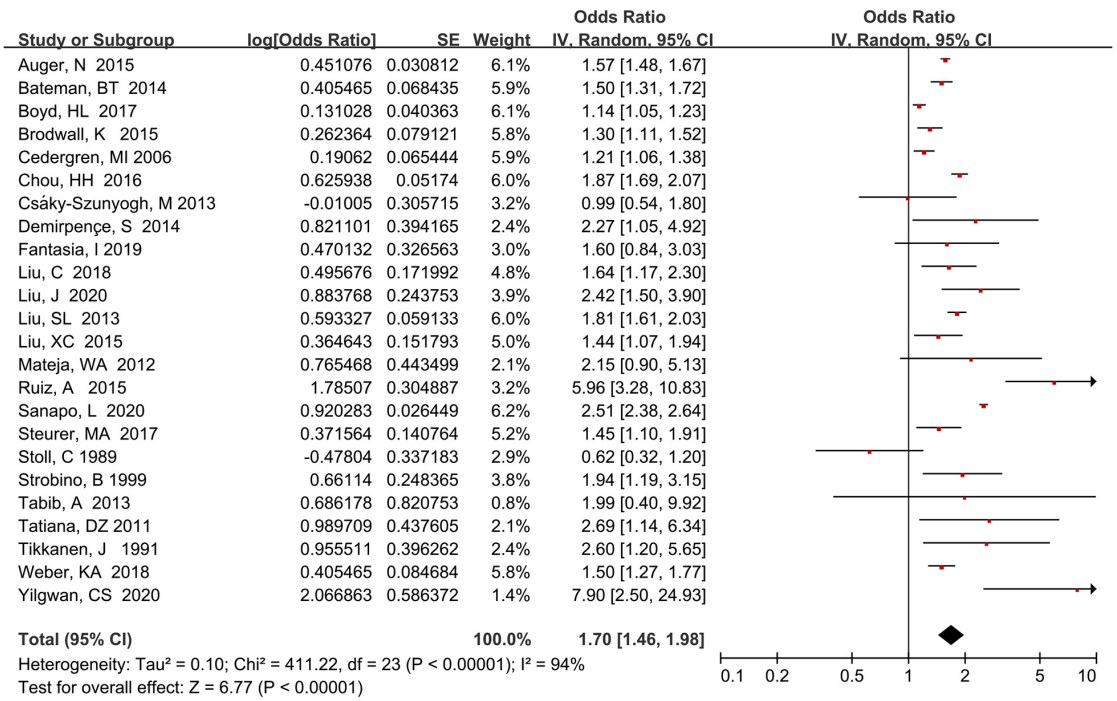

FIGURE 2 | Forest plot of maternal HDP exposure and risk of total CHDs in offspring.

detailed forest plots are provided in **Supplementary Figures 1–3**. Our results indicated that mothers with HDP exposure had a significantly higher risk of most CHD phenotypes including CTD (*OR* = 1.55, 95% CI: 1.33–1.79; *P* < 0.001), TOF (*OR* = 1.35, 95% CI: 1.05–1.72; *P* = 0.020), ASD (*OR* = 1.78, 95% CI: 1.11–2.87; *P* = 0.020),HLHS (*OR* = 2.10, 95% CI: 1.29–3.42; *P* = 0.003), COA (*OR* = 1.73, 95% CI: 1.38–2.17; *P* < 0.001),LVOTO (*OR* = 1.33, 95% CI: 1.06–1.67; *P* = 0.010),and RVOTO (*OR* = 1.69, 95% CI: 1.31–2.18; *P* < 0.001). Nevertheless, there was no substantial heterogeneity except for ASD (*P* < 0.001; I^2 = 94.0%). Additionally, our results indicated that mothers with maternal HDP was not significantly associated with the risk of TGA (*OR* = 1.14, 95% CI: 0.86–1.52; *P* = 0.360), VSD (*OR* = 1.31, 95% CI: 0.86–1.99; *P* = 0.200), AVSD (*OR* = 2.20, 95% CI: 0.91–5.32; *P* = 0.080), and Heterotaxia (*OR* = 1.12, 95% CI: 0.73–1.73; *P* = 0.600). Nevertheless, obvious heterogeneity was observed for several above-mentioned phenotypes except for TGA (*P* = 0.100; I^2 = 48.0%) and Heterotaxia (*P* = 0.750; I^2 = 0.0%).

Subgroup Analysis

Results of subgroup analyses between maternal HDP and risk of total CHDs were outlined in **Table 2**. In general,

Phenotypes	No.	OR(95%CI)	*P* value	Measure of heterogeneity Q	*P* value	I^2(%)
CTD	5	1.55 (1.33−1.79)	<0.001	5.20	0.270	23
TOF	4	1.35 (1.05−1.72)	0.020	2.13	0.550	0
TGA	5	1.14 (0.86−1.52)	0.360	7.70	0.100	48
ASD	6	1.78 (1.11−2.87)	0.020	89.50	<0.001	94
VSD	5	1.31 (0.86−1.99)	0.200	36.84	<0.001	89
AVSD	3	2.20 (0.91−5.32)	0.080	8.90	0.010	78
HLHS	3	2.10 (1.29−3.42)	0.003	4.10	0.130	51
COA	4	1.73 (1.38−2.17)	<0.001	2.66	0.450	0
LVOTO	3	1.33 (1.06−1.67)	0.010	0.29	0.870	0
RVOTO	3	1.69 (1.31−2.18)	<0.001	2.38	0.300	16
Heterotaxia	4	1.12 (0.73−1.73)	0.600	1.23	0.750	0

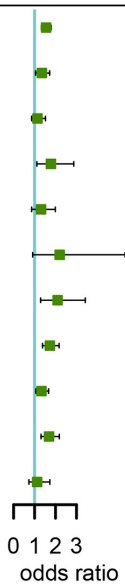

FIGURE 3 | Forest plot of maternal HDP exposure and risk of most CHD phenotypes in offspring.

a significantly increased risk of CHDs was found in most subgroups. Subgroup analyses suggested that different types of HDP (test for subgroup difference [TSD]: I^2 = 90.0%), geographic region (TSD: I^2 = 61.8%), sample sources (TSD: I^2 = 63.0%), sample sizes (TSD: I^2 = 61.5%), and quality assessment (TSD: I^2 = 43.4%), were determined as potential heterogeneity moderators. However, a statistically significant difference was only found in different types of HDP (χ^2 = 29.99; $P < 0.001$) and geographic region (χ^2 = 13.10; P = 0.020), while different sample sources (χ^2 = 2.70; P = 0.100), sample sizes (χ^2 = 2.60; P = 0.110) and quality assessment (χ^2 = 1.77; P = 0.180) were not statistically different. Additionally, subgroup analyses showed that the risk of total CHDs also was significantly increased when data were restricted to specific HDP types (**Figure 4**), such as pre-eclampsia (*OR* = 1.79, 95% CI:1.50–2.13), gestational hypertension (*OR* = 1.16, 95% CI: 1.02–1.31), and chronic hypertension (*OR* = 1.68, 95% CI: 1.49–1.89). Besides, our results showed that the risk of total CHDs was also significantly increased when restricted to specific preeclampsia types, e.g., mild preeclampsia (*OR* = 1.33, 95% CI: 1.16–1.53), severe preeclampsia (*OR* = 2.31, 95% CI: 2.05–2.60), early onset preeclampsia (*OR* = 4.03, 95% CI: 2.63–6.18), and late-onset preeclampsia (*OR* = 1.27, 95% CI: 1.02–1.57) (**Supplementary Figure 4**).

Sensitivity Analysis

Sensitivity analyses were applied to find the possible sources of heterogeneity and to evaluate the effect of various exclusion criteria on pooled risk estimates. Exclusion of poor methodological quality when assessing the association of maternal HDP with the risk of total CHDs did not change the combined results (*OR* = 1.59; 95% CI: 1.34–1.89), but heterogeneity still exists ($P < 0.001$; I^2 = 96.0%). Further exclusion of four old studies (before 2010) also yielded similar results (*OR* = 1.75; 95% CI: 1.48–2.07). Furthermore, removing nine studies that did not control any confounding factors still did not change the combined risk estimate (*OR* = 1.70; 95% CI: 1.42–2.04), but heterogeneity cannot be ignored ($P < 0.001$; I^2 = 96.0%). Besides, removing any single study at a time still did not substantially affect the combined risk estimate (**Figure 5**).

Galbraith Plot

Galbraith plot was performed to find the studies that bring about heterogeneity. Among 24 studies, nine studies were identified after Galbraith plot analysis (**Figure 6**). After excluding these 9 studies, mothers who had HDP exposure compared with those who did not have HDP exposure still had a significantly increased risk of total CHDs in offspring (*OR* = 1.63, 95% CI: 1.50–1.78; $P < 0.001$). But, it is worth noting that there was an obvious decrease in heterogeneity (I^2 decreased from 94.0 to 15.0%).

Publication Bias

Visual inspection of funnel plot showed a mild asymmetry (**Figure 7**), but Egger's test showed no significant substantial publication bias between maternal HDP and the risk of total CHDs in offspring (P = 0.608).

DISCUSSION

Our meta-analysis aimed to synthesize the published literature on the association of maternal HDP with the risk of CHDs

TABLE 2 | Subgroup analysis of association maternal HDP exposure and risk of congenital heart defects in offspring.

Subgroup variables	No. of studies	Pooled OR (95% CI)	Measure of heterogeneity		
			χ^2	*P*	I^2
Geographic region			13.10*	0.020*	61.8%*
Asia	5	1.84 (1.63-2.07)	4.26	0.370	6.0%
Europe	8	1.38 (1.12-1.71)	39.10	<0.001	82.0%
North America	8	1.74 (1.41-2.15)	170.95	<0.001	96.0%
South America	1	2.69 (1.14-6.34)	NA	NA	NA
Oceania	1	1.64 (1.17-2.30)	NA	NA	NA
Africa	1	7.90 (2.50-24.93)	NA	NA	NA
Sample sources			2.70*	0.100*	63.0%*
Community	13	1.54 (1.36-1.75)	116.46	<0.001	90.0%
Hospital	11	1.99 (1.51-2.64)	29.69	0.001	66.0%
Study design			0.15*	0.690*	0.0%*
Case-control studies	7	1.58 (1.02-2.44)	14.25	0.030	58.0%
Cohort studies	17	1.73 (1.46-2.05)	395.96	<0.001	96.0%
Sample sizes			2.60*	0.110*	61.5%*
≤ 2000	8	2.47 (1.45-4.22)	30.02	<0.001	77.0%
>2000	16	1.56 (1.32-1.85)	375.99	<0.001	96.0%
Publication years			1.15*	0.280*	13.2%*
Before 2010	4	1.36 (0.87-2.13)	11.08	0.01	73.0%
2010 or after	20	1.77 (1.50-2.09)	367.72	<0.001	95.0%
Types of HDP			29.99*	<0.001*	90.0%*
PE	10	1.79 (1.50-2.13)	93.24	<0.001	90.0%
GH	6	1.16 (1.02-1.31)	6.81	0.240	27.0%
CH	12	1.68 (1.49-1.89)	23.81	0.010	54.0%
PE superimposed on CH	1	2.60 (1.67-4.05)	NA	NA	NA
Whether the confounding factors were adjusted			0.00*	0.990*	0.0%*
Adjusted	15	1.70 (1.42-2.04)	379.03	<0.001	96.0%
Unadjusted	9	1.70 (1.19-2.44)	31.51	<0.001	75.0%
Quality assessment			1.77*	0.180*	43.4%*
< 7	9	2.23 (1.40-3.55)	35.52	<0.001	78.0%
≥ 7	15	1.59 (1.34-1.89)	375.33	<0.001	96.0%

HPD, hypertensive disorders of pregnancy; OR, Odd Ratios; 95% CI, confidence interval; PE, pre-eclampsia; GH, gestational hypertension; CH, chronic hypertension; NA, not available.
**Test for subgroup differences.*

in offspring. Four principal findings were obtained. First, our study suggested that mothers who had HDP exposure were associated with a 70% increased risk of CHDs in offspring compared with non-exposure. Second, our study indicated that maternal HDP exposure could significantly increase the risk of most CHD phenotypes in offspring including CTD (*OR* = 1.55), TOF (*OR* = 1.35), ASD (*OR* = 1.78), HLHS (*OR* = 2.10), COA (*OR* = 1.73), LVOTO (*OR* = 1.33), and RVOTO (*OR* = 1.69). Third, the results of subgroup analyses indicated that the development risk of total CHDs in offspring had significantly increased when data were confined only to specific HDP types, such as pre-eclampsia (*OR* = 1.79), gestational hypertension (OR = 1.16), and chronic hypertension (*OR* = 1.68). Fourth, our results showed that the risk of total CHDs was also significantly increased when restricted to specific preeclampsia types, e.g., mild preeclampsia (*OR* = 1.33), severe preeclampsia (*OR* = 2.31), early onset preeclampsia (*OR* = 4.03), and late-onset preeclampsia (*OR* = 1.27). These findings indicated that early onset and severe preeclampsia had a higher risk of CHDs than late-onset and mild preeclampsia, respectively, and the increased exposure to the hypertensive disorder could generate more important complications. Besides, our results found that the association of maternal HDP with CHDs still exists after subgroup analyses, sensitivity analyses, and Galbraith plot, which indicated that our findings were credible.

To our knowledge, the potential mechanisms involved in the association of maternal HDP exposure with CHDs risk in offspring remain uncertain. However, several underlying mechanisms have been put forward to try to explain the association of maternal HDP with CHDs risk. The most potential explanation is that maternal HDP can occur in early damage of the vasculogenesis, leading to abnormal development of the placenta (18). Previous studies showed that placental dysplasia may cause alteration in placental genes, oxygen concentration, and protein expression (18). These alterations can lead to altered antioxidant enzyme activity, increased apoptosis, reduction of angiogenic factors, the abnormal balance of growth factors, hypoxic stress, and ultimately to lead to the abnormal development of the fetal cardiovascular system (15, 42, 47). For example, animal studies demonstrated that the blockage of vascular endothelial growth factor (VEGF) receptors resulted in a functional and structural defect in heart valve development, indicating that these receptors are involved in heart valve formation (48, 49). Moreover, animal studies also corroborated that hypoxic stress is associated with abnormal proteins activation and signaling, which may increase the risk of CHD (50). Meanwhile, persisting elevated blood pressure levels may affect cardiovascular health through a variety of mechanisms, including increased afterload, myocardial ischemia, myocardial fibrosis, and mechanical damage on the aortic valve. These alterations may induce abnormally high stress on aortic leaflets, turbulent flow, endothelial injury, and subsequent progression toward alteration in aortic valve morphology, finally causing aortic regurgitation, stenosis, and aortic dilatation, suggesting that persisting hypertension are closely related to cardiac structural abnormalities (51).

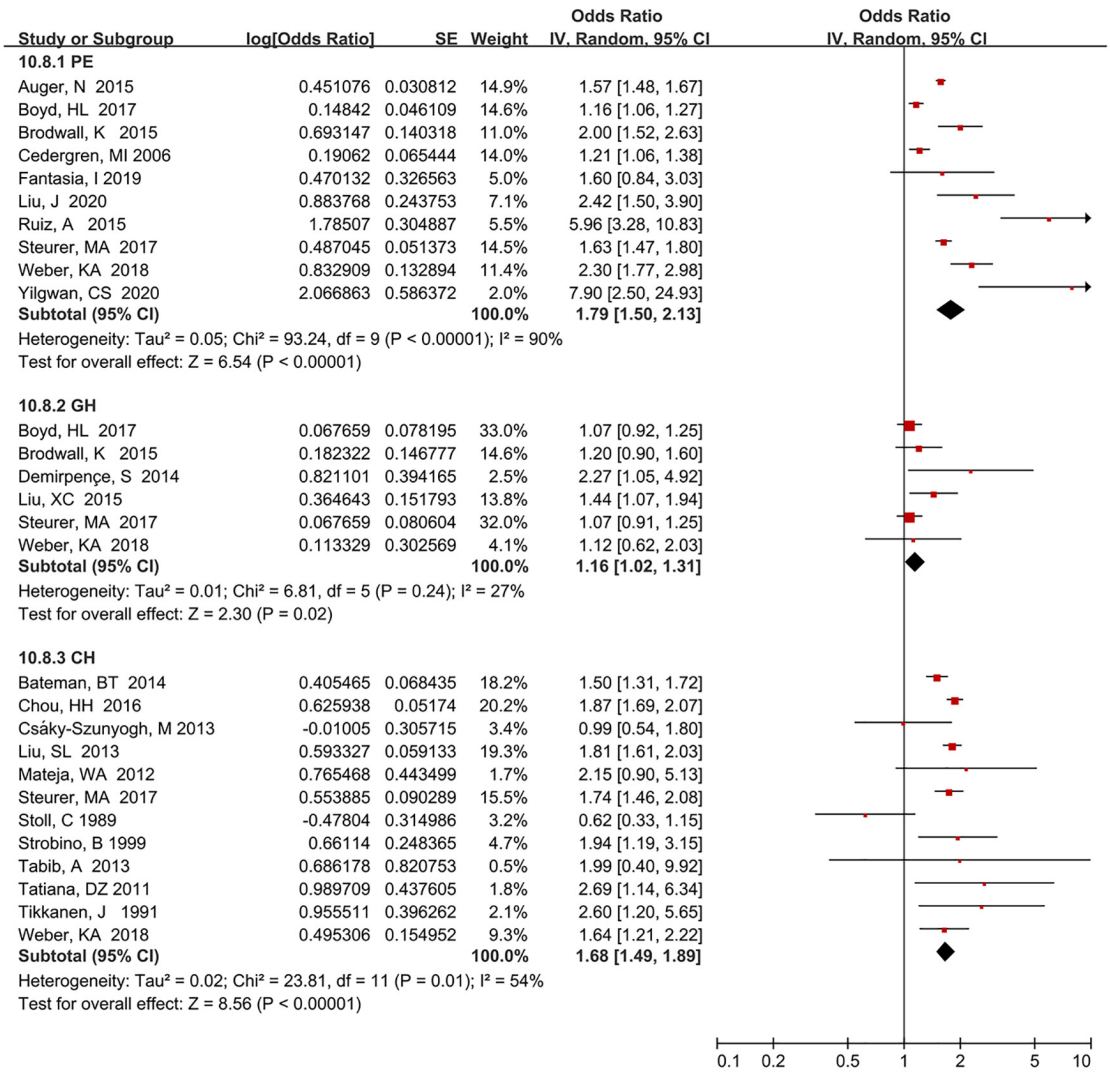

FIGURE 4 | Forest plot of different types of HDP exposure and risk of total CHDs in offspring.

Additionally, there are a few possible explanations for the association of maternal HDP with CHDs risk in offspring. On the one hand, evidence indicates that maternal HDP exposure can lead to compromised blood flow to the developing fetus. Decreasing blood flow to the uterus during pregnancy could cause fetal intracardiac blood flow alterations and cell death, thus affecting normal heart development in the fetus (40, 52). On the other hand, although the heart develops were earlier than the period of pre-eclampsia from the theory of primitive embryo development [in embryology, the period of organogenesis starts 3 weeks and ends 8 weeks (42)], researchers have proposed that pathophysiologic changes in preeclampsia begin well before 20 weeks. Recently study has detected imbalances in angiogenic biomarkers as early as the first trimester in women who later developed preeclampsia (38). Among them, overexpression of the antiangiogenic biomarkers soluble endoglin (sEng) and soluble fms-like tyrosine kinase 1 (sFlt-1) associated with angiogenic placental growth factor and vascular endothelial growth factor begins at the start of pregnancy (38, 53). Meanwhile, a researcher found that a fetal imbalance toward anti-angiogenesis at the trophoblast stage could result in abnormal heart formation (38). Therefore, we can speculate that pre-eclampsia may already have clinical changes in early pregnancy, which may affect the development of the heart and lead to an increased risk of CHDs. Additionally, research showed that gestational hypertension may be in the spectrum of pre-eclampsia and was included in the definition of mild preeclampsia (54). Thus, the effect of pre-eclampsia on CHD may be consistent with that of gestational hypertension on CHD. Furthermore, findings regarding the association of maternal HDP with CHDs subtypes are varied in our study. Despite our study suggesting that maternal HDP may increase the risk for most CHDs, the mechanisms are almost unknown. We think that the differences between HDP and specific CHDs phenotypes could be explained by the fact that the

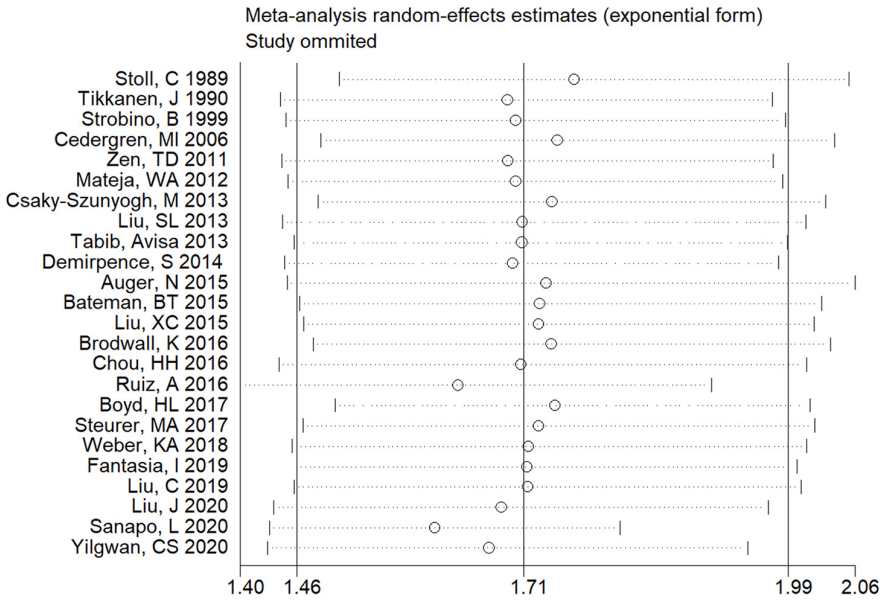

FIGURE 5 | Sensitivity analysis for the association of maternal HDP exposure with risk of overall CHDs in offspring.

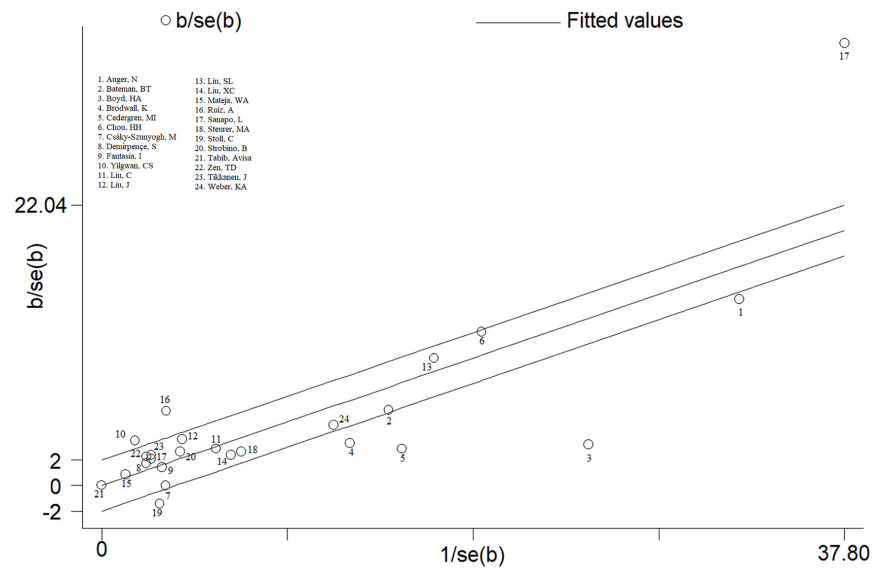

FIGURE 6 | Galbraith plots for maternal HDP exposure and CHDs risk in offspring.

pathophysiology of CHDs is multifactorial, involving genetic and environmental factors.

This systematic review had several strengths compared to the existing meta-analysis. First, as far as we know, our study was the first meta-analysis to independently estimate the association of pre-eclampsia, gestational hypertension, and chronic hypertension with the risk of CHDs. Our results indicated that the risk of total CHDs in offspring had significantly increased when data were restricted to pre-eclampsia (*OR* = 1.79), gestational hypertension (*OR* = 1.16), and chronic hypertension (*OR* = 1.68). Second, compared with the previous review (19), our study supplied up-to-date evidence on this topic and involved a large number of studies that not only included America and Europe populations, but also Asia, Oceania, and Africa populations. With the accumulation of evidence and the expansion of sample size and population, we have enhanced our statistical power to provide generalizable risk estimates. Third, although the previous meta-analysis also estimates the association of maternal hypertension with specific CHDs phenotypes (19), the number of studies included in the

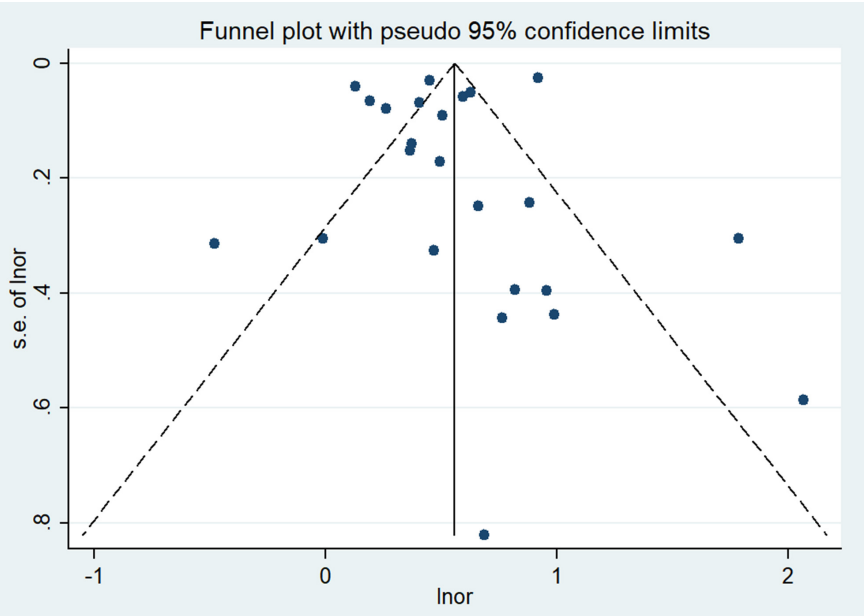

FIGURE 7 | Funnel plot for the association of maternal HDP exposure with risk of overall CHDs in offspring.

analysis is limited, including only 2–3 studies. Our study further enlarged the sample size in our analysis, which may contribute to improving the accuracy and reliability of risk estimates. Therefore, different from the results of the previous study (19), our results suggested a significant association of maternal HDP with most CHD phenotypes, which not only included CTD and ASD, but also TOF, HLHS, COA, LVOTO, and RVOTO. Besides, our study also fully considered the effect of heterogeneity and the most relevant heterogeneity moderators have been identified by subgroup analysis.

However, several limitations should be noted in our study. Firstly, in our review, results were limited to English-language literature, which may lead to possible language bias. Moreover, potential publication bias with under-publication of negative results may influence the findings, and it cannot be ignored. Secondly, substantial heterogeneity was found in the our study. This is not surprising, given the different study populations and methodologies. Based on the results of subgroup analyses, we found that types of HDP and geographic region were the potential source of heterogeneity. The possible explanation was that the risk of CHDs and HDP were not consistent in different geographical regions due to differences in race, medical level, and health awareness. For example, in some developing countries (e.g., Africa and Asia), there are still many pregnant women who do not receive adequate antenatal and pregnancy care because of the limited medical service, and the incidence and mortality of HDP were relatively high in these countries. Moreover, the health awareness of pregnant women in these developing countries is relatively weak, which may lead to the diagnosis delay of HDP, and result in a lack of effective early clinical interventions for HDP. Besides, since the definition of HDP may change over time, bias on outcome detection is difficult to avoid, which may increase clinical heterogeneity between studies. Nevertheless, we should still view the results with caution as the heterogeneity cannot be ignored. Thirdly, both case-control and cohort studies were selected in our study. Case-control studies are widely acknowledged to be prone to recall and selection biases, which restrict the strength and quality of evidence. Although the exposure history of maternal HDP was confirmed through medical records and/or physician-diagnosed self-reporting, the potential bias was unavoidable.

Fourth, considering that other subtypes of HDP were mostly diagnosed after organogenesis in addition to chronic hypertension, it is difficult to establish a causal link between pre-eclampsia or gestational hypertension and CHDs based on existing studies. Therefore, our study was mainly used to evaluate the association of maternal pre-eclampsia or gestational hypertension with CHDs in offspring, and could not explain the causal relationship. Fifth, of note, although our results found that early onset and severe preeclampsia had a higher risk of CHDs than late-onset and mild preeclampsia, respectively, the number of studies included in the analysis is limited, only three and four studies. In the future, more studies was needed to further explore the potential association between different types of preeclampsia and the risk of CHDs, which may contribute to improving the accuracy and reliability of risk estimates. Sixth, it is difficult to accurately evaluate the effect of the management of these disorders or the use of antihypertensive treatment on the occurrence of complications because of the limited information from original studies. Last but not least, the potential limitations including these studies (studies that were old or poor consideration of confounding factors) are inevitable. Although most of the included studies have tried to control for some potential confounding factors and restricting

the analysis to studies that have controlled confounding factors did not substantially change the pooled risk estimate, the possible influences of confounding factors might not be completely omitted. Therefore, further studies with adequate adjustment of potential confounding factors are still warranted to clarify the association of HDP with CHDs in offspring.

CONCLUSION

In conclusion, our findings have two implications significant for the public health of pregnant women. First, our study indicated maternal HDP exposure including pre-eclampsia, gestational hypertension, and chronic hypertension may be associated with an increase in the risk of CHDs. Second, our findings showed that maternal HDP exposure was significantly associated with the risk of most CHD phenotypes in offspring, such as CTD, ASD, and so on. These findings emphasize that maternal HDP exposure could seriously endanger the health of their babies, and lead to an increased risk of death in offspring. Therefore, for pregnancies, especially pregnant women at high risk of HDP, clinical workers should form a coalition of obstetricians, pediatricians, sonographers, and specialists in pregnancy-related hypertensive disease to conduct dynamic monitoring of these pregnant women, and increase cardiac developmental early screening of HDP-exposed infants in order to early intervention, so as to avoid missing the best treatment time and reduce the risk of death in children with CHDs. However, considering that the mechanisms involved in the association between maternal HDP and CHDs in offspring are unclear, further studies are essential to explore the potential mechanisms and find probable interventions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

SZ, LZC, and YJ made substantial contributions concerning: conception and design, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. XQ, TW, JL, JD, YL, LTC, and JQ made substantial contributions concerning: analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published. LZC and YJ was the guarantor for the study. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Krasuski RA, Bashore TM. Congenital heart disease epidemiology in the united states. *Circulation.* (2016) 134:110–3. doi: 10.1161/CIRCULATIONAHA.116.023370
2. Triedman JK, Newburger JW. Trends in congenital heart disease. *Circulation.* (2016) 133:2716–33. doi: 10.1161/CIRCULATIONAHA.116.023544
3. Liu Y, Chen S, Zuhlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol.* (2019) 48:455–63. doi: 10.1093/ije/dyz009
4. Ntiloudi D, Zegkos T, Bazmpani MA, Parcharidou D, Panagiotidis T, Hadjimiltiades S, et al. Pregnancy outcome in women with congenital heart disease: a single-center experience. *Hellenic J Cardiol.* (2018) 59:155–9. doi: 10.1016/j.hjc.2017.08.008
5. Ntiloudi D, Zegkos T, Koutsakis A, Giannakoulas G, Karvounis H. Pregnancy in patients with congenital heart disease a contemporary challenge. *Cardiol Rev.* (2017) 25:326–30. doi: 10.1097/CRD.0000000000000160
6. Uzark K. Challenges of assessing quality of life in congenital heart disease globally. *J Am Coll Cardiol.* (2016) 67:2246–8. doi: 10.1016/j.jacc.2016.03.535
7. Zaidi S, Brueckner M. Genetics and genomics of congenital heart disease. *Circ Res.* (2017) 120:923–40. doi: 10.1161/CIRCRESAHA.116.309140
8. Wang T, Chen L, Yang T, Huang P, Wang L, Zhao L, et al. Congenital heart disease and risk of cardiovascular disease: a meta-analysis of cohort studies. *J Am Heart Assoc.* (2019) 8:e12030. doi: 10.1161/JAHA.119.012030
9. Gaynor JW, Stopp C, Wypij DB, Andropoulos DB, Atallah J, Atz AM, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics.* (2015) 135:816–25. doi: 10.1542/peds.2014-3825
10. Brown MA, Magee LA, Kenny LC, Karumanchi SA, Mccarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens.* (2018) 13:291–310. doi: 10.1016/j.preghy.2018.05.004
11. Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. *Hypertens Res.* (2017) 40:213–20. doi: 10.1038/hr.2016.126
12. Li F, Wang T, Chen L, Zhang S, Chen L, Qin J. Adverse pregnancy outcomes among mothers with hypertensive disorders in pregnancy: a meta-analysis of

cohort studies. *Pregnancy Hypertens.* (2021) 24:107–17. doi: 10.1016/j.preghy.2021.03.001
13. Kibret KT, Chojenta C, Gresham E, Tegegne TK, Loxton D. Maternal dietary patterns and risk of adverse pregnancy (hypertensive disorders of pregnancy and gestational diabetes mellitus) and birth (preterm birth and low birth weight) outcomes: a systematic review and meta-analysis. *Public Health Nutr.* (2018) 22:1–15. doi: 10.1017/S1368980018002616
14. Chou HH, Chiou MJ, Liang FW, Chen LH, Lu TH, Li CY. Association of maternal chronic disease with risk of congenital heart disease in offspring. *CMAJ.* (2016) 188:E438–46. doi: 10.1503/cmaj.160061
15. Boyd HA, Basit S, Behrens I, Leirgul E, Bundgaard H, Wohlfahrt J, et al. Association between fetal congenital heart defects and maternal risk of hypertensive disorders of pregnancy in the same pregnancy and across pregnancies. *Circulation.* (2017) 136:39–48. doi: 10.1161/CIRCULATIONAHA.116.024600
16. Fantasia I, Andrade W, Syngelaki A, Akolekar R, Nicolaides KH. Impaired placental perfusion and major fetal cardiac defects. *Ultrasound Obstet Gynecol.* (2019) 53:68–72. doi: 10.1002/uog.20149
17. Liu J, Zhao G, Xie J, Wu S, Li B, Yao J. There is a strong association between early preeclampsia and congenital heart defects: a large population-based, retrospective study. *Gynecol Obstet Invest.* (2020) 86:1–8. doi: 10.1159/000506804
18. Sanapo L, Donofrio MT, Ahmadzia HK, Gimovsky AC, Mohamed MA. The association of maternal hypertensive disorders with neonatal congenital heart disease: analysis of a United States cohort. *J Perinatol.* (2020) 40:1617–24. doi: 10.1038/s41372-020-00795-9
19. Ramakrishnan A, Lee LJ, Mitchell LE, Agopian AJ. Maternal hypertension during pregnancy and the risk of congenital heart defects in offspring: a systematic review and meta-analysis. *Pediatr Cardiol.* (2015) 36:1442–51. doi: 10.1007/s00246-015-1182-9
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* (2009) 339:b2535. doi: 10.1136/bmj.b2535
21. Lowe SA, Brown MA, Dekker GA, Gatt S, Mclintock CK, Mcmahon LP, et al. Guidelines for the management of hypertensive disorders of pregnancy 2008. *Aust N Z J Obstet Gynaecol.* (2009) 49:242–6.
22. Hypertension in pregnancy. Report of the American college of obstetricians and gynecologists' task force on hypertension in pregnancy. *Obstet Gynecol.* (2013) 122:1122–31. doi: 10.1097/01.AOG.0000437382.03963.88
23. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet.* (2010) 376:631–44. doi: 10.1016/S0140-6736(10)60279-6
24. Wells GA, Shea BJ, O'Connell D, Peterson J, Welch V. *Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in the Meta-Analysis.* (2021). Available online at: www.ohri.ca/programs/clinical_epidemiology/oxford.htm (accessed July 20, 2021).
25. Dersimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials.* (2015) 45:139–45. doi: 10.1016/j.cct.2015.09.002
26. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* (2003) 327:557–60. doi: 10.1136/bmj.327.7414.557
27. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* (1997) 315:629–34. doi: 10.1136/bmj.315.7109.629
28. Stoll C, Alembik Y, Roth MP, Dott B, De Geeter B. Risk factors in congenital heart disease. *Eur J Epidemiol.* (1989) 5:382–91. doi: 10.1007/BF00144842
29. Tikkanen J, Heinonen OP. Risk factors for cardiovascular malformations in Finland. *Eur J Epidemiol.* (1990) 6:348–56. doi: 10.1007/BF00151707
30. Strobino B, Abid S, Gewitz M. Maternal lyme disease and congenital heart disease: a case-control study in an endemic area. *Am J Obstet Gynecol.* (1999) 180:711–6. doi: 10.1016/s0002-9378(99)70277-2
31. Cedergren MI, Kallen BA. Obstetric outcome of 6346 pregnancies with infants affected by congenital heart defects. *Eur J Obstet Gynecol Reprod Biol.* (2006) 125:211–6. doi: 10.1016/j.ejogrb.2005.07.006
32. Zen TD, Rosa RF, Zen PR, Trevisan P, Da SA, Ricachinevsky CP, et al. Gestational and family risk factors for carriers of congenital heart defects in southern Brazil. *Pediatr Int.* (2011) 53:551–7. doi: 10.1111/j.1442-200X.2011.03341.x
33. Mateja WA, Nelson DB, Kroelinger CD, Ruzek S, Segal J. The association between maternal alcohol use and smoking in early pregnancy and congenital cardiac defects. *J Womens Health (Larchmt).* (2012) 21:26–34. doi: 10.1089/jwh.2010.2582
34. Tabib A, Shirzad N, Sheikhbahaei S, Mohammadi S, Qorbani M, Haghpanah V, et al. Cardiac malformations in fetuses of gestational and pre gestational diabetic mothers. *Iran J Pediatr.* (2013) 23:664–8.
35. Liu S, Joseph KS, Lisonkova S, Rouleau J, Van den Hof M, Sauve R, et al. Association between maternal chronic conditions and congenital heart defects: a population-based cohort study. *Circulation.* (2013) 128:583–9. doi: 10.1161/CIRCULATIONAHA.112.001054
36. Csaky-Szunyogh M, Vereczkey A, Kosa Z, Gerencser B, Czeizel AE. Risk and protective factors in the origin of conotruncal defects of heart–a population-based case-control study. *Am J Med Genet A.* (2013) 161A:2444–52. doi: 10.1002/ajmg.a.36118
37. Demirpençe S, Demirpençe BÝ, Meşe T, Arslanoğlu S, Tavlı V, çalkavur Ş, et al. Predictors of postnatal complications and congenital cardiac diseases in infants of mothers with pregestational and gestational diabetes. *Turk Pediatri Ars.* (2014) 49:299–306. doi: 10.5152/tpa.2014.1017
38. Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association between preeclampsia and congenital heart defects. *JAMA.* (2015) 314:1588–98. doi: 10.1001/jama.2015.12505
39. Liu X, Liu G, Wang P, Huang Y, Liu E, Li D, et al. Prevalence of congenital heart disease and its related risk indicators among 90,796 Chinese infants aged less than 6 months in Tianjin. *Int J Epidemiol.* (2015) 44:884–93. doi: 10.1093/ije/dyv107
40. Bateman BT, Huybrechts KF, Fischer MA, Seely EW, Ecker JL, Oberg AS, et al. Chronic hypertension in pregnancy and the risk of congenital malformations: a cohort study. *Am J Obstet Gynecol.* (2015) 212:331–7. doi: 10.1016/j.ajog.2014.09.031
41. Ruiz A, Ferrer Q, Sánchez O, Ribera I, Arévalo S, Alomar O, et al. Placenta-related complications in women carrying a foetus with congenital heart disease. *J Matern Fetal Neonatal Med.* (2016) 29:3271–5. doi: 10.3109/14767058.2015.1121480
42. Brodwall K, Leirgul E, Greve G, Vollset SE, Holmstrom H, Tell GS, et al. Possible common aetiology behind maternal preeclampsia and congenital heart defects in the child: a cardiovascular diseases in norway project study. *Paediatr Perinat Epidemiol.* (2016) 30:76–85. doi: 10.1111/ppe.12252
43. Steurer MA, Baer RJ, Keller RL, Oltman S, Chambers CD, Norton ME, et al. Gestational age and outcomes in critical congenital heart disease. *Pediatrics.* (2017) 140:e20170999. doi: 10.1542/peds.2017-0999
44. Weber KA, Mayo JA, Carmichael SL, Stevenson DK, Winn VD, Shaw GM. Occurrence of selected structural birth defects among women with preeclampsia and other hypertensive disorders. *Am J Epidemiol.* (2018) 187:668–76. doi: 10.1093/aje/kwx269
45. Liu C, Lodge J, Flatley C, Gooi A, Ward C, Eagleson K, et al. Obstetric and perinatal outcomes in pregnancies with isolated foetal congenital heart abnormalities. *J Matern Fetal Neonatal Med.* (2019) 32:2985–92. doi: 10.1080/14767058.2018.1453799
46. Yilgwan CS, Pam VC, Ige OO, Golit WN, Anzaku S, Imade GE, et al. Profile of congenital heart disease in infants born following exposure to preeclampsia. *PLoS One.* (2020) 15:e229987. doi: 10.1371/journal.pone.0229987
47. Sliwa K, Mebazaa A. Possible joint pathways of early pre-eclampsia and congenital heart defects *via* angiogenic imbalance and potential evidence for cardio-placental syndrome. *Eur Heart J.* (2014) 35:680–2. doi: 10.1093/eurheartj/eht485
48. Dor Y, Camenisch TD, Itin A, Fishman GI, Mcdonald JA, Carmeliet P, et al. A novel role for VEGF in endocardial cushion formation and its potential contribution to congenital heart defects. *Development.* (2001) 128:1531–8. doi: 10.1242/dev.128.9.1531
49. Lee YM, Cope JJ, Ackermann GE, Goishi K, Armstrong EJ, Paw BH, et al. Vascular endothelial growth factor receptor signaling is required for cardiac valve formation in zebrafish. *Dev Dyn.* (2006) 235:29–37. doi: 10.1002/dvdy.20559

50. Shi H, O'Reilly VC, Moreau JL, Bewes TR, Yam MX, Chapman BE, et al. Gestational stress induces the unfolded protein response, resulting in heart defects. *Development*. (2016) 143:2561–72. doi: 10.1242/dev.136820
51. Cameli M, Lembo M, Sciaccaluga C, Bandera F, Ciccone MM, D'Andrea A, et al. Identification of cardiac organ damage in arterial hypertension: insights by echocardiography for a comprehensive assessment. *J Hypertens.* (2020) 38:588–98. doi: 10.1097/HJH.0000000000002323
52. Clark EB. Pathogenetic mechanisms of congenital cardiovascular malformations revisited. *Semin Perinatol.* (1996) 20:465–72. doi: 10.1016/s0146-0005(96)80062-0
53. Roberts JM, Bell MJ. If we know so much about preeclampsia, why haven't we cured the disease? *J Reprod Immunol.* (2013) 99:1–9. doi: 10.1016/j.jri.2013.05.003
54. Melamed N, Ray JG, Hladunewich M, Cox B, Kingdom JC. Gestational hypertension and preeclampsia: are they the same disease? *J Obstet Gynaecol Can.* (2014) 36:642–7. doi: 10.1016/S1701-2163(15)30545-4

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REVIEW
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Related Risk Factors and Treatment Management of Psoriatic Arthritis Complicated With Cardiovascular Disease

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Psoriatic arthritis (PsA) is a chronic autoimmune inflammatory joint disease related to psoriasis (PsO). The risk of PsA patients with cardiovascular disease (CVD) is significantly higher than that of the general population. At present, the relevant mechanism is not clear, chronic inflammation and traditional cardiovascular risk factors are the most important factors for the increased risk of CVD in PsA patients. Early assessment of the risk of PsA patients with CVD, and active control of the disease activity of PsA patients and intervention of traditional cardiovascular risk factors can delay the progression of CVD risk. This article reviews the epidemiology and pathogenesis between PsA and CVD, and reviews the latest developments in the risk assessment and management of CVD in PsA patients.

Keywords: psoriatic arthritis, cardiovascular disease, traditional cardiovascular risk factors, inflammation risk, treatment management

INTRODUCTION

According to the World Health Organization, 17.7 million people die from cardiovascular disease (CVD) each year, accounting for 31% of all deaths worldwide (1). Psoriatic arthritis (PsA)is a chronic, inflammatory and immune-mediated disease that affects up to 30% of patients with psoriasis (PsO) (2). PsA was once considered a relatively mild disease, but more and more studies have shown that it can bring a huge economic burden to patients and families, especially with CVD, including Ischemic Heart Disease, all stable and unstable angina, Myocardial infarction, transient ischemic attack, coronary artery insufficiency, peripheral artery disease, stroke, congestive heart failure (3). Studies have found that CVD is the most common comorbidity in patients with PsA (4, 5). At present, with the advent of targeted therapy, the joint and skin performance of PsA patients has been greatly improved. However, due to insufficient recognition or treatment of PsA combined with CVD, serious morbidity and even mortality have been caused (6). The EULAR for PsA pharmacological management in 2019 recommends that when dealing with PsA patients, comorbidities such as metabolic syndrome and CVD should be considered (7). This article will review the research progress in the epidemiology, pathogenesis, risk assessment and management of PsA combined with CVD.

EPIDEMIOLOGY OF PSA WITH CVD

Compared with the general population, the incidence and mortality of CVD in PsA patients have increased (8–11). CVD-related risk factors and morbidity risks in the PsA population are also higher than those in the general population (12, 13). Polachek et al. (14) conducted a meta-analysis and included 11 studies, the results showed that compared with the general population, the incidence of CVD of PsA increased by 43%, and the risk of incidence increased by 55% in 2017. Among them, myocardial infarction, cerebrovascular disease and the risk of heart failure increased by 68%, 22%, and 31%. Schieir et al. (15) stated in another systematic review and meta-analysis that the risk of myocardial infarction in patients with PsA is significantly increased, even after adjustment for traditional cardiovascular risk factors, the risk of PsA combined with CVD is still significantly increased. A large population-based study in 2019 found that the risk of PsA patients with CVD increased by 29%, and also showed that the increase in CVD risk in PsA and PsO was similar (16). However, some studies have found that compared with PsO patients, PsA patients have a higher burden of carotid artery plaque and a higher incidence of combined CVD (17, 18). But compared with RA, AS and diabetes, patients with PsA have a similar CVD risk (19–21). In recent years, studies have shown that CVD is the main cause of death in PsA patients, Juneblad et al. (22) used Swedish national registration data to compare 464 PsA patients with the general population and found that the standard mortality rate of CVD in PsA patients was significantly higher. Clinicians should pay attention to the comorbidities of PsA patients, multidisciplinary cooperation, and reduce mortality.

RISK FACTORS OF PSA WITH CVD

Chronic Inflammation and Autoimmune Factors

The increased risk of CVD cannot be fully explained by traditional cardiovascular risk factors, and PsA inflammation is considered to be the main reason for the increased risk of PsA combined with CVD. There is evidence that the pathogenesis of CVD includes systemic inflammation, insulin resistance, dyslipidemia, angiogenesis, oxidative stress, and endothelial dysfunction (23). Studies have shown that many pro-inflammatory cytokines, including TNF, IL-6, and IL-17, are involved in the pathogenesis of PsA, as well as in the pathogenesis of endothelial dysfunction and atherosclerosis (24) (**Figure 1**). These inflammatory factors suggest that PsA is potentially related to CVD. In addition, systemic inflammation in PsA patients is thought to change lipid structure and function, thereby forming a pro-atherosclerotic profile, this lipid imbalance has been confirmed in PsA cross-sectional studies, although causal data is lacking (25, 26). Systemic inflammation of PsO can lead to insulin resistance, which in turn leads to endothelial dysfunction, atherosclerosis and ultimately CVD (27). In addition to systemic inflammatory factors, chronic recurring inflammation is also involved in the occurrence of PsA-related CVD, because the number and duration of disease activity will increase the risk of CVD. Studies have shown that cumulative inflammation is related to arteriosclerosis in PsA patients, after correcting for traditional cardiovascular risk factors, chronic inflammation still plays an important role in accelerating the development of cardiovascular risk in PsA patients (28–31). The results of a meta-analysis also showed that PsA-related subclinical atherosclerosis and endothelial dysfunction, suggesting that chronic inflammation plays an important role in its pathogenesis, independently and/or in conjunction with traditional cardiovascular risk factors, increase the risk of CVD (32). PsA patients with tendon enthesitis and/or structural damage are at high risk of CVD (33). A cross-sectional study showed that nail involvement in PsA patients is independently related to carotid plaque, and nail involvement is related to severe skin manifestations and joint involvement, which is caused by increased inflammation burden (34). Baseline increases in joint counts, index inflammation counts, and erythrocyte sedimentation rate (ESR) count levels in patients with PsA are independently associated with increases in cardiovascular events (CVE) (35, 36). In short, inflammation is the core mechanism of PsA combined with CVD, however, the data on the effect of PsA-targeted inflammation on cardiometabolism are limited, and further research is needed.

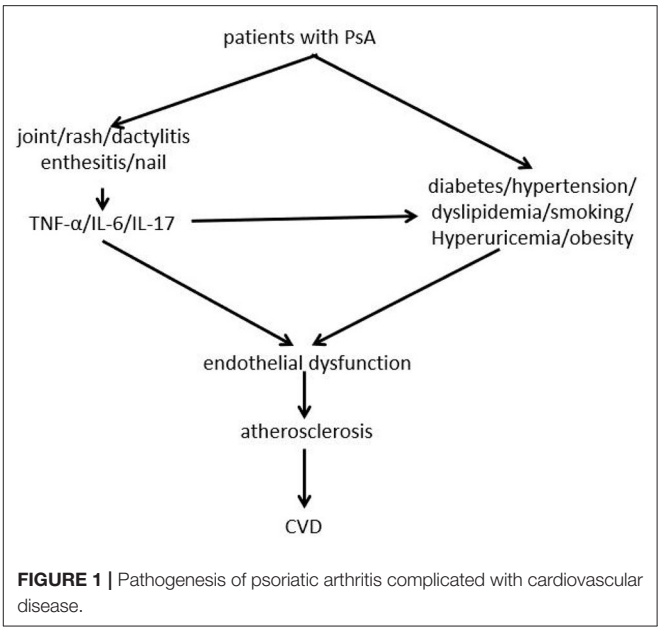

FIGURE 1 | Pathogenesis of psoriatic arthritis complicated with cardiovascular disease.

Traditional Cardiovascular Risk Factors

Studies have found that traditional cardiovascular risk factors (obesity, hypertension, diabetes, dyslipidemia, metabolic syndrome, smoking) are related to PsA, and it also shows that PsA is closely related to increased CVD risk (37). A large study report in 2017 showed that the traditional cardiovascular risk factors of PsA patients are higher than those of RA and PsO (38). In subsequent studies of PsA patients, almost 88% of patients

had at least one modifiable cardiovascular risk factor: smoking 17%, type 2 diabetes 13%, hypertension 45%, dyslipidemia 50%, overweight or obesity >75% (39). Compared with those PsA patients without CVD risk factors, PsA patients with more CVD risk factors showed higher disease activity (40). Among them, the obesity factor is more important, and it has been proven to promote the production of IL-17 in adipose tissue and peripheral tissue, and IL-17 is involved in the pathogenesis of obesity and PsA (41). PsA can produce a variety of pro-inflammatory cytokines, which can interfere with metabolic activities and affect adipose tissue and lipid distribution. This can lead to type 2 diabetes, metabolic syndrome, hyperlipidemia, hypertension, and obesity, which can have a profound impact on the management of PsA patients (42). Hyperuricemia appears to be an independent risk factor for PsA (43). for PsA patients without CVD, serum uric acid concentration is associated with subclinical atherosclerosis (44). Appropriate control of hyperuricemia and metabolic diseases can improve the outcome of cardiovascular disease in PsA and play a preventive role (45).

Genetic Factors

First-degree relatives with a family history of premature cardiovascular event (CVE) (males before the age of 55, females before the age of 65) can significantly increase the risk of CVD in patients with inflammation and the general population (46). At present, there are few genetic research data on PsA patients with CVD, and more data are about the role of genes in the human leukocyte antigen (HLA) region in RA patients with CVD risk. Other genetic polymorphisms in different inflammatory and metabolic pathways located inside and outside the HLA region appear to increase the risk of CVD in RA patients (47, 48).

RISK ASSESSMENT OF PSA WITH CVD

In order to achieve better management and prevention of patients with PsA combined with CVD, it is necessary to carry out relevant assessments of their risks (**Table 1**). Studies have shown that high ESR values are related to the high burden of atherosclerosis and clinical CVD in PsA patients. Another study on the levels of serum cytokines and adhesion molecules related to endothelial function has found that ESR and DAS28 in endothelin-1 and PsA related, suggesting that the progression of PsA combined with CVD may be slowed by controlling ESR and endothelin-1 levels (35, 78). PsA patients have a moderately increased risk of hyperlipoproteinemia (a) which may help improve the CVD risk assessment of PsA patients (79). Imaging examinations such as ultrasound and coronary CT can help assess the risk of CVD in PsA.Study found that 39% of PsA patients showed carotid plaque formation on ultrasound examination (80). Another meta-analysis showed that in patients with PsA, the common carotid artery intima-media thickness (CCA-IMT) increased, and the blood flow-mediated dilatation (FMD) decreased (32). It is suggested that ultrasound can be used to screen and monitor carotid artery plaque, CCA-IMT and brachial artery FMD to predict the possibility of CVD. However, brachial artery FMD is easily affected by the level of technique, which greatly limits its reproducibility and outcome correlation. CCA-IMT

TABLE 1 | Risk assessment of PsA combined with CVD.

Assessment method	Evaluation metrics
Scale	DAPSA, MDA, Framingham, SCORE (8–60,64,65)
Serology	ESR, endothelin-1, hyperlipoproteinemia (a) (35,49–50)
Videography	Ultrasound (CCA-IMT, FMD, carotid plaque, aortic pulse wave velocity),CT coronary angiography (29,32,51–52,57–60)

ultrasound technology is safe and reproducible, but the accuracy of different doctors may vary. Current studies have found that CCA-IMT can be used as a surrogate marker for atherosclerosis and CVD risk, the HR for CCA-IMT increased by 0.1 mm and related CVE was 1.65 (81). After carotid ultrasound assessment, patients with PsA are more often reclassified into a very high-scoring risk category than the control group, which is explained independently by disease activity (82–84). A recent multicenter study also found that both PsO and PsA are associated with an increased prevalence of coronary artery calcification (85). Szentpetery et al. (29) used coronary CT angiography to evaluate the relationship between PsA and coronary plaques and found that the prevalence of PsA coronary plaques was 76%, compared with 44% in the control group, the total plaque volume was even larger and mixed plaques have a higher incidence in PsA. Mixed plaques contain thin cap fibrous atherosclerosis, which helps PsA with CVD and poor prognosis. The course of arterial stiffness is highly correlated with the risk of CVD, and the risk of CVD in PsA patients can be assessed by detecting the aortic pulse wave velocity (53, 81). At present, EULAR recommends the routine use of Framingham and SCORE for risk scores to calculate the 10-year risk of CVD events in PsA patients. This risk score can easily underestimate the CVD risk of PsA patients, even after adjusting for the traditional risk factors of PsA patients (51, 86). In PsA patients, in addition to the traditional CV risk score, the presence of higher DAPSA and carotid plaque can independently predict CVD events (87). Therefore, the risk assessment of patients with PsA combined with CVD is particularly important.

MANAGEMENT RISK FACTORS FOR CVD WITH PSA

Management of Traditional Cardiovascular Risk Factors

The risk of CVD in PsA patients is significantly higher than that of the general population, EULAR recommends that all PsA patients undergo a CVD risk assessment at least once every 5 years to screen and identify risk factors for CVD in order to implement risk management and preventive treatment of CVD, at the same time, it is recommended that when using Framingham and SCORE to assess the 10-year risk of CVD events in PsA patients, if the Framingham score is 10% or the SCORE score is 5%, it is recommended that the patient change lifestyle and use lipid-lowering drugs for treatment (51). For overweight or obese PsA patients, ACR/American Psoriasis Foundation recommends weight loss (88). Weight loss

intervention can increase the proportion of patients with PsA who reach minimum disease activity (MDA) (89, 90). Once the MDA level is reached, the MDA level should ideally be extended to prevent the progression of carotid atherosclerosis and arteriosclerosis in PsA patients (91, 92). In addition, studies have shown that exercise has a significant beneficial effect on PsA on disease activity and CVD risk (93). Schieir et al. (15) found in a systematic review and meta-analysis that traditional risk factors are more common when PsA is combined with CVD. Therefore, they support a more comprehensive CVD prevention strategy for this population, with the goal of reducing inflammation and enhancing management of traditional CVD risk factors.

Reasonable Use of NSAIDs Drugs and Glucocorticoids

There is evidence that cyclooxygenase-2 inhibitors (COXIBs) and NSAIDs increase the risk of CVD. A recent meta-analysis showed that non-selective NSAIDs and COXIBs have an adverse effect on the CVD outcome of PsA patients (52). It may be that the use of NSAIDs is related to arterial stiffness in PsA patients, increasing the risk of CVD (53). Another cohort study from the United Kingdom found that the incidence of major adverse cardiovascular events (MACE) in PsA patients receiving glucocorticoid therapy was significantly higher (49). An 11-year retrospective study showed that the increased burden of inflammation reflected by elevated CRP levels in PsA patients was associated with an increased risk of CV events, while the use of NSAIDs in PsA patients significantly reduced the risk of CVD (3). In PsA patients, the use of NSAIDs or glucocorticoid therapy is associated with a high risk of new-onset hypertension. Doctors should pay attention to the early diagnosis of hypertension during treatment with such drugs, reduce the risk of PsA combined with CVD (50). There are few direct data on this relationship in PsA, and further research is needed. EULAR recommends that NSAIDs should be used cautiously in patients with CVD records or CVD risk factors for PsA, because these drugs are usually essential when dealing with the disease activity

TABLE 2 | Risk of CVD in patients with PsA after drug treatment.

Drug	Favorable evidence for CVD	Unfavorable evidence for CVD
Glucocorticd		1. The incidence of MACE in PsA patients receiving glucocorticoid therapy is significantly higher (49) 2. Glucocorticoid therapy increases the risk of hypertension in PsA patients, leading to an increased risk of CVD (50) 3. Glucocorticoids can eliminate the harm of PsA inflammation to CVD, but it can also increase the risk of CVD (51)
NSAIDs	1. the use of NSAIDs in PsA patients can improve inflammation and significantly reduce the risk of CVD (3)	1. Non-selective NSAIDs and COXIBs have adverse effects on the CVD outcome of PsA patients (52) 2. The use of NSAIDs is associated with arterial stiffness in PsA patients and increases the risk of CVD (53) 3. Treatment of NSAIDs in PsA patients increases the risk of hypertension, leading to an increased risk of CVD (50)
csDMARDs	1. Methotrexate may reduce cardiovascular risk by suppressing inflammation (54) 2. Vascular endothelial function of PsA patients in the MTX group improved more than that in the TNF-αi-MTX group (55) 3. There is no difference in MACE between TNF-αi, MTX and untreated PsA patients (35)	1. Compared with TNF-αi treatment of RA, methotrexate has an increased risk of MACE and stroke (56)
bsDMARDs-TNF-αi	1. TNF-αi inhibitors can delay the progression of subclinical atherosclerosis, reduce arterial stiffness, and reduce the risk of CVD while treating PsA inflammation (57–64) 2. The reduced cardiovascular morbidity observed in PsA patients receiving TNF-αi therapy may be partly due to its beneficial effects on complement (65) 3. TNF-αi targeting systemic inflammation can provide cardioprotection for patients with PsO and/or PsA (66)	
bsDMARDs-IL-17/ IL-12/23	1. In patients with PsO or PsA, compared with TNF-αi, there was no difference in the MACE or mortality of ulinumumab (IL-12/23) initiation of treatment (67)	1. Compared with TNF-αi, patients with PsA using IL-12/23 and IL-17 have a greater MACE risk (68)
tsDMARDs-PDE-4	1. Apremilast can help restore vascular endothelial dysfunction and stability, prevent the progression of atherosclerotic plaque, thereby reducing the risk of CVD (69–71) 2. Compared with TNF-αi, there is no difference in the risk of MACE for major adverse cardiovascular events in PsA patients using Apremilast (68, 72)	1. Apremilast can improve the disease activity of patients with PsO, but cannot improve vascular endothelial function (73)
tsDMARDs-JAKi	1. Tofacitinib treatment of PsA patients increases the risk of dyslipidemia, while the risk of CVE decreases (74–76)	1. A real-world study found that tofacitinib has a higher incidence of MACE when treating PsA patients (77)

of PsA patients, clinicians should evaluate them based on the patient's specific conditions. Then use NSAIDs according to specific treatment guidelines, and glucocorticoids can eliminate the harm of inflammation to CVD, but it will also increase the risk of CVD. When treating patients with active PsA, the lowest effective dose can be given short-term continuous treatment (51).

Control PsA Disease Activity

EULAR proposed that controlling disease activities can reduce the risk of PsA combined with CVD (**Table 2**). Current studies have shown that the use of biologics in PsA patients is related to the reduction of major CVD (57, 72). And proper disease activity control will reduce the use of non-steroidal anti-inflammatory drugs and glucocorticoids, which will ultimately help reduce the incidence of new CVE in these patients (35, 94). The most common first-line csDMARDs for the treatment of PsA patients is methotrexate (MTX) (70.9%), and the most common first-line bsDMARDs is adalimumab (30.8%) (95). There is conflicting evidence regarding the clinical cardiovascular end points of myocardial infarction, stroke, and cardiovascular-related death in PsA patients treated with biologics. A meta-analysis of 10 cohort studies including patients with RA, PsO, and PsA found that MTX treatment can reduce overall cardiovascular risk by 21% and myocardial infarction risk by 18%. MTX may be reduce cardiovascular risk by suppressing inflammation (54). Another study found that the vascular endothelial function of PsA patients in the MTX group improved more than that in the TNF-αi-MTX group (55). A recent meta-analysis of observational studies of 14 RA patients found that compared with TNF-αi treatment, methotrexate has an increased risk of MACE and stroke (56). Eder et al. (35) investigated the incidence of CVE in a large PsA clinic and found that there was no difference in MACE between TNF-αi, MTX, and untreated PsA patients. Studies have found that TNF-αi inhibitors can delay the progression of subclinical atherosclerosis, reduce arterial stiffness, and reduce the risk of CVD while treating PsA inflammation (57–64). The reduced cardiovascular morbidity observed in PsA patients receiving TNF-αi therapy may be partly due to its beneficial effects on complement (65). Another meta-analysis showed that the use of TNF-αi to target systemic inflammation can provide cardioprotection for patients with PsO and/or PsA, and can reduce the risk of CVD (66). A systematic review and meta-analysis by Roubille et al. (52). In 2015 showed that in patients with PsO and PsA, biologics and other DMARDs may be related to reducing the risk of CVD, but compared with RA, the evidence is not conclusive. Data from two large commercial databases in the United States show that in patients with PsO or PsA, compared with TNF-αi, there is no difference in the MACE or mortality of uzumumab (IL-12/23) initiation of treatment (67). A national cohort study in 2021 showed that compared with TNF-αi, patients with PsA using IL-12/23 and IL-17 are at greater MACE risk (68). Studies have found that Apremilast can help restore vascular endothelial dysfunction and stability, prevent the progression of atherosclerotic plaque, thereby reducing the risk of CVD (69–71), this is in contrast to a recent study by Ferguson et al. (73). Studies have found that compared with TNF-αi, there is no difference in the risk of MACE for major adverse cardiovascular events in PsA patients using Apremilast (68, 72). Tofacitinib treatment of PsA patients increases the risk of dyslipidemia, while the risk of CVD decreases (74–76). But a real-world study found that tofacitinib has a higher incidence of MACE when treating PsA patients (77). Regarding the effect of drugs on the incidence and mortality of CVD in the PsA population, large-scale, prospective, adequately controlled and powerful studies are still needed.

CONCLUSION

With the improvement of the level of diagnosis and treatment, more and more evidences show that the CVD burden of PsA patients has increased significantly. In terms of management, it is recommended to intervene in the traditional risk factors of CVD that are increased in PsA, and then further research is needed on the impact of anti-inflammatory treatments, especially DMARDs and biological agents (including TNF-αi inhibitors) on the burden of CVD. In addition to considering traditional risk factors, chronic and systemic inflammation may lead to the accelerated development of atherosclerosis, which can be measured by some non-invasive techniques, early identification, early treatment, and reduced incidence rate and death rate.

AUTHOR CONTRIBUTIONS

ZZ: literature search and writing. QG and DM: suggestions and revision points. XW and HW: literature search. CZ and LZ: propose. GZ: provide ideas and suggestions. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. WHO. *World Health Statistics Overview 2019: Monitoring Health for the SDGs, Sustainable Development Goals*. Geneva: World Health Organization (2019).
2. Gottlieb A, Merola JF. Psoriatic arthritis for dermatologists. *J Dermatolog Treat*. (2020) 31:662–79. doi: 10.1080/09546634.2019.1605142
3. Lam SH, So H, Cheng IT, Li EK, Wong P, Li TK, et al. Association of C-reactive protein and non-steroidal anti-inflammatory drugs with cardiovascular events in patients with psoriatic arthritis: a time-dependent Cox regression

analysis. *Ther Adv Musculoskelet Dis.* (2021) 13:1759720X211027712. doi: 10.1177/1759720X211027712
4. Esposito M, Giunta A, Mazzotta A, Zangrilli A, Babino G, Bavetta M, et al. Efficacy and safety of subcutaneous anti-tumor necrosis factor-alpha agents, etanercept and adalimumab, in elderly patients affected by psoriasis and psoriatic arthritis: an observational long-term study. *Dermatology.* (2012) 225:312–9. doi: 10.1159/000345623
5. Maximilian R, Garbe C, Petersen J, Augustin M, Kirsten N, Biermann MHC, et al. Epidemiology, comorbidity and risk factors for psoriatic arthritis: a health insurance claims database analysis. *Acta Derm Venereol.* (2021) 101:adv00566. doi: 10.2340/00015555-3879
6. So H, Tam LS. Cardiovascular disease and depression in psoriatic arthritis: multidimensional comorbidities requiring multidisciplinary management. *Best Pract Res Clin Rheumatol.* (2021) 35:101689. doi: 10.1016/j.berh.2021.101689
7. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis.* (2020) 79:700–12. doi: 10.1136/annrheumdis-2020-217159
8. Karmacharya P, Ogdie A, Eder L. Psoriatic arthritis and the association with cardiometabolic disease: a narrative review. *Ther Adv Musculoskelet Dis.* (2021) 13:1759720X21998279. doi: 10.1177/1759720X21998279
9. Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, et al. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. *J Eur Acad Dermatol Venereol.* (2013) 27(Suppl. 3):12–29. doi: 10.1111/jdv.12163
10. Jamnitski A, Symmons D, Peters MJ, Sattar N, McInnes I, Nurmohamed MT. Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review. *Ann Rheum Dis.* (2013) 72:211–6. doi: 10.1136/annrheumdis-2011-201194
11. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis.* (2015) 74:326–32. doi: 10.1136/annrheumdis-2014-205675
12. Kibari A, Cohen AD, Gazitt T, Bitterman H, Lavi I, Feldhamer I, et al. Cardiac and cardiovascular morbidities in patients with psoriatic arthritis: a population-based case control study. *Clin Rheumatol.* (2019) 38:2069–75. doi: 10.1007/s10067-019-04528-y
13. Landgren AJ, Bilberg A, Eliasson B, Larsson I, Dehlin M, Jacobsson L, et al. Cardiovascular risk factors are highly overrepresented in Swedish patients with psoriatic arthritis compared with the general population. *Scand J Rheumatol.* (2020) 49:195–9. doi: 10.1080/03009742.2019.1672783
14. Polachek A, Touma Z, Anderson M, Eder L. Risk of cardiovascular morbidity in patients with psoriatic arthritis: a meta-analysis of observational studies. *Arthritis Care Res.* (2017) 69:67–74. doi: 10.1002/acr.22926
15. Schieir O, Tosevski C, Glazier RH, Hogg-Johnson S, Badley EM. Incident myocardial infarction associated with major types of arthritis in the general population: a systematic review and meta-analysis. *Ann Rheum Dis.* (2017) 76:1396–404. doi: 10.1136/annrheumdis-2016-210275
16. Charlton R, Green A, Shaddick G, Snowball J, Nightingale A, Tillett W, et al. Risk of type 2 diabetes and cardiovascular disease in an incident cohort of people with psoriatic arthritis: a population-based cohort study. *Rheumatology*. (2019) 58:144–8. doi: 10.1093/rheumatology/key286
17. Eder L, Jayakar J, Shanmugarajah S, Thavaneswaran A, Pereira D, Chandran V, et al. The burden of carotid artery plaques is higher in patients with psoriatic arthritis compared with those with psoriasis alone. *Ann Rheum Dis.* (2013) 72:715–20. doi: 10.1136/annrheumdis-2012-201497
18. Skornicki M, Prince P, Suruki R, Lee E, Louder A. Clinical burden of concomitant joint disease in psoriasis: a US-linked claims and electronic health records database analysis. *Adv Ther.* (2021) 38:2458–71. doi: 10.1007/s12325-021-01698-7
19. Fragoulis GE, Evangelatos G, Tentolouris N, Fragkiadaki K, Panopoulos S, Konstantonis G, et al. Higher depression rates and similar cardiovascular comorbidity in psoriatic arthritis compared with rheumatoid arthritis and diabetes mellitus. *Ther Adv Musculoskelet Dis.* (2020) 12:1759720X20976975. doi: 10.1177/1759720X20976975
20. Lauper K, Courvoisier DS, Chevallier P, Finckh A, Gabay C. Incidence and prevalence of major adverse cardiovascular events in rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. *Arthritis Care Res.* (2018) 70:1756–63. doi: 10.1002/acr.23567
21. Rueda-Gotor J, Llorca J, Corrales A, Parra JA, Portilla V, Genre F, et al. Cardiovascular risk stratification in axial spondyloarthritis: carotid ultrasound is more sensitive than coronary artery calcification score to detect high-cardiovascular risk axial spondyloarthritis patients. *Clin Exp Rheumatol.* (2018).
22. Juneblad K, Rantapaa-Dahlqvist S, Alenius GM. Disease activity and increased risk of cardiovascular death among patients with psoriatic arthritis. *J Rheumatol.* (2016) 43:2155–61. doi: 10.3899/jrheum.160070
23. Yim KM, Armstrong AW. Updates on cardiovascular comorbidities associated with psoriatic diseases: epidemiology and mechanisms. *Rheumatol Int.* (2017) 37:97–105. doi: 10.1007/s00296-016-3487-2
24. Ramonda R, Lo Nigro A, Modesti V, Nalotto L, Musacchio E, Iaccarino L, et al. Atherosclerosis in psoriatic arthritis. *Autoimmun Rev.* (2011) 10:773–8. doi: 10.1016/j.autrev.2011.05.022
25. Shrestha A, Bahce-Altuntas A, Mowrey W, Broder A. Active peripheral inflammation is associated with pro-atherogenic lipid profile in psoriatic arthritis. *Semin Arthritis Rheum.* (2016) 46:286–90. doi: 10.1016/j.semarthrit.2016.05.011
26. Garg N, Krishan P, Syngle A. Atherosclerosis in psoriatic arthritis: a multiparametric analysis using imaging technique and laboratory markers of inflammation and vascular function. *Int J Angiol.* (2016) 25:222–8. doi: 10.1055/s-0036-1584918
27. Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. *Exp Dermatol.* (2011) 20:303–7. doi: 10.1111/j.1600-0625.2011.01261.x
28. Shen J, Shang Q, Li EK, Leung YY, Kun EW, Kwok LW, et al. Cumulative inflammatory burden is independently associated with increased arterial stiffness in patients with psoriatic arthritis: a prospective study. *Arthritis Res Ther.* (2015) 17:75. doi: 10.1186/s13075-015-0570-0
29. Szentpetery A, Healy GM, Brady D, Haroon M, Gallagher P, Redmond CE, et al. Higher coronary plaque burden in psoriatic arthritis is independent of metabolic syndrome and associated with underlying disease severity. *Arthritis Rheumatol.* (2018) 70:396–407. doi: 10.1002/art.40389
30. Lai YC, Yew YW. Psoriasis as an independent risk factor for cardiovascular disease: an epidemiologic analysis using a national database. *J Cutan Med Surg.* (2016) 20:327–33. doi: 10.1177/1203475415602842
31. Eder L, Thavaneswaran A, Chandran V, Cook R, Gladman DD. Increased burden of inflammation over time is associated with the extent of atherosclerotic plaques in patients with psoriatic arthritis. *Ann Rheum Dis.* (2015) 74:1830–5. doi: 10.1136/annrheumdis-2014-205267
32. Di Minno MN, Ambrosino P, Lupoli R, Di Minno A, Tasso M, Peluso R, et al. Cardiovascular risk markers in patients with psoriatic arthritis: a meta-analysis of literature studies. *Ann Med.* (2015) 47:346–53. doi: 10.3109/07853890.2015.1031822
33. Lorenzo A, Pardo E, Charca L, Pino M, Queiro R. Enthesitis and joint erosions are disease traits associated with cardiovascular risk in psoriatic arthritis. *Clin Rheumatol.* (2020) 39:2973–79. doi: 10.1007/s10067-020-05088-2
34. Colunga-Pedraza IJ, Galarza-Delgado DA, Azpiri-Lopez JR, Rodriguez-Romero AB, Guajardo-Jauregui N, Cardenas-de la Garza JA, et al. Nail involvement in psoriatic arthritis patients is an independent risk factor for carotid plaque. *Ann Rheum Dis.* (2021) 80:1629–31. doi: 10.1136/annrheumdis-2021-220782
35. Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. *Ann Rheum Dis.* (2016) 75:1680–6. doi: 10.1136/annrheumdis-2015-207980
36. Kaeley GS, Eder L, Aydin SZ, Gutierrez M, Bakewell C. Dactylitis: a hallmark of psoriatic arthritis. *Semin Arthritis Rheum.* (2018) 48:263–73. doi: 10.1016/j.semarthrit.2018.02.002
37. Puig L. Cardiometabolic comorbidities in psoriasis and psoriatic arthritis. *Int J Mol Sci.* (2017) 19. doi: 10.3390/ijms19010058
38. Radner H, Lesperance T, Accortt NA, Solomon DH. Incidence and prevalence of cardiovascular risk factors among patients with rheumatoid arthritis, psoriasis, or psoriatic arthritis. *Arthritis Care Res.* (2017) 69:1510–8. doi: 10.1002/acr.23171
39. Eder L, Harvey P, Chandran V, Rosen CF, Dutz J, Elder JT, et al. Gaps in diagnosis and treatment of cardiovascular risk factors in patients with

psoriatic disease: an international multicenter study. *J Rheumatol.* (2018) 45:378–84. doi: 10.3899/jrheum.170379
40. Ferraz-Amaro I, Prieto-Pena D, Palmou-Fontana N, Martinez-Lopez D, de Armas-Rillo L, Garcia-Dorta A, et al. The number of traditional cardiovascular risk factors is independently correlated with disease activity in patients with psoriatic arthritis. *Medicina.* (2020) 56. doi: 10.3390/medicina56080415
41. Chehimi M, Vidal H, Eljaafari A. Pathogenic role of IL-17-producing immune cells in obesity, and related inflammatory diseases. *J Clin Med.* (2017) 6. doi: 10.3390/jcm6070068
42. Scarpa R, Caso F, Costa L, Peluso R, Del Puente A, Olivieri I. Psoriatic disease 10 years later. *J Rheumatol.* (2017) 44:1298–301. doi: 10.3899/jrheum.161402
43. Tsuruta N, Imafuku S, Narisawa Y. Hyperuricemia is an independent risk factor for psoriatic arthritis in psoriatic patients. *J Dermatol.* (2017) 44:1349–52. doi: 10.1111/1346-8138.13968
44. Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Paz-Carreira J, et al. Asymptomatic hyperuricemia and serum uric acid concentration correlate with subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease. *Semin Arthritis Rheum.* (2009) 39:157–62. doi: 10.1016/j.semarthrit.2008.06.001
45. AlJohani R, Polachek A, Ye JY, Chandran V, Gladman DD. Characteristic and outcome of psoriatic arthritis patients with hyperuricemia. *J Rheumatol.* (2018) 45:213–7. doi: 10.3899/jrheum.170384
46. Semb AG, Ikdahl E, Hisdal J, Olsen IC, Rollefstad S. Exploring cardiovascular disease risk evaluation in patients with inflammatory joint diseases. *Int J Cardiol.* (2016) 223:331–6. doi: 10.1016/j.ijcard.2016.08.129
47. Lopez-Mejias R, Genre F, Remuzgo-Martinez S, Robledo G, Llorca J, Corrales A, et al. Vitamin D receptor GATG haplotype association with atherosclerotic disease in patients with rheumatoid arthritis. *Atherosclerosis.* (2016) 245:139–42. doi: 10.1016/j.atherosclerosis.2015.12.011
48. Garcia-Bermudez M, Lopez-Mejias R, Genre F, Castaneda S, Llorca J, Gonzalez-Juanatey C, et al. Interferon regulatory factor 5 genetic variants are associated with cardiovascular disease in patients with rheumatoid arthritis. *Arthritis Res Ther.* (2014) 16:R146. doi: 10.1186/ar4608
49. Li L, Hagberg KW, Peng M, Shah K, Paris M, Jick S. Rates of cardiovascular disease and major adverse cardiovascular events in patients with psoriatic arthritis compared to patients without psoriatic arthritis. *J Clin Rheumatol.* (2015) 21:405–10. doi: 10.1097/RHU.0000000000000306
50. Lee MS, Chang CH, Lin RY, Lai MS. Risks of hypertension associated with cyclosporine, nonsteroidal anti-inflammatory drugs, and systemic glucocorticoids in patients with psoriasis: a nationwide population-based nested case-control study in Taiwan. *Pharmacoepidemiol Drug Saf.* (2016) 25:133–40. doi: 10.1002/pds.3890
51. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis.* (2017) 76:17–28. doi: 10.1136/annrheumdis-2016-209775
52. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis.* (2015) 74:480–9. doi: 10.1136/annrheumdis-2014-206624
53. Fohse FK, Rollefstad S, Ikdahl E, Wibetoe G, Sexton J, Hisdal J, et al. Degree of arterial stiffness is comparable across inflammatory joint disease entities. *Scand J Rheumatol.* (2021) 76:17–28. doi: 10.1080/03009742.2021.1920169
54. Micha R, Imamura F, Wyler von Ballmoos M, Solomon DH, Hernan MA, Ridker PM, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. *Am J Cardiol.* (2011) 108:1362–70. doi: 10.1016/j.amjcard.2011.06.054
55. Deyab G, Hokstad I, Whist JE, Smastuen MC, Agewall S, Lyberg T, et al. Methotrexate and anti-tumor necrosis factor treatment improves endothelial function in patients with inflammatory arthritis. *Arthritis Res Ther.* (2017) 19:232. doi: 10.1186/s13075-017-1439-1
56. Singh S, Fumery M, Singh AG, Singh N, Prokop LJ, Dulai PS, et al. Comparative risk of cardiovascular events with biologic and synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res.* (2020) 72:561–76. doi: 10.1002/acr.23875
57. Lee JL, Sinnathurai P, Buchbinder R, Hill C, Lassere M, March L. Biologics and cardiovascular events in inflammatory arthritis: a prospective national cohort study. *Arthritis Res Ther.* (2018) 20:171. doi: 10.1186/s13075-018-1669-x
58. Brezinski EA, Follansbee MR, Armstrong EJ, Armstrong AW. Endothelial dysfunction and the effects of TNF inhibitors on the endothelium in psoriasis and psoriatic arthritis: a systematic review. *Curr Pharm Des.* (2014) 20:513–28. doi: 10.2174/13816128200414021312385 2
59. Di Minno MN, Iervolino S, Zincarelli C, Lupoli R, Ambrosino P, Pizzicato P, et al. Cardiovascular effects of Etanercept in patients with psoriatic arthritis: evidence from the cardiovascular risk in rheumatic diseases database. *Expert Opin Drug Saf.* (2015) 14:1905–13. doi: 10.1517/14740338.2015.1111870
60. Shen J, Shang Q, Tam LS. Targeting inflammation in the prevention of cardiovascular disease in patients with inflammatory arthritis. *Transl Res.* (2016) 167:138–51. doi: 10.1016/j.trsl.2015.05.006
61. Vlachopoulos C, Gravos A, Georgiopoulos G, Terentes-Printzios D, Ioakeimidis N, Vassilopoulos D, et al. The effect of TNF-a antagonists on aortic stiffness and wave reflections: a meta-analysis. *Clin Rheumatol.* (2018) 37:515–26. doi: 10.1007/s10067-017-3657-y
62. Eder L, Joshi AA, Dey AK, Cook R, Siegel EL, Gladman DD, et al. Association of tumor necrosis factor inhibitor treatment with reduced indices of subclinical atherosclerosis in patients with psoriatic disease. *Arthritis Rheumatol.* (2018) 70:408–16. doi: 10.1002/art.40366
63. Ortolan A, Ramonda R, Lorenzin M, Pesavento R, Spinazze A, Felicetti M, et al. Subclinical atherosclerosis evolution during 5 years of anti-TNF-alpha treatment in psoriatic arthritis patients. *Clin Exp Rheumatol.* (2021) 39:158–61.
64. Lorenzo Martin JA, Pardo Campo E, Pino Martinez M, Colazo Burlato M, Queiro Silva MR. Psoriatic arthritis: interaction between cardiometabolic diseases and inflammatory burden of the disease. *Reumatol Clin.* (2021) 51:240–7. doi: 10.1016/j.reumae.2021.05.003
65. Hokstad I, Deyab G, Wang Fagerland M, Lyberg T, Hjeltnes G, Forre O, et al. Tumor necrosis factor inhibitors are associated with reduced complement activation in spondylarthropathies: an observational study. *PLoS ONE.* (2019) 14:e0220079. doi: 10.1371/journal.pone.0220079
66. Yang ZS, Lin NN, Li L, Li Y. The effect of TNF inhibitors on cardiovascular events in psoriasis and psoriatic arthritis: an updated meta-analysis. *Clin Rev Allergy Immunol.* (2016) 51:240–7. doi: 10.1007/s12016-016-8560-9
67. Lee MP, Desai RJ, Jin Y, Brill G, Ogdie A, Kim SC. Association of ustekinumab vs TNF inhibitor therapy with risk of atrial fibrillation and cardiovascular events in patients with psoriasis or psoriatic arthritis. *JAMA Dermatol.* (2019) 155:700–7. doi: 10.1001/jamadermatol.2019.0001
68. Pina Vegas L, Le Corvoisier P, Penso L, Paul M, Sbidian E, Claudepierre P. Risk of major adverse cardiovascular events in patients initiating biologics/apremilast for psoriatic arthritis: a nationwide cohort study. *Rheumatology.* (2021) 47:578–82. doi: 10.1093/rheumatology/keab522
69. Mazzilli S, Lanna C, Chiaramonte C, Cesaroni GM, Zangrilli A, Palumbo V, et al. Real life experience of apremilast in psoriasis and arthritis psoriatic patients: preliminary results on metabolic biomarkers. *J Dermatol.* (2020) 47:578–82. doi: 10.1111/1346-8138.15293
70. De La Rosa IA, López-Montilla MD, Pérez-Sánchez C, Ábalos-Aguilera MD, Ruiz-Ponce M, Jiménez-Gómez Y. SAT0331 Inflammatory markers and adipokines related to cardiovascular risk and metabolic comorbidities in psoriatic arthritis *in vivo* effects of apremilast. In: *Annual European Congress of Rheumatology, EULAR 2018, Amsterdam, 13–16 June 2018* (2018).
71. Imam F, Al-Harbi NO, Al-Harbi MM, Ansari MA, Al-Asmari AF, Ansari MN, et al. Apremilast prevent doxorubicin-induced apoptosis and inflammation in heart through inhibition of oxidative stress mediated activation of NF-kappaB signaling pathways. *Pharmacol Rep.* (2018) 70:993–1000. doi: 10.1016/j.pharep.2018.03.009
72. Persson R, Hagberg KW, Qian Y, Vasilakis-Scaramozza C, Jick S. The risks of major cardiac events among patients with psoriatic arthritis treated with apremilast, biologics, DMARDs or corticosteroids. *Rheumatology.* (2021) 60:1926–31. doi: 10.1093/rheumatology/keaa683

73. Ferguson LD, Cathcart S, Rimmer D, Semple G, Brooksbank K, Paterson C, et al. Effect of the phosphodiesterase 4 inhibitor apremilast on cardiometabolic outcomes in psoriatic disease-results of the IMAPA study. *Rheumatology.* (2021) 71:1387–95. doi: 10.1093/rheumatology/keab474
74. Gladman DD, Charles-Schoeman C, McInnes IB, Veale DJ, Thiers B, Nurmohamed M, et al. Changes in lipid levels and incidence of cardiovascular events following tofacitinib treatment in patients with psoriatic arthritis: a pooled analysis across phase III and long-term extension studies. *Arthritis Care Res.* (2019) 71:1387–95. doi: 10.1002/acr.23930
75. Xie W, Xiao S, Huang Y, Sun X, Zhang Z. Effect of tofacitinib on cardiovascular events and all-cause mortality in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis of randomized controlled trials. *Ther Adv Musculoskelet Dis.* (2019) 11. doi: 10.1177/1759720X19895492
76. Yang X, Wan M, Cheng Z, Wang Z, Wu Q. Tofacitinib inhibits ox-LDL-induced adhesion of THP-1 monocytes to endothelial cells. *Artif Cells Nanomed Biotechnol.* (2019) 47:2775–82. doi: 10.1080/21691401.2019.1573740
77. Burmester GR, Curtis JR, Yun H, FitzGerald O, Winthrop KL, Azevedo VF, et al. An integrated analysis of the safety of tofacitinib in psoriatic arthritis across phase III and long-term extension studies with comparison to real-world observational data. *Drug Saf.* (2020) 43:379–92. doi: 10.1007/s40264-020-00904-9
78. Przepiera-Bedzak H, Fischer K, Brzosko M. Serum interleukin-18, fetuin-A, soluble intercellular adhesion molecule-1, and endothelin-1 in ankylosing spondylitis, psoriatic arthritis, and SAPHO syndrome. *Int J Mol Sci.* (2016) 17. doi: 10.3390/ijms17081255
79. Garcia-Gomez C, Martin-Martinez MA, Fernandez-Carballido C, Castaneda S, Gonzalez-Juanatey C, Sanchez-Alonso F, et al. Hyperlipoproteinaemia(a) in patients with spondyloarthritis: results of the cardiovascular in rheumatology (CARMA) project. *Clin Exp Rheumatol.* (2019) 37:774–82.
80. Lucke M, Messner W, Kim ES, Husni ME. The impact of identifying carotid plaque on addressing cardiovascular risk in psoriatic arthritis. *Arthritis Res Ther.* (2016) 18:178. doi: 10.1186/s13075-016-1074-2
81. Ikdahl E, Rollefstad S, Wibetoe G, Olsen IC, Berg IJ, Hisdal J, et al. Predictive value of arterial stiffness and subclinical carotid atherosclerosis for cardiovascular disease in patients with rheumatoid arthritis. *J Rheumatol.* (2016) 43:1622–30. doi: 10.3899/jrheum.160053
82. Palmou-Fontana N, Martinez-Lopez D, Corrales A, Rueda-Gotor J, Genre F, Armesto S, et al. Disease activity influences cardiovascular risk reclassification based on carotid ultrasound in patients with psoriatic arthritis. *J Rheumatol.* (2020) 47:1344–53. doi: 10.3899/jrheum.190729
83. Martinez-Vidal MP, Andres M, Jovani V, Santos-Ramirez C, Romera C, Fernandez-Carballido C. Role of carotid ultrasound and systematic coronary risk evaluation charts for the cardiovascular risk stratification of patients with psoriatic arthritis. *J Rheumatol.* (2020) 47:682–9. doi: 10.3899/jrheum.181223
84. Ibanez-Bosch R, Restrepo-Velez J, Medina-Malone M, Garrido-Courel L, Paniagua-Zudaire I, Loza-Cortina E. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients: a study based on carotid ultrasound. *Rheumatol Int.* (2017) 37:107–12. doi: 10.1007/s00296-016-3617-x
85. Tinggaard AB, Hjuler KF, Andersen IT, Winther S, Iversen L, Bottcher M. Prevalence and severity of coronary artery disease linked to prognosis in psoriasis and psoriatic arthritis patients: a multi-centre cohort study. *J Intern Med.* (2021) 290:693–703. doi: 10.1111/joim.13311
86. Martinez-Vidal MP, Fernandez-Carballido C. Is the SCORE chart underestimating the real cardiovascular (CV) risk of patients with psoriatic arthritis? Prevalence of subclinical CV disease detected by carotid ultrasound. *Joint Bone Spine.* (2018) 85:327–32. doi: 10.1016/j.jbspin.2017.07.002
87. Lam SHM, Cheng IT, Li EK, Wong P, Lee J, Yip RM, et al. DAPSA, carotid plaque and cardiovascular events in psoriatic arthritis: a longitudinal study. *Ann Rheum Dis.* (2020) 79:1320–6. doi: 10.1136/annrheumdis-2020-217595
88. Singh JA, Guyatt G, Ogdie A, Gladman DD, Deal C, Deodhar A, et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Care Res.* (2019) 71:2–29. doi: 10.1002/acr.23789
89. Klingberg E, Bilberg A, Bjorkman S, Hedberg M, Jacobsson L, Forsblad-d'Elia H, et al. Weight loss improves disease activity in patients with psoriatic arthritis and obesity: an interventional study. *Arthritis Res Ther.* (2019) 21:17. doi: 10.1186/s13075-019-1810-5
90. Di Minno MN, Peluso R, Iervolino S, Russolillo A, Lupoli R, Scarpa R, et al. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor alpha blockers. *Ann Rheum Dis.* (2014) 73:1157–62. doi: 10.1136/annrheumdis-2012-202812
91. Cheng IT, Shang Q, Li EK, Wong PC, Kun EW, Law MY, et al. Effect of achieving minimal disease activity on the progression of subclinical atherosclerosis and arterial stiffness: a prospective cohort study in psoriatic arthritis. *Arthritis Rheumatol.* (2019) 71:271–80. doi: 10.1002/art.40695
92. Cheng IT, Li EK, Wong PC, Law MY, Yim IC, Lai BT, et al. Treat to target and prevention of subclinical atherosclerosis in psoriatic arthritis-which target should we choose? *Rheumatology.* (2020) 59:2881–92. doi: 10.1093/rheumatology/keaa025
93. Kessler J, Chouk M, Ruban T, Prati C, Wendling D, Verhoeven F. Psoriatic arthritis and physical activity: a systematic review. *Clin Rheumatol.* (2021) 40:4379–89. doi: 10.1007/s10067-021-05739-y
94. Castaneda S, Vicente-Rabaneda EF, Garcia-Castaneda N, Prieto-Pena D, Dessein PH, Gonzalez-Gay MA. Unmet needs in the management of cardiovascular risk in inflammatory joint diseases. *Expert Rev Clin Immunol.* (2020) 16:23–36. doi: 10.1080/1744666X.2019.1699058
95. Pina Vegas L, Sbidian E, Penso L, Claudepierre P. Epidemiologic study of patients with psoriatic arthritis in a real-world analysis: a cohort study of the French health insurance database. *Rheumatology.* (2021) 60:1243–51. doi: 10.1093/rheumatology/keaa448

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Machine Learning Analyzed Weather Conditions as an Effective Means in the Predicting of Acute Coronary Syndrome Prevalence

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Background: The prediction of the number of acute coronary syndromes (ACSs) based on the weather conditions in the individual climate zones is not effective. We sought to investigate whether an artificial intelligence system might be useful in this prediction.

Methods: Between 2008 and 2018, a total of 105,934 patients with ACS were hospitalized in Lesser Poland Province, one covered by two meteorological stations. The predicted daily number of ACS has been estimated with the Random Forest machine learning system based on air temperature (°C), air pressure (hPa), dew point temperature (Td) (°C), relative humidity (RH) (%), wind speed (m/s), and precipitation (mm) and their daily extremes and ranges derived from the day of ACS and from 6 days before ACS.

Results: Of 840 pairwise comparisons between individual weather parameters and the number of ACS, 128 (15.2%) were significant but weak with the correlation coefficients ranged from −0.16 to 0.16. None of weather parameters correlated with the number of ACS in all the seasons and stations. The number of ACS was higher in warm front days vs. days without any front [40 (29–50) vs. 38 (27–48), respectively, $P < 0.05$]. The correlation between the predicted and observed daily number of ACS derived from machine learning was 0.82 with 95% CI of 0.80–0.84 ($P < 0.001$). The greatest importance for machine learning (range 0–1.0) among the parameters reached Td daily range with 1.00, pressure daily range with 0.875, pressure maximum daily range with 0.864, and RH maximum daily range with 0.853, whereas among the clinical parameters reached hypertension daily range with 1.00 and diabetes mellitus daily range with 0.28. For individual seasons and meteorological stations, the correlations between the predicted and observed number of ACS have ranged for spring from 0.73 to 0.77 (95% CI 0.68–0.82), for summer from 0.72 to 0.76 (95% CI 0.66–0.81), for autumn from 0.72 to 0.83 (95% CI 0.67–0.87), and for winter from 0.76 to 0.79 (95% CI 0.71–0.83) ($P < 0.001$ for each).

Conclusion: The weather parameters have proven useful in predicting the prevalence of ACS in a temperate climate zone for all the seasons, if analyzed with an artificial intelligence system. Simultaneously, the analysis of individual weather parameters or frontal scenarios has provided only weak univariate relationships. These findings will require validation in other climatic zones.

Keywords: weather, acute coronary syndrome, myocardial infarction, machine learning, artificial intelligence, prediction

INTRODUCTION

When I look out the window, I can forecast whether today's see of practice will be busy or not. This unwritten, intuitive observation often works in the case of an interventional cardiologist treating patients with acute coronary syndromes (ACS). Nevertheless, this common truth is insufficiently proven and does not allow for any practical recommendations to be drawn. A seasonal variation in the prevalence of acute coronary syndromes (ACS) and cardiovascular morbidity is a conventional wisdom. Already in 1926, an association was noted between coronary thrombosis and cold weather in New England during winter (1).

Although weather is a complex phenomenon, usually the impact of only individual weather parameters on ACS prevalence has been analyzed so far. Bayentin et al. (2) have shown that cold temperatures during winter months and hot periods during the summer are associated with a 12% increase in the daily hospital admission rate for ischemic heart disease. In a large Swedish registry, one incorporating more than 280,000 patients, an increase in minimum air temperature by 7.4°C was associated with the reduction of the prevalence of the ACS ratio by 2.8% (3). In contrast, Schwartz et al. have revealed that with each 1°C temperature decrease the mortality ratio rises by 0.49% and the frequency of all-cause, circulatory, coronary heart disease, and ST-segment elevation myocardial infarction (STEMI) death (4). Blazejczyk et al. (5) have shown that the number of deaths attributed to a strong heat stress was five times higher and the total mortality was almost 10% higher in June 2019 than the average for the period of 2010–2018 in Poland. Also, the exposure to an acute air pressure decrease more than 10.7 hPa within 7 days before STEMI increased the rate of STEMI (odds ratio 1.12, 95% CI 1.03–1.21) (6). In the population of New York state, certain demographic groups including the elderly, males, people with Medicaid insurance, people living in warmer areas, or in areas with a high PM2.5 concentration were more prone to cold acute myocardial infarction (MI) effects than others (7). Barnett et al. (8) have proved that inhabitants of colder countries such as North Sweden, North Korea, or Finland are less prone to ACS with temperature changes. This is most likely caused by better protection against cold temperature including clothes as well as housing and metabolic adaptation by inhabitants of these cold areas as observed in the Indians of Tierra del Fuego, Arctic Indians, and Inuits (9). In turn, in Poland, an increase in mortality by 9–19% on cold stress days was noted mainly in the so-called "cool" cities characterized by a clear thermal optimum, approximately in the range of 5–30°C of the Universal Thermal Climate Index (UTCI) (10).

Despite a lot of univariate associations between weather parameter and the prevalence of ACS, their prediction in a given geographical or climatic zone and season is so far ineffective. On the other hand, data concerning a multifactorial approach to this issue are limited (11). Data mining and machine learning techniques seem to be the optimal choices for the reasons that they are trying to predict non-linear and complex relationships between many parameters (12, 13). Among algorithms mostly used in meteorological and climatological studies, the Random Forest method is widely applied (14, 15). Therefore, we sought to investigate if multiple weather conditions analyzed together with an artificial intelligence system are useful in predicting the prevalence of ACS in a temperate climate zone. Lesser Poland Province, being the area of interest, is located in Central Europe where the global circulation model constitutes a westerly advection dependent also on the low pressure systems allocated in north-west Europe in both a cold and warm half-year.

METHODS

Study Design and Population

Between 1 January 2008 and 31 December 2018, a total of 105,934 patients with were hospitalized in the north part of Lesser Poland Province. The region of interest had a population of 1,812,272 inhabitants in 2014 and in this period was served by two meteorological stations in Tarnow (Station A, 50.03 N, 20.98 E) and Krakow (Station B, 50.08 N, 19.8 E), both located approximately 200 m above sea level (**Supplementary Figure 1**). In the area represented by stations A and B, 30,143 and 75,791 of patients with ACS were treated, respectively.

The studied population was composed of patients who had been admitted to emergency medical services, emergency departments, or hospital wards and their diagnosis was conducted by the treating physician and coded at discharge according to the International Classification of Diseases (ICD) classification as unstable angina (UA) (I.20.0), ST-segment elevation myocardial infarction (STEMI) including acute transmural MI of the anterior wall (I21.0), of the inferior wall (I21.1), of other sites (I21.2), or non-ST-segment elevation myocardial infarction (NSTEMI) including acute transmural MI of an unspecified site (I21.3), acute subendocardial MI (I21.4), or unspecified acute MI (I21.9). The exclusion criteria for this study were an age of <18 years and doubled records of the same patient

who was transferred between two different units due to the same incident. The clinical characteristics of the studied patients, including age, sex, diabetes mellitus (E10–E14), hypertension (I10–I15), duration of hospitalization, history of renal failure (N18–N19) or stroke (I62–I64), and in-hospital mortality, were obtained from the Polish National Health Fund (NHF) registry. This study protocol complied with the Declaration of Helsinki was approved by the Ethical Committee of the Jagiellonian University (approval number 1072.6120.88.2020).

Meteorological Data and Definitions

Meteorological data were obtained from the Institute of Meteorology and Water Management-National Research Institute (IMWM-NRI) operating as the National Weather Service. The weather registry included air pressure (P) (hPa), air temperature (T) (°C), dew point temperature (Td) (°C), relative humidity (RH (%), wind speed (WS) (m/s), and precipitation (RR) (mm) as measured in accordance with the World Meteorological Organization's standards and regulations (16). All the data were collected at synoptic stations each hour a day with the use of calibrated instruments, i.e., barometers, dry and wet bulb thermometers, anemometers, and rain gauges, respectively. Most of measurements were in parallel conducted with dedicated automated sensors for further validation. All the meteorological variables, with their daily extremes, including maximum (T_max) or minimum (T_min) temperature, maximum (Td_max) or minimum (Td_min) of dew point temperature, maximum (P_max) or minimum (P_min) of air pressure, maximum (RH_max) or minimum (RH_min) of relative humidity, maximum (WS_max) or minimum (WS_min) of wind speed, and maximum (RR_max) or minimum (RR_min) of precipitation, were analyzed for the day of ACS and for 6 days prior to ACS itself. The daily ranges of the aforementioned variables were defined as the difference between the maximum and minimum value within each analyzed day and expressed as the range of temperature (T_range), range of dew point temperature (Td_range), range of air pressure (P_range), range of relative humidity (RH_range), range of wind speed (WS_range), and range of precipitation (RR_range). To indicate the day prior to the index ACS for which the weather conditions were analyzed included was a subscript with values from 1 to 6. For example, RH_max_2 means a maximum relative humidity 2 days prior to the index ACS. Furthermore, a 3-h air pressure tendency (P_{3h}_tend) and a 6-h aggregated amount of precipitation (RR_{6h}) were added to the overall analysis. Any negative value of P_{3h}_tend expresses pressure decrease, whereas any positive value of P_{3h}_tend expresses pressure increase.

Finally, the catalog of synoptic scenarios in the upper Vistula river basin covering the area of Lesser Poland Province (17) was used to distinguish the type and direction of air masses advection as well as the type of pressure pattern together with the type of frontal system. Synoptic maps also served as the source of information of frontal systems distinguished by a surface weather analysis supported by upper air information (18). Strong horizontal temperature, moisture, wind gradient, as well as the vertical shear of a horizontal wind and high vorticity as the attributes of the boundaries between air masses were identified and every front was classified as cold, warm, quasi-stationary, or occluded.

Weather seasons were established on the basis of meteorological rules as follows: spring (1st March to 31st May), summer (1st June to 31th August), autumn (1st September to 30th November), and winter (1st December to 28/29th February).

Statistics

Statistical analysis was performed with SPSS Statistics software (version 25.0.0.2, IBM Incorporation, USA). Continuous variables are expressed as median (interquartile range) and categorical variables are expressed as number (percentage). Continuous variables were first checked for normal distribution by the Shapiro–Wilk test. Differences between two continuous variables were compared by the Student's *t*-test or the Mann–Whitney *U* test, if distribution was normal or different than normal, respectively. ANOVA followed by the *post-hoc* Bonferroni test was used to compare the differences in the three or more groups with normally distributed data, whereas non-normally distributed data were analyzed by the Kruskal–Wallis test and the differences between the individual groups were identified using a test for multiple comparisons of mean ranks. Categorical variables were analyzed by the chi-squared test or the Fisher's exact test. The association between two variables with a normal or non-normal distribution was assessed by the Pearson or Spearman test, respectively. A two-tailed *P*-value of <0.05 was considered as statistically significant.

Predictions With Machine Learning System

Machine learning analysis was performed using the R package with the Random Forest algorithm (19). We examined models with repeated 10-fold cross-validation (10 repeats), which partitions the original sample into 10 disjoint subsets, uses seven of those subsets in the training process, and then makes predictions about the remaining subset. We trained an ensemble classifier by using the results of a set of constituent classifiers by taking a (weighted) vote of their individual predictions. The predictive learning model was based on artificial intelligence with the Random Forest algorithm. The latter is a decision tree-based method constructed by creating a series of decision trees from bootstrapped training samples (20). The decision tree split is a random process, where a new division of data is constructed, rather than using the full set of predictors. The model takes predictions from individual learning algorithm as an input to build an ensemble learning predictive model that classified required meteorological parameters up to 6 days before the day with a specific number of ACS. The variable importance of each weather parameter was a derivative of all its measurements obtained on the day of ACS and 6 days before ACS. For example, the variable importance for T_max means value calculated for all the maximum temperatures collected within 7 days. The training and testing datasets were driven from meteorological parameters, their derivatives, and were combined with the date and day of the week for each number of ACS, as there was found a decreasing trend in the numbers of ACS between 2008 to 2018, as well as significant differences in their

TABLE 1 | Baseline clinical characteristics.

	All patients $n = 105,902$	UA $n = 55,786$	STEMI $n = 20,042$	NSTEMI $n = 30,074$	*P*-value
Age, years	68 (60–76)	67 (60–75)	66 (57–76)	70 (61–79)	<0.001
Male	65,859 (62.2)	33,828 (60.6)	13,180 (65.9)	18,851 (62.7)	<0.001
Comorbidities					
Diabetes mellitus type 1 or 2	37,419 (35.3)	19,452 (34.9)	6,530 (32.6)	11,437 (38.0)	<0.001
Hypertension	75,418 (71.2)	39,474 (70.6)	13,799 (68.9)	22,145 (73.6)	<0.001
Renal failure	4,798 (4.5)	2,074 (3.7)	804 (4.0)	1,920 (6.4)	<0.001
History of stroke	7,211 (6.8)	3,407 (6.1)	1,432 (7.1)	2,372 (7.9)	<0.001
Outcome					
Length of hospitalization, days	6 (3–9)	7 (4–9)	5 (4–9)	5 (3–9)	<0.001
In-hospital death	4,649 (4.4)	583 (1.0)	1,967 (9.8)	2,099 (7.0)	<0.001

Data are shown as median (interquartile range) or numbers (percentage), ACS, acute coronary syndrome; UA, unstable angina; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; P-value for differences between UA, NSTEMI and STEMI.

TABLE 2 | Seasonal weather characteristics at both the meteorological stations.

Weather parameter	Season	Station A	Station B	*P*-value
T_max, °C	Spring	15.1 (9.6–20.4)	14.5 (9.0–19.6)	<0.001
	Summer	24.9 (21.4–28.3)	24.3 (20.9–27.5)	<0.001
	Autumn	14.3 (9.3–19.1)	13.4 (8.7–18.6)	<0.001
	Winter	3.2 (−0.5–6.8)	2.4 (−0.9–5.7)	<0.001
T_min, °C	Spring	4.4 (0.7–8.2)	3.8 (0.1–7.7)	<0.001
	Summer	13.2 (10.8–15.8)	13.1 (10.9–15.5)	0.021
	Autumn	5.7 (2.2–9.3)	4.9 (1.1–8.5)	<0.001
	Winter	−1.9 (−6.2–0.9)	−2.9 (−6.8 to −0.3)	<0.001
P_max, hPa	Spring	1,018 (1,013–1,023)	1,019 (1,013–1023)	<0.001
	Summer	1,018 (1,014–1,020)	1,018 (1,015–1,021)	<0.001
	Autumn	1,021 (1,016–1,026)	1,021 (1,017–1,026)	0.075
	Winter	1,022(1,015–1,028)	1,022 (1,015–1,028)	0.027
P_min, hPa	Spring	1,013 (1,007–1,018)	1,013 (1,007–1,018)	<0.001
	Summer	1,013 (1,010–1,016)	1,014 (1,010–1,016)	<0.001
	Autumn	1,016 (1,011–1,021)	1,016 (1,011–1,021)	0.286
	Winter	1,015 (1,008–1,022)	1,015 (1,008–1,022)	0.255
RH_max, %	Spring	95 (91–98)	95 (91–97)	0.002
	Summer	96 (93–98)	95 (92–97)	<0.001
	Autumn	97 (93–98)	96 (95–98)	<0.001
	Winter	94 (89–97)	96 (93-−98)	<0.001
RH_min, %	Spring	44 (34-60)	47 (37–64)	<0.001
	Summer	44 (37–57)	46 (38–58)	<0.001
	Autumn	61 (49–74)	65 (52–79)	<0.001
	Winter	69 (59–79)	75 (65–83)	<0.001
WS_max, m/s	Spring	3 (3–4)	6 (5–8)	<0.001
	Summer	3 (2–3)	6 (4–7)	<0.001
	Autumn	3 (2–4)	5 (4–7)	<0.001
	Winter	3 (2–4)	6 (4–8)	<0.001

Data are shown as median (interquartile range), T, daily temperature; P, air pressure; RH, relative air humidity; WS, wind speed;max, maximum daily value; min, minimum daily value; P-value for comparisons between station A and B.

distribution between Monday and Saturday or Sunday. The Random Forest was used to build a predictive model, as well as to give information about the learning process itself. In this study, the variable importance of each parameter was examined to quantify how a meteorological condition or clinical characteristic is important in the prediction of the number of ACS per day. The higher the variable importance value (results ranged from 0 to 1), the more important the given parameter was in the training of the model. The prediction performed with the Random Forest algorithm was finally adjusted for age, sex, diabetes mellitus, arterial hypertension, renal failure, and history of stroke.

RESULTS

Study Population

The demographic and clinical characteristics of the studied patients are shown in **Table 1**. In the whole study period, unstable angina was the most frequent diagnosis comprising 52.7% of all the patients with ACS, while STEMI occurred in fewer than one-fifth of patients (**Table 1**). Patients with STEMI were the youngest ($P < 0.001$), with the highest percentage being males ($P < .001$). Only 1% of patients with UA died during index hospitalization, whereas the highest in-hospital mortality occurred in the STEMI population ($P < 0.001$). Simultaneously, patients with NSTEMI were characterized by the highest percentage of diabetes mellitus, hypertension, renal failure, and history of stroke (all $P < 0.001$) (**Table 1**).

The total number of acute coronary syndromes has been decreasing since 2013 (**Supplementary Table 1**). Between 2008 and 2018, the annual number of UA decreased by 67% and STEMI by 47%. Simultaneously, the absolute number of patients with NSTEMI increased during the analyzed period by 39%. In 2018, hypertension was identified more frequently than in 2008 (68.1 vs. 65.8%, $P = 0.002$, respectively), but diabetes mellitus (30.0 vs. 34.5%, $P < 0.001$), renal failure (2.4 vs. 4.7%, $P < .001$), and a history of stroke (4.0 vs. 7.7%, $P < 0.001$) were identified less frequently. The mortality rate was similar in 2018 vs. 2008 (4.7 vs. 4.6%, $P = 0.377$).

Patients with ACS were hospitalized most frequently on Mondays ($P < 0.0001$, **Supplementary Table 2**) without significant trends in the annual cycle (**Supplementary Figure 2**). UA was most frequent on Mondays ($P < 0.0001$), while STEMI ($P < 0.0001$) or NSTEMI ($P < 0.0001$) was most frequent on Saturdays. The oldest patients with a median age of 69 years were admitted on weekends. Also, renal failure (5.1 vs. 4.1%, $P = 0.002$) or stroke (7.3 vs. 6.7%, $P = 0.002$) was more frequent, while in-hospital death was higher (6.7 vs. 3.9%, $P < 0.001$) in patients admitted during weekends as compared with working days.

General Meteorological Characteristics

Both the stations are located relatively close. So, for all the seasons, most of the weather characteristics had a similar

TABLE 3 | The correlations between the number of acute coronary syndrome (ACS) and the weather conditions as measured in the day of ACS.

		Station A				Station B			
		Spring	**Summer**	**Autumn**	**Winter**	**Spring**	**Summer**	**Autumn**	**Winter**
T_max °C	r	0.01	−0.06	0.00	**−0.12**	−0.06	−0.03	−0.01	−0.02
	P	0.87	0.06	0.96	**<0.001**	0.07	0.28	0.70	0.61
T_min, °C	r	−0.01	−0.00	−0.06	**−0.14**	−0.06	−0.04	0.02	**−0.07**
	P	0.89	0.93	0.08	**<0.001**	0.07	0.20	0.46	**0.03**
T_range, °C	r	0.01	**−0.07**	0.06	0.04	−0.02	−0.01	−0.04	**0.08**
	P	0.68	**0.03**	0.07	0.17	0.45	0.78	0.18	**0.01**
P_max, hPa	r	0.02	−0.02	0.03	0.06	−0.03	−0.01	−0.04	0.05
	P	0.46	0.56	0.30	0.06	0.30	0.83	0.17	0.13
P_min, hPa	r	0.02	−0.03	0.02	0.02	−0.03	−0.02	−0.03	0.04
	P	0.55	0.29	0.45	0.57	0.37	0.50	0.31	0.27
P_range, hPa	r	0.01	0.04	0.01	**0.08**	−0.01	0.03	−0.02	0.02
	P	0.79	0.25	0.70	**0.02**	0.77	0.28	0.63	0.53
P_{3h}_tend, hPa	r	−0.05	−0.00	0.02	0.04	−0.01	0.04	−0.01	−0.04
	P	0.10	0.90	0.51	0.23	0.74	0.19	0.84	0.22
Td_max, °C	r	−0.01	0.03	−0.01	**−0.10**	−0.04	−0.02	0.01	−0.02
	P	0.79	0.38	0.81	**0.002**	0.21	0.45	0.85	0.57
Td_min, °C	r	−0.02	0.03	−0.04	**−0.14**	−0.02	−0.02	0.02	−0.06
	P	0.63	0.36	0.25	**<0.001**	0.44	0.52	0.60	0.07
Td_range, °C	r	0.02	−0.01	**0.07**	**0.12**	−0.03	−0.00	−0.02	**0.09**
	P	0.67	0.82	**0.03**	**<0.001**	0.30	0.96	0.44	**0.003**
RH_max, %	r	−0.03	0.05	**0.11**	0.02	0.04	0.02	−0.01	0.05
	P	0.35	0.11	**<0.001**	0.57	0.16	0.44	0.82	0.15
RH_min, %	r	0.00	**0.09**	−0.02	−0.01	0.06	0.03	0.02	0.00
	P	0.99	**0.005**	0.45	0.87	0.08	0.30	0.59	0.99
RH_range, %	r	−0.01	**−0.07**	0.06	0.02	−0.05	−0.03	−0.02	0.02
	P	0.67	**0.02**	0.05	0.56	0.15	0.39	0.55	0.56
RR_{6h}, mm	r	−0.03	0.01	−0.01	−0.03	0.02	0.03	0.05	−0.05
	P	0.29	0.64	0.82	0.43	0.62	0.42	0.13	0.14
WS_max, m/s	r	0.02	0.00	**−0.07**	0.02	−0.04	0.06	**0.07**	−0.01
	P	0.54	0.97	**0.03**	0.62	0.26	0.05	**0.04**	0.83

r, correlation coefficient; T, daily temperature; P, air pressure; P_{3h}tend, daily 3-hour pressure tendency; RH, relative air humidity; Td, dew point temperature; RR_{6h}, cumulative amount of precipitation within 6 h; WS, wind speed; max, maximum daily value; min, minimum daily value; range, daily range; The significant associations are highlighted with bold.

distribution. However, due to differences in their geographical location, the median values of most of the meteorological characteristics calculated for the study period of 11 years were different in both the stations (**Table 2**). The highest absolute differences between both the stations concerned with air temperature, relative humidity, and wind speed. Station A had higher maximum and minimum temperatures than station B in all the seasons, with the median T_max value in summer reaching 24.9°C as compared to 24.3°C in station B. Station A had lower median values of RH_min also in all the seasons, with the biggest difference for winter. Median values of wind speed in station A were equal to 3 m/s, while for station B they reached 5 m/s for autumn and 6 m/s for the rest of the year (**Table 2**).

Acute Coronary Syndrome Prevalence vs. Individual Weather Parameters

Analysis comparing individual weather parameters derived from the day of ACS and the 6 preceding days with the number of ACS in the index day including their seasonal distribution concerned 420 pairwise comparisons for each station separately. Of them, in station A 88 (21.0%) and in station B 40 (9.5%) were significant but weak, with the correlation coefficients ranged from −0.16 to 0.16 (**Table 3** and **Supplementary Table 3**).

In both the stations, 16 (13.3%) of the weather parameters derived from the day of ACS incident were significantly correlated with ACS number. In the case of 5 (4.2%) parameters recoded in station A (T_min, T_max, Td_min, Td_range, and RH_max), correlation coefficients were higher than |0.10| (**Table 3**).

In both the stations, in total, 66 (18.3%) of the weather parameters recorded at least once, 1 to 3 days prior to ACS incident, were significantly correlated with the number of ACS in the given index day (**Supplementary Table 3**). In the case of 14 (3.9%) measurements, the correlation coefficients were higher than |0.10|, including 13 in station A in winter (T_max_{1-3}, Td_max_{1-3}, T_min_{1-3}, Td_min_{1-3}, and Td_range_3) and one in station B in spring (WS_max_3), while in station A in winter, the

TABLE 4 | Median values of ACS in relation to the occurrence of a specific atmospheric front.

	No front $N = 2,339$	Cold front $N = 361$	Warm front $N = 517$	Quasi–stationary front $N = 221$	Occluded front $N = 341$	Different fronts $N = 239$	*P*–value[#]
The whole period	38 (27–48)	40 (29–52)	40 (29–50)*	37 (28–49)	37 (27–48)	38 (27–51)	**0.012**
January	37 (25–48)	40 (31–51)	37 (25–48)	42 (30–49)	39 (28–52)	48 (36–62)	0.155
February	40 (29–51)	41 (29–56)	40 (27–58)	41 (32–48)	40 (31–49)	47 (33–59)	0.861
March	40 (29–48)	44 (29–55)	46 (29–56)	37 (21–57)	39 (31–46)	40 (28–52)	0.708
April	36 (25–50)	42 (37–52)	39 (30–52)	39 (36–54)	37 (30–46)	38 (28–55)	0.481
May	37 (28–48)	45 (32–50)	**46 (30–54)***	34 (30–42)	**30 (23–45)***	36 (30–45)	**0.015**
June	37 (26–47)	40 (33–59)	39 (28–47)	32 (27–42)	38 (28–45)	35 (25–57)	0.276
July	35 (26–46)	34 (32–44)	38 (30–46)	34 (27–46)	32 (23–41)	34 (24–51)	0.423
August	36 (27–45)	32 (27–43)	38 (27–47)	48 (26–56)	**28 (20–38)***	26 (21–48)	**0.017**
September	38 (28–48)	39 (31–52)	42 (31–50)	39 (33–49)	36 (22–53)	40 (26–47)	0.805
October	40 (28–50)	41 (32–54)	46 (32–56)	39 (32–51)	45 (35–53)	37 (31–52)	0.388
November	38 (28–52)	39 (26–55)	38 (29–52)	31 (23–50)	46 (40–62)	44 (33–50)	0.284
December	34 (25–46)	36 (23–45)	37 (25–50)	**28 (23–47)***	**56 (44–60)***	36 (25–50)	**0.019**

*Data are shown as median (interquartile range), [#]ANOVA Kruskal-Wallis for differences in six groups, *P < 0.05 vs. no-front days for post-hoc comparisons. The significant differences are highlighted with bold.*

lower T_max, Td_max, T_min, Td_min, or the higher T_range and Td_range in the 3 days preceding the higher number of ACS in the index day.

In both the stations, in total, 46 (12.8%) of the weather parameters recorded at least once, 4 to 6 days prior to ACS incident, were significantly correlated with the number of ACS in the given index day. In the case of 15 (4.2%) measurements, the correlation coefficient was higher than |0.10|. All of them were found in station A, 13 in winter (T_max_{4-6}, T_min_{4-6}, Td_min_{4-6}, Td_range_{4-6}, and P_range_5) and 2 in autumn ($RH_max_{5,6}$).

Acute Coronary Syndrome Prevalence vs. Frontal Analysis

In the years 2008–2018, 58% of ACS occurred during days without any fronts as they constitute almost 60% of all the analyzed days. The remaining ACS happened on days with cold (11%) or warm (10%) fronts or during days with quasi-stationary frontal systems (9%), occluded fronts (6%), or with different fronts in the course of the self-same same day (6%).

In the whole period studied, especially in spring months, the number of ACS was the highest during days with cold or warm fronts, but a significant difference in the number of ACS was found only between warm front days and days without any front (**Table 4**). In summer, autumn, and winter, there were no significant differences in the median number of ACS across the different frontal scenarios. The occurrence and type of front was associated with different ACS distribution in May, August, and December (**Table 4**). The number of ACS in days with an occluded front was the lowest in May and August, while in December this was the highest. In the remaining months, there were no significant differences in ACS distribution.

Machine Learning-Based Prediction for Acute Coronary Syndrome Prevalence

The correlation between the predicted and observed number of ACS per day was 0.82 with a CI of 0.80–0.84 ($P < 0.0001$) (**Figure 1A**). Of all the weather parameters, the highest variable importance for machine learning (range 0–1) involved dew point temperature daily range, air pressure daily range and its maximum, and RH maximum with 1.00, 0.875, 0.864, and 0.853, respectively (**Figure 1B**). Among the clinical parameters, the variable importance for hypertension was 1.00, the variable importance for diabetes mellitus was 0.28, the variable importance for a history of stroke was 0.10, the variable importance for chronic kidney disease was 0.07, the variable importance for median age was 0, and the variable importance for sex was 0 (**Figure 1C**).

For individual seasons, the correlations between the observed and predicted number of ACS (**Figure 2**) within the operations of station A were for spring 0.77 (CI 0.72–0.82), for summer 0.76 (CI 0.71–0.81), for autumn 0.83 (CI 0.80–0.87), and for winter 0.79 (CI 0.75–0.83) ($P < 0.0001$ for each correlation). The analogous correlations for station B were for spring 0.73 (CI 0.68–0.78), for summer 0.72 (CI 0.66–0.77), for autumn 0.72 (CI 0.67–0.78), and for winter 0.76 (CI 0.71–0.81) ($P < 0.0001$ for each prediction).

Of all the analyzed meteorological parameters, the most important in the machine learning model with a variable importance of more than 0.8 was for station A in spring RH_max, T_max, and P_range, in summer Td_max, T_range, and RH_range, in autumn T_range, and in winter P_min, P_range, and Td_max (**Figure 3**). For station B, the meteorological parameters with a variable importance of more than 0.8 were in spring P_max, RH_max, Td_range, P_{3h}tend, and P_min, in summer RH_max, in autumn Td_range, P_range, and $P_{3h_}$tend, and in winter Td_range and T_range.

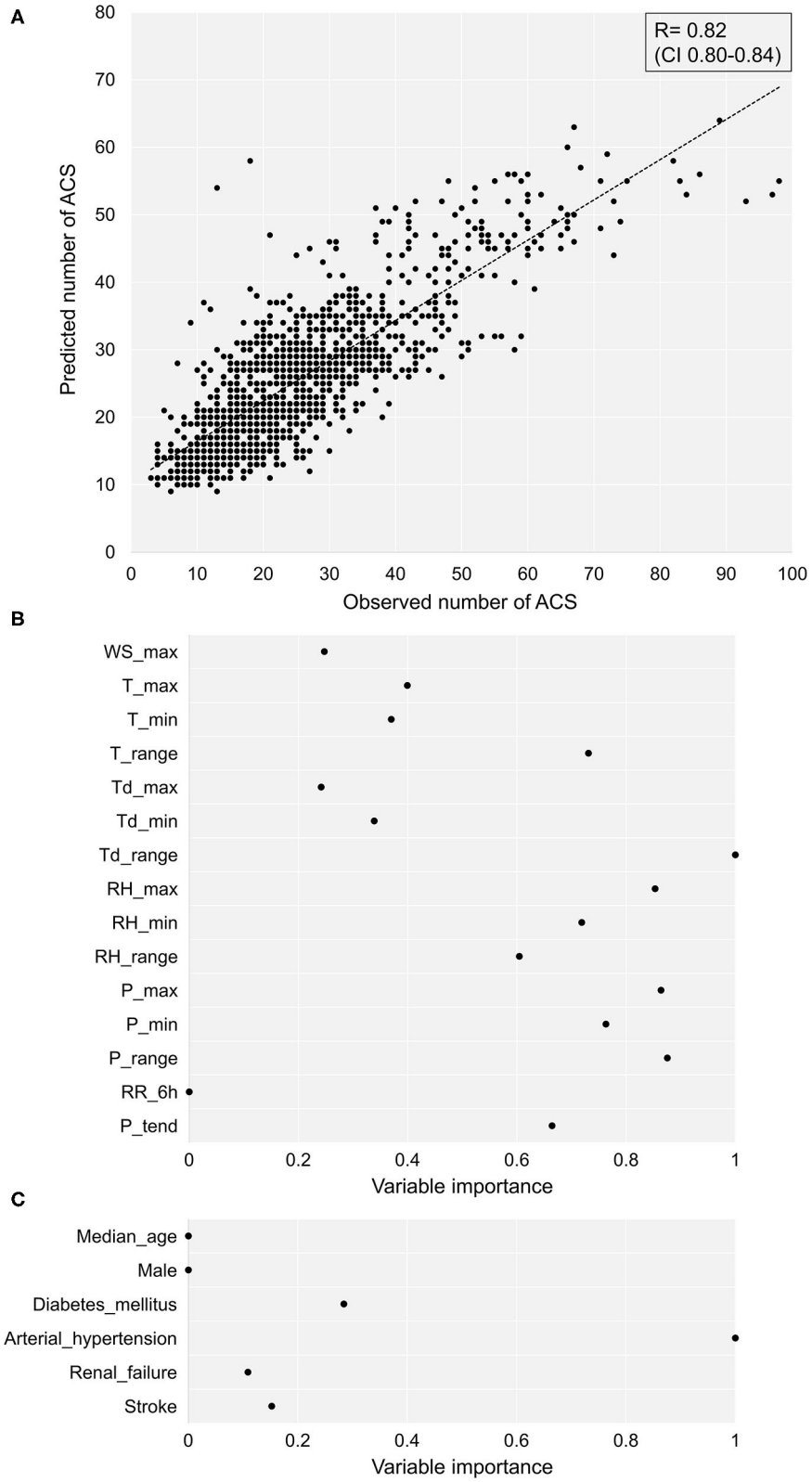

FIGURE 1 | The predicted vs. observed numbers of ACS. **(A)** The correlation between the predicted vs. observed number of ACS per day. **(B)** The importance of individual weather conditions for machine learning. **(C)** The importance of clinical parameters for machine learning. ACS, acute coronary syndrome; T, temperature; P, air pressure; P_{3h}_tend, daily 3 hours pressure tendency, RH, relative air humidity, Td, dew point temperature, RR_{6h}, precipitation, WS, wind speed, max, maximum daily value, min, minimum daily value, range, daily range.

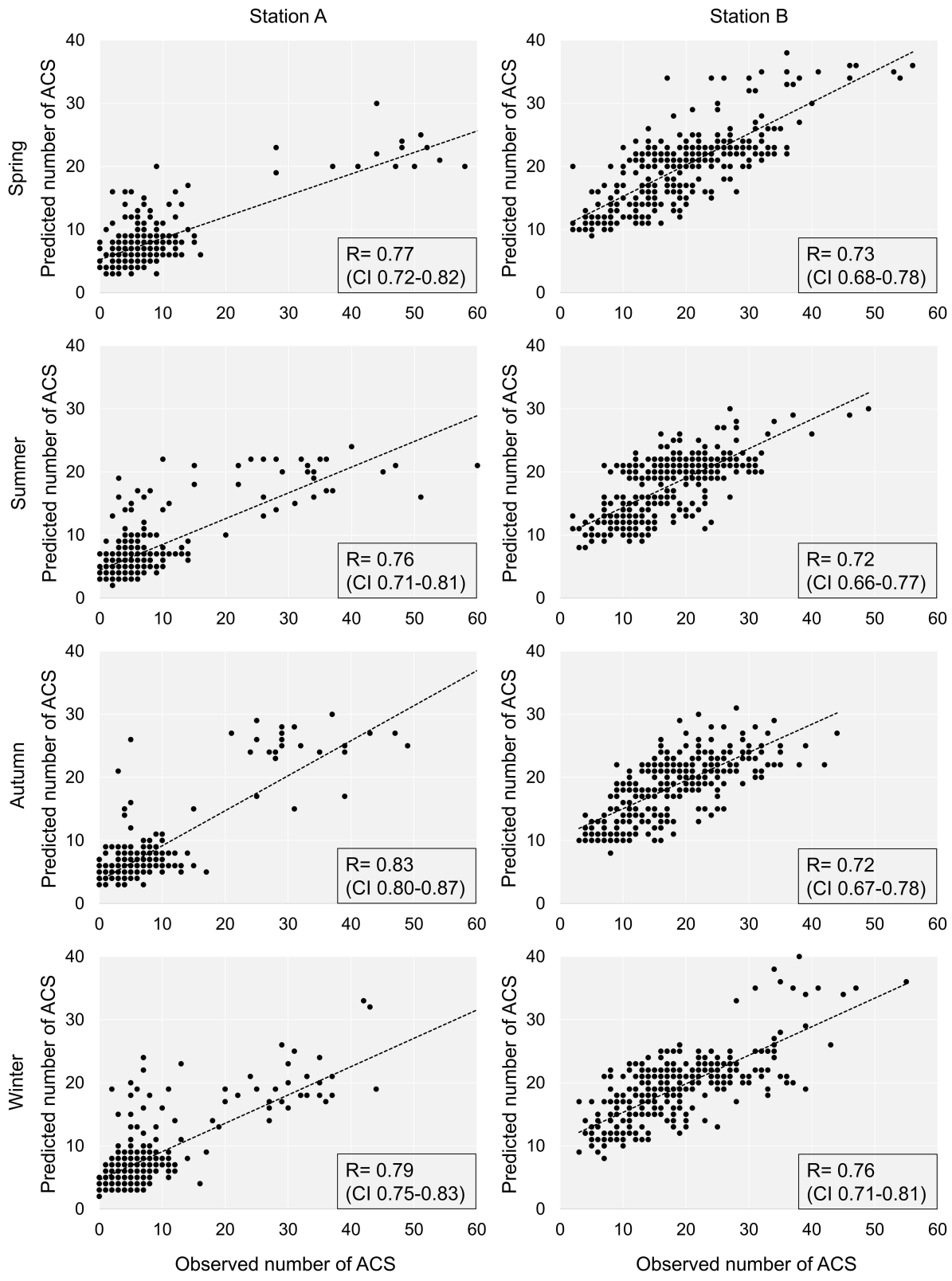

FIGURE 2 | The predicted vs. observed numbers of ACS in individual seasons and meteorological stations. ACS, acute coronary syndrome.

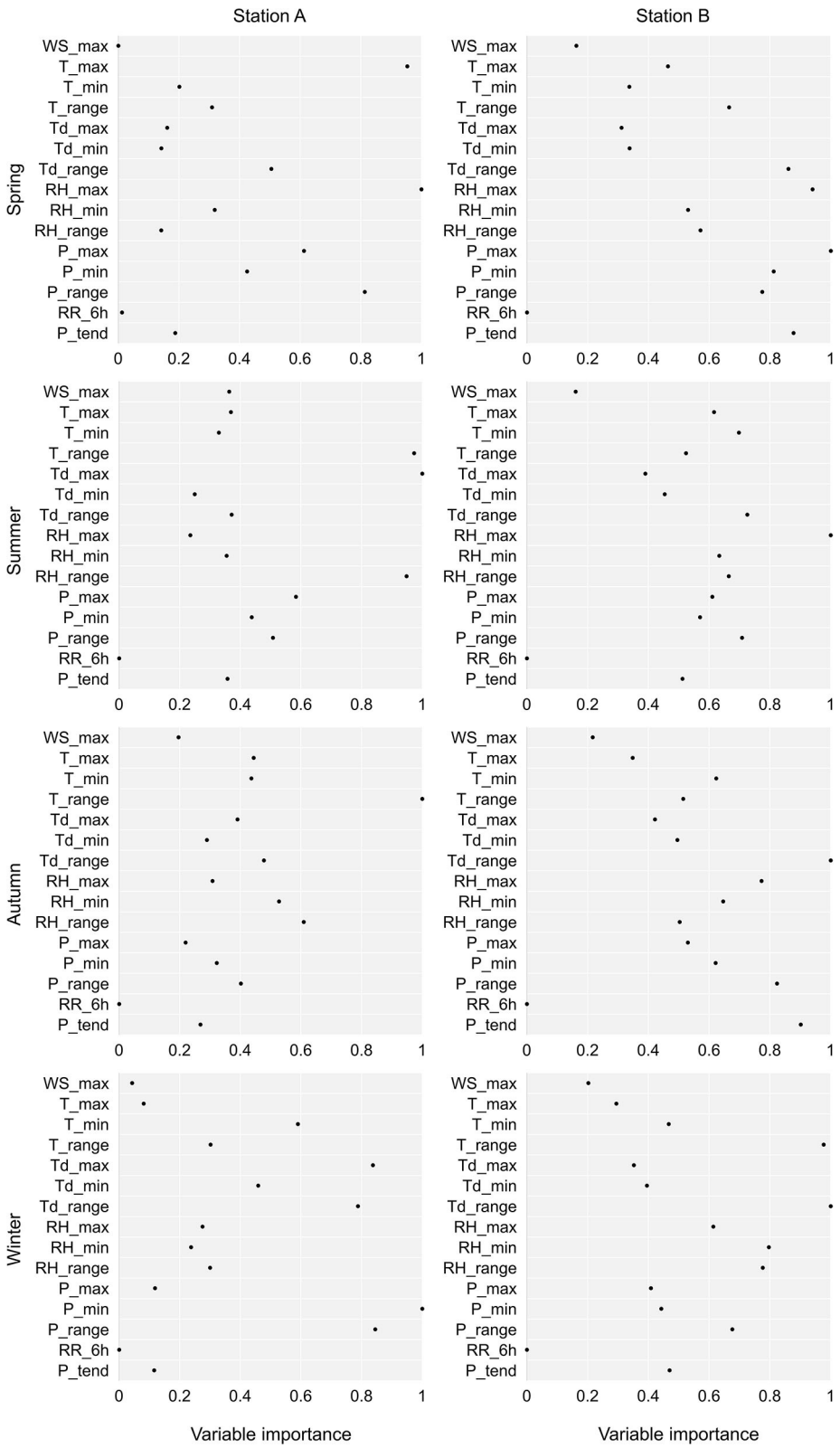

FIGURE 3 | The importance of weather conditions in prediction of the number of ACS with machine learning in relation to the season and the meteorological station. T, temperature; P, air pressure; P_{3h}_tend, daily 3 h pressure tendency; RH, relative air humidity; Td, dew point temperature; RR_{6h}, precipitation; WS, wind speed; max, maximum daily value; min, minimum daily value; range, daily range.

DISCUSSION

Summary of Findings

To the best of our knowledge, this study is the first study to demonstrate that weather parameters analyzed with an artificial intelligence system using machine learning accurately predict the daily number of ACS in a temperate climate zone. The accuracy of this prediction turned out to be irrespective of the season and location of the meteorological station. Machine learning system has produced a unique prediction pattern based on a broad set of weather data including their absolute values, several hour tendencies, and also their dynamic changes derived from the day of ACS and 6 days prior to ACS. Of all the analyzed meteorological parameters in this specific population, the most influential on these predictions was both the daily ranges of dew point temperature and air pressure, as well as the maximum value of air pressure and of relative humidity. On the other hand, analysis of atmospheric fronts as well as individual weather parameters provided several univariate and significant relationships; however, ones not universal and only specific to a selected season and station. Thus, this study provides evidence indicating that artificial intelligence algorithms used for the analysis of weather conditions together might be a valuable and clinically important tool estimating the everyday risk of ACS.

Univariate Relationships Between Weather and Acute Coronary Syndrome Prevalence

In this study, we observed significant but weak correlations between individual weather parameters and ACS prevalence. Unfortunately, these relationships were not repeatable for all the seasons and meteorological stations, thus their predictive value was useless. The WHO Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) project (21) showed that a 10°C decrease was associated with a 13% increase of the total number of myocardial infarctions or coronary deaths. For an atmospheric pressure, a V-shaped relationship was found with a minimum of the daily event rate at 1,016 hPa. Simultaneously, a 10-hPa decrease below or a 10-hPa increase above 1,016 hPa was associated with a 12 or 11% increase in ACS event rate, respectively. Swedish analysis (3) indicated a higher ACS prevalence in the days with air temperatures of <0°C, while ACS rate was lower when temperatures rose to 3–4°C. Equally Canadian data (22) revealed that cold days with a temperature below the 1st percentile of temperature distribution were associated with a 29% increase in acute MI rate (95% CI 15–45) and high temperatures above the 99th percentile increased coronary heart disease hospitalizations by 6% (95% CI 1–11) as compared with the days with an optimal temperature. Low air temperatures were a significant risk factor for hospital admissions from diseases of the circulatory system also in the Iberian Peninsula, regardless of calculated meteorological index (23). Urban and Kyselý (24) have found that apparent temperature and physiologically equivalent temperature appear to be more universal predictors of heat- and cold-related mortality than UTCI when both the urban and rural environments were of concern. In turn, significant cold-related mortality in the rural region showed potential for UTCI to become a useful tool in cold exposure assessments. Michelozzi et al. (25) have analyzed the impact of high environmental temperatures on hospital admissions in 12 European cities participating in the Assessment and Prevention of Acute Health Effects of Weather Conditions in Europe project. They found that high temperatures have a specific impact on respiratory admissions, particularly in the elderly population, but the underlying mechanisms were unclear. In turn, high temperature was associated with an increased cardiovascular mortality, but not cardiovascular admissions. These relationships also remain not elucidated. In this study, the strongest univariate correlations concerned with temperature and dew point temperature only in winter in station A. These results indicate that a universal ACS prediction based on single individual weather parameters does not work. It may be due to the fact of significant day-to-day variability of weather conditions in Southern Poland, described also by Piotrowicz (26).

Given the complex nature of the weather, in the next step, we focused on the influence of atmospheric fronts on the occurrence of ACS. The median daily number of ACS was higher on days with warm fronts compared to days without any front, especially in spring. Recently, Boussoussou et al. (27) have observed in patients with acute cardiovascular diseases in the area of Budapest a 9.5% increase in hospitalizations associated with cold or occluded fronts. This effect was 10% stronger in a situation of day-to-day front replacement from warm or stationary to a cold one. In Europe, active frontal weather occurs in 40% of days in a year and frontal systems induce substantial and dynamic modifications of weather conditions, including significant air pressure and wind speed shifts, as well as temperature changes (28). Therefore, the approach to assess the number of ACS depending on the type of front seemed to be particularly justified, but again it turned out that the results were not repeatable for individual seasons as well as for shorter time intervals such as months.

Weather Parameters Analyzed With Artificial Intelligence for Prediction of Acute Coronary Syndrome Prevalence

The lack of a satisfactory predictive value of individual weather parameters as well as frontal analysis has become an argument for applying a more sophisticated analytical method. In this study, artificial intelligence with machine learning using the Random Forest system was used to predict the number of ACS based on the weather characteristics. Ambale-Venkatesh et al. (29) have tested random survival forest to predict six cardiovascular outcomes in comparison to standard risk scores. They found that artificial intelligence added to traditional methods improves the prediction accuracy of cardiovascular events in an initially asymptomatic population. In turn, Wang et al. (30) have shown that the Random Forest displayed a satisfying performance compared to traditional linear regression models for heatstroke prediction based on meteorological and socioeconomic factors. The feature identification process of building a machine learning model that combined both the data-driven methodology and domain knowledge resulted in comprehensive variables in complex sets. Our machine learning-based analysis showed

seasonal and regional differences in the influence of atmospheric processes on ACS prevalence indicating the most influential weather parameters specific to a given time and place. Weather elements act as stimuli, especially when they reach extreme values or their parameters change in a short time interval. Some of them act permanently, being intensified by synergism with others finally forming a stimulant weather complex. Thermal and moisture conditions are one of the most important factors, which profile the human heat budget. In this study, the most influential on the prevalence of ACS was maximum relative humidity and the daily range of dew point temperature describing temperatures at which the concentration of water vapor in the air was saturated. A low temperature activates the thermoreceptors of the hypothalamic-pituitary-adrenal axis and stimulates adrenal glands to secrete adrenalin, which causes vasoconstriction and blood pressure elevation. Finally, increased shear stress may induce atherosclerotic plaque rupture. Simultaneously, cold weather increases diuresis and diminishes serum volume deteriorating its rheological properties (31). In contrast, a high temperature leads to parasympathetic nervous system stimulation, vasodilatation, and a decrease in blood pressure (32). Mechanical stimuli caused, in turn, by atmospheric circulation, particularly pressure and frontal systems, fluctuations that affect the human body through air pressure and wind speed. In this study, the maximum and daily range of atmospheric pressure was found to be the most influential for a learning machine process with specific differences for separate seasons.

First, weather conditions vary across different climate zones; therefore, analysis with a machine learning model for our specific region cannot be one-to-one extrapolated to other regions, with local validation being required each time. Second, particular caution must be exercised when interpreting the results of meteorological variables with local effects, such as precipitation, even if they were included in regional analyses. Third, for patients with NSTEMI, the date of hospital admission does not precisely reflect the time of symptom onset due to the delay effect associated with the diagnosis process, while the timing of symptoms for patients with STEMI can be considered fairly accurate. Fourth, in this study, solar radiation characteristics were not analyzed. Although they are important for human body, their effects are gradual and their availability is limited what would make a study difficult for further implementation. Finally, the clinical characteristics of the studied groups are limited; hence, the National Health System has to collect data selectively.

CONCLUSION

Our findings indicate that weather conditions are useful for the prediction of the number of ACS in a temperate climate zone, if analyzed with an artificial intelligence system. Simultaneously, the analysis of individual weather parameters or frontal scenarios, although separately providing weak univariate relationships, was insufficient for a reproducible prognosis in different seasons and locations. The adoption of these novel findings in other climatic zones might be clinically relevant, but would require local validation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Bioethics Committee of the Jagiellonian University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AW, PM, and JZ: conception. AW and PM: data collection and manuscript drafting. BB and JZ: data analysis. BB, AW, JN, and JZ: data interpretation and revision of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.830823/full#supplementary-material

REFERENCES

1. Wolff L, White PD. Acute coronary occlusion. *The Boston Med Surg J.* (1926) 195:13–25. doi: 10.1056/nejm192607011950102
2. Bayentin L, El Adlouni S, Ouarda TB, Gosselin P, Doyon B, Chebana F. Spatial variability of climate effects on ischemic heart disease hospitalization rates for the period 1989–2006 in Quebec. *Canada Int J Health Geogr.* (2010) 9:5. doi: 10.1186/1476-072X-9-5
3. Mohammad MA, Koul S, Rylance R, Fröbert O, Alfredsson J, Sahlén A, et al. Association of weather with day-to-day incidence of myocardial infarction: a swedeheart nationwide observational study. *JAMA Cardiol.* (2018) 3:1081–9. doi: 10.1001/jamacardio.2018.3466
4. Schwartz BG, Qualls C, Kloner RA, Laskey WK. Relation of total and cardiovascular death rates to climate system, temperature, barometric pressure, and respiratory infection. *Am J Cardiol.* (2015) 116:1290–7. doi: 10.1016/j.amjcard.2015.07.050
5. Błażejczyk K, Twardosz R, Wałach P, Czarnecka K, Błażejczyk A. Heat strain and mortality effects of prolonged central European heat wave—an example of June 2019 in Poland. *Int J Biometeorol.* (2022) 66:149–161. doi: 10.1007/s00484-021-02202-0
6. Hong Y, Graham MM, Rosychuk RJ, Southern D, McMurtry MS. The effects of acute atmospheric pressure changes on the occurrence of ST-elevation myocardial infarction: a case-crossover study. *Can J Cardiol.* (2019) 35:753–60. doi: 10.1016/j.cjca.2019.02.015
7. Lin S, Soim A, Gleason KA, Hwang SA. Association between low temperature during winter season and hospitalizations for ischemic heart diseases in New York state. *J Environ Health*. (2016) 78:66–74.

8. Barnett AG, Dobson AJ, McElduff P, Salomaa V, Kuulasmaa K, Sans S, et al. Project. Cold periods and coronary events: an analysis of populations worldwide. *J Epidemiol Community Health.* (2005) 59:551–7. doi: 10.1136/jech.2004.028514
9. De Lorenzo F, Sharma V, Scully M, Kakkar VV. Cold adaptation and the seasonal distribution of acute myocardial infarction. *QJM: Int J Med.* (1999) 92:747–51. doi: 10.1093/qjmed/92.12.747
10. Kuchcik M. Mortality and thermal environment (UTCI) in Poland Polandyocardial infarction. i*Int J Biometeorol.* (2021) 65:1529–529:doi: 10.1007/s00484-020-01995-w
11. Sherazi SWA, Bae JW, Lee JY. A soft voting ensemble classifier for early prediction and diagnosis of occurrences of major adverse cardiovascular events for STEMI and NSTEMI during 2-year follow-up in patients with acute coronary syndrome. *PLoS ONE.* (2021) 16:e0249338. doi: 10.1371/journal.pone.0249338
12. Suzuki S, Yamashita T, Sakama T, Arita T, Yagi N, Otsuka T, et al. Comparison of risk models for mortality and cardiovascular events between machine learning and conventional logistic regression analysis. *PLoS ONE.* (2019) 14:e0221911. doi: 10.1371/journal.pone.0221911
13. Khera R, Haimovich J, Hurley NC, McNamara R, Spertus JA, Desai N, et al. Use of machine learning models to predict death after acute myocardial infarction. *JAMA Cardiol.* (2021) 6:633–41. doi: 10.1001/jamacardio.2021.0122
14. McGovern A, Elmore KL, Gagne DJ II. Haupt SE, Karstens CD, Lagerquist R, et al. Using artificial intelligence to improve real-time decision-making for high-impact weather. *Bull Amer Meteor Soc.* (2017) 98:2073–90. doi: 10.1175/BAMS-D-16-0123.1
15. Hutengs C, Vohland M. Downscaling land surface temperatures at regional scales with random forest regression. *Remote Sens Environ.* (2016) 178:1270–41. doi: 10.1016/j.rse.2016.03.006
16. World Meteorological Organization. Guide to Instruments and Methods of Observation (WMO-No.8.). Volume I-Measurement of meteorological variables. (2018). Available online at: https://library.wmo.int/index.php?id=12407&lvl=notice_display#.YOdcARMzaI
17. Niedzwiedz T. Catalogue of synoptic situations in the upper Vistula river basin (since 1873.09) University of Silesia. (2019). Available online at: http://klimat.wnoz.us.edu.pl (updated by the author)
18. Sanders F, A. Proposed method of surface map analysis. *Monthly Weather Rev.* (1999) 127:945–55. doi: 10.1175/1520-0493(1999)127<0945:APMOSM>2.0.CO;2
19. Liaw A, Wiener M. Classification and regression by random Forest. *R News.* (2002) 2:18–22.
20. Shameer K, Pugalenthi G, Kandaswamy KK, Sowdhamini R. 3dswap-pred: prediction of 3D domain swapping from protein sequence using random forest approach. *Protein Pept Lett.* (2011) 18:1010–20. doi: 10.2174/092986611796378729
21. Danet S, Richard F, Montaye M, Beauchant S, Lemaire B, Graux C. et al. Unhealthy effects of atmospheric temperature and pressure on the occurrence of myocardial infarction and coronary deaths a 10-year survey: the Lille-world health organization MONICA project (monitoring trends and determinants in cardiovascular disease). *Circulation.* (1999) 100:e1–e7. doi: 10.1161/01.CIR.100.1.e1
22. Bai L, Li Q, Wang J, Lavigne E, Gasparrini A, Copes R, et al. Increased coronary heart disease and stroke hospitalizations from ambient temperatures in Ontario. *Heart.* (2018) 104:673–9. doi: 10.1136/heartjnl-2017-311821
23. Santurtún A, Almendra R, Fdez-Arroyabe P, Sanchez-Lorenzo A, Royé D, Zarrabeitia, et al. Predictive value of three thermal comfort indices in low temperatures on cardiovascular morbidity in the Iberian peninsula. *Sci Total Env.* (2020) 729:138969. doi: 10.1016/j.scitotenv.2020.138969
24. Urban A, Kyselt indices in low temperatures on cardiovascular morbidity in the Iberian penintariorction and coronary deaths sion analysisascular events for STE*Int J Environ Res Public Health.* (2014) 11:952–67. doi: 10.3390/ijerph110100952
25. Michelozzi P, Accetta G, De Sario M, D'Ippoliti D, Marino C, Baccini M, et al. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. *Am J Respir Crit Care Med.* (2009) 179:383–89. doi: 10.1164/rccm.200802-217OC
26. Piotrowicz K. (2010). *Seasonal and Long-Term Weather Type Variability in Krakow*. Institute of Geography and Spatial Management. Krakow: Jagiellonian University.
27. Boussoussou M, Boussoussou N, Meresz G, Rakovics M, Entz L, Nemes A. Atmospheric fronts as minor cardiovascular risk factors, a new approach to preventive cardiology. *J Cardiol.* (2020) 75:196–202. doi: 10.1016/j.jjcc.2019.07.009
28. Wypych A, Bochenek B, Rozycki M. Atmospheric moisture content over Europe and the Northern Atlantic. *Atmosphere.* (2018) 9:18. doi: 10.3390/atmos9010018
29. Ambale-Venkatesh B, Yang X, Wu CO, Liu K, Hundley WG, McClelland R. et al. Cardiovascular event prediction by machine learning the multi-ethnic study of atherosclerosis. *Circ Res.* (2017) 121:1092–101. doi: 10.1161/CIRCRESAHA.117.311312
30. Wang Y, Song Q, Du Y, Wang J, Zhou J, Du Z, et al. A random forest model to assess heatstroke occurrence for heatwave prediction in China. *Sci Total Environ.* (2019) 650:3048–53. doi: 10.1016/j.scitotenv.2018.09.369
31. Schäuble CL, Hampel R, Breitner S, Rückerl S, Rne R, Phipps R, et al. Short-term effects of air temperature on blood markers of coagulation and inflammation in potentially susceptible individuals. *Occup Environ Med.* (2012) 69:670 Meddoi: 10.1136/oemed-2011-100469
32. Brook RD, Weder AB, Rajagopalan S. gopalan S. "Environmental hypertensionology" the effects of environmental factors on blood pressure in clinical practice and research. *J Clin Hypertens (Greenwich).* (2011) 13:836–42. doi: 10.1111/j.17951-7176.2011.00543.x

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Cost-effectiveness of Direct Oral Anticoagulant vs. Warfarin Among Atrial Fibrillation Patients With Intermediate Stroke Risk

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Background: Several studies have shown the cost-effectiveness of direct oral anticoagulants (DOACs), compared with warfarin, to prevent atrial fibrillation (AF) related complications. However, few have reported cost-effectiveness of DOACs in AF patients with intermediate stroke risk. Thus, we investigated the cost-effectiveness of DOACs vs. warfarin in non-valvular AF patients with intermediate stroke risk using national representative data.

Methods: We identified 7,954 newly diagnosed non-valvular AF patients (≥18 years) with intermediate stroke risk (CHA_2DS_2-VASc score: 1 for men and 2 for women) using the national healthcare utilization data from August 1, 2016, to July 31, 2019. Annual incidence rate of AF-related composite outcomes (heat failure, myocardial infarction, ischemic stroke, intracerebral hemorrhage, and gastrointestinal bleeding) was estimated. Cost-effectiveness was estimated using a Markov chain model with the transition probability of 1 year. The willingness-to-pay (WTP) was set at $32,000 per quality-adjusted life-year (QALY) gained.

Results: The total cost of warfarin, rivaroxaban, apixaban, dabigatran and edoxaban was $2,874, $5,761, $5,151, $5,761 and $5,851, respectively. The QALYs gained were 10.83, 10.95, 11.10, 10.49 and 10.99 years, respectively. The incremental cost-effectiveness ratio of rivaroxaban, apixaban, dabigatran and edoxaban was $29,743.99, $8,426.71, -$8,483.04 and $18,483.55, respectively. The WTP was set at $32,000. DOACs (except dabigatran) were more cost-effective compared with warfarin because they did not exceed the WTP in the base-case analysis.

Conclusion: Our findings showed that DOACs were more cost-effective than warfarin in non-valvular AF patients with intermediate stroke risk.

Keywords: atrial fibrillation, cost-effectiveness, anticoagulants, warfarin, intermediate stroke risk

INTRODUCTION

The global incidence and prevalence of atrial fibrillation (AF) have increased rapidly in elderly people (1). In the Republic of Korea, AF prevalence is estimated to be 2.1% among those aged more than 65 years, and it is expected to rise to 5.8% by 2060 due to rapid population aging (2). Accordingly, the risk of complications (including stroke) and the related cost of treating AF have increased steadily (3). In the United States, the estimated incremental cost for treating AF patients reached $26 billion during 2004–2006 (4). In Europe, AF-related costs increased up to €3,000 per patient-year from 1990 to 2009 (5).

Use of anticoagulants is of importance in preventing cardiovascular complications in patients with AF. AF increases the risk of developing a thrombus due to turbulent flow in the left atrium. The thrombus from the left atrium can cause embolization in a primary organ or tissue, leading to complications such as stroke or systemic embolism, myocardial infarction (MI), and heart failure (HF) (6–8). To prevent these complications, vitamin K antagonists or direct oral anticoagulants (DOACs; rivaroxaban, apixaban, dabigatran, and edoxaban) are prescribed to patients with AF.

Based on mounting evidence on the DOACs had more cost-effective than warfarin (9–12), guidelines in Europe and the USA recommend preferential use of DOACs over warfarin to prevent cardiovascular complications in patients with AF (13, 14). In line with this, use of DOACs to prevent stroke is subsidized in AF patients since 2015 in the Republic of Korea (15). However, this reimbursement scheme is limited to AF patients with high stroke risk (defined as a CHA_2DS_2-VASc score of 2 or higher), as most previous studies on the cost-effectiveness of DOACs included AF patients with high stroke risk or did not consider the risk of stroke (16). Some studies have investigated the cost-effectiveness of DOACs after a stratification on individuals regarding stroke risk (9, 17, 18). To the best of our knowledge, no purposely designed study has investigated the cost-effectiveness of DOACs by focusing on the intermediate stroke risk group.

Therefore, this study investigated the cost-effectiveness of DOACs and warfarin among AF patients with intermediate stroke risk by using national representative data.

MATERIALS AND METHODS

Data Source

In this study, we used data from the Health Insurance Review and Assessment (HIRA) on the demographics (age and sex), diagnosis [International Classification of Disease 10th Revision (ICD-10) codes and date of diagnosis], in-hospital mortality, information on prescriptions (date and chemical name), and cost. Because the HIRA database covers almost 98% of the total population (15), sampling or selection bias was minimized.

This study was approved by the Institutional Review Board of Yonsei University Health System (2021–1748–001), and informed consent was waived.

Study Population

Of the 781,583 individuals who visited hospitals with the AF code (ICD-10: I48) between August 1, 2016, and July 31, 2019, we further identified 7,954 non-valvular AF patients using the following inclusion criteria (**Supplementary Figure 1**):

Individuals who were not diagnosed with AF (or valvular AF) and AF-related complications from August 1, 2015, to July 31, 2016;
Individuals who visited outpatient clinics at least twice or were admitted to a hospital at least once for AF (ICD-10: I48, I48.0, and I48.1);
Adults (aged ≥ 18 years) who took warfarin or DOACs (rivaroxaban, apixaban, dabigatran and edoxaban) and we excluded AF patients with prescriptions of both DOACs and warfarin during the study period;
Individuals with intermediate stroke risk (defined as the CHA2DS2-VASc score of 1 in men or 2 in women).

CHA_2DS_2-VASc Score

To calculate the CHA_2DS_2-VAS_c score (an indicator of stroke risk), this study set the index date for each participant. The index date is defined as the date of admission or of the second outpatient visit for AF, whichever came earlier. The CHA_2DS_2-VAS_c score was calculated based on the demographics on the index date and healthcare utilization 1 year prior to the index date. The CHA_2DS_2-VAS_c score is the sum of the scores of each component. One point was given to those who aged 65–75 years; those with a history of hypertension, diabetes, congestive HF, or vascular disease (MI or a peripheral vascular disease); and women. Two points were given to those aged 75 years or older and those with a history of stroke or systemic embolism. The ICD-10 codes used for calculating the CHA_2DS_2-VAS_c score are presented in **Table 1.**

Composite Outcome Measure

In this study, we calculated annual rates of the composite outcome of the following AF-related complications: HF, MI, ischemic stroke (IS), intracerebral hemorrhage (ICH), and gastrointestinal (GI) bleeding. For each composite outcome, there were records of outpatient visits at least twice or admission at least once. If the definition is satisfied no matter how many times an event occurs within a year, the analysis was conducted with one event occurrence. The ICD-10 codes used for calculating the composite outcome are presented in **Table 2**.

Cost-Effectiveness Analysis

A Markov chain decision-analysis model was constructed to evaluate the cost-effectiveness of DOACs compared with warfarin in intermediate stroke risk patients. We categorized health status into healthy with AF, post-health event (post-HF, post-IS, post-ICH, post-GI bleeding, or post-MI), and death. All health events, except for GI bleeding, were assumed to remain in the post-disease state or to transition to the death state. GI bleeding was assumed to transition to the healthy with AF state or death state (**Supplementary Figure 2**).

This study assumed the transition of health status in a 1-year cycle. Transient probabilities were determined by the annual

TABLE 1 | Definition of CHA_2DS_2-VAS_c score components (ICD-10).

Disease	ICD-10 code	
Hypertension	I10, I11, I12, I13, I15	Essential (primary) hypertension, hypertensive heart disease, hypertensive renal disease, hypertensive heart and renal disease, secondary hypertension
Heart failure	I50	Heart failure
Stroke (IS, ICH)	I60, I61, I62, I63, I64	Subarachnoid hemorrhage, intracerebral hemorrhage, other non-traumatic intracranial hemorrhage, cerebral infarction, stroke, not specified as hemorrhage or infarction
Myocardial infarction	I21, I22	Acute myocardial infarction, subsequent myocardial infarction
Peripheral artery disease	I70, I71	Atherosclerosis, aortic aneurysm and dissection

IS, ischemic stroke; ICH, intracranial hemorrhage.

TABLE 2 | Definition of health event (ICD-10).

Disease	ICD-10 code		Inclusion criteria
Heart failure	I50	Heart failure	Admission ≥1 or outpatient department ≥2
Myocardial infarction	I21	Acute myocardial infarction	Admission ≥1 or outpatient department ≥2
	I22	Subsequent myocardial infarction	
Ischemic stroke	I63	Cerebral infarction	Admission ≥1 or outpatient department ≥2 + brain imaging (CT, MRI)
Intracranial hemorrhage	I60	Subarachnoid hemorrhage	Admission ≥1 or outpatient department ≥2+ brain imaging (CT, MRI)
	I61	Intracerebral hemorrhage	
	I62	Other non-traumatic intracranial hemorrhage	
Gastrointestinal bleeding	K22.6	Gastro-esophageal laceration-hemorrhage syndrome	Admission ≥1 or outpatient department ≥2
	K25	Gastric ulcer	
	K26	Duodenal ulcer	
	K27	Peptic ulcer, site unspecified	
	K28	Gastrojejunal ulcer	
	K92.2	Gastrointestinal hemorrhage, unspecified	

ICD, International Classification of Disease 10th Revision (ICD-10) code; CT, computed tomography; MRI, magnetic resonance imaging.

incidence rates of five diseases (HF, MI, IS, ICH, and GI bleeding). The Markov chain decision-analysis model was repeated for 20 cycles. The discount rate was set as 4.5% (19).

This study took the perspective of a Korea healthcare system. All cost incurred from the point of view of Korean payers (medicine cost, cost due to health event) were included the cost consisted of medication cost, health event-related cost, and post-health event cost. Annual costs of medication were defined as 365 times the daily medication price. Health event-related cost was defined as the average admission cost for each health event. Post-event cost was estimated by subtracting the medication cost and event-related cost from the total costs. The willingness-to-pay (WTP) was set at $32,000 per quality-adjusted life-year (QALY) to reflect the South Korean gross domestic product ($31,494 in 2020). All costs were converted to USD (1 USD=1,000 KRW). We used the QALYs provided by previous studies (20–25).

Sensitivity Analysis

Deterministic sensitivity analysis (DSA) was performed to examine which input parameter among those used in the above cost-effectiveness analysis most affects the model. In addition, probabilistic sensitivity analysis (PSA) was performed using a Monte Carlo simulation (10,000 times). The parameter used in sensitivity analysis shown in **Supplementary Table 2.**

All analyses were performed in TreeAge Pro 2020 (TreeAge Software, Inc., Williamstown, MA, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The input parameter used to this analysis is shown in **Supplementary Table 1**.

We derived the annual incidence rate from a nationwide database. The annual incidence rate of IS was 0.75, 1.07, 1.50, 4.55, and 1.33% for warfarin, rivaroxaban, apixaban, dabigatran and edoxaban, respectively, with a CHA_2DS_2-VAS_c score = 1. Patients with CHA_2DS_2-VAS_c score = 2 had annual incidence rates of IS of 1.52, 0.64, 0.62, 0.53 and 0.64% for warfarin, rivaroxaban, apixaban, dabigatran and edoxaban, respectively. The utilities of warfarin, rivaroxaban, apixaban, dabigatran and edoxaban were 0.987, 0.994, 0.998, 0.970 and 0.998, respectively (**Table 3**). Their annual medication costs were $19.490, $795.420, $470.968, $870.890 and $670.010, respectively (**Table 4**).

TABLE 3 | Fatality and utility used in base-case analysis.

Model parameter	Base-case value (raw)	Base-case value (%/year)	Distribution
Fatality			
Heart failure	4/1,223	0.32%	Beta
Myocardial infarction	0/61	0.00%	Beta
Ischemic stroke	2/92	2.17%	Beta
Intracranial hemorrhage	1/8	12.50%	Beta
GI bleeding	1/54	1.85%	Beta
Utility			
Warfarin (20)	0.987	0.987	Gamma
Rivaroxaban (20)	0.994	0.994	Gamma
Dabigatran (21)	0.970	0.970	Gamma
Apixaban (21)	0.998	0.998	Gamma
Edoxaban (21)	0.998	0.998	Gamma
Heart failure (22)	0.69	0.69	Beta
Myocardial infarction (23)	0.84	0.84	Beta
Ischemic stroke (24)	0.41	0.41	Beta
Intracranial hemorrhage (24)	0.56	0.56	Beta
GI bleeding (25)	0.70	0.70	Beta

GI, gastrointestinal.

TABLE 4 | Cost used in base-case analysis.

Model parameter	Base-case value (raw)	Base-case value (%/year)	Distribution
Cost($)			
Medication cost (yearly)			
Warfarin	19.490	19.490	Gamma
Rivaroxaban	795.426	795.426	Gamma
Apixaban	470.968	470.968	Gamma
Dabigatran	870.890	870.890	Gamma
Edoxaban	670.010	670.010	Gamma
Event-related cost (per event)			
Heart failure	2,964.92	2,964.92	Gamma
Myocardial infarction	7,482.15	7,482.15	Gamma
Ischemic stroke	4,557.36	4,557.36	Gamma
Intracranial hemorrhage	7,108.77	7,108.77	Gamma
GI bleeding	1,583.03	1,583.03	Gamma

GI, gastrointestinal.

In the base-case analysis, the total cost of warfarin, rivaroxaban, apixaban, dabigatran and edoxaban in non-valvular AF patients was $2,874, $6,379, $5,151, $5,761 and $5,851, respectively (**Table 5**). The QALYs gained were 10.83, 10.95, 11.10, 10.49 and 10.99 years, respectively. The incremental cost-effectiveness ratios (ICERs) of rivaroxaban, apixaban, dabigatran and edoxaban (compared with warfarin) were $29,743.99, $8,426.71, −$8,483.04 and $18,483.55 each, respectively, and these estimates did not exceed the WTP threshold ($32,000 per QALY). Rivaroxaban, apixaban, and edoxaban were thus cost-effective compared with warfarin.

TABLE 5 | Base-case analysis result comparing warfarin and DOACs.

Strategy	Cost ($)	Incremental cost	QALY	ICER ($/QALY)
Warfarin	2,874	Ref.	10.83	Ref.
Rivaroxaban	6,379	3,505	10.95	29,743.99
Apixaban	5,151	2,276	11.10	8,426.71
Dabigatran	5,761	2,886	10.49	−8,483.04
Edoxaban	5,851	2,976	10.99	18,483.55

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; DOACs, direct oral antagonist oral anticoagulants.

In the deterministic sensitivity analysis, the input parameter most affecting the ICER was the drug cost in all analyses of DOACs compared with warfarin (**Supplementary Figures 3–6**). In a probabilistic sensitivity analysis, rivaroxaban, apixaban, dabigatran and edoxaban were cost-effective at 21.19, 49.73, 22.3, and 9.97% compared with warfarin, respectively (**Table 6**). In the acceptability curves for warfarin and DOACs, the ICERs of apixaban and rivaroxaban were lower than that of warfarin at the WTP ($32,000; **Figure 1**). The cost-effectiveness scatter plot is presented in **Supplementary Figure 7**.

DISCUSSION

This study is the first to investigate the cost-effectiveness of DOACs compared with warfarin in South Korean non-valvular AF patients with intermediate stroke risk with fully independent from pharmaceutical company. In the base-case analysis, apixaban was the best alternative treatment to warfarin (with an ICER of $8,426.71). Rivaroxaban was also cost-effective compared with warfarin (with an ICER of $29,743.99). However, Dabigatran was not cost effective than warfarin (With an ICER of -$8,483.04). Although edoxaban exhibited an ICER of $18,483.55, it was not cost-effective compared with warfarin in the sensitivity analysis.

It is well known based on previous studies that the cost-effectiveness of DOACs is higher than that of warfarin (26, 27), which is consistent with our findings. Furthermore, the present study showed that apixaban and rivaroxaban were cost-effective compared with warfarin in both the base-case and sensitivity analyses (28, 29), which is consistent with previous studies (28–33). By contrast, our sensitivity analysis showed dabigatran and edoxaban to be less cost-effective than warfarin among patients with AF, which is not consistent with previous studies (33, 34). This discrepancy may stem from the difference in study population: the previous studies did not consider stroke risk (26, 27), while the present study focused on the intermediate stroke risk group.

There is little evidence in previous literature on the cost-effectiveness of DOACs in AF patients with intermediate stroke risk, and only a few investigated the cost-effectiveness of DOACs compared with warfarin while considering stroke risk (9, 17, 18). A UK study, which included 1,000 AF patients, showed

TABLE 6 | The PSA result of DOACs and warfarin.

	Cost ($)					QALYs				
	Warfarin	**Rivaroxaban**	**Dabigatran**	**Apixaban**	**Edoxaban**	**Warfarin**	**Rivaroxaban**	**Dabigatran**	**Apixaban**	**Edoxaban**
Mean ± SD	3,024 ± 218	6,431 ± 426	6,765 ± 495	5,132 ± 327	5,787 ± 383	10.72 ± 0.71	10.84 ± 0.71	10.87 ± 0.73	11.11 ±0.74	10.60 ± 0.69
Median	3,015	6,420	6,749	5,773	5,773	10.73	10.85	10.89	11.11	10.61
Minimum	2,333	4,967	5,152	4,463	4,463	7.76	7.88	8.31	8.31	7.83
Maximum	3,890	8,176	8,925	7,557	7,557	13.5	13.32	14.01	14.72	13.04
Sum	30,242,571	64,310,937	67,652,251	57,873,216	57,873,216	107,216.51	108,407.77	108,713.93	111,061.42	106,007.53
Size (n)	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000	10,000
Variance	47,351	181,617	245,238	146,479	146,479	0.51	0.5	0.53	0.55	0.47
Variance/Size	5	18	25	15	15	0	0	0	0	0
SQRT (variance/size)	2	4	5	4	4	0.01	0.01	0.01	0.01	0.01

SD, standard deviation; SQRT, square root; PSA, probabilistic sensitivity analysis; DOACs, direct oral antagonist oral anticoagulants; QALY, quality-adjusted life year.

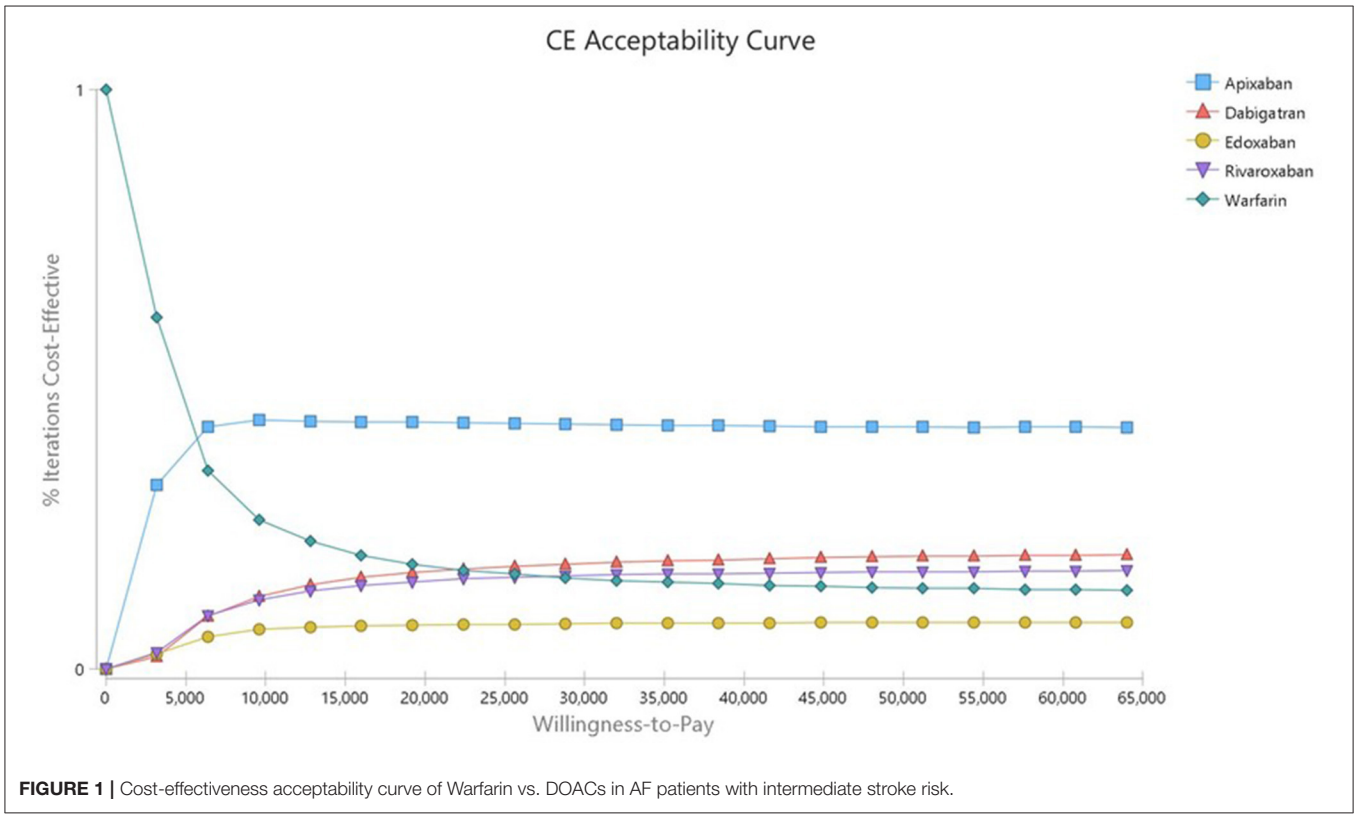

FIGURE 1 | Cost-effectiveness acceptability curve of Warfarin vs. DOACs in AF patients with intermediate stroke risk.

that apixaban was more cost-effective than aspirin among AF patients with intermediate stroke risk, both having an ICER of $26,852 for a CHADS score of 1 and $14,001 for a CHA_2DS_2-VASc score of 1, respectively (17). However, our study included 7,954 AF patients with intermediate stroke risk, and the ICER of apixaban was $8,426.71 per QALY. A recent study from the Republic of Korea on AF patients with a CHA_2DS_2-VASc score of 1 (N=805) found that rivaroxaban was more cost-effective than warfarin (with an ICER of $98,051 per QALY) (9). The present study (N=7,954) included AF patients with intermediate stroke risk (having a CHA_2DS_2-VASc score of 1 in men 2 in women) and showed that the ICERs of apixaban and rivaroxaban were $8,426.71 and $29,743.99 per QALY, respectively.

In accordance with the previous studies, our findings clearly showed that DOACs were more cost-effective than warfarin. The higher cost-effectiveness of DOACs (vs. warfarin) in AF patients with intermediate stroke risk aligns with the current recommendations from Europe and the USA (13, 14). Nonetheless, DOACs are not subsidized in AF patients with intermediate stroke risk in many countries including the UK, USA, and China. In Korea, National Health Insurance program covers almost 100% of the Korean population (15). Thus, present study may provide evidence on the need for including AF patients

with intermediate stroke risk as the beneficiary group of the DOACs' subsidy scheme.

Although our study included all AF patients in Korea during the study period and used real-world hospital utilization data to estimate cost-effectiveness, there are some limitations to be noted. First, the generalizability of the findings to other countries is limited since this study only included Koreans. Although many studies have been conducted in the West, they reported results similar to this study. Second, as an inherent issue of cost-effectiveness research, our findings are based on several assumptions. We assumed that the cost only included medication and health-related costs. Another assumption was that the transition probability evaluated the incidence of health events within 1 year. The other assumption was that we didn't consider health losses related to aging. To examine uncertainty, we performed a sensitivity analysis using Monte Carlo simulation. Third, in this study, the patients who had switched to the counter group had been excluded. The cost-effectiveness of warfarin depends on the time in therapeutic range (TTR), which was not evaluated in the present study (35). Warfarin users with poor TTR maintenance or minor bleeding episodes which were not included in clinical outcome, might underestimate cost of warfarin group. Fourth, because health events usually proceeded by systemic embolism and limitations of diagnosis existed in claims data. We could not consider systemic embolism as a final health event. Thus, considering the preventative effect of DOACs on systemic embolism (36, 37), our estimates might have been underestimated the cost-effectiveness of DOACs.

Lastly, only direct costs related to clinical events were considered in this study. As warfarin has a narrow therapeutic window and interactions with food or drugs, there may be indirect costs related to monitoring of the international normalized ratio, clinic visits, time spent during traveling and waiting, and consultation. This issue may have led to the underestimation of the cost-effectiveness of DOACs vs. warfarin.

In summary, we evaluated the cost-effectiveness of DOACs and warfarin using real-world hospital utilization data. The data of the study might be affected by reimbursement criteria of DOAC, not included the intermediate stroke risk patients in Korea. However, in this group of patients, the incidence of clinical events was substantial and DOAC has shown to be cost effective.

However, because it has been only a few years since DOACs were subsidized in South Korea, the long-term follow-up data are not sufficient to evaluate cost-effectiveness of DOACs and warfarin. Considering the result, the reimbursement scope of DOAC should be extended to the intermediate stroke risk patients who would benefit from DOAC. Therefore, future research on this topic might be necessary.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

The health economic model was designed by J-BK and CK and performed by JChoi and WK. JChoi reviewed literature and drafted the manuscript, which was reviewed and revised by CK, J-BK, SS, and JCho. YK supported statistical method. Results were reviewed and interpreted by CK and J-BK. All authors contributed directly or indirectly to this study and agreed to manuscript submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.849474/full#supplementary-material

REFERENCES

1. Fang MC, Chen J, Rich MW. Atrial fibrillation in the elderly. *Am J Med.* (2007) 120:481–7. doi: 10.1016/j.amjmed.2007.01.026
2. Joung B, Lee JM, Lee KH, Kim TH, Choi EK, Lim WH, et al. 2018 Korean guideline of atrial fibrillation management. *Korean Circ J.* (2018) 48:1033–80. doi: 10.4070/kcj.2018.0339
3. Sheikh A, Patel NJ, Nalluri N, Agnihotri K, Spagnola J, Patel A, et al. Trends in hospitalization for atrial fibrillation: epidemiology, cost, and implications for the future. *Prog Cardiovasc Dis.* (2015) 58:105–16. doi: 10.1016/j.pcad.2015.07.002
4. Kim MH, Johnston SS, Chu B-C, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes.* (2011) 4:313–20. doi: 10.1161/CIRCOUTCOMES.110.958165
5. Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda J-G, Van Gelder IC. The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace.* (2011) 13:1375–85. doi: 10.1093/europace/eur194
6. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: a systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J.* (2009) 30:1038–45. doi: 10.1093/eurheartj/ehn579
7. Perino AC, Kaiser DW, Lee RJ, Fan J, Askari M, Schmitt SK, et al. Incidence and outcomes of patients with atrial fibrillation and major bleeding complications: from the TREAT-AF study. *J Interv Card Electrophysiol.* (2021) 62:133–42. doi: 10.1007/s10840-020-00873-0
8. Andrade J, Khairy P, Dobrev D, Nattel S. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. *Circ Res.* (2014) 114:1453–68. doi: 10.1161/CIRCRESAHA.114.303211
9. Kim H, Kim H, Cho SK, Kim JB, Joung B, Kim C. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. *Korean Circ J.* (2019) 49:252–63. doi: 10.4070/kcj.2018.0220
10. Wei H, Cui C, Cui X, Liu Y, Li D. Cost-effectiveness analysis of dabigatran, rivaroxaban and warfarin in the prevention of stroke in

patients with atrial fibrillation in China. *BMC Health Serv Res.* (2021) 21:96. doi: 10.1186/s12913-021-06084-1
11. Athanasakis K, Boubouchairopoulou N, Karampli E, Tarantilis F, Savvari P, Bilitou A, et al. Cost effectiveness of apixaban versus warfarin or aspirin for stroke prevention in patients with atrial fibrillation: a Greek perspective. *Am J Cardiovasc Drugs.* (2017) 17:123–33. doi: 10.1007/s40256-016-0204-1
12. Lopes RD, Berger SE, Di Fusco M, Kang A, Russ C, Afriyie A, et al. A review of global health technology assessments of non-VKA oral anticoagulants in non-valvular atrial fibrillation. *Int J Cardiol.* (2020) 319:85–93. doi: 10.1016/j.ijcard.2020.06.061
13. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation.* (2019) 74:104–32. doi: 10.1161/CIR.0000000000000719
14. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) *Eur Heart J.* (2021) 42:373-498. doi: 10.1093/eurheartj/ehaa798
15. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea health Insurance review and assessment (HIRA) data as a resource for health research: Strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci.* (2017) 32:718–28. doi: 10.3346/jkms.2017.32.5.718
16. Shen NN, Wu Y, Wang N, Kong LC, Zhang C, Wang JL, et al. Direct oral anticoagulants vs. vitamin-K antagonists in the elderly with atrial fibrillation: a systematic review comparing benefits and harms between observational studies and randomized controlled trials. *Front Cardiovasc Med.* (2020) 7:132. doi: 10.3389/fcvm.2020.00132
17. Lip GY, Lanitis T, Mardekian J, Kongnakorn T, Phatak H, Dorian P. Clinical and economic implications of apixaban versus aspirin in the low-risk nonvalvular atrial fibrillation patients. *Stroke.* (2015) 46:2830–7. doi: 10.1161/STROKEAHA.115.009995
18. Wu B, Kun L, Liu X, He B. Cost–effectiveness of different strategies for stroke prevention in patients with atrial fibrillation in a health resource-limited setting. *Cardiovasc Drugs Ther.* (2014) 28:87–98. doi: 10.1007/s10557-013-6490-9
19. Health Insurance Review and Assessment Service (HIRA). *Guidelines for Economic Evaluation of Pharmaceuticals in Korea.* (2021). HIRA
20. Gage BF, Cardinalli AB, Owens D. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med.* (1996) 156:1829–36. doi: 10.1001/archinte.1996.00440150083009
21. Zhao YJ, Lin L, Zhou HJ, Tan KT, Chew AP, Foo CG, et al. Cost-effectiveness modelling of novel oral anticoagulants incorporating real-world elderly patients with atrial fibrillation. *Int J Cardiol.* (2016) 220:794–801. doi: 10.1016/j.ijcard.2016.06.087
22. Wouters OJ, Naci H, Samani NJ. QALYs in cost-effectiveness analysis: an overview for cardiologists. *Heart.* (2015) 101:1868–73. doi: 10.1136/heartjnl-2015-308255
23. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making.* (2006) 26:410–20. doi: 10.1177/0272989X06290495
24. Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM, et al. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. *Neurology.* (2013) 81:1588–95. doi: 10.1212/wnl.0b013e3182a9f45f
25. Kongnakorn T, Lanitis T, Annemans L, Thijs V, Goethals M, Marbaix S, et al. Stroke and systemic embolism prevention in patients with atrial fibrillation in Belgium: comparative cost effectiveness of new oral anticoagulants and warfarin. *Clin Drug Investig.* (2015) 35:109–19. doi: 10.1007/s40261-014-0253-7
26. Kasmeridis C, Apostolakis S, Ehlers L, Rasmussen LH, Boriani G, Lip GY. Cost effectiveness of treatments for stroke prevention in atrial fibrillation: focus on the novel oral anticoagulants. *Pharmacoeconomics.* (2013) 31:971–80. doi: 10.1007/s40273-013-0090-1
27. Ferreira J, Mirco A. Systematic review of cost-effectiveness analyses of novel oral anticoagulants for stroke prevention in atrial fibrillation. *Rev Port Cardiol.* (2015) 34:179–91. doi: 10.1016/j.repce.2014.08.016
28. Lanitis T, Cotté F, Gaudin A, Kachaner I, Kongnakorn T, Durand-Zaleski I. Stroke prevention in patients with atrial fibrillation in France: comparative cost-effectiveness of new oral anticoagulants (apixaban, dabigatran, and rivaroxaban), warfarin, and aspirin. *J Med Econ.* (2014) 17:587–98. doi: 10.3111/13696998.2014.923891
29. Athanasakis K, Karampli E, Tsounis D, Bilitou A, Kyriopoulos J. Cost-effectiveness of apixaban vs. other new oral anticoagulants for the prevention of stroke: an analysis on patients with non-valvular atrial fibrillation in the Greek healthcare setting. *Clin Drug Investig.* (2015) 35:693–705. doi: 10.1007/s40261-015-0321-7
30. Hersi AS, Osenenko KM, Kherraf SA, Aziz AA, Sambrook RJ. Cost-effectiveness of apixaban for stroke prevention in non-valvular atrial fibrillation in Saudi Arabia. *Ann Saudi Med.* (2019) 39:265–78. doi: 10.5144/0256-4947.2019.265
31. Lee S, Mullin R, Blazawski J, Coleman CI. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. *PLoS ONE.* (2012) 7:e47473. doi: 10.1371/journal.pone.0047473
32. Pinyol C, Cepeda JM, Roldan I, Roldan V, Jimenez S, Gonzalez P, et al. A systematic literature review on the cost-effectiveness of apixaban for stroke prevention in non-valvular atrial fibrillation. *Cardiol Ther.* (2016) 5:171–86. doi: 10.1007/s40119-016-0066-2
33. Magnuson EA, Vilain K, Wang K, Li H, Kwong WJ, Antman EM, et al. Cost-effectiveness of edoxaban vs warfarin in patients with atrial fibrillation based on results of the ENGAGE AF–TIMI 48 trial. *Am Heart J.* (2015) 170:1140–50. doi: 10.1016/j.ahj.2015.09.011
34. Dilokthornsakul P, Nathisuwan S, Krittayaphong R, Chutinet A, Permsuwan U. Cost-effectiveness analysis of non-vitamin K antagonist oral anticoagulants versus warfarin in Thai patients with non-valvular atrial fibrillation. *Heart Lung Circ.* (2020) 29:390–400. doi: 10.1016/j.hlc.2019.02.187
35. Hospodar AR, Smith KJ, Zhang Y, Hernandez I. Comparing the cost effectiveness of non-vitamin k antagonist oral anticoagulants with well-managed warfarin for stroke prevention in atrial fibrillation patients at high risk of bleeding. *Am J Cardiovasc Drugs.* (2018) 18:317–25. doi: 10.1007/s40256-018-0279-y
36. Martha JW, Pranata R, Raffaelo WM, Wibowo A, Akbar MR. Direct acting oral anticoagulant vs. warfarin in the prevention of thromboembolism in patients with non-valvular atrial fibrillation with valvular heart disease-a systematic review and meta-analysis. *Front Cardiovasc Med.* (2021) 8:764356. doi: 10.3389/fcvm.2021.764356
37. Yang Q, Lang X, Quan X, Gong Z, Liang Y. Different oral antithrombotic therapy for the treatment of ventricular thrombus: an observational study from 2010 to 2019. *Int J Clin Pract.* (2022) 2022:1–12. doi: 10.1155/2022/7400860

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Adiposity-Related Predictors of Vascular Aging From a Life Course Perspective–Findings From the Helsinki Birth Cohort Study

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The main objective of this study was to study predictors of vascular health with focus on adiposity-related factors. Glucose metabolism, blood lipids, inflammatory markers and body composition were assessed 15 years before assessment of vascular health which was assessed with pulse wave velocity (PWV) in 660 subjects born 1934–44. In a univariate analysis in women the strongest association with PWV was seen for age, systolic blood pressure, dysglycemia, dyslipidemia, inflammatory markers and body fat percentage measured in late midlife and PWV measured 15 years later. In men age, body mass index (BMI), systolic blood pressure, dysglycemia, and body fat percentage in late midlife were associated with PWV. One novel finding was that adiposity-related factors were strong predictors of vascular health, something not fully encapsulated in BMI, lean body mass or body fat percentage alone. A higher fat mass index was associated with worse vascular health, which was not ameliorated by a higher lean mass index. Our findings stress the importance to study body composition and fat and lean body mass simultaneously because of their close interaction with each other also in relation to vascular health.

Keywords: vascular aging, blood pressure, body composition, pulse wave velocity, lean body mass, body fat percentage, prenatal programming

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WHAT IS KNOWN ABOUT TOPIC

- Arterial stiffness is closely linked with blood pressure and arteriosclerosis.
- Other factors that contribute to arterial stiffness include impaired glucose regulation, low grade chronic inflammation and oxidative stress which are associated with adiposity. However, the overall influence of adiposity and body composition on vascular health has received little interest.

WHAT THIS STUDY ADDS

- Adiposity-related factors were strong predictors of vascular health, something not encapsulated in BMI, lean body mass or body fat percentage alone. A higher fat mass index was associated with worse vascular health, which was not ameliorated by a higher lean mass index.
- The study findings stress the importance to study body composition and fat and lean body mass simultaneously also in relation to vascular health.

INTRODUCTION

With increasing age cardiovascular disease (CVD) morbidity and mortality increase (1). Arteriosclerosis and atherosclerosis are major underlying factors influencing CVD morbidity. Both aging and hypertension are major CVD risk factors associated with the arteriosclerotic process and strongly linked to overall vascular health (2, 3). One of the core components in vascular health is believed to be arterial stiffness which is closely linked with blood pressure and arteriosclerosis (4–8).

Other factors that contribute to arterial stiffness include impaired glucose regulation, low grade chronic inflammation and oxidative stress (9–11). Several of these factors are associated with overweight and obesity and an unfavorable body composition. However, the overall influence of adiposity and body composition on vascular health has received little interest.

There is a large individual variation in the overall aging process, including vascular aging (12). This could partly be explained by factors that are active early in life; consequently, the importance to focus upon health and disease from a life course perspective has been stressed (13). Non-communicable chronic diseases (NCDs) including CVD and type 2 diabetes are known to have risk factors originating early in life, as a consequence of what is often called "early life programming" (14, 15).

The main aim of the present study was to study adiposity-related predictors of vascular health by using unique longitudinal phenotypic data from participants in the Helsinki Birth Cohort Study (HBCS) available from prenatal life until the ninth decade of life.

METHODS

Helsinki Birth Cohort Study (HBCS) consists of an epidemiological study cohort including men and women born at Helsinki University Hospital and Helsinki City Maternity Hospital between 1934 and 1944 and who attended child welfare clinics in the city, the majority also attended schools in the city of Helsinki. Details of the birth records, child welfare clinics and school health records have been described previously (14). From the epidemiological cohort we identified 8,760 people (4,630 men and 4,130 women) who were born at Helsinki University Hospital and who were living in Finland in 1971, when a unique identification number was allocated to each member of the Finnish population.

For a clinical study in the years 2001-04 we used random-number tables to select a subset of people from the initial study group who were still alive and living in Finland. In order to achieve a sample size in excess of 2,000 people for this clinical study, we selected 2,902 subjects for evaluation. Of these subjects, 2,003 attended a clinic after an overnight fast. A 2-hr 75 g oral glucose tolerance test (OGTT) was performed and blood samples were drawn for laboratory assessment including plasma glucose, insulin, blood lipids and inflammatory markers. Plasma glucose concentrations were measured according to a hexokinase method, whereas plasma insulin concentrations were determined by two-site immunometric assay (16, 17). Serum total cholesterol and triglyceride concentrations were measured with the use of standard enzymatic methods (18, 19). Height was measured with a Kawi stadiometer. Weight was measured on a Seca Alpha 770 scale. Blood pressure was measured from the right arm while the subject was in the sitting position and was recorded as the mean of two successive readings from a standard sphygmomanometer. Body composition was assessed at baseline by bioelectrical impedance analysis using the InBody 3.0 eight-polar tactile electrode system (Biospace Co, Ltd, Seoul, Korea) (20). The instrument estimates lean body mass and body fat mass by segmental multi-frequency (5, 50, 250, and 500 kHz) analysis. The measurements were made with the subject standing in light indoor clothing on the four foot electrodes on the platform of the analyzer and gripping the two palm and thumb electrodes.

Fat and lean mass indices were calculated as follows: fat mass index (FMI, kg/m^2) = fat mass/height^2 and lean mass index (LMI, kg/m^2) = lean mass/height^2 (21). We divided the study cohort based upon sex-specific median values for fat and lean mass indices. Four groups were created separately for women and men; those are: (A) low LMI and low FMI, (B) high LMI and low FMI, (C) low LMI and high FMI and (D) high LMI and high FMI.

Leisure-time physical activity (LTPA) was assessed by using a validated Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study 12-month LTPA history questionnaire (22). The subjects were asked to fill in frequency (occasions per month), average duration and intensity of each type of activity performed during the previous 12 months. For each type of activity we signed a metabolic equivalent of task (MET) -value based on available databases. To calculate the volume of LTPA in MET-hours (METh), MET values were multiplied with the average duration and frequency of activities per week.

From the original clinical study cohort (n = 2,003), 1,404 people who were alive and living within 100 km distance from our study clinic in Helsinki were invited to participate in a clinical follow-up in 2011. A total of 1,094 participants attended the clinical examination between 2011 and 2013. Those participants alive and living within 100 km distance from our study clinic were invited to a clinical follow-up in 2017-18. Eight hundred and fifteen people from the original clinical study cohort took part in a study to assess vascular health with pulse wave velocity (PWV) measurements (23). Of these 660 participants had valid data on both PWV and body composition and were included in the study. PWV was measured between the carotid and femoral artery with mechanotransducer sensors using the Complior (ALAM Medical, France) at rest and in supine position. The following equation was used: PWV = 0.8 × (direct distance between a. carotis and a. fermoralis measuring site/Δ time between upstroke

TABLE 1 | Baseline clinical characteristics of the study participants divided into four groups of carotid-femoral pulse wave velocity (CFPWV)* in the 15-year follow-up.

	I	II	III	IV	*P* for linearity
Women, *n*	69	107	112	72	
CFPWV (m/s)	<10.05	10.05–12.00	12.05–14.50	>14.50	
Age (years)	61 (3)	61 (3)	61 (3)	62 (3)	0.016
Height (cm)	163 (5)	164 (6)	163 (5)	164 (6)	0.62
Years of education	13.2 (3.6)	12.7 (3.5)	12.4 (3.4)	12.3 (3.6)	0.093
BP (mmHg)					
Systolic	134 (19)	139 (17)	144 (18)	145 (25)	<0.001
Diastolic	84 (9)	87 (9)	88 (10)	87 (11)	0.12
MAP	101 (11)	104 (11)	106 (11)	106 (14)	0.003
Pulse rate (bpm)	66 (9)	69 (10)	69 (10)	72 (11)	<0.001
P-glucose (mmol/l)					
Fasting	5.35 (0.83)	5.29 (0.47)	5.51 (1.06)	5.56 (0.96)	0.041
2-hr	6.39 (2.40)	6.61 (1.60)	7.52 (3.31)	7.65 (2.16)	<0.001
Cholesterol (mmol/l)	5.86 (1.11)	5.83 (0.96)	6.07 (1.01)	6.13 (1.24)	0.047
LDL-cholesterol (mmol/l)	3.54 (0.93)	3.48 (0.84)	3.69 (0.87)	3.69 (1.07)	0.13
HDL-cholesterol (mmol/l)	1.82 (0.44)	1.77 (0.44)	1.77 (0.47)	1.72 (0.37)	0.19
Triglycerides (mmol/l)	1.12 (0.48)	1.30 (0.60)	1.40 (0.77)	1.57 (0.91)	<0.001
BMI (kg/m^2)	25.7 (3.0)	26.8 (4.4)	27.0 (4.9)	26.4 (3.3)	0.30
LBM (kg)	47.1 (4.5)	48.0 (5.5)	47.7 (5.5)	47.1 (5.0)	0.84
Fat percentage (%)	30.2 (6.2)	32.7 (6.6)	32.6 (6.4)	33.1 (5.4)	0.014
LMI	17.7 (1.2)	17.7 (1.5)	17.9 (1.7)	17.5 (1.4)	0.83
FMI	7.9 (2.4)	9.0 (3.2)	9.0 (3.5)	8.9 (2.4)	0.073
hsCRP (mmol/l)	1.9 (1.9)	2.7 (3.0)	2.8 (3.2)	2.8 (3.4)	0.045
TNF-alfa (pg/ml)	7 (5)	19 (47)	11 (13)	18 (43)	0.27
Smoking history	25 (36)	49 (46)	40 (36)	24 (33)	0.36
METh/week	39 (26)	40 (25)	41 (28)	34 (24)	0.38
Use of lipid-lowering drugs	7 (10)	8 (7)	20 (18)	10 (14)	0.13
Use of BP-lowering drugs	18 (26)	22 (21)	27 (24)	22 (31)	0.42
Use of diabetes drugs	0 (0)	0 (0)	4 (4)	3 (4)	0.017
Men, *n*	57	88	92	63	
CFPWV (m/s)	<10.05	10.05–11.80	11.85–14.80	>14.85	
Age (years)	60 (2)	61 (2)	61 (3)	62 (3)	0.020
Height (cm)	177 (6)	177 (6)	177 (6)	178 (6)	0.59
Years of education	12.9 (3.9)	14.0 (4.0)	13.3 (3.8)	13.4 (3.7)	0.83
BP (mmHg)					
Systolic	137 (21)	141 (16)	145 (18)	145 (17)	0.003
Diastolic	87 (11)	89 (9)	89 (10)	89 (10)	0.21
MAP	103 (13)	106 (10)	108 (11)	108 (11)	0.024
Pulse rate (bpm)	66 (11)	64 (11)	66 (10)	68 (11)	0.23
P-glucose (mmol/l)					
Fasting	5.51 (0.57)	5.69 (0.61)	5.92 (1.26)	5.95 (0.79)	0.002
2-hr	7.35 (2.91)	6.79 (2.02)	7.75 (3.82)	7.57 (2.60)	0.23
Cholesterol (mmol/l)	4.84 (1.03)	4.72 (1.12)	4.66 (1.09)	4.85 (1.03)	0.95
LDL-cholesterol (mmol/l)	3.75 (0.71)	3.72 (0.80)	3.62 (0.90)	3.62 (0.86)	0.28
HDL-cholesterol (mmol/l)	1.47 (0.34)	1.45 (0.35)	1.42 (0.37)	1.45 (0.32)	0.56
Triglycerides (mmol/l)	1.14 (0.42)	1.22 (0.49)	1.22 (0.86)	1.25 (0.44)	0.34
BMI (kg/m^2)	26.3 (3.2)	25.9 (2.8)	26.6 (3.2)	27.3 (2.8)	0.027
LBM (kg)	65.4 (8.4)	63.5 (5.9)	64.8 (6.2)	66.0 (7.5)	0.38
Fat percentage (%)	20.7 (4.6)	21.0 (4.7)	21.8 (5.6)	23.3 (4.4)	0.003
LMI	20.7 (1.7)	20.4 (1.3)	20.6 (1.4)	20.9 (1.6)	0.42
FMI	5.5 (1.9)	5.6 (1.7)	5.9 (2.2)	6.4 (1.8)	0.005

(Continued)

TABLE 1 | Continued

	I	II	III	IV	*P* for linearity
hsCRP (mmol/l)	1.7 (2.4)	1.6 (2.2)	2.2 (3.0)	2.1 (2.5)	0.21
TNF-alfa (pg/ml)	14 (25)	18 (49)	24 (60)	13 (23)	0.71
Smoking history	34 (60)	67 (76)	61 (66)	47 (75)	0.28
METh/week	36 (27)	38 (27)	38 (22)	36 (22)	0.98
Use of lipid-lowering drugs	8 (14)	19 (22)	16 (17)	14 (22)	0.44
Use of BP-lowering drugs	10 (18)	29 (33)	25 (27)	17 (27)	0.48
Use of diabetes drugs	2 (4)	0 (0)	4 (4)	2 (3)	0.55

Values are given as mean and SD or proportions and percentages. Values are mean and SD or n and %. BMI, body mass index; BP, blood pressure; MAP, mean arterial blood pressure; LBM, lean body mass; LMI, lean mass index; FMI, fat mass index; CFPWV, carotid-femoral pulse wave velocity; METh, metabolic equivalent hours. [*] *CFPWV sex-specific categories corresponding to 20, 50, and 80th percentiles of total distribution.*

of pressure waves). A scaling factor of 0.8 was used because direct distance leads to overestimation of real PWV (24). Two recordings were performed in supine position.

Written informed consent was obtained from each subject participating before any procedures were carried out. The Coordinating Ethics Committee, Hospital District of Helsinki and Uusimaa approved the study.

STATISTICS

Data are presented as means with standard deviation (SD) or as counts (n) with percentages (%). Statistical significances for linearity across categories of carotid-femoral pulse wave velocity (CFPWV) and characteristics of the study participants were evaluated by using the Cochran–Armitage test for trend and analysis of variance (ANOVA) (with an appropriate contrast) (orthogonal). CFPWV values were divided into sex-specific four level categories (ordinals) corresponding to 20, 50, and 80th percentiles of the total distribution. The crude and adjusted relationship between body composition grouping and CFPWV were analyzed by using general linear models. In the case of violation of the assumptions (e.g., non-normality), a bootstrap-type test was used. Correlation coefficients were calculated by the Pearson method. The normality of variables was evaluated graphically and by using the Shapiro–Wilk W test. Stata 16.1 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

RESULTS

Table 1 shows baseline characteristics in 2001-04 of the study participants at a mean age of 61 years grouped into percentiles according to PWV measured 15 years later in 2017-18, separately for women and men. Mean age of the participants in 2017-18 was 75.8 (SD 2.7) and 75.6 (SD 2.4) years in women and men, respectively. Mean BMI at follow-up was 25.8 (SD 3.1) and 26.6 (SD 4.3) kg/m^2, respectively. Follow-up time was 14.7 (SD 0.9) years (range 12.5–16.8 years).

A univariate analysis was performed in order to identify variables with the strongest association with PWV. In women age, systolic blood pressure and mean arterial pressure, fasting and 2-h plasma glucose, total cholesterol, triglycerides, body fat percentage, pulse rate and hsCRP all measured in late midlife were associated with PWV measured 15 years later.

In men age, body mass index (BMI), systolic blood pressure, mean arterial pressure, fasting plasma glucose, body fat percentage and fat mass index in late midlife were associated with PWV measured 15 years later.

LTPA, smoking and lean body mass were not associated with PWV, nor was the inflammatory marker TNF-alfa. Neither birth weight nor BMI at 7 years of age were associated with PWV.

Adiposity-related variables showed a strong association with PWV in the univariate analyses are therefore focused upon in greater details. The relationships between LMI and FMI and the median-split categories of body composition in women and men are shown in **Figure 1**. **Figure 2** shows the crude unadjusted differences between the groups in relation to PVW. There is a statistically significant difference between the groups, with lower PWV values in groups A and B (both low FMI) compared to groups C and D (both high FMI). No sex differences were observed, nor any interactions between group and sex.

Table 2 shows linear regression models predicting PWV at follow-up based upon the four body composition categories in women and men combined and separately in women and men. Group B (high LMI and low FMI) was set as the reference group in further analyses. There were statistically significant differences between Group B (reference group) and Group C (low LMI and high FMI) and Group D (high LMI and high FMI) when women and men were combined. The trends and the beta values were similar also when women and men were analyzed separately. There was no significant difference between Group A (low LMI and low FMI) and Group B suggesting that a higher lean mass index was not associated with a better PWV in the presence of a low fat mass index. In a similar way there were no statistically significant differences between Groups C and D suggesting that a higher lean mass index was not associated with better vascular health in the presence of a high fat mass index.

DISCUSSION

In this study we assessed predictors of vascular health in old individuals from a life course perspective. Early life factors, in

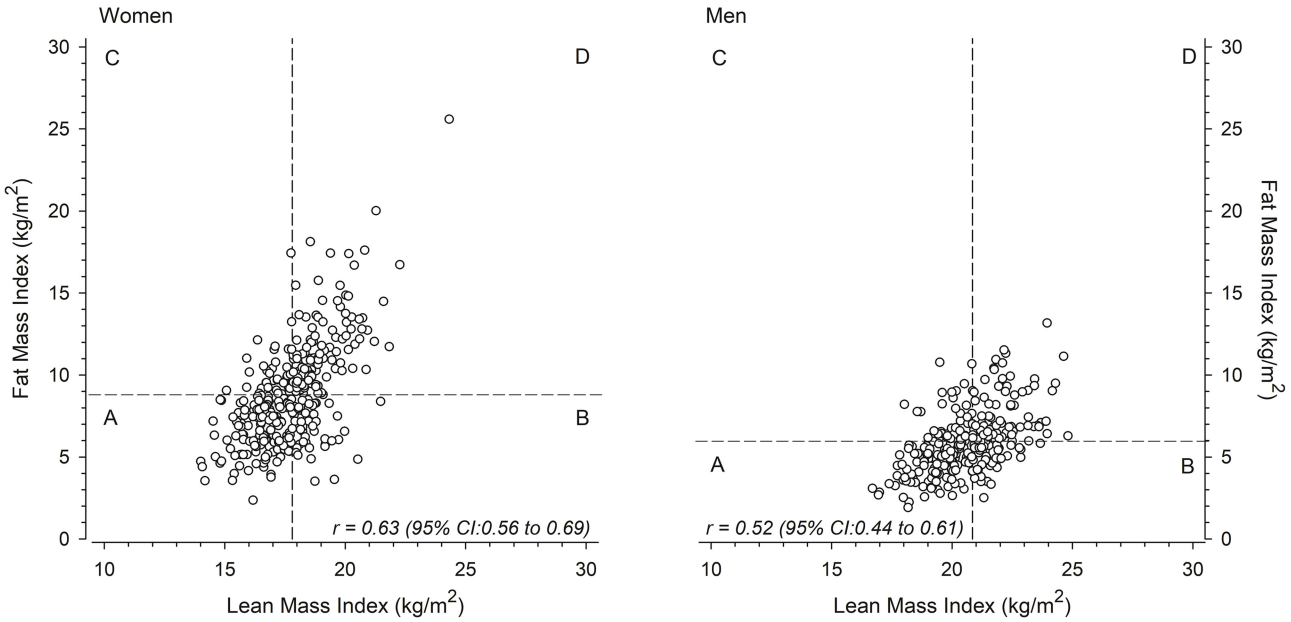

FIGURE 1 | Mean lean mass index-fat mass index scatter plots for women (left) and men (right) divided into four groups (A, B, C, D) around the sex-specific median.

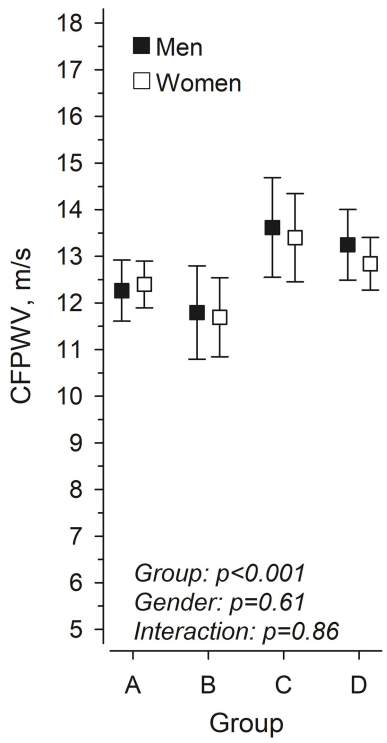

FIGURE 2 | Pulse wave velocity in women and men at mean age 76 years according to body composition at 61 years, in four groups based on lean mass index (LMI) and fat mass index (FMI). (A) low LMI and low FMI, (B) high LMI and low FMI, (C) low LMI and high FMI, and (D) high LMI and high FMI.

this case birth weight and body mass index at age 7 years, did not predict vascular health in the ninth decade of life. As expected, blood pressure in late midlife was a strong predictor of PWV in old age among men and women. Further, this study showed sex differences in predictors of PWV. In men primarily systolic blood pressure, fasting plasma glucose and adiposity related factors were associated with PWV during a 15-year follow-up. Interestingly in women the same factors seemed to be of importance but also markers of inflammation and lipid metabolism were associated with PWV measured in old age. Further a novel finding was that adiposity-related factors were strong predictors of vascular health, something not fully encapsulated in body mass index, lean body mass or body fat percentage alone. A higher fat mass index was associated with worse vascular health and was not ameliorated by a higher lean mass index. Our findings stress the importance to study fat and lean body mass simultaneously because of their close interaction with each other.

It is well known that blood pressure and arterial stiffness are closely correlated, also shown in the present study (5, 8). Besides the well-known association between blood pressure and arterial stiffness several other factors have also been proposed to be associated with arterial stiffness. These include non-hemodynamic factors like chronic low-grade inflammation, dyslipidemia and an impairment in glucose regulation (9–11). Our findings support these previous reports, but we also report sex differences in factors predicting arterial stiffness. In men systolic blood pressure, dysglycemia and a higher body fat percentage were predictors of arterial stiffness, while in

TABLE 2 | Regression models predicting pulse wave velocity 15 years later based upon body composition groups in men and women combined and separately in women and men.

	Model I β (95% CI)	Model II β (95% CI)	Model III β (95% CI)
ALL			
B	Reference	Reference	Reference
A	0.09 (−0.02–0.20), $p = 0.12$	0.08 (−0.02–0.19), $p = 0.15$	0.08 (−0.03–0.19), $p = 0.18$
C	0.18 (0.08–0.28), $p < 0.001$	0.17 (0.07–0.27), $p < 0.001$	0.15 (0.05–0.24), $p = 0.002$
D	0.18 (0.07–0.29), $p < 0.001$	0.17 (0.06–0.28), $p = 0.002$	0.12 (0.01–0.23), $p = 0.028$
Women			
B	Reference	Reference	Reference
A	0.11 (−0.04–0.27), $p = 0.15$	0.11 (−0.05–0.26), $p = 0.18$	0.11 (−0.04–0.26), $p = 0.15$
C	0.18 (0.05–0.31), $p = 0.007$	0.15 (0.02–0.28), $p = 0.021$	0.13 (0.01–0.26), $p = 0.042$
D	0.18 (0.02–0.33), $p = 0.024$	0.16 (0.01–0.31), $p = 0.038$	0.10 (−0.05–0.25), $p = 0.18$
Men			
B	Reference	Reference	Reference
A	0.06 (−0.10–0.23), $p = 0.43$	0.06 (−0.10–0.22), $p = 0.49$	0.04 (−0.12–0.21), $p = 0.60$
C	0.18 (0.04–0.32), $p = 0.012$	0.18 (0.04–0.32), $p = 0.012$	0.15 (0.01– to 0.30), $p = 0.042$
D	0.19 (0.03–0.34), $p = 0.020$	0.18 (0.02–0.34), $p = 0.023$	0.14 (−0.02–0.31), $p = 0.081$

Model I, Crude. Model II, Adjusted for age, LTPA, smoking history. Model III, Model II + further adjustment for systolic blood pressure, pulse rate, fasting blood glucose and cholesterol. β, standardized regression coefficient; A, low lean mass index and low fat mass index; B, high lean mass index and low fat mass index; C, low lean mass index and high fat mass index; D, high lean mass index and high fat mass index.

women also dyslipidemia and inflammation related factors were predicting arterial stiffness.

Since dyslipidemia, dysglycemia and a low-grade chronic inflammation are all closely associated with overweight and obesity we wanted to focus upon the importance of body composition from a holistic point, simultaneously taking lean and fat mass into account (25). It is often assumed that a high lean body mass could ameliorate the negative effects of a higher fat mass. In order to be able to study the impact of fat and lean mass on vascular health we divided the study participants into four groups according to sex-specific median values for fat and lean mass indices. The group with low fat mass index and high lean mass index was set as the reference group. This because we hypothesized that those with a higher lean body mass and lower fat mass would be those with the best vascular health. In the present study we show that a higher fat mass index was associated with worse vascular health, which was not ameliorated by a higher lean body mass. The present findings are supported by findings from the Southampton Women's survey in the UK reporting that most vascular measurements in children at 8 to 9 years of age were related to BMI, and fat and lean mass contributed differently and PWV was positively associated with fat mass index. The authors conclude that "differences in vascular structure and function in relation to BMI probably represent combinations of adverse effects of fat mass, adaptive effects of body size, and relatively protective effects of lean mass" (26).

Factors active in early life and influencing e.g., fetal growth and childhood growth have been associated with a large number of NCDs including hypertension and type 2 diabetes (14, 15). Consequently, these factors have been proposed to be associated with vascular aging. In fact, an Austrian study reported that being born preterm or SGA were associated with higher PWV in a cohort studied at a mean age of 16 years (27). However, in the present study with a follow-up into the ninth decade of life we could not find any association between early life factors and vascular health when simultaneously taking into account factors active in later life. We have previously shown that body mass index at birth is positively associated with adult lean and fat mass indices (28). Therefore, we studied whether the influence of fat mass index on vascular health was mediated by body size at birth. However, based on the mediation models (data not shown) this was not the case.

Our findings suggest that lean mass without simultaneously taking fat mass into account is not a good predictor of vascular health among older people. These findings are supported by previous studies focusing upon physical performance among elderly people (29, 30). We believe that fat mass is to a certain degree confounding lean mass because individuals with a high fat mass tend to also have higher lean mass than those with low fat mass. Therefore, it is challenging to use lean mass as a predictor of various health outcomes without simultaneously accounting for the influence of fat mass (31). Overweight and obesity are known to be associated with several adverse health outcomes including CVD and Type 2 diabetes. The underlying mechanisms could include similar factors as those identified in predicting vascular health in the present study. Obesity is associated with a systemic low-grade inflammation and insulin resistance which are also known to contribute to the development of atherosclerosis (32, 33).

Strengths of the present study include a longitudinal study design with a 15-year clinical follow-up time and a register-based follow-up throughout the life course. We made assessment of body composition instead of relying solely on BMI, which allowed us to study fat and lean mass separately

as well as simultaneously. Measurement of vascular health was based on measurements of carotid-femoral pulse wave velocity which is a valid way to measure arterial stiffness and predictive of fatal and non-fatal CVD as well as overall mortality (34, 35).

This study has some limitations. Our design was longitudinal, but we had no information on the participants PWV at baseline and therefore, we were not able to assess the change in PWV over the follow-up. Bioelectrical impedance analysis was used to determine body composition. The use of dual-energy x-ray absorptiometry would have ensured better validity but between-day precision of InBody 3.0 has been reported to be 2.7% and when compared to fat-free mass assessed by DXA scan, percent root mean square error of InBody 3.0 was 6%, which can be considered acceptable (20). As typical in studies including older adults, there was a loss of participants in the follow-up. Our participants were Europeans and the results may therefore not be generalizable to other populations.

Our findings stress the importance to study body composition and fat and lean body mass simultaneously because of their close interaction with each other also in relation to vascular health.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Coordinating Ethics Committee, Hospital District of Helsinki and Uusimaa. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JE contributed to research study design and interpretation of results and writing of manuscript. HK contributed to statistical analyses. MS, HK, and NW contributed to clinical data curation. All authors contributed to critical reading of the manuscript and interpretation of the results and approved the final submitted version.

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REFERENCES

1. Costantino S, Paneni F, Cosentino F. Ageing, metabolism and cardiovascular disease. *J Physiol.* (2016) 15:594:2061–73. doi: 10.1113/JP270538
2. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective studies collaboration. age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* (2002) 360:1903–13. doi: 10.1016/S0140-6736(02)11911-8
3. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet*. (2012) 380:2224–60. doi: 10.1016/S0140-6736(12)61766-8
4. Safar ME. Arterial stiffness as a risk factor for clinical hypertension. *Nat Rev Cardiol.* (2018) 15:97–105. doi: 10.1038/nrcardio.2017.155
5. Nilsson PM, Boutouyrie P, Laurent S. Vascular aging: A tale of EVA and ADAM in cardiovascular risk assessment and prevention. *Hypertension.* (2009) 54:3–10. doi: 10.1161/HYPERTENSIONAHA.109.129114
6. Benetos A, Salvi P, Lacolley P. Blood pressure regulation during the aging process: the end of the 'hypertension era'? *J Hypertens.* (2011) 29:646–52. doi: 10.1097/HJH.0b013e3283424be0
7. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cífková R, Cosentino F, et al. The role of vascular biomarkers for primary and secondary prevention. a position paper from the European society of cardiology working group on peripheral circulation: endorsed by the association for research into arterial structure and physiology (ARTERY) society. *Atherosclerosis.* (2015) 241:507–32. doi: 10.1016/j.atherosclerosis.2015.05.007
8. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation.* (2003) 107:2864–9. doi: 10.1161/01.CIR.0000069826.36125.B4
9. Gottsäter M, Östling G, Persson M, Engström G, Melander O, Nilsson PM. Non-hemodynamic predictors of arterial stiffness after 17 years of follow-up: the Malmö diet and cancer study. *J Hypertens.* (2015) 33:957–65. doi: 10.1097/HJH.0000000000000520
10. Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. *Hypertension.* (2017) 70:660–7. doi: 10.1161/HYPERTENSIONAHA.117.07802
11. Gottsäter M, Hindy G, Orho-Melander M, Nilsson PM, Melander O. A genetic risk score for fasting plasma glucose is independently associated with arterial stiffness: a mendelian randomization study. *J Hypertens.* (2018) 36:809–14. doi: 10.1097/HJH.0000000000001646
12. Nilsson PM. Early vascular aging (EVA): consequences and prevention. *Vasc Health Risk Manag.* (2008) 4:547–52. doi: 10.2147/VHRM.S1094
13. Olsen MH, Angell SY, Asma S, Boutouyrie P, Burger D, Chirinos JA, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet commission on hypertension. *Lancet.* (2016) 388:2665–712. doi: 10.1016/S0140-6736(16)31134-5
14. Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. *N Engl J Med.* (2005) 353:1802–9. doi: 10.1056/NEJMoa044160
15. Visentin S, Grumolato F, Nardelli GB, Di Camillo B, Grisan E, Cosmi E. Early origins of adult disease: low birth weight and vascular remodeling. *Atherosclerosis.* (2014) 237:391–9. doi: 10.1016/j.atherosclerosis.2014.09.027

16. Kunst A, Draeger B, Ziegenhorn J. UV-methods with hexokinase and glucose-6-phosphate dehydrogenase. In: Bergmeyer HU, editors. *Methods of Enzymatic Analysis*. Weinheim: Verlag Chemie (1983). p. 163–72.
17. Sobey WJ, Beer SF, Carrington CA, Clark PM, Frank BH, Gray IP, et al. Sensitive and specific two-site immunoradiometric assays for human insulin, proinsulin, 65-66 split and 32-33 split proinsulins. *Biochem J.* (1989) 260:535–41. doi: 10.1042/bj2600535
18. Lie RF, Schmitz JM, Pierre KJ, Gochman N. Cholesterol oxidase-based determination, by continuous-flow analysis of total and free cholesterol in serum. *Clin Chem.* (1976) 22:1627–30. doi: 10.1093/clinchem/22.10.1627
19. Fossati P, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. *Clin Chem.* (1982) 28:2077–80. doi: 10.1093/clinchem/28.10.2077
20. Malavolti M, Mussi C, Poli M, Fantuzzi AL, Salvioli G, Battistini N, et al. Cross-calibration of eight-polar bioelectrical impedance analysis versus dual-energy X-ray absorptiometry for the assessment of total and appendicular body composition in healthy subjects aged 21-82 years. *Ann Hum Biol.* (2003) 30:380–91. doi: 10.1080/0301446031000095211
21. Janssen I, Baumgartner RN, Ross R, Rosenberg IH, Roubenoff R. Skeletal muscle cutpoints associated with elevated physical disability risk in older men and women. *Am J Epidemiol.* (2004) 159:413–21. doi: 10.1093/aje/kwh058
22. Lakka TA, Salonen JT. Intra-person variability of various physical activity assessments in the kuopio ischaemic heart disease risk factor study. *Int J Epidemiol.* (1992) 21:467–72. doi: 10.1093/ije/21.3.467
23. Sundholm JKM, Litwin L, Rönö K, Koivusalo SB, Eriksson JG, SarkolaT. Maternal obesity and gestational diabetes: Impact on arterial wall layer thickness and stiffness in early childhood - RADIEL study six-year follow-up. *Atherosclerosis.* (2019) 284:237–44. doi: 10.1016/j.atherosclerosis.2019.01.037
24. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens.* (2012) 30:445–8 doi: 10.1097/HJH.0b013e32834fa8b0
25. Chait A, den Hartigh LJ. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. *Front Cardiovasc Med*. (2020) 7:22. doi: 10.3389/fcvm.2020.00022
26. Sletner L, Mahon P, Crozier SR, Inskip HM, Godfrey KM, Chiesa S, et al. Childhood fat and lean mass: differing relations to vascular structure and function at age 8-9-years. *Arterioscler Thromb Vasc Biol.* (2018) 38:2528–37. doi: 10.1161/ATVBAHA.118.311455
27. Stock K, Schmid A, Griesmaier E, Gande N, Hochmayr C, Knoflach M, et al. The impact of being born preterm or small for gestational age on early vascular aging in adolescents. *J Pediatr.* (2018) 201:49–54. doi: 10.1016/j.jpeds.2018.05.056
28. Ylihärsilä H, Kajantie E, Osmond C, Forsén T, Barker DJ, Eriksson JG. Body mass index during childhood and adult body composition in men and women aged 56-70 y. *Am J Clin Nutr.* (2008) 87:1769–75. doi: 10.1093/ajcn/87.6.1769
29. Bouchard DR, Beliaeff S, Dionne IJ, Brochu M. Fat mass but not fat-free mass is related to physical capacity in well-functioning older individuals: nutrition as a determinant of successful aging (NuAge)–the quebec longitudinal study. *J Gerontol A Biol Sci Med Sci.* (2007) 62:1382–8. doi: 10.1093/gerona/62.12.1382
30. Matta J, Mayo N, Dionne IJ, Gaudreau P, Fülöp T, Tessier D, et al. Interrelated factors favoring physical performance and activity in older adults from the NuAge cohort study. *Exp Gerontol.* (2014) 55:37–43. doi: 10.1016/j.exger.2014.03.013
31. Mikkola TM, Kautiainen H, von Bonsdorff MB, Salonen MK, Wasenius N, Kajantie E, et al. Body composition and changes in health-related quality of life in older age: a 10-year follow-up of the helsinki birth cohort study. *Qual Life Res.* (2020) 29:2039–50. doi: 10.1007/s11136-020-02453-1
32. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. *Nat Rev Endocrinol.* (2017) 13:633–43. doi: 10.1038/nrendo.2017.90
33. Ye J. Mechanisms of insulin resistance in obesity. *Front Med.* (2013) 7:14–24. doi: 10.1007/s11684-013-0262-6
34. Zhong Q, Hu MJ, Cui YJ, Liang L, Zhou MM, Yang YW, et al. Carotid-femoral pulse wave velocity in the prediction of cardiovascular events and mortality: an updated systematic review and meta-analysis. *Angiology*. (2018) 69:617–29. doi: 10.1177/0003319717742544
35. Laurent S, Boutouyrie P, Cunha PG, Lacolley P, Nilsson PM. Concept of extremes in vascular aging. *Hypertension.* (2019) 74:218–28. doi: 10.1161/HYPERTENSIONAHA.119.12655

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The Effect of Periodontal Treatment on the Reactive Hyperemia Index. A 1-Year Follow-Up Pilot Study

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Background: Periodontitis is a chronic multifactorial inflammatory disease of the supportive tissues of the teeth. In more recent years, remarkable epidemiological and pathophysiological associations between periodontitis and cardiovascular disease (CVD) have been presented. Whether or not treatment of periodontitis is valuable for primary or secondary prevention of cardiovascular disease, has not yet been fully established. In this practice-based pilot study we focused on primary prevention of cardiovascular disease, by investigating the effect of periodontal treatment on the earliest detectable stage of CVD; endothelial dysfunction.

Methods: Otherwise healthy periodontitis and non-periodontitis participants 45–70 years of age were included in the study. One year after completing periodontal (non-surgical and surgical) treatment of the periodontitis patients and 1 year after inclusion of the controls, all baseline measurements were repeated. Full-mouth examinations were performed by a periodontist to determine their Periodontal Inflamed Surface Area (PISA) score and other dental parameters. To assess the cardiovascular conditions, endothelial function through the reactive hyperemia index (RHI) assessed by the EndoPAT^{TM}, and several physical and biochemical parameters were measured.

Results: 21 patients with diagnosed, untreated periodontitis and 21 participants without periodontitis were included in this follow-up study. After periodontal therapy in the periodontitis patients, the PISA reduced significantly. The RHI did not show a significant improvement after treatment of the periodontitis patients (-0.1 ± 0.8, $p = 0.524$). Similarly, other secondary cardiovascular outcome measurements, hsCRP, total cholesterol, HDL cholesterol, triglycerides, HbA1c, and systolic blood pressure did not improve significantly after periodontal treatment. Controls did not show any significant changes in the RHI, in other CVD parameters and in the PISA after 1-year follow-up.

Conclusion: In this practice-based pilot study, periodontal treatment did not improve the endothelial function in otherwise healthy adults with periodontitis. Future studies

are needed to be of larger size and could focus on periodontitis patients with co-morbidities to investigate whether periodontal treatment has secondary preventive effect on endothelial function and other CVD parameters.

Clinical Trial Registration: [www.ClinicalTrials.gov], identifier [ISRCTN55656827].

Keywords: periodontitis, dental health, cardiovascular disease, endothelial dysfunction, EndoPAT—pulse wave velocity, periodontal treatment, cardiovascular prevention

INTRODUCTION

Periodontitis is a chronic multifactorial inflammatory disease of the supportive tissues of the teeth (1). It is the most common oral disease, and the sixth most common human disease, affecting 30–50% and approximately 10% of the global adult population in its most severe form (2, 3). Periodontitis starts with localized inflammation of the gingiva that is initiated by bacteria in the dental plaque. As a result of inflammation, the tissues surrounding the tooth are infiltrated by neutrophils, macrophages and activated lymphocytes. The subsequent state is periodontitis, with progressive loss of alveolar bone and tooth attachment and ultimately tooth loss. Bacteria and cytokines from the periodontal inflammatory lesions are dispersed throughout the body and acute phase reactants [C-reactive protein (CRP), fibrinogen] are produced (4). Although bacteria are necessary for periodontitis to take place, a susceptible host is also needed. Consequently, several risk factors for periodontitis have been established, including smoking, diabetes mellitus, socio-economic position, psychosocial factors, and genetic predispositions (5). Interestingly, some genetic risk variants for cardiovascular diseases show overlap with identified genetic variants of periodontitis (6).

The first study that found positive epidemiological evidence for the association between periodontitis and atherosclerosis was in 1989 by Mattila et al. (7). In more recent years, remarkable pathological and epidemiological associations between these two diseases have been presented, though without final conclusions (8–11). The explanation of the association between periodontitis and CVD generally fall into two categories: (a) microbial mechanisms, which through vascular invasion may locally affect the development of the atheroma lesions; and (b) inflammatory and immunologic mechanisms that directly influence the pathobiology of the atheroma lesion (12). Most pathophysiological links between these two diseases are based on the possible common inflammatory background between periodontitis and CVD (13, 14).

The possible link between CVD and periodontitis is of great public health importance because of the high prevalence of both diseases and the potential impact on public health if risk modification or therapeutic opportunities could be identified. Whether or not treatment of periodontitis is valuable for primary or secondary prevention of cardiovascular disease, have not yet been fully established. The majority of the intervention trials, aimed to study this purpose, has examined the effect of periodontal treatment on markers of systemic inflammation, focusing primarily on the role of common inflammatory pathways (15).

Endothelial dysfunction has been recognized as the critical junction between CVD risk factors and clinical disease, and is the earliest detectable stage of CVD (16). Tonetti et al. sought to assess the effect on intensive periodontal treatment on endothelial function measured by Flow-Mediated dilatation (FMD) of the brachial artery. The FMD was greater, and thus improved, in the intensive-treatment group than in the control-treatment group 60 days after therapy (absolute difference 0.9%; 95% CI, 0.1–1.7; $P = 0.02$) and 180 days after therapy (difference, 2.0%; 95% CI, 1.2–2.8; $P < 0.001$). The degree of improvement was associated with improvement in measures of periodontal disease (17). More recent studies did not find clinical evidence for a positive effect on endothelial function after periodontal therapy, and therefore a possible cause-to-effect relationship remains controversial (18, 19).

In this pilot study we focused on possible primary prevention of CVD in a practice-based setting. Accordingly, the primary aim of this study was to determine the effect of periodontal treatment on endothelial function as assessed by the reactive hyperemia index (RHI) in otherwise healthy patients with periodontitis. Secondary aims were to investigate the effect of periodontal treatment on other parameters, including high sensitive C-reactive Protein (hsCRP), (systolic) blood pressure, cholesterol (HDL, LDL, and total), triglycerides and glycosylated hemoglobin (HbA1c).

MATERIALS AND METHODS

Study Design

This dental-practice based clinical intervention study was a 1-year follow-up, of our prospective cross-sectional study as published previously (20). The study was approved by the Medical Ethics Committee, Isala Academy, Zwolle, the Netherlands (NL43083.075.13) and has been registered in the ISRCTN trial registry with study ID ISRCTN55656827. All participants provided written consent for participation at baseline and at the time of follow-up. This study was performed in accordance with the Declaration of Helsinki guidelines for human research, 1964, and amended in 2013 (64th World Medical Association General Assembly, Fortaleza, Brazil). Data were collected, analyzed and interpreted by the authors.

Participants

We included periodontitis patients and control subjects, between 45 and 69 years of age, without known systemic diseases and with at least 10 teeth. At baseline, all subjects were included in our previously published prospective cross-sectional study (20). The

periodontitis patients received periodontal treatment after the baseline measurements. One year after completing periodontal treatment, these patients were recruited for participation in this follow-up study. The control group was also recruited for participation in this follow-up study, 1 year after the baseline measurements. All mentioned measurements below were performed at baseline and after 1 year of follow-up.

Measures of Dental Health

All participants underwent a full-mouth periodontal examination performed by two trained periodontists at the Practice for Periodontology Zwolle (PPZ). Inter observer agreement of these two periodontists was examined by comparing individual measurements of 10 random participants. The statistically determined intraclass correlation coefficient of 0.81 represented an excellent reliability according to Fleiss (21). Periodontitis was initially diagnosed and staged according to the consensus report of the World Workshop on the classification of periodontal and peri-implant diseases and conditions (22). The Periodontal Inflamed Surface Area (PISA) score was applied. This scoring tool calculated the amount of inflamed periodontal tissue in square millimeters and quantified the total inflammatory burden resulting from periodontitis (23). The PISA score was calculated after extensive periodontal examination, including periodontal probing pocket depth (PD), plaque score and bleeding on probing (BOP). All measurements were performed on all teeth, on six sites per tooth using a manual periodontal standard probe. Rather than presenting mean pocket probing results and bleeding on probing scores, we regarded it essential for the current study to use the PISA score because it is the best integrative and overall score for quantifying the inflammatory burden posed by periodontitis. Moreover, it can be easily and broadly interpreted and applied by clinicians as well as patients.

Measures of General Health

All participants completed questionnaires to collect data on their medical history, perceived health, parental history, lifestyle, socio-economic status, and oral hygiene.

At least 2 weeks after the periodontal examination, the participants were examined by a trained nurse at the Department of Cardiology of the Isala hospital, Zwolle. Physical examinations were performed, and blood pressure (BP), heart rate (HR), body mass index (BMI), waist-to-hip ratio (WHR), and electrocardiogram measurements (ECG) were obtained. Venous blood was collected to determine levels of high sensitive C-reactive Protein [hsCRP (mg/L)], total cholesterol (mmol/L), HDL-cholesterol (mmol/L), LDL-cholesterol (mmol/L), triglycerides (mmol/L), estimated Glomerular Filtration Rate (eGFR ml/min/1.73 m^2) and glycosylated hemoglobin [HbA1c (%)].

Measures of Cardiovascular Condition

As primary outcome we performed an endothelial function assessment by the EndoPAT^{TM} (Itmar Medical, Israel), based on non-invasive Peripheral Arterial Tone (PAT) signal technology measuring endothelium-mediated changes in vascular tone using bio-sensors placed on the fingertips. This endothelial function assessment is validated vs. the invasive gold standard (intracoronary infusion of acetylcholine). It is a short and operator independent endothelial dysfunction test, that is easy practice or office based performable (24). The final result of the EndoPAT^{TM} is the Reactive Hyperemia Index (RHI), which is a ratio of the post-to-pre occlusion PAT amplitude of the tested arm, divided by the post- to pre- occlusion ratio of the control arm. A RHI score of 1.67 and below correlates to endothelial dysfunction (25, 26).

Periodontal Treatment

All periodontitis patients received periodontal treatment, including training in oral hygiene, and counseling on control of risk factors (e.g., smoking, alcohol usage and overweight/obesity). Supra- and subgingival bacterial plaque and calculus was removed by comprehensive, meticulous periodontal scaling and root planning performed by an experienced dental hygienist in the specialized periodontal practice using local anesthesia. When the non-surgical treatment had insufficient effect on the pocket depth and bleeding score, or when residual pockets deeper than 5 mm were still present, surgical treatment by a periodontist was incorporated. Surgical treatment consisted of procedures to reduce or eliminate periodontal pockets and create an acceptable gingival contour that facilitates oral hygiene and periodontal maintenance. Selective teeth that could not be saved were extracted. Finishing procedures included post-treatment evaluation with review and reinforcement of daily oral hygiene when appropriate. Thereafter, patients were enrolled in a periodontal maintenance program of 3–4 times a year performed by the dental hygienist of the specialized periodontal practice.

Controls

The controls without periodontitis were educated in oral hygiene and were counseled on control of risk factors for

TABLE 1 | Characteristics of the study population.

	Total	Periodontitis	Control
	n = 42	*n* = 21	*n* = 21
Age	54.1 ± 6.3	55.4 ± 7.1	52.9 ± 5.4
Gender			
Male	17 (40.5)	10 (47.6)	7 (33.3)
Female	25 (59.5)	11 (52.4)	14 (66.7)
BMI	24.3 ± 3.2	25.4 ± 3.8	23.2 ± 1.8
Waist to hip ratio	0.9 (0.8–0.9)	0.9 (0.2–1.0)	0.9 (0.8–0.9)
Smoking	4 (9.5)	4 (19.0)	0 (0.0)
Alcohol servings/week*	4.0 ± 4.1	2.2 ± 2.7	5.4 ± 4.5
Education			
Primary	3 (7.1)	2 (9.5)	1 (4.8)
Secondary	18 (42.9)	8 (38.1)	10 (47.6)
Tertiary	21 (50.0)	11 (52.4)	10 (47.6)
Positive family history for CVD	17 (40.5)	7 (33.3)	10 (47.6)

**Alcohol servings/week: 8 missing. Values represent mean ± standard deviation, number of subjects (%), or median (Q1–Q3). There were no statistically significant differences between the periodontitis and the controls.*

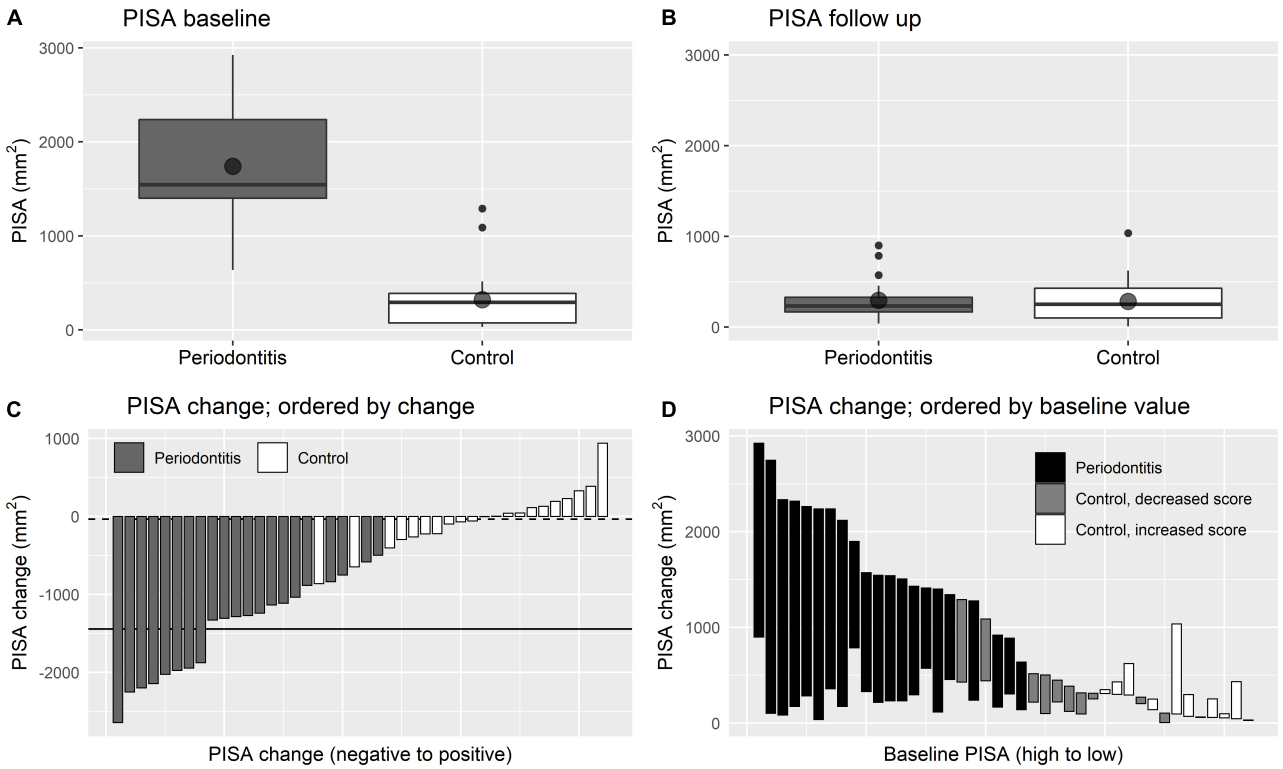

FIGURE 1 | Changes in PISA score. **(A,B)** Are boxplots showing the distribution of PISA score at baseline and at follow up, respectively. Point shapes indicate sample means. **(C,D)** Are waterfall plots showing the change of PISA score while ordered by the extent of PISA change and ordered by baseline PISA score, respectively. In **(C)** the solid line indicates mean PISA change for periodontitis patients and the dashed line indicates mean change for controls.

periodontitis (e.g., stress and smoking). The dental health was maintained by their own dental hygienist 1–2 times a year.

TABLE 2 | Changes in dental health.

	Baseline	Follow-up	Change	*p*-value
All				
PISA score	1030.1 ± 868.0	290.0 ± 226.0	−740.2 ± 872.2	<0.001
Teeth	28.0 (26.0–28.0)	27.0 (25.0–28.0)	0.0 (−0.3 to 0.0)	0.005
Plaque score	40.6 ± 28.1	15.1 ± 9.9	−25.5 ± 30.1	<0.001
Bleeding score	43.8 ± 31.1	15.1 ± 9.8	−28.7 ± 33.2	<0.001
Periodontitis				
PISA score	1740.7 ± 612.5	295.9 ± 221.6	−1444.8 ± 612.4	<0.001
Teeth	28.0 (24.0–28.5)	26.0 (22.0–28.0)	0.0 (−2.5 to 0.0)	0.017
Plaque score	60.6 ± 19.4	12.8 ± 7.2	−47.8 ± 19.1	<0.001
Bleeding score	67.6 ± 18.4	13.2 ± 9.0	−54.4 ± 19.9	<0.001
Control				
PISA score	319.6 ± 330.3	284.0 ± 235.7	−35.6 ± 376.6	0.670
Teeth	28.0 (26.0–28.0)	28.0 (26.0–28.0)	0.0 (0.0–0.0)	0.102
Plaque score	20.7 ± 20.0	17.4 ± 11.7	−3.3 ± 21.2	0.485
Bleeding score	20.0 ± 21.2	17.1 ± 10.3	−2.9 ± 21.6	0.544

Values represent mean ± standard deviation, or median (Q1–Q3). Group differences were tested by a paired t-test or Wilcoxon signed rank test.

Statistics

Descriptive statistics [mean ± standard deviations (SD), Median (Q1–Q3) or numbers (%) of subjects] were used to present patient characteristics and results, depending on the distribution. Between group differences were tested by the Fisher's exact test or Chi-square test for categorical variables and independent *t*-tests for quantitative variables. Change scores were calculated by subtracting old values from new values. Hence a negative value indicates a lower follow up value, i.e., decrease. Within group differences/changes were tested using the McNemar test for categorical variables and the paired *t*-test or the Wilcoxon signed ranks test for quantitative variables, depending on the distribution of change. The significance level was set at a *p*-value of 0.05. All analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, United States). Figures were created using RStudio version 1.4.1717 (R version 4.0.3).

RESULTS

Inclusion

At baseline, 27 patients with untreated periodontitis and 27 controls without periodontitis were included. Of these 54 participants, 12 subjects (6 periodontitis patients and 6 control subjects) were lost to follow-up, because of refusing to participate. Thus 21 periodontitis patients and 21 non-periodontitis controls

TABLE 3 | Changes in cardiovascular conditions.

	Baseline	Follow-up	Change	*p*-value
All				
Endothelial function (RHI)	2.5 ± 0.7	2.4 ± 0.9	−0.1 ± 0.8	0.424
hsCRP	1.1 (0.6–2.3)	0.75 (0.0–1.9)	−0.3 (−0.6 to 0.3)	0.123
Total cholesterol	5.4 ± 0.8	5.3 ± 0.8	−0.1 ± 0.7	0.350
HDL cholesterol	1.7 ± 0.5	1.7 ± 0.4	0.0 ± 0.2	0.705
LDL cholesterol	3.3 ± 0.9	3.2 ± 0.8	−0.1 ± 0.6	0.173
Triglycerides	1.0 (0.7–1.2)	0.9 (0.7–1.1)	0.0 (−0.2 to 0.1)	0.634
HbA1c	36.1 ± 2.7	36.3 ± 2.6	0.3 ± 1.3	0.195
Systolic BP	126.3 ± 15.2	123.2 ± 11.3	−3.1 ± 13.4	0.113
Periodontitis				
Endothelial function (RHI)	2.5 ± 0.6	2.4 ± 1.0	−0.1 ± 0.8	0.524
hsCRP	1.2 (0.6–2.8)	1.0 (0.0–2.5)	−0.3 (−0.7 to 0.5)	0.339
Total cholesterol	5.2 ± 0.8	5.1 ± 0.7	−0.1 ± 0.4	0.185
HDL cholesterol	1.6 ± 0.5	1.6 ± 0.4	−0.0 ± 0.2	0.787
LDL cholesterol	3.1 ± 0.8	3.0 ± 0.7	−0.2 ± 0.4	0.101
Triglycerides	1.0 (0.6–1.4)	0.9 (0.8–1.4)	0.0 (−0.2 to 0.4)	0.490
HbA1c	36.9 ± 2.6	36.8 ± 2.5	−0.0 ± 1.2	0.858
Systolic BP	129.3 ± 16.6	125.4 ± 11.0	−3.9 ± 13.8	0.208
Control				
Endothelial function (RHI)	2.5 ± 0.8	2.4 ± 0.7	−0.1 ± 0.8	0.623
hsCRP	0.9 (0.6–1.7)	0.6 (0.0–1.4)	−0.2 (−0.4 to 0.1)	0.169
Total cholesterol	5.7 ± 0.8	5.6 ± 0.9	−0.1 ± 0.9	0.693
HDL cholesterol	1.7 ± 0.4	1.8 ± 0.4	0.0 ± 0.2	0.438
LDL cholesterol	3.5 ± 0.9	3.4 ± 0.9	−0.1 ± 0.7	0.578
Triglycerides	0.9 (0.7–1.2)	0.8 (0.7–1.1)	−0.1 (−0.2 to 0.0)	0.099
HbA1c	35.3 ± 2.6	35.9 ± 2.6	0.6 ± 1.3	0.062
Systolic BP	123.3 ± 13.4	121.1 ± 11.4	−2.3 ± 11.1	0.357

RHI missing at follow-up: 8 (6 periodontitis and 2 control). Values represent mean ± standard deviation, or median (Q1–Q3). Group differences were tested by a paired t-test or Wilcoxon signed rank test.

were included in this follow-up study. There was no significant difference at baseline between the age, gender, BMI, PISA score, and endothelial function between the total 54 participants and the 42 participants included for follow-up.

Participants

The study population consisted of 40.5% ($n = 17$) male and 59.5% ($n = 25$) female participants. The mean age was 54.1 ± 6.3 years. All participants were Caucasian. Fifty percent ($n = 21$) of these participants were tertiary educated, and 42.9% ($n = 18$) were secondary educated. Forty-one percent of the participants had a positive family history for CVD. The characteristics of these 42 participants are presented in **Table 1**. There was no significant change in periodontitis risk factors between baseline and follow-up (BMI $p = 0.791$, waist to hip ratio $p = 0.259$, smoking $p = 1.000$, alcohol intake $p = 0.798$).

Dental Health

Figure 1 and **Table 2** show baseline values, 1-year follow-up values and changes in dental health. The inflammatory burden of the periodontitis patients improved significantly after periodontal treatment: 1 year after completing the periodontal treatment, the mean decrease of the PISA score was −1444.8 mm^2 ± 612.4 ($p < 0.001$). In the control group, mean decrease of the PISA score was −35.6 mm^2 ($p = 0.670$). **Figure 1C** visualizes an association of baseline PISA score with PISA change.

The mean decrease of the plaque score was −47.8% ± 19.1 and the mean decrease of the bleeding score was −54.4% ± 19.9. Due to selective tooth extraction, as part of the periodontal treatment, the number of teeth also significantly decreased ($p = 0.017$). The dental health of the control group did not significantly change during the follow-up period.

Cardiovascular Health

Data on cardiovascular conditions at baseline and after the follow-up period of the periodontitis and controls are shown in **Table 3**. Endothelial function, the primary outcome, expressed as RHI, did not show a significant improvement after treatment of the periodontitis patients (RHI −0.1 ± 0.8, $p = 0.524$). **Figures 2A,B** illustrates the minor changes in endothelial function, expressed by the RHI, observed from baseline to 1 year after completing periodontal therapy. In **Figures 2C,D** we present waterfall plots to demonstrate the change of the endothelial function ordered by the extent of the RHI change and ordered by the RHI at baseline. Due to technical problems with the EndoPAT^{TM}, the RHI of 8 subjects (6 periodontitis

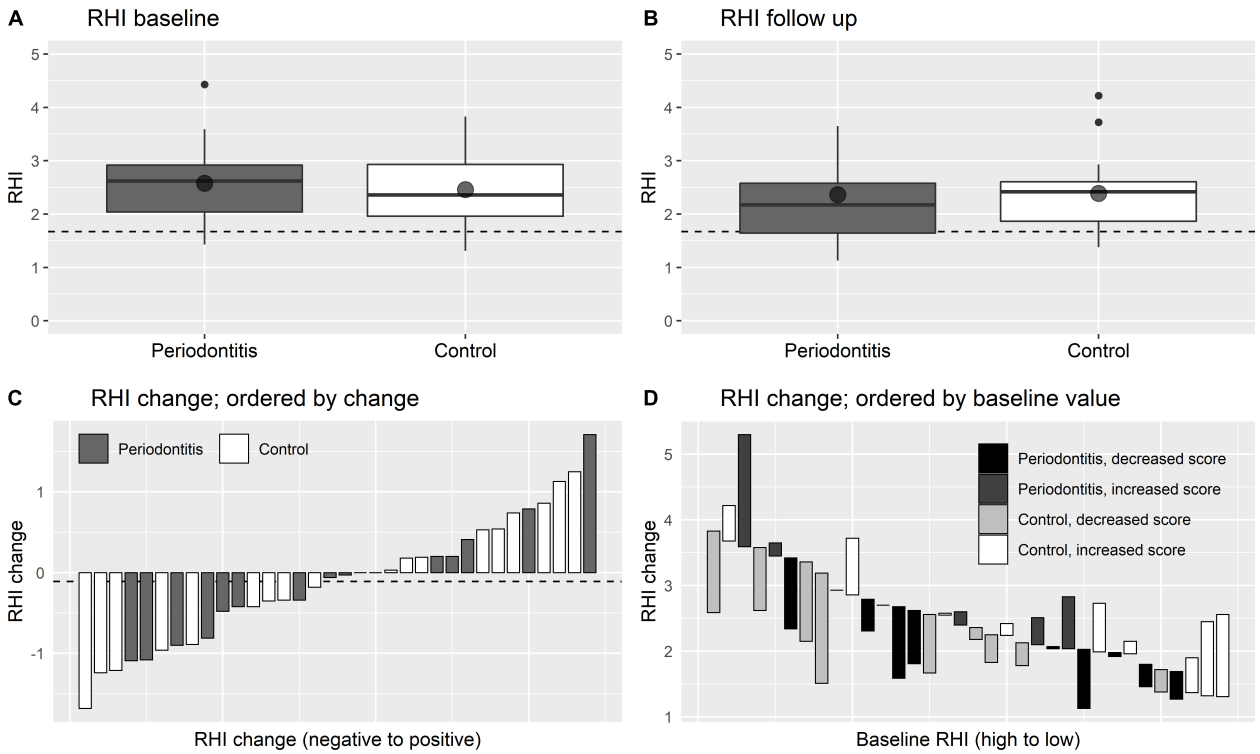

FIGURE 2 | Changes in endothelial function (RHI). **(A,B)** Are boxplots showing the distribution of RHI at baseline and at follow up, respectively Point shapes indicate sample means. The dashed line presents RHI cut-off score of 1.67 that correlates to endothelial dysfunction. **(C,D)** Are waterfall plots showing the change of RHI while ordered by the extent of RHI change and ordered by baseline RHI, respectively. In **(C)** the dotted line indicates mean RHI change for periodontitis patients.

TABLE 4 | Differences in cardiovascular change between periodontitis patients and controls.

	Change periodontitis	Change control	Difference	*p*-value
All				
Endothelial function (RHI)	−0.1 ± 0.8	−0.1 ± 0.8	−0.1 (NA)	0.960
hsCRP	−0.3 (−0.7 to 0.5)	−0.2 (−0.4 to 0.1)	−0.1 (NA)	0.880
Total cholesterol	−0.1 ± 0.4	−0.1 ± 0.9	−0.0 (−0.5 to 0.4)	0.839
HDL cholesterol	−0.0 ± 0.2	0.0 ± 0.2	−0.1 (−0.2 to 0.1)	0.452
LDL cholesterol	−0.2 ± 0.4	−0.1 ± 0.7	−0.1 (−0.4 to 0.3)	0.689
Triglycerides	0.0 (−0.2 to 0.4)	−0.1 (−0.2 to 0.0)	−0.1 (NA)	0.232
HbA1c	−0.0 ± 1.2	0.6 ± 1.3	−0.6 (−1.4 to 0.2)	0.121
Systolic BP	−3.9 ± 13.8	−2.3 ± 11.1	−1.6 (−9.4 to 6.2)	0.677

Values represent mean ± standard deviation, or median (Q1–Q3). Group differences were tested by an independent t-test or Mann-Whitney U-test.

patients and 2 control subjects) was unknown. Similarly, all other secondary cardiovascular outcome measurements, hsCRP, total cholesterol, HDL cholesterol, triglycerides, HbA1c, and systolic blood pressure did not significantly improve after periodontal therapy.

After the 1-year follow-up period of the controls, none of the cardiovascular variables significantly changed.

Association Between Periodontal Improvement and Cardiovascular Health

Table 4 emphasizes that there were no significant differences in change of the cardiovascular variables after treatment of the periodontitis patients compared to the control group. **Figure 3** illustrates that there was no significant association between the decrease of the PISA score, periodontal improvement, and the endothelial function, expressed in RHI.

DISCUSSION

The current clinical intervention follow-up study aimed to investigate the effect of periodontal treatment on endothelial function, in otherwise healthy adults. The clinical results showed that significant decrease of the inflammatory burden after periodontal treatment did not improve the endothelial function,

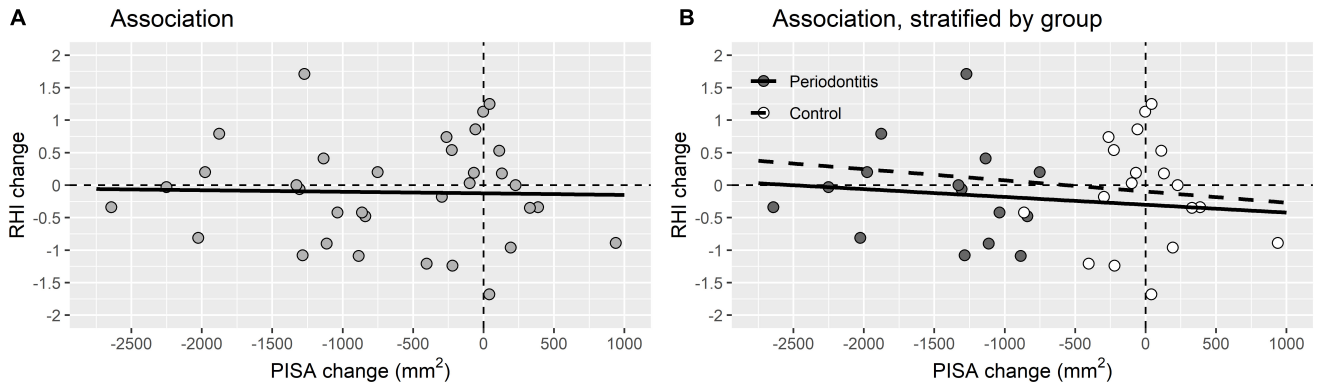

FIGURE 3 | Association between periodontal improvement and endothelial function. **(A)** Association between PISA change and RHI change for the total study population (R^2 linear = 6.549E-4). **(B)** Association between PISA change and RHI change stratified by periodontitis patients (R^2 linear = 0.008) and control group (R^2 linear = 0.006) **(B)**.

as measured by the RHI with the EndoPAT^{TM}, or other cardiovascular parameters after 1-year follow-up.

Positive effects of periodontal treatment on endothelial function and other cardiovascular parameters that were demonstrated in previous intervention studies, focused more on patients already suffering from CVD. Correspondingly, levels of hsCRP of the included untreated periodontitis patients were somewhat lower than previously studies reported (27, 28). In this study we focused on otherwise healthy adults, without a history of CVD. Only 5 participants suffered from endothelial dysfunction at baseline. The mean baseline endothelial function, expressed in RHI, in our study population was higher than the RHI cut-off score of 1.67 that correlates to endothelial dysfunction. Probably, because the RHI at baseline was well within normal limits, a positive effect of periodontal treatment could not be expected. Besides, we used the EndoPAT^{TM} device for measuring endothelial function. This device might not be sensitive enough to detect small differences in endothelial function.

Some systematic reviews support the positive effects of periodontal treatment on CVD risk parameters, especially 6 months after the treatment. This effect extinguished after a follow-up time of 12 months (29). We have chosen consciously for a follow-up period of 1 year, because intervention studies with a 1-year follow-up time are scarce. Furthermore, an even more extended follow-up time, with cardiovascular events as hard endpoint, is needed to confirm or reject the causal relation between periodontitis and CVD. However, these kind of studies are challenging, due to methodological, financial and most important, ethical considerations (30).

Despite numerous publications investigating the association between periodontitis and CVD, there is still no consensus whether periodontitis plays a pathophysiological role in CVD (8). Ever since the publication of the first studies indicating an association, this topic received substantial professional and public interest. Consequently, this subject generated debates between researchers, caused wide-scale media coverage and prompted involved professional organizations to issue official statements. It remains essential to understand the quality of the underlying literature to be able to perform a critical appraisal. Regrettably, we must be aware of poor reporting and misinforming, concerning the clinical trials evaluating the effect of periodontal treatment on CVD (31).

A limitation of this study is the relatively small study group. Although the effect of periodontal treatment on endothelial function in periodontitis patients has been suggested in the literature, this has rarely been investigated in exclusively, otherwise healthy periodontitis patients. We are the first study that investigated asymptomatic healthy periodontitis patients from the dental practice, using the endothelial function assessment by the EndoPAT. We focused on this specific patient population, to investigate whether the apparently otherwise healthy periodontitis patients in the dental practice are possibly at risk for a CVD event in the future and whether periodontal treatment can reduce such risk for a CVD event. Due to this explorative nature of the study, a proper power-analysis was not applicable. In retrospect, enlargement of the study population would have strengthened the current study. Besides, we included patients who visited a specialized dental clinic for periodontology. It must be taken into account that these patients may not fully representative of the general population.

With the current pilot study, we have attempted to add further knowledge to the once-wide gap between dentistry and general medicine, aimed to identify patients at risk for CVD in an earlier stage. In conclusion, periodontitis and CVD are complex inflammatory diseases with shared modifiable and non-modifiable risk factors. Periodontal treatment as primary or secondary prevention of CVD could be focused on direct control of periodontitis and changing modifiable risk factors of both. In this study, we did not find an improvement of endothelial function or other cardiovascular parameters after highly effective periodontal treatment including non-surgical and surgical therapy. Future studies are needed to be a larger size and could focus on periodontitis patients with co-morbidities, whether periodontal treatment has secondary preventive effect on endothelial function and other CVD parameters.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee, Isala Academy, Zwolle, the Netherlands (NL43083.075.13). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HD, EV, AH, JL, and BL contributed to conception and design of the study. EV and HD included the patients and arranged the clinical measurements. HD organized the database and wrote the first draft of the manuscript. HD and ME performed the statistical analysis. HD, ME, AH, JL, and BL wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCES

1. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet.* (2005) 366:1809–20.
2. Papapanou PN, Susin C. Periodontitis epidemiology: is periodontitis under-recognized, over-diagnosed, or both? *Periodontol 2000.* (2017) 75:45–51. doi: 10.1111/prd.12200
3. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. *J Dent Res.* (2014) 93:1045–53. doi: 10.1177/0022034514552491
4. Loos BG. Systemic markers of inflammation in periodontitis. *J Periodontol.* (2005) 76:2106–15. doi: 10.1902/jop.2005.76.11-s.2106
5. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nat Rev Dis Prim.* (2017) 3:1–14.
6. Aarabi G, Zeller T, Seedorf H, Reissmann DR, Heydecke G, Schaefer AS, et al. Genetic susceptibility contributing to periodontal and cardiovascular disease. *J Dent Res.* (2017) 96:610–7. doi: 10.1177/0022034517699786
7. Mattila KJ, Nieminen MS, Valtonen VV, Rasi VP, Kesäniemi YA, Syrjälä SL, et al. Association between dental health and acute myocardial infarction. *BMJ.* (1989) 298:779–81. doi: 10.1136/bmj.298.6676.779
8. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, et al. Periodontitis and cardiovascular diseases: consensus report. *J Clin Periodontol.* (2020) 47:268–88.
9. Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, et al. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American heart association. *Circulation.* (2012) 125:2520–44. doi: 10.1161/CIR.0b013e31825719f3
10. Pietropaoli D, Del Pinto R, Ferri C, Wright JT Jr, Giannoni M, Ortu E, et al. Poor oral health and blood pressure control among US hypertensive adults: results from the national health and nutrition examination survey 2009 to 2014. *Hypertension.* (2018) 72:1365–73. doi: 10.1161/hypertensionaha.118.11528
11. Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, et al. Periodontitis is associated with hypertension: a systematic review and meta-analysis. *Cardiovasc Res.* (2020) 116:28–39. doi: 10.1093/cvr/cvz201
12. Schenkein HA, Papapanou PN, Genco R, Sanz M. Mechanisms underlying the association between periodontitis and atherosclerotic disease. *Periodontol 2000.* (2020) 83:90–106. doi: 10.1111/prd.12304
13. Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. *J Clin Periodontol.* (2013) 40(Suppl. 1): S51–69.
14. Martínez-García M, Hernández-Lemus E. Periodontal inflammation and systemic diseases: an overview. *Front Physiol.* (2021) 12:709438. doi: 10.3389/fphys.2021.709438
15. Liu W, Cao Y, Dong L, Zhu Y, Wu Y, Lv Z, et al. Cardiovascular disease in people with periodontitis (review). *Cochrane Database Syst Rev.* (2019) 9:CD009197.
16. Gimbrone MAJ, Garcia-Cardena G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ Res.* (2016) 118:620–36. doi: 10.1161/CIRCRESAHA.115.306301
17. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, et al. Treatment of periodontitis and endothelial function. *N Engl J Med.* (2007) 356:911–20.
18. Ronsoni RM, Saffi MAL, Gonçalves MVM, Nakayama IH, Luz Leiria TL. Periodontal therapy and endothelial function in coronary artery disease: a randomized controlled trial. *Oral Dis.* (2018) 24:1349–57. doi: 10.1111/odi.12909
19. Okada A, Murata T, Matin K, Ariyoshi M, Otsuka R, Yamashita M, et al. Effect of advanced periodontal self-care in patients with early-stage periodontal diseases on endothelial function: an open-label, randomized controlled trial. *PLoS One.* (2021) 16:e0257247. doi: 10.1371/journal.pone.0257247
20. Donders HCM, Veth EO, van 't Hof AWJ, de Lange J, Loos BG. The association between periodontitis and cardiovascular risks in asymptomatic healthy patients. *Int J Cardiol Cardiovasc Risk Prev.* (2021) 11:200110. doi: 10.1016/j.ijcrp.2021.200110
21. Fleiss JL. *The Design and Analysis of Clinical Experiments*. New York, NY: Wiley (1999).
22. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant diseases and conditions. *J Clin Periodontol.* (2018) 45:S162–70.
23. Nesse W, Abbas F, van der Ploeg I, Spijkervet FKL, Dijkstra PU, Vissink A. Periodontal inflamed surface area: quantifying inflammatory burden. *J Clin Periodontol.* (2008) 35:668–73. doi: 10.1111/j.1600-051X.2008.01249.x
24. Rubinshtein R, Kuvin JT, Soffler M, Lennon RJ, Lavi S, Nelson RE, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J.* (2010) 31:1142–8. doi: 10.1093/eurheartj/ehq010
25. Bonetti PO, Pumper GM, Higano ST, Holmes DR, Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *J Am Coll Cardiol.* (2004) 44:2137–41. doi: 10.1016/j.jacc.2004.08.062

26. Matsuzawa Y, Kwon T-G, Lennon RJ, Lerman LO, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. *J Am Heart Assoc.* (2015) 4:e002270. doi: 10.1161/JAHA.115.002270
27. Teeuw WJ, Slot DE, Susanto H, Gerdes VE, Abbas F, D'Aiuto F, et al. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. *J Clin Periodontol.* (2014) 41:70–9. doi: 10.1111/jcpe.12171
28. Orlandi M, Suvan J, Petrie A, Donos N, Masi S, Hingorani A, et al. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: a systematic review and meta-analysis. *Atherosclerosis.* (2014) 236:39–46. doi: 10.1016/j.atherosclerosis.2014.06.002
29. Zardawi F, Gul S, Abdulkareem A, Sha A, Yates J. Association between periodontal disease and atherosclerotic cardiovascular diseases: revisited. *Front Cardiovasc Med.* (2021) 7:625579. doi: 10.3389/fcvm.2020.625579
30. Herrera D, Molina A, Buhlin K, Klinge B. Periodontal diseases and association with atherosclerotic disease. *Periodontol 2000.* (2020) 83:66–89. doi: 10.1111/prd.12302
31. Shaqman M, Al-Abedalla K, Wagner J, Swede H, Gunsolley JC, Ioannidou E. Reporting quality and spin in abstracts of randomized clinical trials of periodontal therapy and cardiovascular disease outcomes. *PLoS One.* (2020) 15:e0230843. doi: 10.1371/journal.pone.0230843

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ORIGINAL RESEARCH
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Age-Related Differences for Cardiorespiratory Fitness Improvement in Patients Undergoing Cardiac Rehabilitation

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Objective: We investigated age-related differences for peak oxygen uptake (peak VO_2) improvement with exercise training during cardiac rehabilitation (CR).

Patients and Methods: This was a retrospective cohort study of the Mayo Clinic Rochester CR program including adult patients who attended CR (≥1 session) for any eligible indication between 1999 and 2017 and who had a cardiopulmonary exercise test pre and post CR with VO_2 data (peak respiratory exchange ratio ≥1.0). Younger (20–49 yrs), midlife (50–64 yrs), and older adults (≥65 yrs) were compared using ANOVA for delta and percent change in peak VO_2; and percentage of peak VO_2 responders (>0% change).

Results: 708 patients (age: 60.8 ± 12.1 years; 24% female) met inclusion criteria. Delta and percent change in peak VO_2 was lower for older adults (1.6 ± 3.2 mL.kg.min^{-1}; 12 ± 27%) compared with younger (3.7 ± 4.0 mL.kg.min^{-1}, $p < 0.001$; 23 ± 28%, $p = 0.002$) and midlife adults (2.8 ± 3.8 mL.kg.min^{-1}, $p < 0.001$; 17 ± 28%, $p = 0.04$). For midlife, delta change, but not percent change in peak VO_2 was significantly lower ($p = 0.02$) compared with younger. Percentage of responders was only different between older and younger (72 vs. 86%; $p = 0.008$). Sensitivity analyses in non-surgical patients showed similar differences for delta change, and differences in percent change remained significant between older and younger adults (10 ± 20% vs. 16 ± 18%; $p = 0.04$).

Conclusions: In CR patients, older adults had lower improvement in cardiorespiratory fitness than younger and midlife adults. While excluding surgical patients reduced age-related differences, older adults still had lower cardiorespiratory fitness improvement during CR. These findings may have implications for individualizing CR programming in aging populations to reduce future cardiovascular risk.

Keywords: peak oxygen uptake (VO_2), exercise capacity, older adult, peak VO_2 responder, peak VO_2 non-responder, exercise training

INTRODUCTION

Early outpatient (phase II) cardiac rehabilitation (CR) is internationally recognized as a class 1A recommendation for patients following a cardiovascular-related event or procedure (1, 2). CR is comprehensive secondary prevention encompassing multifaceted strategies to optimize cardiovascular risk reduction, foster healthy behaviors, and promote an active lifestyle (1). While CR originated primarily for middle-aged patients with coronary artery disease, the aging spectrum for cardiac rehabilitation has broadened over time with a range of eligible diagnoses and applications. In particular, benefits for aging populations include improvements in survival, exercise capacity, frailty, body composition, quality of life, symptom management, cognition, and socialization (3, 4).

Exercise training is an integral component of CR programs (1, 2), and exerts a multi-system effect on improving cardiovascular health (5). One of the most important benefits of exercise training in CR is the improvement in cardiorespiratory fitness, referred to as peak oxygen uptake (peak VO_2) when directly measured using gas exchange analysis (6). Peak VO_2 reflects an integrated ability to transport oxygen around the body, encompassing pulmonary function (ventilation and diffusion), right and left ventricular function (systolic and diastolic), ventricular-arterial coupling, vascular function (to accommodate and efficiently transport blood), and the ability of muscle cells to receive and use oxygen for aerobic energy production as well as communicating metabolic demands to the cardiovascular control center (7). Cardiorespiratory fitness is a strong predictor of cardiovascular events and all-cause mortality (6, 7), and has been shown to improve risk classification beyond traditional risk factors (7). Furthermore, changes in peak VO_2 during CR are highly predictive of future readmissions for cardiovascular disease and all-cause mortality, with each 1 $ml.kg.min^{-1}$ increase in peak VO_2 associated with a 21% reduction in cardiovascular events and a 13% reduction in all-cause mortality (8).

It is well-established that cardiorespiratory fitness declines with increasing age (9–11), however the influence of age on the trainability of cardiorespiratory fitness is less clear, with evidence suggesting either little or no difference (12–14) or a reduction (15, 16) in trainability with increasing age. There are limited data evaluating the influence of age on cardiorespiratory fitness response during a CR program, particularly using directly measured peak VO_2. Banks et al. investigated percent change in peak VO_2 during cardiac rehabilitation across age decades, finding those in the younger age categories (<50 years), tended to show a greater percent change in peak VO_2 than adults in each other age decade (16). However, this study excluded patients that did not respond to CR with increases in peak VO_2. Therefore, it is unclear how non-responders may influence the age-related differences in peak VO_2 improvements in a CR population.

The purpose of our study was to investigate age-related differences in peak VO_2 response to an exercise-based CR program. We hypothesized that improvements in peak VO_2 during CR are attenuated with increasing age. And furthermore, that with increasing age there will be a lower proportion of patients who are peak VO_2 responders (i.e., elicit a change in peak $VO_2 > 0\%$) during CR.

METHODS

Study Population

This was a historical cohort of consecutive patients residing in Olmsted County, Minnesota, who underwent CR at Mayo Clinic Rochester between June 1999 and July 2017. Patients enrolled in CR were included if they were 18 years or older and had completed a cardiopulmonary exercise test (CPET) pre and post cardiac rehabilitation, with peak VO_2 data and peak respiratory exchange ratio $\geq$1.0 (indicative of sufficient exertion) (17). If, over follow-up, patients were enrolled in cardiac rehabilitation multiple times, only their earliest program enrollment was included. The CPET performed closest to the cardiac rehabilitation enrollment and discharge was included in the study, including CPETs for diagnostic purposes. This study was approved by the Mayo Clinic and Olmsted Medical Center (whose patients attended CR at Mayo Clinic) Institutional Review Boards and, per MN statute. Only patients who had provided authorization to use their medical records for medical research were included.

Cardiac Rehabilitation Program

The CR program at Mayo Clinic in Rochester, Minnesota is based on guidelines from the American Association of Cardiovascular and Pulmonary Rehabilitation, American Heart Association, and American College of Cardiology. It is a comprehensive secondary prevention program that encompasses core components including exercise training and physical activity counseling, weight management and nutritional counseling, cardiovascular risk factor management, medication management and adherence, stress management, depressive symptom management, and social support networking. All patients are prescribed 36 exercise sessions which were typically completed at a frequency of two to three times per week over 12–18 weeks. Each exercise session consisted of 20–45 min of structured aerobic exercise and 10–15 min of resistance training, following an individualized prescription from an exercise physiologist depending on physical capabilities and/or limitations. Exercise was commonly prescribed at a moderate intensity using ratings of perceived exertion of 12–14 on the 6–20 Borg Scale (18). On days of the week with no supervised CR sessions, patients were encouraged to engage in physical activity independently for at least 30 min consistent with the prescribed exercise program.

CPET Data Collection

Symptom-limited CPETs were conducted by trained exercise physiologists under the supervision of a cardiologist, using institutionally derived incremental exercise protocols for treadmill or cycle ergometer (19). Cardiac medications were not withheld prior to CPET. A gas exchange metabolic system (MGC Diagnostics, St Paul, Minnesota, USA) was used to quantify VO_2, carbon dioxide production (VCO_2), respiratory exchange ratio (RER), ventilation (V_E), and ventilatory equivalent for VCO_2 (VE/VCO_2) according to the American Heart Association

Exercise Standards Statement for Testing and Training (20). Peak values were obtained during the final minute of exercise. Predicted peak VO_2 was calculated using Wasserman-Hansen and FRIEND registry prediction equations (21, 22). We further calculated the percentage of predicted peak VO_2 achieved using our directly measured peak VO_2. As a measure of exercise capacity, peak workload was converted to estimated metabolic equivalents (METs) using FRIEND registry equations for treadmill and cycle (23, 24). Peak oxygen pulse (mL/beat) was calculated as peak VO_2 (in mL/min) divided by peak heart rate (beats/min) (25). The CPET data were extracted electronically from an institutional registry. To evaluate accuracy, a fraction of the data were reviewed by a clinical investigator (J.L.T). If relevant data were missing, electronic medical records were reviewed, and data were manually extracted.

Clinical Data Collection

Patient demographic and clinical characteristics were extracted electronically using resources of the Rochester Epidemiology Project (REP) (26), a record linkage system that captures data on health conditions (diagnoses, procedures, and other vital information) for all Olmsted County residents who receive medical care at Mayo Clinic or Olmsted Medical Center and its allied health care centers (27, 28). Clinical variables were operationalized as per the International Classification of Diseases-9 and 10 (ICD-9 and−10) (29). This data extraction approach has been previously validated and reported (30, 31). A random sample of these variables was reviewed in duplicate for validation (A.C.S, J.M.I), with an excellent inter-observer agreement (all $\kappa > 0.85$).

Statistical Analysis

The overarching aim of this analysis was to evaluate possible age-related differences in peak VO_2 response from participation in an exercise-based CR program. To achieve this, differences in patient demographics and exercise testing outcomes were compared among different age groups across the lifespan (older adults ≥65 years; midlife adults 50–64 yrs; younger adults 20–49 yrs) (32, 33) and age decades. Groups were initially compared using analysis of variance (ANOVA) for continuous variables and Pearson's chi-squared for categorical data. Continuous data are reported as mean values and standard deviations (SD), and categorical data as frequencies and percentages. Age-group differences for delta and percent change in relative peak VO_2 and peak workload from pre to post CR, as well as the proportion of patients classified as peak VO_2 responders (i.e., >0% change in peak VO_2) were also compared with ANOVA. Pre-planned *post-hoc* comparisons were conducted with pairwise *t*-test and Bonferroni correction for multiple comparisons. Due to the variation between age groups in surgical CR indications, we performed sensitivity analyses excluding patients with surgical indications to evaluate whether this influenced our results. Furthermore, we used linear regression to determine whether female sex influenced the delta or percent change in relative peak VO_2, within age groups, with data reported as unstandardized estimate (95% confidence interval). We used logistic regression to determine whether female sex influenced the likelihood of a peak VO_2 response within age groups, with data reported as odds ratio (95% confidence interval). A p-value < 0.05 was considered statistically significant unless otherwise stated. All analyses were performed using BlueSky Statistics software v. 7.10 (Bluesky Statistics LLC, Chicago, IL, USA).

RESULTS

Patient Demographics

A total of 708 patients met the inclusion criteria for this study. Patient demographic characteristics are outlined by age group in **Table 1** and age decade in **Supplementary Table 1**. On average, 24% of the study population were female, with the highest proportion of females in the younger adult group. With increasing age, there was a higher proportion of patients with CR indication for percutaneous coronary intervention (PCI) ($p < 0.001$) and a lower proportion of patients with surgical CR indications ($p = 0.002$), specifically related to heart transplant ($p < 0.001$). The proportion of patients with comorbidities increased with age ($p < 0.05$) with the exception of chronic heart failure, chronic kidney disease, and smoking, which were not different between groups ($p > 0.05$). Similarly, the proportion of patients prescribed standard cardiac medications increased with age ($p < 0.05$), with the exception of calcium channel blocker and anticoagulant classes, which were not different between groups ($p > 0.05$).

Baseline Exercise Testing Variables

Baseline CPET characteristics are presented by age group in **Table 2** and age decade in **Supplementary Table 2**. With increasing age, patients had a lower resting HR and peak exercise HR, and a higher systolic blood pressure at rest and peak exercise. Baseline cardiorespiratory fitness (absolute and relative peak VO_2) and peak workload (in estimated METs) was similar between younger and midlife adults, but lower in older adults. In contrast, younger adults achieved a lower percentage of predicted peak VO_2 compared with both midlife and older adults. On average, ratings of perceived exertion (RPE) and RER were indicative of maximal exertion (RPE: 18.2 ± 0.9; RER: 1.19 ± 0.09), and there were no differences between groups. Sensitivity analyses, which excluded surgical patients, produced similar trends and statistical results for baseline exercise variables (**Table 3**). On average, baseline CPET was 6.8 ± 13.5 weeks prior to cardiac rehabilitation commencement, which reduced to 3.5 ± 10.2 weeks when surgical patients were excluded from analysis.

Post Exercise Testing and CR Program Outcomes

CR program variables and outcomes for percentage of predicted VO_2, change in peak VO_2, change in peak workload (in estimated METs), and proportion of peak VO_2 responders are presented by age group in **Table 2** and age decade in **Supplementary Table 2**. On average, patients improved relative peak VO_2 from pre to post CR by 2.5 ± 3.7 $mL.kg.min^{-1}$ ($p < 0.001$), with an average percent change in relative peak VO_2 of 16 ± 28% ($p < 0.001$). All age groups significantly improved peak VO_2

TABLE 1 | Patient demographics by age group.

Demographic variable	Total ($n = 708$)	Younger adults ($n = 115$)	Midlife adults ($n = 324$)	Older adults ($n = 269$)	*p*-value
Age (years)	60.8 ± 12.1	41.2 ± 7.5	58.1 ± 4.3	72.5 ± 5.1	<0.001
Female	167 (24%)	40 (35%)	67 (21%)	60 (22%)	0.008
Body mass index ($kg.m^{-2}$)	29.5 ± 5.3	29.3 ± 6.2	29.8 ± 5.5	29.2 ± 4.6	0.437
Indication for cardiac rehabilitation					
Acute coronary syndrome	196 (28%)	27 (23%)	90 (28%)	79 (29%)	0.497
PCI	223 (31%)	18 (16%)	105 (32%)	100 (37%)	<0.001
Surgical	173 (24%)	41 (36%)	82 (25%)	50 (19%)	0.002
Heart transplant	100 (14%)	30 (26%)	56 (17%)	14 (5%)	<0.001
CABG	36 (5%)	4 (3%)	15 (5%)	17 (6%)	0.448
Valve	33 (5%)	6 (5%)	8 (2%)	19 (7%)	0.029
Other‡	115 (16%)	29 (25%)	46 (14%)	50 (19%)	0.017
Co-morbidities					
Myocardial infarction	260 (37%)	32 (28%)	110 (34%)	118 (44%)	0.004
Hypertension	560 (79%)	61 (53%)	253 (78%)	246 (91%)	<0.001
Chronic heart failure	248 (35%)	48 (42%)	110 (34%)	90 (33%)	0.255
Dyslipidemia	642 (91%)	83 (72%)	301 (93%)	258 (96%)	<0.001
Arrhythmia	561 (79%)	78 (68%)	261 (81%)	222 (83%)	0.004
Stroke	153 (22%)	15 (13%)	53 (16%)	85 (32%)	<0.001
Chronic kidney disease	217 (31%)	27 (23%)	102 (31%)	88 (33%)	0.18
COPD	288 (41%)	31 (27%)	135 (42%)	122 (45%)	0.003
Diabetes	423 (60%)	45 (39%)	199 (61%)	179 (67%)	<0.001
Peripheral artery disease	97 (14%)	5 (4%)	34 (10%)	58 (22%)	<0.001
Smoking	451 (64%)	64 (56%)	209 (65%)	178 (66%)	0.134
Medications					
β-blocker	550 (78%)	80 (70%)	243 (75%)	227 (84%)	0.002
ACE Inhibitor or ARB	389 (55%)	51 (44%)	170 (52%)	168 (62%)	0.002
Calcium channel blocker	179 (25%)	23 (20%)	75 (23%)	81 (30%)	0.055
Diuretics	305 (43%)	39 (34%)	118 (36%)	148 (55%)	<0.001
Salicylates or anti-platelet	501 (71%)	66 (57%)	224 (69%)	211 (78%)	<0.001
Anticoagulant	139 (20%)	27 (23%)	48 (15%)	64 (24%)	0.012
Cholesterol lowering	566 (80%)	69 (60%)	264 (81%)	233 (87%)	<0.001

Age groups: younger adults 20–49 yrs; Midlife adults 50–64 yrs; Older adults ≥65 yrs.

Continuous data are presented as mean ± SD and categorical data presented as n (%). p-values are reported for trend across group comparisons.

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

‡*Breakdown of other category includes, stable angina (4%), heart failure (2%), dyspnea (<1%), sudden cardiac death (<1%), peripheral artery disease (<1%), pericarditis or myocarditis (<1%), or non-specified cardiac event (8%).*

($p < 0.001$) from pre to post CR (**Table 2**). However, the change in relative peak VO_2 was lower with increasing age, with significant differences between younger and midlife adults (mean difference = 0.9 $mL.kg.min^{-1}$; $p = 0.02$), younger and older adults (mean difference = 2.1 $mL.kg.min^{-1}$; $p < 0.001$), and midlife and older adults (mean difference 1.2 $mL.kg.min^{-1}$; $p < 0.001$) (**Figure 1A**). Percent change in relative peak VO_2 was also lower with increasing age, although differences between groups were only significant for younger and older adults (mean difference = 11%; $p = 0.002$), and midlife and older adults (mean difference = 5%; $p = 0.04$) (**Figure 1B**). On average, 77% of patients showed an improvement in peak VO_2 (>0% change) from pre to post cardiac rehabilitation. While response rate showed a lower trend with increasing age, the response rate was only significantly different between younger and older adults (86 vs. 72%, respectively; $p = 0.008$). Change in peak workload was lower for older adults compared with younger adults (0.6 ± 1.1 vs. 1.0 ± 1.2 METs; $p = 0.007$), however percent change in peak workload was not different between groups. On average, there was an improvement in percentage of predicted VO_2 from 75 ± 22% to 83 ± 22%, however levels remained significantly lower for younger adults compared with midlife adults (74 ± 22 vs. 84 ± 24; $p < 0.001$) and older adults (74 ± 22 vs. 86 ± 18; $p < 0.001$). Older adults completed a significantly greater number of CR sessions than younger adults (30 ± 11 vs. 24 ± 14 sessions; $p < 0.001$) and midlife adults (30 ± 11 vs. 26 ± 13 sessions; $p < 0.001$), and older adults were in the program for a longer period than younger adults (17 ± 9 vs. 13 ± 9 weeks;

TABLE 2 | Exercise testing and cardiac rehabilitation variables by age group.

Outcome variable	Total ($n = 708$)	Younger adults ($n = 115$)	Midlife adults ($n = 324$)	Older adults ($n = 269$)	*p*-value
Baseline CPET variables					
CPET timing prior to program commencement (weeks)	6.8 ± 13.5	10.9 ± 16.5	7.0 ± 13.5	4.7 ± 11.5	<0.001
Resting HR (beat.min^{-1})	68 ± 12	72 ± 13	69 ± 11	66 ± 11	<0.001[a,b,c]
Resting SBP (mmHg)	115 ± 20	106 ± 18	112 ± 18	122 ± 20	<0.001[a,b,c]
Resting DBP (mmHg)	70 ± 12	68 ± 15	71 ± 11	70 ± 11	0.038[a]
Peak exercise HR (beat.min^{-1})	127 ± 23	135 ± 27	129 ± 23	120 ± 20	<0.001[a,b,c]
Peak exercise SBP (mmHg)	153 ± 35	141 ± 37	154 ± 38	158 ± 30	<0.001[a,b]
Peak exercise DBP (mmHg)	66 ± 17	62 ± 18	66 ± 17	66 ± 15	0.066
Peak exercise RPE	18.2 ± 0.9	18.2 ± 0.8	18.2 ± 1.0	18.2 ± 0.8	0.828
Peak exercise RER	1.19 ± 0.09	1.20 ± 0.11	1.19 ± 0.09	1.18 ± 0.09	0.177
Peak workload (estimated METs)	6.8 ± 1.6	7.0 ± 1.8	7.0 ± 1.7	6.4 ± 1.4	<0.001[b,c]
Peak absolute VO_2 (L.min^{-1})	1.76 ± 0.66	1.85 ± 0.79	1.90 ± 0.69	1.56 ± 0.48	<0.001[b,c]
Peak relative VO_2 (mL.kg.min^{-1})	20.0 ± 6.7	21.0 ± 8.1	21.1 ± 7.1	18.2 ± 4.9	<0.001[b,c]
% predicted peak VO_2 (Wasserman-Hansen)	75 ± 22	63 ±21	76 ± 24	80 ± 19	<0.001[a,b]
% predicted peak VO_2 (FRIEND-registry)	79 ± 33	67 ± 26	81 ± 38	82 ± 27	<0.001[a,b]
Peak oxygen pulse (mL.beat^{-1})	13.8 ± 4.2	13.4 ± 4.8	14.5 ± 4.3	13.1 ± 3.8	<0.001[a,b,c]
Post CPET and CR program variables					
CPET timing following program commencement (weeks)	14.9 ± 10.7	14.9 ± 10.7	16.3 ± 10.2	15.7 ± 9.3	0.367
CR program duration (weeks)	15.5 ± 10.1	12.9 ± 9.0	15.2 ± 11.0	16.9 ± 9.0	0.001[b]
CR program exercise sessions	27.0 ± 12.7	23.9 ± 13.5	25.5 ± 13.4	30.2 ± 10.9	<0.001[b,c]
Delta change in peak relative VO_2 (mL.kg.min^{-1})	2.5 ± 3.7	3.7 ± 4.0	2.8 ± 3.8	1.6 ± 3.2	<0.001[a,b,c]
Percent change in peak relative VO_2 (%)	16 ± 28	23 ± 28	17 ± 28	12 ± 27	0.001[b,c]
Delta change in peak workload (METs)	0.7 ± 1.1	1.0 ± 1.2	0.8 ± 1.1	0.6 ± 1.1	0.007[b]
Percent change in peak workload (%)	14 ± 24	17 ± 23	14 ± 22	12 ± 25	0.170
Proportion of VO_2 responders (*n*, %)	546 (77%)	99 (86%)	253 (78%)	194 (72%)	0.010 [b]
% predicted peak VO_2 (Wasserman-Hansen)	83 ± 22	74 ± 22	84 ± 24	86 ± 18	<0.001[a,b]
% predicted peak VO_2 (FRIEND-registry)	86 ± 37	77 ± 26	88 ± 44	87 ± 30	0.017[a,b]

Age groups: younger adults 20–49 yrs; Midlife adults 50–64 yrs; Older adults ≥65 yrs. Continuous data presented as mean ± SD and categorical data presented as n (%).
Post-hoc comparisons with Bonferroni correction for multiple comparisons, reveal significant differences ($p < 0.05$) between [a]young and midlife adults; [b]young and older adults; and [c]midlife and older adults.
CPET, cardiopulmonary exercise test; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPE, rating of perceived exertion; RER, respiratory exchange ratio; METs, metabolic equivalent; VO_2, oxygen uptake.

$p = 0.001$). The post CPET occurred on average 15.9 ± 9.3 weeks following CR commencement, and within 0.4 ± 11.5 weeks of CR completion.

For sensitivity analyses excluding surgical patients (**Table 3**), the average improvement in relative peak VO_2 was moderately lower (2.2 ± 3.3 mL.kg.min^{-1}) than the primary analysis, as well as the average percent change in relative peak VO_2 (11 ± 20%). Change in relative peak VO_2 remained lower for older adults compared with younger adults (mean difference = 1.9 mL.kg.min^{-1}; $p < 0.001$) and midlife adults (mean difference = 1.0 mL.kg.min^{-1}; $p < 0.001$) (**Figure 1C**). Differences in the percent change of relative VO_2 were less pronounced between older and younger adults (mean difference = 6%; $p = 0.04$), and there were no longer differences between younger and midlife adults or midlife and older adults (**Figure 1D**). There was no longer an effect of age group for proportion of VO_2 responders. Moreover, percentage change in peak workload was not different between age groups.

In **Supplementary Table 3**, we display changes in peak VO_2 for specific CR indications such as acute coronary syndrome (ACS), PCI, heart transplant, and coronary artery bypass graft (CABG)/valve surgery. Numerically, the ACS sub-group showed a similar trend to our non-surgical cohort. In the PCI sub-group, younger adults show a considerably higher delta and percent change in peak VO_2 when compared to both midlife and older adults. In the CABG/valve and other sub-groups, delta and percent change in peak VO_2 are markedly reduced in older adults compared with younger and midlife adults. In the heart transplant sub-group, all age groups showed dramatically higher delta and percent change in peak VO_2 compared with other CR indications, however in contrast to other CR indications, older adults showed markedly higher improvements in peak VO_2 than younger and midlife adults.

We did not find an association of female sex for delta and percent change in peak VO_2, respectively, in younger adults [−0.7 (−2.3 to 0.8) ml.kg.min^{-1}; $p = 0.34$ and 7.4 (−3.3 to 18.1)

TABLE 3 | Exercise testing variables by age group—non-surgical patients.

Outcome variable	Total ($n = 534$)	Younger adults ($n = 74$)	Midlife adults ($n = 241$)	Older adults ($n = 219$)	*p*-value
Baseline CPET variables					
CPET timing prior to program commencement (weeks)	2.2 ± 9.0	3.4 ± 10.9	2.3 ± 9.1	1.7 ± 8.1	0.358
Resting HR (beat.min^{-1})	67 ± 11	71 ± 13	68 ± 10	66 ± 10	0.002[b]
Resting SBP (mmHg)	117 ± 19	108 ± 17	114 ± 17	123 ± 19	<0.001[a,b,c]
Resting DBP (mmHg)	71 ± 10	71 ± 10	72 ± 10	70 ± 10	0.021[c]
Peak exercise HR (beat.min^{-1})	130 ± 22	143 ± 24	135 ± 20	121 ± 18	<0.001[a,b,c]
Peak exercise SBP (mmHg)	163 ± 29	155 ± 32	165 ± 30	162 ± 27	0.032[a]
Peak exercise DBP (mmHg)	67 ± 16	65 ± 16	68 ± 17	66 ± 15	0.200
Peak exercise RPE	18.2 ± 0.8	18.1 ± 0.7	18.2 ± 0.9	18.2 ± 0.8	0.411
Peak exercise RER	1.19 ± 0.09	1.20 ± 0.11	1.20 ± 0.09	1.9 ± 0.10	0.251
Peak workload (estimated METs)	7.1 ± 1.5	7.6 ± 1.6	7.4 ± 1.5	6.5 ± 1.35	<0.001[b,c]
Peak absolute VO_2 (L.min^{-1})	1.90 ± 0.62	2.18 ± 0.69	2.10 ± 0.61	1.59 ± 0.45	<0.001[b,c]
Peak relative VO_2 (mL.kg.min^{-1})	21.3 ± 6.2	23.7 ± 7.2	22.9 ± 6.4	18.7 ± 4.5	<0.001[b,c]
% predicted peak VO_2 (Wasserman-Hansen)	81 ± 18	72 ± 16	83 ± 20	82 ± 17	<0.001[a,b]
% predicted peak VO_2 (FRIEND-registry)	86 ± 31	78 ± 23	90 ± 37	84 ± 26	0.009[a]
Peak oxygen pulse (mL.beat^{-1})	14.6 ± 4.0	15.2 ± 4.4	15.6 ± 3.8	13.2 ± 3.7	<0.001[b,c]
Post CPET and CR program variables					
CPET timing following program commencement (weeks)	15.7 ± 7.5	14.5 ± 8.3	16.2 ± 8.2	15.5 ± 6.3	0.071
CR program duration (weeks)	16.0 ± 7.3	14.6 ± 7.9	16.7 ± 8.1	15.8 ± 5.9	0.072
CR program exercise sessions	29 ± 12	27 ± 14	28 ± 13	31 ± 10	<0.001[b,c]
Delta change in peak relative VO_2 (mL.kg.min^{-1})	2.2 ± 3.3	3.4 ± 3.9	2.5 ± 3.5	1.5 ± 2.7	<0.001[b,c]
Percent change in peak relative VO_2 (%)	11 ± 19	16 ± 18	12 ± 18	10 ± 20	0.043[b]
Delta change in peak workload (METs)	0.6 ± 1.0	0.8 ± 1.1	0.6 ± 1.0	0.6 ± 1.0	0.280
Percent change in peak workload (%)	11 ± 19	13 ± 17	10 ± 17	12 ± 22	0.483
Proportion of VO_2 responders (n, %)	416 (78%)	64 (86%)	191 (79%)	161 (74%)	0.053
% predicted peak VO_2 (Wasserman-Hansen)	89 ± 20	82 ± 19	91 ± 22	89 ± 17	0.007[a]
% predicted peak VO_2 (FRIEND-registry)	92 ± 38	88 ± 24	96 ± 46	90 ± 31	0.085

Age groups: younger adults 20–49 yrs; Midlife adults 50–64 yrs; Older adults ≥65 yrs. Continuous data presented as mean ± SD and categorical data presented as n (%).
Post-hoc comparisons with Bonferroni correction for multiple comparisons, reveal significant differences ($p < 0.05$) between [a]young and midlife adults; [b]young and older adults; and [c]midlife and older adults.
CPET, cardiopulmonary exercise test; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPE, rating of perceived exertion; RER, respiratory exchange ratio; METs, metabolic equivalent; VO_2, oxygen uptake.

%; $p = 0.17$] or older adults [−0.2 (−1.1 to 0.7) ml.kg.min^{-1}; $p = 0.71$; and 0.1 (−7.6 to 7.7) %; $p = 0.98$]. There was trend toward an influence of female sex in midlife adults for delta change in peak VO_2 [−1.0 (−2.0 to 0.0) ml.kg.min^{-1}; $p = 0.05$] but not percent change in peak VO_2 [−3.1 (−10.7 to 4.5) %; $p = 0.42$]. There was also no influence of female sex on likelihood of peak VO_2 response for younger adults [0.6 (0.2–1.9); $p = 0.42$], midlife adults [1.1 (0.6–2.1); $p = 0.82$], or older adults [1.2 (0.6–2.3); $p = 0.57$].

DISCUSSION

This study investigated age-related differences for improving cardiorespiratory fitness (peak VO_2) and exercise capacity (as peak workload) during a CR program. All age groups significantly improved peak VO_2 from pre to post CR, however when evaluating patients with any CR indication, we found significant attenuation in peak VO_2 improvement with increasing age, from younger adults to midlife adults, and midlife adults to older adults. Although older adults improved peak VO_2, their percent change in peak VO_2 was significantly lower when compared with both younger adults and midlife adults; and older adults were less likely to show a peak VO_2 response (>0% change) to the CR program compared with younger adults. When surgical patients were excluded from the analysis, age-related differences for percent change in peak VO_2 were reduced, however older adults still achieved a lower improvement in cardiorespiratory fitness during CR. Percent change in peak exercise workload showed no age-related differences throughout CR.

Previous research in healthy populations has shown that cardiorespiratory fitness decreases by approximately

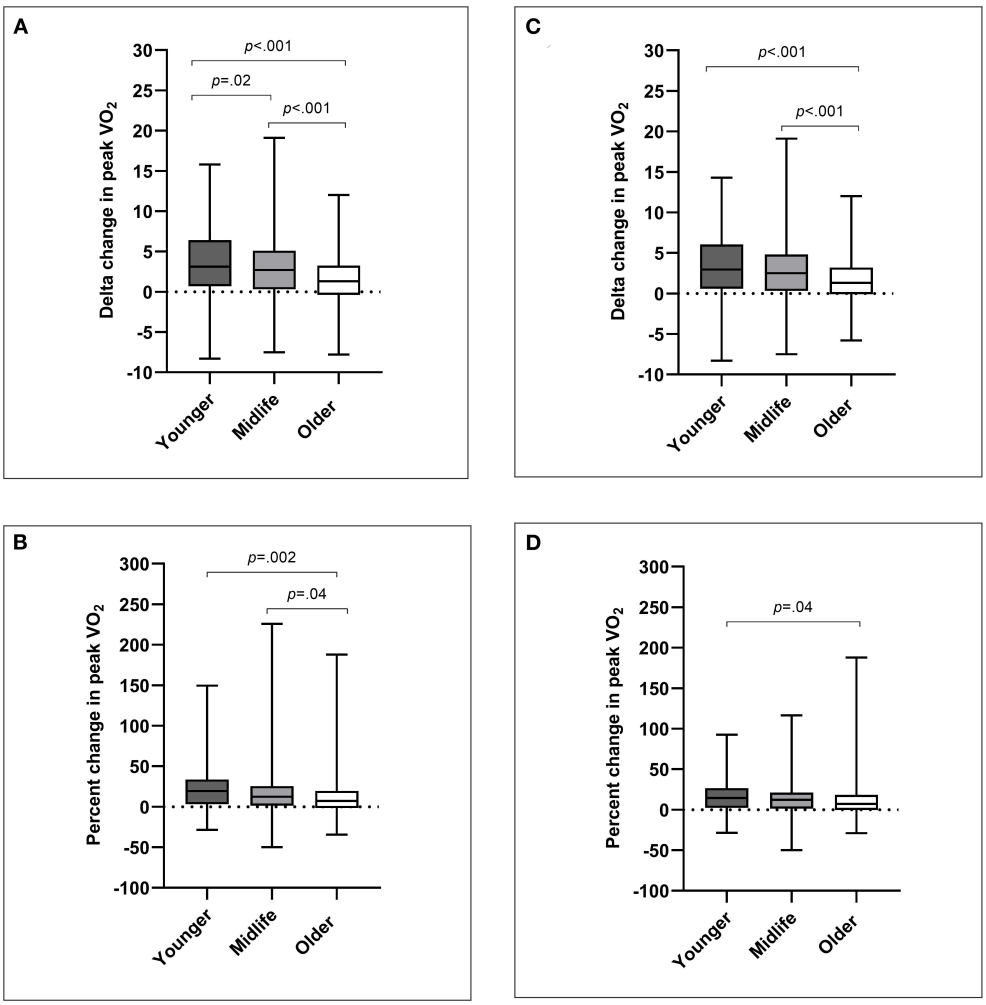

FIGURE 1 | Age-related differences in cardiorespiratory fitness as: **(A)** delta change in peak VO_2 for all CR indications; **(B)** percent change in peak VO_2 for all CR indications; **(C)** delta change in peak VO_2 for non-surgical CR indications; **(D)** percent change in peak VO_2 for non-surgical CR indications. Data are presented as box and whisker plots with median line, and minimum to maximum.

1-MET (equivalent to 3.5 ml.kg.min^{-1}) with each increasing age decade (10, 34). In the current study, the differences between age-decades using directly measured peak VO_2 at the beginning of CR were much less pronounced (mean difference $\sim$ 1.0 ml.kg.min^{-1}). Our results were similar to the differences between age-decades reported by Banks et al. (16) (mean difference in peak VO_2 = 1.8 ml.kg.min^{-1}) in their patients with coronary artery disease undergoing CR. With regards to changes in peak VO_2 with exercise training, our findings were also similar to Banks et al., with older patients attending CR showing both lower delta and percent change in peak VO_2. These results are in contrast to studies in healthy populations showing similar percent change in peak VO_2 between age groups with exercise training (12–14). The Heritage Family Study investigated the variability in peak VO_2 response to a standardized exercise training program in a healthy population. They found that while older adults had a lower delta change in relative peak VO_2, the percent change from baseline was similar to younger adults (12). Robinson et al. (35) also found that healthy younger and older adults had similar percent change in peak VO_2 with combined training (aerobic + resistance). In the same study, both young and older adults showed significant improvements in peak VO_2 with high intensity interval training, however, the percent change was much greater in the younger adults (35). Therefore, differences in training intensity could have influenced our age-related differences in peak VO_2 improvement.

Currently there are limited published data showing the influence of peak VO_2 improvement during CR, as a percent change from baseline, on major adverse cardiovascular events. However, the differences in delta change for relative peak VO_2 that we found between our age groups could be considered

clinically meaningful, as each 1 ml.kg.min^{-1} increase in peak VO_2 during cardiac rehabilitation has been shown to reduce cardiovascular events by 21% and all-cause mortality by 13% (8). Recent work by Carbone et al. (36) found that the percentage of predicted peak VO_2 at the end of CR was a stronger predictor of long-term survival rather than change in peak VO_2 during CR. While our results showed younger adults had greater improvements in peak VO_2 during CR, midlife and older adults maintained a significantly higher percentage of predicted peak VO_2 at the end of CR, compared with the younger adults. A potential bias with this outcome is that older adults who are able to complete a CPET pre and post CR could be more likely to have a higher fitness level and may not be representative of the average older adult attending CR.

Notably, our midlife and older adults also achieved a significantly higher percentage of predicted peak VO_2 at the beginning of CR (∼76–80%), compared with our younger adults (∼63%). Lower baseline peak VO_2 has consistently been shown to be a strong predictor for peak VO_2 response with exercise training (37, 38). Although mean baseline peak VO_2 was lower for older adults, the mean percentage of predicted peak VO_2 was lower for younger adults, and this likely contributed to the greater improvements in peak VO_2 during CR. The lower initial fitness level in our younger adults was in part related to the increased prevalence of heart transplant. Indeed, when we excluded surgical patients from the analysis, the mean relative peak VO_2 at baseline increased by 2.7 ml.kg.min^{-1} (13%) in our younger adults and 1.8 ml.kg.min^{-1} (9%) in our midlife adults, with minimal change in our older adults (0.5 ml.kg.min^{-1}; 3%). In non-surgical patients, the age-related differences between younger and midlife adults diminished. Therefore, differences in patient populations among age groups may contribute to bias that CR is less effective for improving peak VO_2 with increasing age. Previous research has shown that females have a lower improvement in peak VO_2 than males during CR (39). We found a trend toward female adults in midlife achieving a lower delta change for peak VO_2 improvement, however, there was no significant influence of sex on peak VO_2 improvement or likelihood for peak VO_2 response in any age group.

Multimorbidity may have contributed to the lower improvement in peak VO_2 in our older adults. Having a higher number of comorbidities has been associated with lower improvements in cardiorespiratory fitness (40) and other CR outcomes (41). Although our older adults attended more sessions and were in the program for longer, they also had a higher prevalence of peripheral artery disease, stroke, myocardial infarction, and chronic obstructive pulmonary disease. This is consistent with the work of Listerman et al. (41), showing that patients with a higher number of comorbidities may be prescribed a greater number of CR sessions than patients with a lower number of comorbidities.

Our study has a number of limitations that warrant discussion. Firstly, patients were from a single-center, were predominately male (75%), and the majority of the population in this region (Olmsted County) are White. Secondly, the retrospective nature of this study can present several sources of bias, and only including patients with pre- and post-CR CPET data may contribute to selection bias. These factors might affect the generalizability, but not the internal validity of our findings. Medication differences between age groups could not be accounted for in our ANOVA *post-hoc* analyses. Using an Analysis of Covariance (ANCOVA), we explored the interactions between medication status and change in peak VO_2, in this case we only found an interaction between delta change in peak VO_2 and angiotensin-converting enzyme or angiotensin II receptor blocker. When including this medication status as a covariate with ANCOVA, the effect of age group on delta change in peak VO_2 remained significant ($p < 0.001$). Similarly, differences in baseline CPET timing between groups could not be accounted for in our ANOVA *post-hoc* analyses. Using ANCOVA, an interaction was found between baseline CPET timing and percent change in peak VO_2, but not delta change in peak VO_2. When including baseline CPET timing as a covariate with ANCOVA, the effect of age group on percent change in peak VO_2 remained significant ($p < 0.001$). Moreover, when surgical patients were excluded, baseline CPET timing was not different between age groups. Likewise, although informative, we had limited sample size to evaluate statistical significance between age groups for specific CR indications (e.g., ACS, PCI, CABG, heart transplant). Finally, due to the absence of exercise prescription data during the cardiac rehabilitation program, we could not evaluate whether the greater improvement in peak VO_2 of younger adults was influenced by exercise training being of a higher relative intensity or longer duration.

CONCLUSION

This study found significant improvements in peak VO_2 for all age groups during a CR program. However, there was a significant attenuation in both delta and percent change in peak VO_2, from younger to midlife adults, and midlife to older adults with any CR referral diagnosis. Older adults also showed a significantly lower rate of VO_2 response to a CR program compared with younger adults. Age-related differences were influenced by a higher prevalence of heart transplant in our younger age group. In non-surgical patients, age-related differences in percent change of peak VO_2 were less pronounced, however older adults still had lower peak VO_2 improvement during CR. These findings may have implications for individualizing CR programming based on age and comorbid conditions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Mayo Clinic Institutional Review Board

Olmsted Medical Center Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JT, JM-I, AC-S, JS, RS, RT, BJ, TO, and AB contributed to study conception and design. JT, JM-I, AC-S, and JS contributed to data collection and analysis. JT and JM-I contributed to the statistical analysis. JT drafted the manuscript. JM-I, AC-S, JS, RS, RT, BJ, TO, and AB critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.872757/full#supplementary-material

REFERENCES

1. Balady Gary J, Williams Mark A, Ades Philip A, Bittner V, Comoss P, Foody JoAnne M, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update. *Circulation.* (2007) 115:2675–82. doi: 10.1161/CIRCULATIONAHA.106.180945
2. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol.* (2020) 28:460–95. doi: 10.1177/2047487320913379
3. Schopfer DW, Forman DE. Cardiac rehabilitation in older adults. *Can J Cardiol.* (2016) 32:1088–96. doi: 10.1016/j.cjca.2016.03.003
4. Lutz AH, Delligatti A, Allsup K, Afilalo J, Forman DE. Cardiac rehabilitation is associated with improved physical function in frail older adults with cardiovascular disease. *J Cardiopulm Rehabil Prev.* (2020) 40:310–8. doi: 10.1097/HCR.0000000000000537
5. Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. *J Physiol.* (2009) 587(Pt 23):5551–8. doi: 10.1113/jphysiol.2009.179432
6. Kaminsky LA, Arena R, Ellingsen Ø, Harber MP, Myers J, Ozemek C, et al. Cardiorespiratory fitness and cardiovascular disease - The past, present, and future. *Prog Cardiovasc Dis.* (2019) 62:86–93. doi: 10.1016/j.pcad.2019.01.002
7. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a Scientific Statement From the American Heart Association. *Circulation.* (2016) 134:e653–99. doi: 10.1161/CIR.0000000000000461
8. Mikkelsen N, Cadarso-Suarez C, Lado-Baleato O, Diaz-Louzao C, Gil CP, Reeh J, et al. Improvement in VO2peak predicts readmissions for cardiovascular disease and mortality in patients undergoing cardiac rehabilitation. *Eur J Prev Cardiol.* (2020) 27:811–9. doi: 10.1177/2047487319887835
9. Kaminsky LA, Arena R, Myers J, Peterman JE, Bonikowske AR, Harber MP, et al. Updated reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the fitness registry and the importance of exercise national database (FRIEND). *Mayo Clin Proc.* (2022) 97:285–93. doi: 10.1016/j.mayocp.2021.08.020
10. Loe H, Steinshamn S, Wisløff U. Cardio-respiratory reference data in 4631 healthy men and women 20-90 years: the HUNT 3 fitness study. *PLoS ONE.* (2014) 9:e113884. doi: 10.1371/journal.pone.0113884
11. Letnes JM, Dalen H, Aspenes ST, Salvesen Ø, Wisløff U, Nes BM. Age-related change in peak oxygen uptake and change of cardiovascular risk factors. The HUNT Study. *Prog Cardiovasc Dis.* (2020) 63:730–7. doi: 10.1016/j.pcad.2020.09.002
12. Skinner JS, Jaskólski A, Jaskólska A, Krasnoff J, Gagnon J, Leon AS, et al. Age, sex, race, initial fitness, and response to training: the HERITAGE Family Study. *J Appl Physiol.* (2001) 90:1770–6. doi: 10.1152/jappl.2001.90.5.1770
13. Støren Ø, Helgerud J, Sæbø M, Støa EM, Bratland-Sanda S, Unhjem RJ, et al. The effect of age on the V?O2max response to high-intensity interval training. *Med Sci Sports Exerc.* (2017) 49:78–85. doi: 10.1249/MSS.0000000000001070
14. Pollock ML, Gaesser GA, Butcher JD, Després J-P, Dishman RK, Franklin BA, et al. ACSM position stand: the recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc.* (1998) 30:975–91. doi: 10.1249/00005768-199806000-00032
15. Woo JS, Derleth C, Stratton JR, Levy WC. The influence of age, gender, and training on exercise efficiency. *J Am Coll Cardiol.* (2006) 47:1049–57. doi: 10.1016/j.jacc.2005.09.066
16. Banks L, Cacoilo J, Carter J, Oh PI. Age-related improvements in peak cardiorespiratory fitness among coronary heart disease patients following cardiac rehabilitation. *J Clin Med.* (2019) 8:310. doi: 10.3390/jcm8030310
17. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 focused update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J.* (2018) 39:1144–61. doi: 10.1093/eurheartj/ehw180
18. Borg G. *Borg's Perceived Exertion and Pain Scales*. Champaign, IL: Human Kinetics (1998).
19. Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. *Circulation.* (2012) 126:2465–72. doi: 10.1161/CIRCULATIONAHA.112.110460
20. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation.* (2013) 128:873–934. doi: 10.1161/CIR.0b013e31829b5b44
21. de Souza e Silva CG, Kaminsky LA, Arena R, Christle JW, Araújo CGS, Lima RM, et al. A reference equation for maximal aerobic power for treadmill and cycle ergometer exercise testing: analysis from the FRIEND registry. *Eur J Prev Cardiol.* (2018) 25:742–50. doi: 10.1177/2047487318763958
22. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation.* (2012) 126:2261–74. doi: 10.1161/CIR.0b013e31826fb946
23. Kokkinos P, Kaminsky LA, Arena R, Zhang J, Myers J. New generalized equation for predicting maximal oxygen uptake (from the fitness registry and the importance of exercise national database). *Am J Cardiol.* (2017) 120:688–92. doi: 10.1016/j.amjcard.2017.05.037
24. Kokkinos P, Kaminsky LA, Arena R, Zhang J, Myers J. A new generalized cycle ergometry equation for predicting maximal oxygen uptake: The Fitness Registry and the Importance of Exercise National Database (FRIEND). *Eur J Prev Cardiol.* (2018) 25:1077–82. doi: 10.1177/2047487318772667

25. Forman DE, Myers J, Lavie CJ, Guazzi M, Celli B, Arena R. Cardiopulmonary exercise testing: relevant but underused. *Postgrad Med.* (2010) 122:68–86. doi: 10.3810/pgm.2010.11.2225
26. St Sauver JL, Grossardt BR, Finney Rutten LJ, Roger VL, Majerus M, Jensen DW, et al. Rochester epidemiology project data exploration portal. *Prev Chronic Dis.* (2018) 15:E42. doi: 10.5888/pcd15.170242
27. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ III. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. *Mayo Clin Proc.* (2012) 87:1202–13. doi: 10.1016/j.mayocp.2012.08.012
28. Yawn BP, Yawn RA, Geier GR, Xia Z, Jacobsen SJ. The impact of requiring patient authorization for use of data in medical records research. *J Fam Pract.* (1998) 47:361–5.
29. National Center for Health Statistics (U.S.) CoCCCoPaHA, World Health Organization. *The International Classification of Diseases, 9th Revision, Clinical Modification: ICD. 9. CM.* Ann Arbor, MI: Commission on Professional and Hospital Activities (1978).
30. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ III, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *Am J Epidemiol.* (2011) 173:1059–68. doi: 10.1093/aje/kwq482
31. Melton LJ III. History of the rochester epidemiology project. *Mayo Clin Proc.* (1996) 71:266–74. doi: 10.4065/71.3.266
32. Centers for Disease Control and Prevention, AARP, American Medical Association. *Promoting Preventive Services for Adults 50-64: Community and Clinical Partnerships*. Atlanta, GA: National Association of Chronic Disease Directors (2009).
33. Centers for Disease Control and Prevention, Administration on Aging, Agency for Healthcare Research and Quality, and Centers for Medicare and Medicaid Services. *Enhancing Use of Clinical Preventive Services Among Older Adults*. Washington, DC: AARP (2011).
34. Kaminsky LA, Arena R, Myers J. Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: data from the fitness registry and the importance of exercise national database. *Mayo Clin Proc.* (2015) 90:1515–23. doi: 10.1016/j.mayocp.2015.07.026
35. Robinson MM, Dasari S, Konopka AR, Johnson ML, Manjunatha S, Esponda RR, et al. Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. *Cell Metab.* (2017) 25:581–92. doi: 10.1016/j.cmet.2017.02.009
36. Carbone S, Kim Y, Kachur S, Billingsley H, Kenyon J, De Schutter A, et al. Peak oxygen consumption achieved at the end of cardiac rehabilitation predicts long-term survival in patients with coronary heart disease. *Eur Heart J Qual Care Clin Outcomes.* (2021). doi: 10.1093/ehjqcco/qcab032. [Epub ahead of print].
37. Witvrouwen I, Pattyn N, Gevaert AB, Possemiers N, Van Craenenbroeck AH, Cornelissen VA, et al. Predictors of response to exercise training in patients with coronary artery disease – a subanalysis of the SAINTEX-CAD study. *Eur J Prev Cardiol.* (2019) 26:1158–63. doi: 10.1177/2047487319828478
38. De Schutter A, Kachur S, Lavie CJ, Menezes A, Shum KK, Bangalore S, et al. Cardiac rehabilitation fitness changes and subsequent survival. *Eur Heart J Qual Care Clin Outcomes.* (2018) 4:173–9. doi: 10.1093/ehjqcco/qcy018
39. Rengo JL, Khadanga S, Savage PD, Ades PA. Response to exercise training during cardiac rehabilitation differs by sex. *J Cardiopulm Rehabil Prev.* (2020) 40:319–24. doi: 10.1097/HCR.0000000000000536
40. Ozemek C, Laddu D, Hauer T, Rouleau C, Campbell T, Wilton S, et al. Abstract 10666: the influence of multimorbidity on cardiorespiratory fitness and mortality in patients completing cardiac rehabilitation. *Circulation.* (2019) 140(Suppl_1):A10666. Available online at: https://www.ahajournals.org/doi/10.1161/circ.140.suppl_1.10666
41. Listerman J, Bittner V, Sanderson BK, Brown TM. Cardiac rehabilitation outcomes: impact of comorbidities and age. *J Cardiopulm Rehabil Prev.* (2011) 31:342–8. doi: 10.1097/HCR.0b013e31822f189c

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SYSTEMATIC REVIEW
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Polypills for Primary Prevention of Cardiovascular Disease: A Systematic Review and Meta-Analysis

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Purpose: To evaluate the effect of polypills on the primary prevention of cardiovascular (CV) events using data from clinical trials.

Methods: We searched PubMed, Web of Science, EBSCO, and SCOPUS throughout May 2021. Two authors independently screened articles for the fulfillment of inclusion criteria. The RevMan software (version 5.4) was used to calculate the pooled risk ratios (RRs) and mean differences (MDs), along with their associated confidence intervals (95% CI).

Results: Eight trials with a total of 20653 patients were included. There was a significant reduction in the total number of fatal and non-fatal CV events among the polypill group [RR (95% CI) = 0.71 (0.63, 0.80); *P*-value < 0.001]. This reduction was observed in both the intermediate-risk [RR (95% CI) = 0.76 (0.65, 0.89); *P*-value < 0.001] and high-risk [RR (95% CI) = 0.63 (0.52, 0.76); *P*-value < 0.001] groups of patients. Subgroup analysis was performed based on the follow-up duration of each study, and benefits were only evident in the five-year follow-up duration group [RR (95% CI) = 0.70 (0.62, 0.79); *P*-value < 0.001]. Benefits were absent in the one-year-or-less interval group [RR (95% CI) = 0.77 (0.47, 1.29); *P*-value = 0.330]. Additionally, there was a significant reduction in the 10-year predicted cardiovascular risk in the polypill group [MD (95% CI) = −3.74 (−5.96, −1.51); *P*-value< 0.001], as compared to controls.

Conclusion: A polypill regimen decreases the incidence of fatal and non-fatal CV events in patients with intermediate- and high- cardiovascular risk, and therefore may be an effective treatment for these patients.

Keywords: primary prevention, cardiovascular events, antihypertensives, polypill, lipid-lowering

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INTRODUCTION

Globally, the prevalence of cardiovascular disease (CVD) has almost doubled in the last 30 years, with CVD mortality increasing from 12.1 million cases in 1990 to 18.6 million cases in 2019. The leading cause of these numbers include suboptimal preventive methods and uncontrolled atherosclerotic cardiovascular disease (ASCVD) risk factors (1, 2). To combat these issues, the World Heart Federation launched a global campaign to reduce premature mortality due to CVD

by 25 percent by 2025 (3). In fact, Atherosclerotic cardiovascular diseases are due to a chronic lifetime exposure of individuals to CVD risk factors such as high blood pressure levels (4). In 2003, Wald and Law coined the term polypill to describe a combination of active pharmaceutical components that had the potential to reduce the burden of cardiovascular diseases by more than 80% (5). The polypill has proven to increase adherence rates for secondary prevention, which is significant because roughly one third of people face adherence issues to blood pressure or lipid lowering medications, and that a large proportion of all CVD events (about 9% in Europe) is due to poor adherence to vascular medications alone (6, 7). However, the use of such a pill in primary prevention – especially for those with an intermediate to high risk of cardiovascular disease – is not well-understood, given that no studies have been performed to assess the long-term effectiveness of such an intervention (8). Intermediate risk is defined is defined by a Framingham score of 10–20% or an INTERHEART score of 10–15, while high risk is defined by a Framingham score of >20% or an INTERHEART score of >16. Despite its cost-effectiveness and ease of use, multiple drawbacks have hampered the wide scale prescription of polypills, most notably physician hesitancy and the inability to tailor doses according to patient needs (9). Trials were designed to investigate the benefits of polypill use, yet they generally assessed the improvement in CVD in terms of risk factors such as blood pressure and lipid profiles rather than clinical outcomes such as fatal and non-fatal cardiovascular events (8). Moreover, these studies were usually performed in developing countries and could not be generalized to developed countries (10). New trials have since been published that account

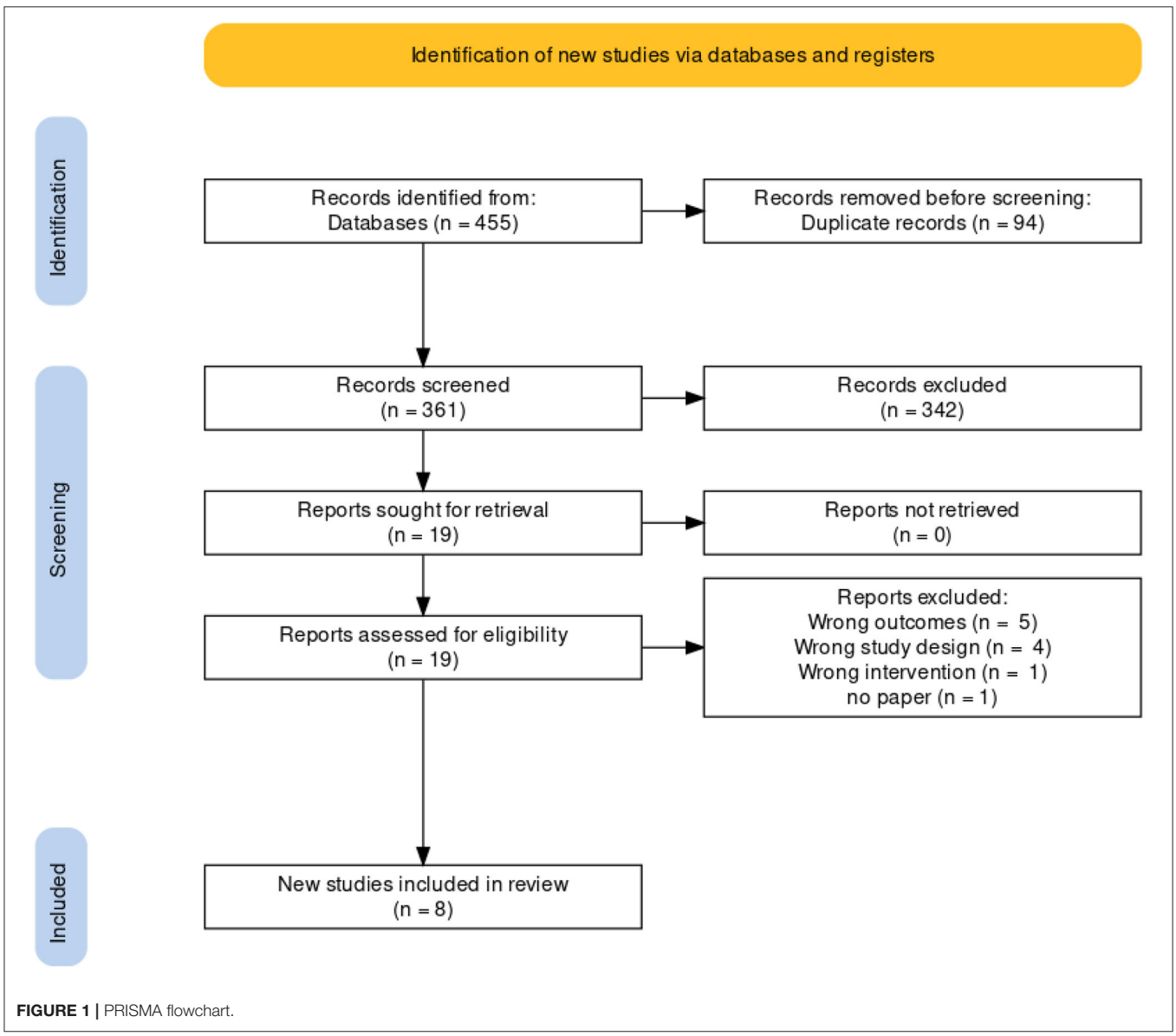

FIGURE 1 | PRISMA flowchart.

for such problems. Considering the newly published studies, the aim of this meta-analysis is to focus on assessing the effectiveness of polypills in preventing clinical outcomes as strokes and Myocardial infarctions and mortality rather than assessing their effect on lipid or blood pressure changes,such parameters have already been discussed in several previous studies so centered our attention on tangible clinical outcomes instead. We also discussed possible solutions to any drawbacks that this treatment might possess.

METHODS

Search and Identification of Studies

A comprehensive literature search was carried out in May 2021 on the following databases: PUBMED, WOS, EBSCO, and SCOPUS. Search terms used were (polypill OR "fixed dose" OR "drug combination" OR "drug combinations") AND ("heart outcomes prevention" OR "primary prevention" OR "Framingham score" OR "estimated 10-year cardiovascular risk"). Reviews and book chapters were excluded. Additional manual searches were performed through the "related articles" feature in PubMed. Lastly, all references from the reviewed articles were checked for any articles that might have been missed in the original literature search.

Selection Process and Inclusion Criteria

Once the searches were completed, the software programme Covidence was used to perform the de-duplication of citations and for the screening process. From the searches, two review authors (M.A, O.K) reviewed the title and abstract of each paper and retrieved potentially relevant references. Following this initial screening, we obtained the full text of potentially relevant studies, and the two authors (M.A, O.K) independently screened them using predetermined inclusion criteria. The inclusion criteria are as follows: (1) trials that include the use of a fixed-dose combination of at least 2 drugs, one of them being a lipid lowering- and the other being a blood pressure lowering-drug; (2) trials that include (even if not limited to) primary prevention of cardiovascular disease in patients with at least one cardiovascular risk factor or calculated cardiovascular risk score but no previous cardiovascular events; and (3) trials that either report the effect of the FDC on the incidence of cardiovascular events such as stroke or MI or that report the 10-year predicted cardiovascular risk (Framingham Score) after FDC use. Disagreements were resolved by discussion and a decision was reached after agreement between the reviewers. We only included trials in our meta-analysis and excluded any observational studies, case reports, and non-English articles.

Outcomes

The primary outcome was the effect of Polypill on total fatal and non-fatal cardiovascular events as Myocardial infarction, stroke, heart failure or angina. Secondary outcomes were effect of polypill on the predicted 10-year cardiovascular risk for the studies which lacked data regarding our primary outcome, so the mean difference of the cardiovascular risk score was used as a predictor of these fatal and non-fatal CV events. The number of participants who discontinued treatment due to adverse effects and the total adverse events along with myalgia were also analyzed.

Data Extraction

Two review authors (O.K, M.A) independently extracted data and consulted the principal investigator when needed. They extracted details of the study design, participant characteristics, study setting, intervention, and comparator. They also extracted outcome data, which included the composite of death from cardiovascular causes and adverse events such as myocardial infarction, stroke, heart failure, resuscitated cardiac arrest, arterial revascularization, and angina. The study quality was assessed as part of the data extraction strategy with RoB 2 revised Cochrane risk-of-bias tool for randomized trials. The tool is structured into a fixed set of domains of bias, focussing on trial's design, conduct, and reporting. In each domain, signaling questions elicit information about features of the trial that are relevant to risk of bias. A judgement about the risk of bias in each domain is generated based on answers to the signaling questions. Judgement can express 'some concerns', be 'Low' or 'High' risk of bias (11). Quality of evidence was assessed using GRADE approach through tools on their website gradepro.

Statistical Analysis

A meta-analysis was carried out to evaluate the impact of a fixed-dose combination of lipid lowering and blood pressure lowering drugs, as compared to placebo or non-pharmacological intervention among participants without cardiovascular disease that were at an intermediate or high risk of developing CVD. RevMan 5.4 was used for statistical analysis. If we detected heterogeneity among studies (p-value <0.05), we used leave one out test or subgroup analysis to resolve the heterogeneity. We used fixed effects model if we observed no heterogeneity among studies, otherwise a random effects model was used if a significant heterogeneity was observed (p-value < 0.05). Our analysis followed the PRISMA Statement Checklist to ensure a high-quality review (12).

RESULTS

Study Inclusion

Four hundred and fifty five publications were extracted from literature search and, after the removal of duplicates, 361 moved on to the next stage of review. After title and abstract screening, 18 studies were eligible for a full-text review. Of these, eight studies were eligible for inclusion in our meta-analysis. A detailed description is illustrated in the PRISMA flow chart (**Figure 1**). Of the eight trials included, six contained data that compared the incidence of fatal and non-fatal cardiovascular events – such as stroke, myocardial infarction, heart failure, cardiovascular death, and revascularisation – between patients who received a polypill treatment and those who received placebos/minimal pharmacological care. Two studies did not contain information about CV events, so we instead compared the mean difference in the 10-year predicted cardiovascular risk between patients who

TABLE 1 | Summary of the included studies (13–21).

ID	NCT	Study region	Design	Duration	Study arms	Endpoints (outcomes) conclusion	Conclusion
TIPS 3 - (16)	NCT01646437	India Philippines Colombia Bangladesh Canada Malaysia Indonesia Tunisia Tanzania	Double-blind, RCT of polypill vs. placebo	4.25 years	1-Experimental: Polycap vs. matching placebo 2-Experimental: Aspirin vs. matching placebo 3-Experimental: Vitamin D vs. matching placebo	Primary: 1- composite of CV events, which includes major CVD (ie, CV death, non-fatal stroke, non-fatal MI) 2- heart failure, resuscitated cardiac arrest, or arterial revascularization. 3- Secondary outcomes are (1) major CVD and (2) the composite ofmajor CVD, heart failure, resuscitated cardiac arrest, arterial revascularization, or angina with evidence of ischemia 3- cancer 4- heart failure, resuscitated cardiac arrest, arterial revascularization, or angina with evidence of ischemia. Other outcomes: 1- all-cause mortality 2- incident and recurrent CV events 3- visual acuity 3- age-related macular degeneration 4- cognitive function 5- adverse events (including bleeding 6- economic analysis related outcomes	Results of the TIP-3 study will be key to determining the appropriateness of FDC therapy as a strategy in the global prevention of CVD
HOPE 3, (26)	NCT00468923	Canada (in Asians)	Quadruple, RCT of polypill vs. placebo	5.6 years	Placebo Comparator: Rosuvastatin Placebo Comparator: Candesartan/HCT	primary: 1- The composite of; Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke. 2- resuscitated cardiac arrest, non-fatal myocardial infarction, heart failure, arterial revascularizations Secondary: 1- Total mortality 2- The components of the co-primary endpoints	Candesartan/ hydrochlorothiazide had fewer effects in reducing blood pressure in Chinese and rosuvastatin reduced low-density lipoprotein cholesterol to a lesser extent in Asians compared with non-Asians. There was no overall reduction in clinical events with lowering blood pressure in either Asians or non-Asians, whereas there were clear and consistent benefits with lipid lowering in both. Despite extensive analyses, there is no obvious explanation for the observed findings. Future studies need to include larger numbers of individuals from different regions of the world to ensure that the results of trials are applicable globally.

(Continued)

TABLE 1 | Continued

ID	NCT	study region	Design	Duration	Study Arms	Endpoints (outcomes) conclusion	Conclusion
Polyiran	NCT01271985	Iran	A two-group, pragmatic, cluster randomized trial of polypill vs. minimal care	5 years	Experimental: polypill and minimal care (polypill arm) no intervention: minimal care	1- primary outcome: occurrence of MCVE within five years of enrolment 2- Secondary outcomes: a- non-cardiovascular causes of death (including neoplastic, respiratory, hepatic, renal and other medical causes), b- adherence to the polypill, c- effects of the interventions on MCVE, d- changes in blood pressure and low-density lipoprotein (LDL) cholesterol during the trial.	Use of a fixed-dose combination of aspirin, atorvastatin, and two blood pressure-lowering drugs was associated with a significantly lower risk of major cardiovascular events in individuals aged 50–75 years in a real-life setting. This pragmatic trial provides evidence that a polypill strategy could be considered as part of preventive programmes to reduce cardiovascular disease burden among eligible adults, especially in LMICs
HOPE 4	NCT01826019	Colombia and Malaysia	Cluster-randomized controlled trial of polypill Vs. usual care	12 months	Experimental: combinations of anti-hypertensive medications (both low and high doses) and a lipid lowering agent (e.g., statin) No intervention: usual care	Primary outcomes: 1- change in Framingham Risk Score (FRS) between the intervention and control after1 year 2- Difference in major CV events at 6 years Secondary outcomes: 1- Change in systolic BP (SBP) 2- Proportion of participants with well-controlled blood pressure at 6 and 12 months 3- Change in HDL, LDL, total cholesterol, triglycerides, and glucose levels 4- Change in smoking status 5- Change in IHRS and ChRS 6- no. of participants recieving anti-hypertensives 7- clinical events (e.g. death, CVD development, hospitalizations)	This strategy is effective, pragmatic, and has the potential to substantially reduce cardiovascular disease compared with current strategies that are typically physician based.
SCCS, (20)	NCT02278471	United States	Open-label, parallel RCT comparing polypill to usual care	12 months	Experimental arm: Polypill No Intervention arm: Usual Care	Primary outcomes: 1- Systolic Blood Pressure 2-Medication Adherence-Percentage of Pills Taken 3-LDL Cholesterol Secondary Outcome Measures: 1-Systolic Blood Pressure 2- Medication Adherence 3- Drug Metabolite Profile 4- Insulin Resistance 5 – *Inflammatory* Profile	A polypill-based strategy led to greater reductions in systolic blood pressure and LDL cholesterol level than were observed with usual care in a socioeconomically vulnerable minority population

(Continued)

TABLE 1 | Continued

ID	NCT	study region	Design	Duration	Study Arms	Endpoints (outcomes) conclusion	Conclusion
Soliman, (21)	NCT00567307	Sri Lanka	Open-label, parallel RCT comparing Polypill to Standard Practice	3 months	Experimental: The Red Heart Pill 2b (Polypill) (A) Active Comparator: Standard Practice Group (B)	1- Reduction of the Estimated 10-year Total Cardiovascular Risk Score	Polypill was simpler and achieved comparable risk factor reductions, highlighting its potential usefulness in the prevention of CVD. Further studies assessing the Polypill in developing countries should take into consideration the study design lessons and challenges that we encountered.
Malekzadeh et al. (18)	ISRCTN43076122	Iran	Double- blind, parallel RCT of polypill vs placebo	12 months	Experimental: polypill non- interventional: placebo	Primary outcome measure Combined cardiovascular events (MI, new onset angina, coronary artery surgery, stroke or sudden cardiac death) Secondary outcome measures 1. Total mortality 2. Gastrointestinal bleeding	The effects of the polypill on blood pressure and lipid levels were less than anticipated, raising questions about the reliability of the reported compliance. There is a case for a fully powered trial of a polypill for the prevention of cardiovascular disease.

received the polypill and patients who received placebos/minimal care. We were able to extract this outcome from a third study as well, so its results were included along with the other two in the Meta-Analysis. The summary and the risk of bias of the included studies are shown in **Table 1** and **Figure 2**, respectively. The quality of evidence table is presented in **Table 2**.

Analyses

The total number of patients included in the polypill treatment group of our meta-analysis is 10,240, with a mean age of 61.1. The placebo/minimal care group included 10,413 patients, with a mean age of 61.38. Females represented 43.7% of the total study population, and males represented 56.4%. Detailed baseline characteristics are shown in **Table 3**.

The total number of patients in the six included clinical trials with the outcome of fatal and non-fatal cardiovascular events is 20,147. Of the 9,993 who received a polypill, 432 experienced a fatal or non-fatal cardiovascular event, as compared to 619 out of 10,154 in the placebo/minimal care group. The pooled risk ratio for patients in the polypill treatment group was 0.71 (95% CI 0.63 to 0.80, p value > 0.00001), as compared to patients in the placebos/minimal care group. No publication bias was observed. We also found no statistically significant heterogeneity among the included studies ($p = 0.49$), as shown in **Figure 3**.

We performed subgroup analysis because trials varied according to their follow-up duration. We ran one analysis for the three trials that had a follow-up period of 12 months or less, and another analysis for the three that reported a 5-year follow-up period. The pooled risk ratio of the 12-months-or-less follow-up subgroup between patients who received the polypill treatment and patients who received minimal care was 0.77 (95% CI 0.47 to 1.29, p-value $= 0.33$). We found no statistically significant heterogeneity among the three studies ($p = 0.77$), as shown in **Figure 4**. The pooled risk ratio of the 5-year follow-up subgroup between patients who received the polypill treatment and patients who received placebos was 0.70 (95% CI 0.62 to 0.79, p-value < 0.00001). No statistically significant heterogeneity was found among the studies ($p = 0.15$), as shown in **Figure 4**.

We performed a third subgroup analysis, as four clinical trials studied patients with an intermediate risk of cardiovascular disease, while two trials studied patients with a high risk of cardiovascular disease. The pooled risk ratio between patients who received the polypill treatment and patients who received placebos/minimal care in the intermediate-risk subgroup was 0.76 (95% CI 0.65 to 0.89, p value $= 0.0005$). We found no statistically significant heterogeneity among the four studies ($p = 0.86$), as shown in **Figure 5**. The pooled risk ratio between patients who received the polypill treatment and patients who received placebos/minimal care in the high-risk subgroup was 0.63 (95% CI 0.52 to 0.76, p-value > 0.00001). No statistically significant heterogeneity was found between the studies ($p = 0.28$), as shown in **Figure 5**.

The total number of patients in the three trials that were analyzed for the difference in 10-year predicted cardiovascular disease risk is 1,805 (854 received the polypill treatment and 951 received placebos/minimal care). The pooled mean difference for patients in the polypill group was −3.74 (95% CI −5.96 to −1.51,

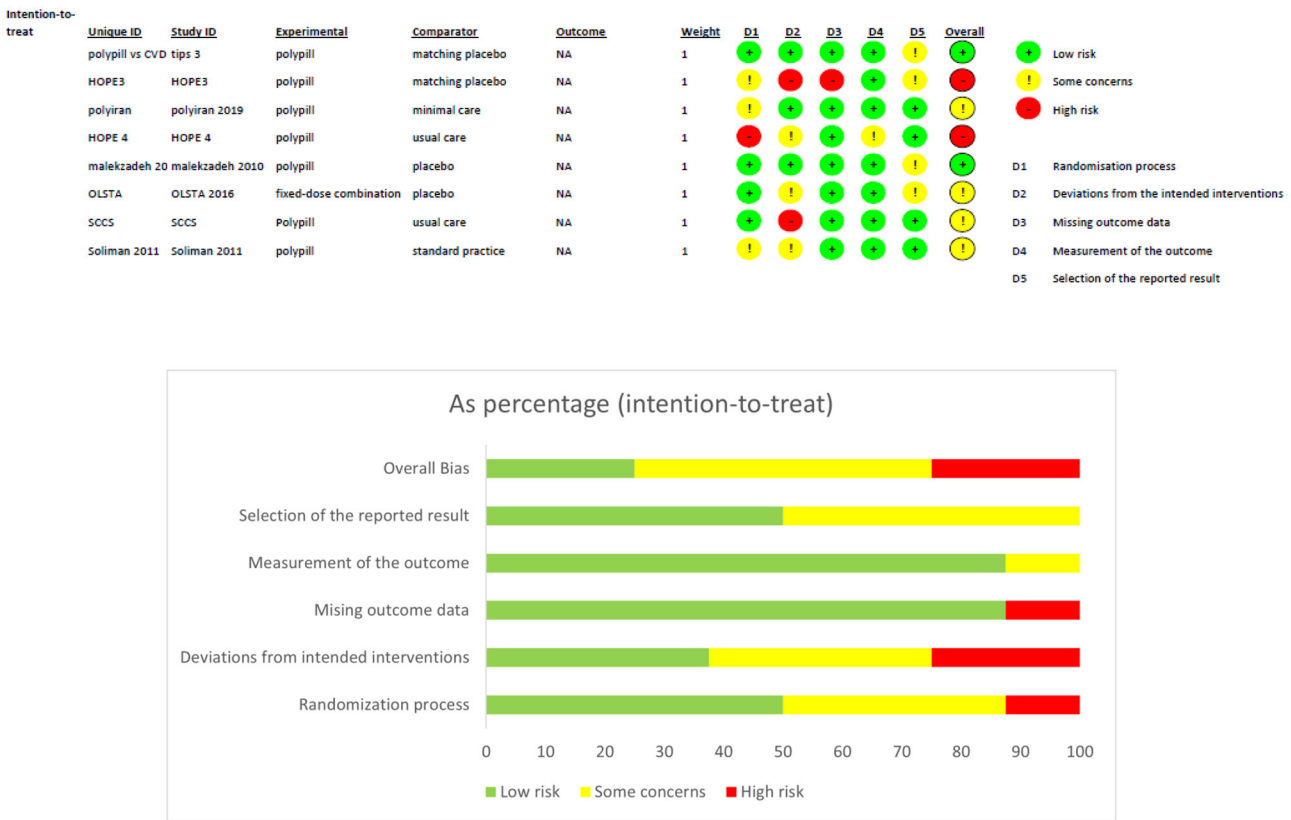

FIGURE 2 | Risk of bias assessment and graph.

p-value = 0.001), as compared to those in the minimal-care group. No statistically significant heterogeneity was found among the three included studies ($p = 0.69$), as shown in **Figure 6**.

Safety

Five studies reported the total number of adverse events experienced by patients. Five hundred and forty one out of a total of 6,457 patients in the polypill group experienced adverse events, compared to 408 out of 6,387 patients in the minimal care/placebo group. The pooled risk ratio of total adverse events between patients who received the polypill treatment and patients who received minimal care/placebo was 1.03 (95% CI 0.70 to 1.51, p-value = 0.87). Statistically significant heterogeneity was found among the five studies, which was not resolved by using leave-one-out test ($p < 0.00001$), as shown in **Figure 7**.

Discontinuation of treatment due to adverse events was reported in three of the eight clinical trials that were included in our meta-analysis. Two hundred and sixty two out of the 6,282 patients in the polypill group of these trials discontinued the polypill due to adverse events, while 157 in the placebo/minimal care group discontinued treatment due to adverse events. The pooled risk ratio of discontinuation due to adverse events between patients who received the polypill treatment and patients who received minimal care/placebo was 1.80 (95% CI 1.12 to 2.87, p-value = 0.01). We found statistically significant heterogeneity among the three studies), as shown in **Figure 8**, so we performed leave-one-out test by removing (26) study, and the heterogeneity was solved ($p = 0.73$) and the results were (RR = 1.40, [95% CI = 1.12 to 1.75], $P = 0.003$).

In the included clinical trials, myalgia was found to be the most reported adverse event. Three of the eight trials in our meta-analysis reported myalgia. Of the 6,146 patients in the polypill group of these three trials, myalgia was reported in 56 patients; of the 6,131 patients in the minimal care/placebo group, myalgia was reported in 50 patients. The pooled risk ratio of myalgia between patients who received the polypill treatment and patients who received minimal care/placebo was 1.15 (95% CI 0.81 to 1.64, p-value = 0.44). We found no statistically significant heterogeneity among the three trials ($p = 0.65$), as shown in **Figure 9**.

DISCUSSION

Our meta-analysis suggests that a polypill regimen for primary prevention in patients with intermediate- to high-cardiovascular risk reduces the incidence of fatal and non-fatal cardiovascular outcomes, including death from cardiovascular causes, myocardial infarction, stroke, heart failure, resuscitated cardiac arrest, arterial revascularization, and angina. Eight studies met inclusion criteria, wherein the pooled outcomes

TABLE 2 | Quality of evidence table using GRADE approach.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)		
Total fatal and non fatal cardiovascular events												
6	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	None	432/9993 (4.3%)	619/10154 (6.1%)	RR 0.71 (0.63 to 0.80)	18 fewer per 1,000 (from 23 fewer to 12 fewer)	⨁⨁⨁◯ Moderate	Critical
Difference in 10 year predicted cardiovascular risk												
3	Randomized trials	Serious	Not serious	Serious[a]	Not serious	None	854	951	-	MD 3.74 lower (5.96 lower to 1.51 lower)	⨁⨁⨁◯◯ Low	Critical
Total adverse events												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	541/6457 (8.4%)	408/6387 (6.4%)	RR 1.03 (0.70 to 1.51)	2 more per 1,000 (from 19 fewer to 33 more)	⨁⨁⨁ High	Important

CI, confidence interval; MD, mean difference; RR, risk ratio.

[a]There are different follow up durations in the studies so by performing subgroup analysis to duration less than 12 months and less than 5 years heterogeneity was resolved. There is also another subgrouping that may account for this heterogeneity which is based on the cardiovascular risk into intermediate and high subgroups so we performed also a subgroup analysis for this and again this resolved the heterogeneity.

of 10,240 patients receiving a polypill were compared with 10,413 patients who did not receive a polypill. Previous studies revealed that the effect of the polypill on fatal and non-fatal ASCVD events was uncertain (8). This may have been due to low-quality evidence, since previous trials had a short duration and were not designed to assess the clinical outcome of the polypill (rather, the data used in analysis were mainly reported as adverse events). The previous trials had several disadvantages that were overcome in the trials included in our meta-analysis, and results could not be generalized because they were restricted to low income and non-developed countries. In our analysis, the HOPE 3 study included 21 countries throughout the world, such as the United States, Australia, and multiple countries in Europe. The TIPS 3 study also included patients from North America. Another major pitfall of previous trials was that they often reported the effect of the polypill on the CV risks themselves, such as blood pressure and blood lipid levels, rather than clinical outcomes. Again, this issue was resolved in our meta-analysis by several trials that were specifically designed to assess the effect of the polypill on a composite of CV deaths, MI, stroke, and revascularisation. In these studies, such as TIPS 3, HOPE 3, and PolyIran, we witnessed a pooled risk ratio between the polypill and comparator groups of 0.70 (95% CI 0.62 to 0.79, p-value > 0.00001). In studies that did not report these outcomes, we instead analyzed the 10-year predicted cardiovascular risk – for example, the SCCS and Soliman trials showed a significant -3.74 (95% CI -5.96 to -1.51, p-value $= 0.001$) mean difference between treatment and minimal care/placebo groups.

Interestingly, the efficacy of the polypill was witnessed in a phase 4 study performed on 1,193 patients in Mexico – the treatment showed even better-than-expected improvement of all-cause mortality and vascular-related mortality, as compared to a phase 3 trial, after the use of the CNIC-Ferrer polypill (22). Lastly, the problem of short trial duration – rendering the evidence of previous studies uncertain – was corrected by multiple trials in our analysis having a mean follow up of 5 years. Apart from the trial design of previous studies, the polypill treatment itself was flawed in multiple ways, with the inability to tailor dosage and individualize therapy as the most pressing issue. However, a range of different formulations and doses – as opposed to only one – might surmount this problem. Patients could potentially be stratified based on their risk scores, with a different formulation and different dose used in each stratum. Additionally, as was done in the TIPS 3 study, any patient who might still have uncontrolled blood pressure or dyslipidaemia could be prescribed additional medication. Another barrier of previous research was the agreement of patients to use a polypill while being asymptomatic, as well as their fear of adverse events while using pharmaceutically active components. However, an interview surveying Australian patients showed that they favored using a prophylactic approach (23). Our meta-analysis showed no significant difference in the total adverse events between the polypill and the comparator group ($p = 87$), which suggests that the polypill is safe to use as a preventive measure over long periods of time. The willingness of physicians to prescribe polypills to their patients was also considered, as many seemed reluctant about the

TABLE 3 | Baseline characteristics of patients (13–21).

	Study arms		Number of patients in each group		Age (years)			
ID	**Intervention (the name and the form of the durg)**	**Control (placeob or another durg)**	**Intervention**	**Control**	**Intervention**	**Control**	**Cardiovascular risk**	**Blood pressure (mmHg)**
TIPS 3 - (16)	1- Polycap (thiazide 25 mg, atenolol 100 mg, ramipril 10 mg, simvastatin 40 mg) taken once daily 2- Aspirin 75 mg daily 3- Vitamin D 60,000 IU monthly	Matching placebo	5,713		63.9 (6.6)		—	SBP: 144.5 (16.8) DBP: 83.9 (9.7)
HOPE 3	1- polypill (Candesartan 16 mg/HCT 12.5 mg) 2- Rosuvastatin 10 mg	Placebo	(Candesartan /HCTZ) Asian: 3,118 non-asians: 3,238	Asian: 3123 non-asians: 3,226	Asian: 64.75 (5.99) non-asians: 66.40 (6.62)	Asian: 64.88 (6.02) non-asians: 66.41 (6.58)	Framingham risk score, N (%): (polypill) Asian: 23.28 (13.41) non asian: 21.37 (11.99) (placebo) asian: 22.68 (13.31) non-asians: 21.22 (11.96)	(polypill) Asian: 139.86 (14.15)/82.55 (9.14) Non-Asian: 136.61 (15.16) / 81.38 (9.58) (placebo) Asian: 139.82 (14.44) / 82.31 (9.00) Non-Asians: 135.96 (14.9) / 81.21 (9.45)
Polyiran	1- polypill 1, (hydrochloro thiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg and enalapril 5 mg.) 2- (those who develop cough at follow up): polypill 2, (valsartan 40 mg instead of enalapril 5 mg)	Minimal care	3,421	3,417	mean (95%CI) 59.3 (59.0–59.6)	59.7 (59.4–60.1)	—	polypill: SBP: 130.2 DBP: 78.5 minimal care: SBP: 131.9 DBP: 79.2
HOPE 4	Polypill: combination of two antihypertensives included an angiotensin receptor blocker or angiotensin converting enzyme inhibitor coupled with a diuretic or calcium channel blocker, with atorvastatin at 20 mg or rosuvastatin at 10 mg	Usual care	644	727	65.1 (9.1)	65.8 (9.7)	Control: 35.5% (22.3) Intervention: 32.6% (21.4)	Control: SBP: 151.7 (15.6) DBP: 85.3 (11.9) intervention: SBP: 152.1 (15.4) DBP: 84.7 (12.0)
SCCS	(polypill) once daily containing: Atorvastatin 10 mg, amlodipine 2.5 mg, losartan 25 mg, and hydrochlorothiazide 12.5 mg.	Usual care	148	155	56 (6)	56 (6)	Control: 13.0 ± 10.1 Intervention: 12.4 ± 8.9	SBP: control: 140 (17) intervention: 140 (18)

(Continued)

TABLE 3 | Continued

ID	Study arms		Number of patients in each group		Age (years)		Cardiovascular risk	Blood pressure (mmHg)
	Intervention (the name and the form of the durg)	Control (placeob or another durg)	Intervention	Control	Intervention	Control		
Soliman et al. (21)	The polypill (Red Heart pill 2b): -aspirin (75 mg), -simvastatin (20 g), -lisinopril (10 mg) and -hydrochlorothiazide (12.5 mg)	Standard practice (management of their CVD risk according to the usual care given to participants in similar conditions)	105	111	59.0 ± 6.9	59.2 ± 7.4	Polypill: 44.1 ± 20.3 standard practice: 41.6 ± 19.8	SBP: 165.2 ± 18.2
Malekzadeh	Polypill: • Aspirin (81 mg) • Enalapril (2.5 mg) • Etorvastatin (20 mg) • Hydrochlorothiazide (12.5 mg)	Placebo	241	234	59.0 ± 6.5	59.1 ± 7.3	—	Polypill: SBP: 124.8 ± 17.3 DBP: 78.4 ± 10.4 placebo: SBP: 130.3 ± 17.4 DBP: 81.2 ± 9.7
OLSTA	1- FDC therapy (40 mg olmesartan medoxomil, 20 mg rosuvastatin) 2- 40 mg olmesartan medoxomil 3- 20 mg rosuvastatin	Placebo	1-FDC therapy group = 61 2-Olmesartan medoxomil group = 36 3-Rosuvastatin group = 36	29	1-FDC therapy group = 61.9 (8.1) 2-Olmesartan medoxomil group = 59.5 (6.9) 3-Rosuvastatin group = 61.8 (8.0)	62.5 (8.2)		-Intervention: 1-FDC therapy group = SBP: 150.6 (11.9) DBP: 92.0 (7.4) 2-Olmesartan medoxomil group = SBP: 150.6 (15.5) DBP: 93.3 (5.0) 3-Rosuvastatin group = SBP: 148.9 (13.3) DBP: 92.9 (6.5) -Control: SBP: 152.2 (14.5) DBP: 92.5 (7.0)

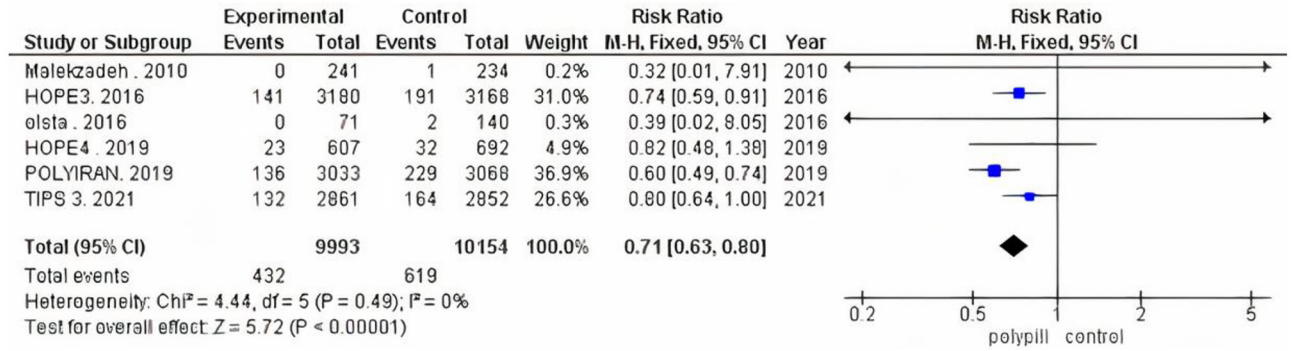

FIGURE 3 | Forest plot of total fatal and non-fatal CV events.

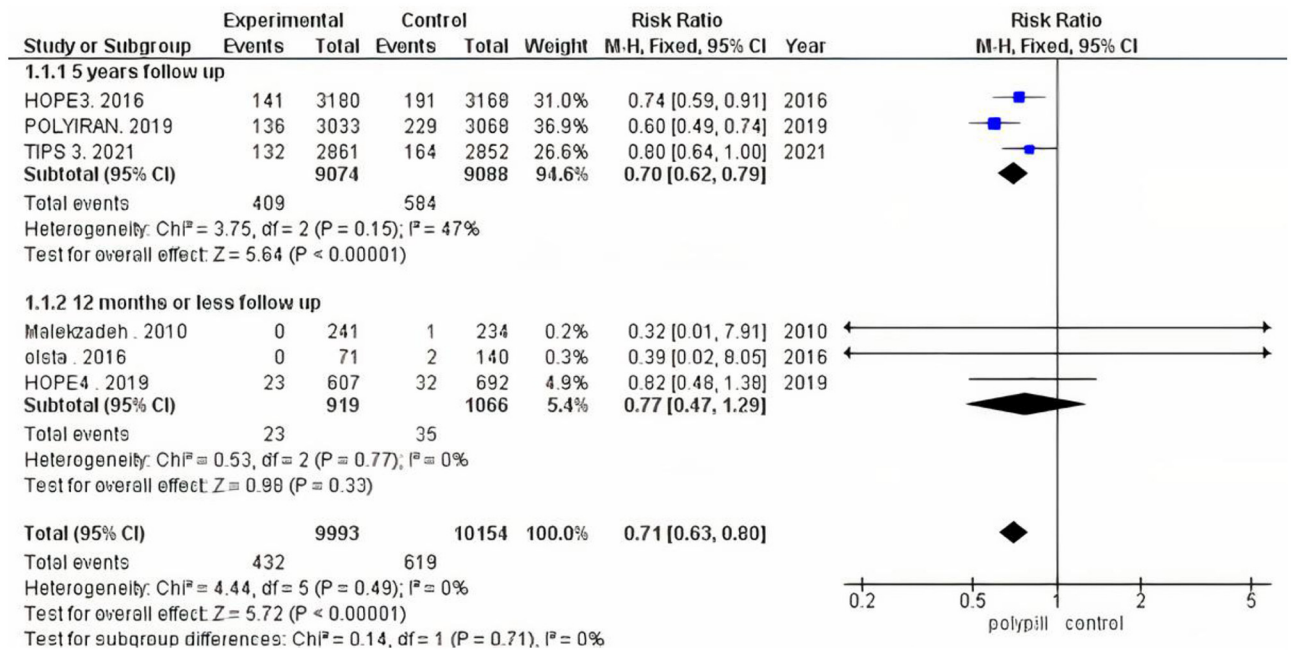

FIGURE 4 | Forest plot of the 12-months-or-less and 5-year follow-up subgroup analysis.

risk-benefit ratio of such a treatment. This meta-analysis may therefore serve as evidence to convince hesitant physicians about the benefits of these fixed-dose combination drugs. The advantages of a polypill regimen, as proven by our meta-analysis, include a decrease in the incidence of fatal and non-fatal CV events. In addition, polypill treatment is cost effective (24, 25); however, cost reductions may still be required in some developing countries (26).

There are many areas of interest that require further study regarding polypill use in primary prevention for intermediate- and high- cardiovascular risk patients. Firstly, additional research is needed in order to determine the most convenient drug combination possible for the reduction of the incidence of ASCVD events. Secondly, polypill trials that stratify patients according to their cardiovascular risk score should be designed and conducted.

Implication for Future Practice

Evidence has shown that a risk-based strategy is better than a blood pressure-based approach or a combination (blood pressure and risk) strategy in terms of cardiovascular disease prevention (9). For that reason, we suggest that the prescription and use of a polypill be based upon risk scores, as shown in studies such as the TIPS 3, HOPE 4, and SCCS trials. Efficient CVD prevention should include the judicious use of evidence-based protocols, founded in the practices of risk-based management and a team approach. Strategies to reduce CVD should integrate socioenvironmental approaches

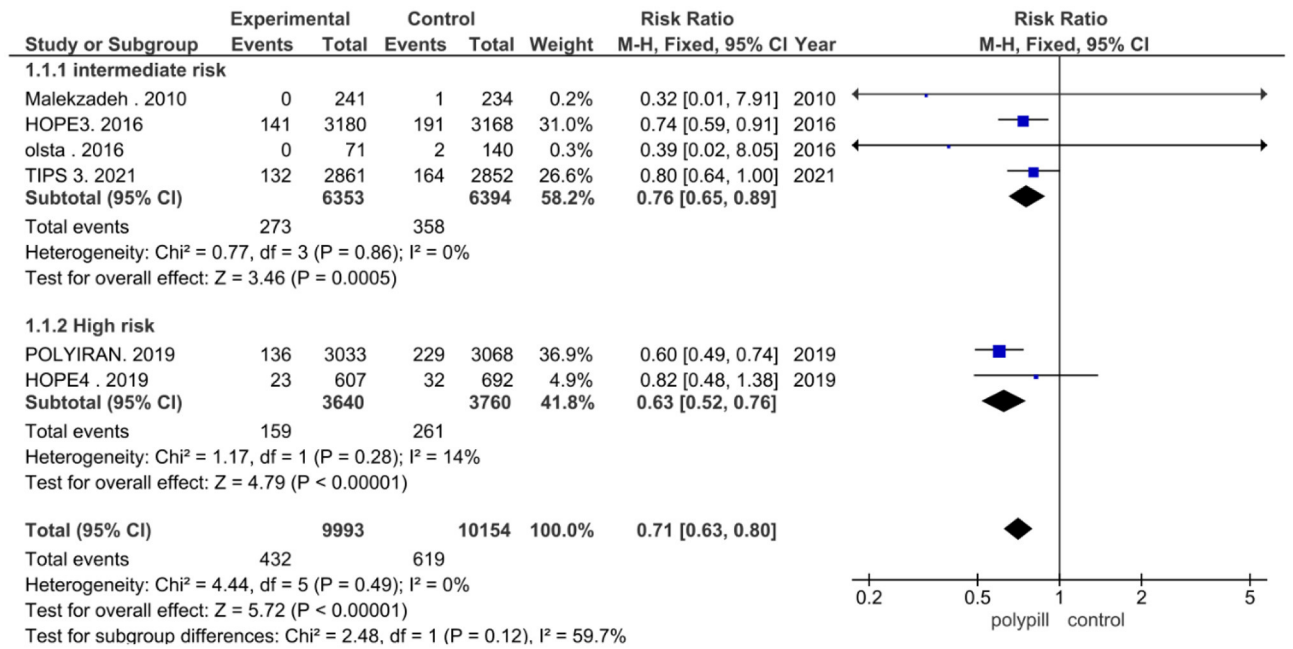

FIGURE 5 | Forest plot according to risk stratification: intermediate and high-risk patients subgroup analysis.

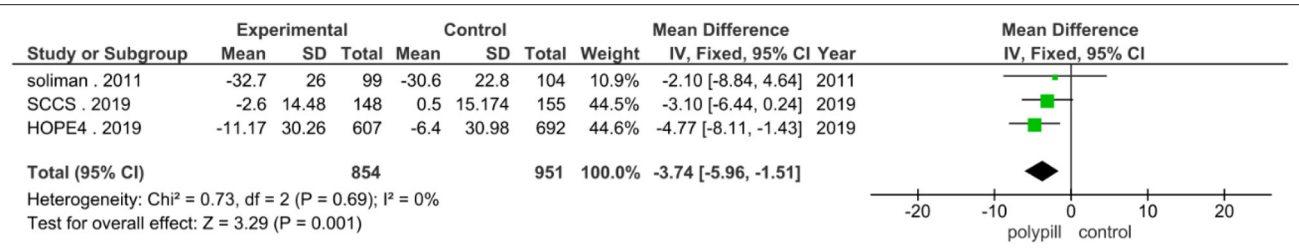

FIGURE 6 | Forest plot of the difference in the 10-year predicted cardiovascular risk.

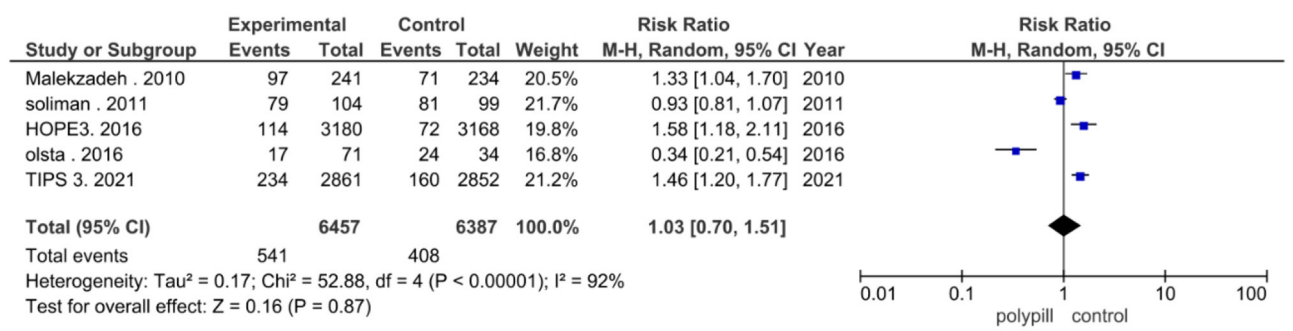

FIGURE 7 | Forest plot of the total adverse events.

and community resources into physician care, as well. This multidimensional treatment plan was successfully illustrated in the HOPE 4 study, which proved that a comprehensive model of care involving physicians and family substantially improved blood pressure control and reduced cardiovascular disease risk (13, 27).

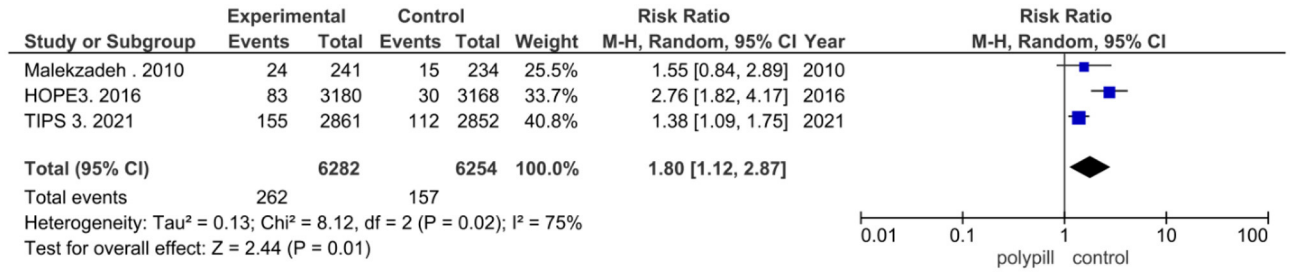

FIGURE 8 | Forest plot of treatment discontinuation due to adverse events.

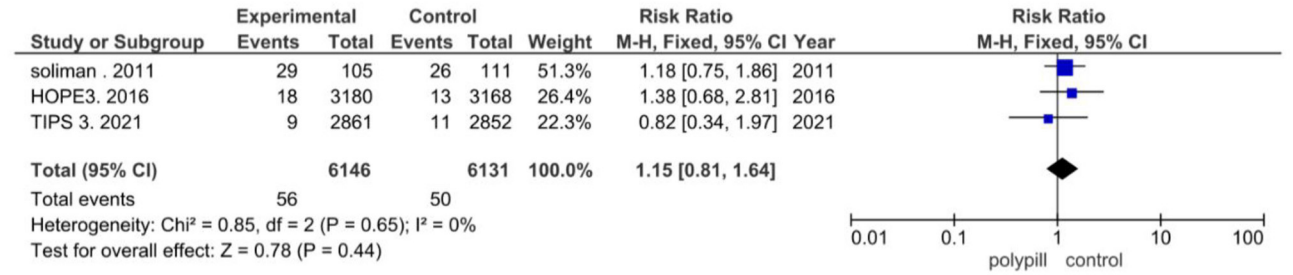

FIGURE 9 | Forest plot of myalgia.

Limitations of This Meta-Analysis

Due to the lack of clinical outcomes in some studies (such as the SCCS and Soliman trials), we had to utilize the difference in 10-year predicted cardiovascular risk as another assessment tool in our analysis.

CONCLUSION

A polypill that combines a lipid-lowering and blood pressure-lowering drug reduces the incidence of fatal and non-fatal cardiovascular events in patients with an intermediate and high risk of cardiovascular disease and could be used as a primary preventive approach in these patients. Limitations of previous studies regarding the polypill were all corrected by the results of the new trials that were included in this meta-analysis. The fear that the polypill may be a scattergun approach in primary prevention, leaving a rather asymptomatic population sentenced to lifelong treatment, was disproven by our study.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

OK: design and concept and writing and review. KM: data analysis and interpretation. MA: data extraction. JS: review and editing. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Circulation*. (2019) 140:e596–646. doi: 10.1161/CIR.0000000000000678
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 Study. *J Am College Cardiol*. (2020) 76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
3. Dugani S, Gaziano TA. 25 by 25: Achieving global reduction in cardiovascular mortality. *Current Cardiolo Reports*. (2016). 18:10. doi: 10.1007/s11886-015-0679-4
4. Vasan RS, Massaro JM, Wilson PW, Seshadri S, Wolf PA, Levy D, et al. Antecedent blood pressure and risk of cardiovascular disease: the Framingham heart study. *Circulation*. (2002). 105:48–53. doi: 10.1161/hc0102.101774
5. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ (Clinical research ed.)*. (2003) 326:1419. doi: 10.1136/bmj.326.7404.1419
6. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis

of prevalence and clinical consequences. *Europ Heart J*. (2013) 34:2940–8. doi: 10.1093/eurheartj/eht295
7. Wald DS, Bestwick JP, Raiman L, Brendell R, Wald NJ. Randomised trial of text messaging on adherence to cardiovascular preventive treatment (INTERACT trial). *PloS ONE*. (2014) 9:e114268. doi: 10.1371/journal.pone.0114268
8. de Cates AN, Farr MR, Wright N, Jarvis MC, Rees K, Ebrahim S, et al. Fixed-dose combination therapy for the prevention of cardiovascular disease. *Cochrane Database Sys.* (2014) 4:CD009868. doi: 10.1002/14651858.CD009868.pub2
9. Roy A, Naik N, Srinath Reddy K. Strengths and limitations of using the polypill in cardiovascular prevention. *Current Cardiol Reports*. (2017) 19:45. doi: 10.1007/s11886-017-0853-y
10. Sukonthasarn A, Chia YC, Wang JG, Nailes J, Buranakitjaroen P, Van Minh H, et al. The feasibility of polypill for cardiovascular disease prevention in Asian Population. *J Clin Hyperten (Greenwich, Conn.)*. (2021) 23:545–55. doi: 10.1111/jch.14075
11. Sterne J, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ (Clin Res ed)*. (2019) 366:4898. doi: 10.1136/bmj.l4898
12. Page MJ, McKenzie JE, Bossuyt, PM, Boutron I, Hoffmann TC et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Res ed.)*. (2021) 372:n71. doi: 10.1136/bmj.n71
13. Kernan WN, Launer LJ, Goldstein LB. What is the future of stroke prevention?: debate: polypill vs. personalized risk factor modification. *Stroke*. (2010) 41(10 Suppl):S35–8. doi: 10.1161/STROKEAHA.110.592022
14. Lonn EM, Bosch J, López-Jaramillo P, Zhu J, Liu L, Pais P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. *N Eng J Med*. (2016) 374:2009–20. doi: 10.1056/NEJMoa1600175
15. Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, Gharavi A, et al. (2019). Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. *Lancet*. 394:672–83. doi: 10.1016/S0140-6736(19)31791-X
16. Yusuf S, Joseph P, Dans A, Gao P, Teo K, Xavier D, et al. International polycap study 3 investigators. polypill with or without aspirin in persons without cardiovascular disease. *N Eng J Med*. (2021) 384:216–28. doi: 10.1056/NEJMoa2028220
17. Park JS, Shin JH, Hong TJ, Seo HS, Shim WJ, Baek SH, et al. Efficacy and safety of fixed-dose combination therapy with olmesartan medoxomil and rosuvastatin in Korean patients with mild to moderate hypertension and dyslipidemia: an 8-week, multicenter, randomized, double-blind, factorial-design study (OLSTA-D RCT: OLmesartan rosuvaSTAtin from Daewoong). *Drug Design, Develop Therap*. (2016) 10:2599–609. doi: 10.2147/DDDT.S112873
18. Malekzadeh F, Marshall T, Pourshams A, Gharravi M, Aslani A, Nateghi A, et al. A pilot double-blind randomised placebo-controlled trial of the effects of fixed-dose combination therapy ('polypill') on cardiovascular risk factors. *Int J Clin Prac*. (2010) 64:1220–7. doi: 10.1111/j.1742-1241.2010.02412.x
19. Schwalm JD, McCready T, Lopez-Jaramillo P, Yusoff K, Attaran A, Lamelas P, et al. A community-based comprehensive intervention to reduce cardiovascular risk in hypertension (HOPE 4): a cluster-randomised controlled trial. *Lancet*. (2019) 394:1231–42. doi: 10.1016/S0140-6736(19)31949-X
20. Muñoz D, Uzoije P, Reynolds C, Miller R, Walkley D, Pappalardo S, et al. Polypill for cardiovascular disease prevention in an underserved population. *N Eng J Med*. (2019) 381:1114–23. doi: 10.1056/NEJMoa1815359
21. Soliman EZ, Mendis S, Dissanayake WP, Somasundaram NP, Gunaratne PS, Jayasingne, et al. A polypill for primary prevention of cardiovascular disease: a feasibility study of the world health organization. *Trials*. (2011) 12:3. doi: 10.1186/1745-6215-12-3
22. Castellano JM, Verdejo J, Ocampo S, Rios MM, Gómez-Álvarez E, Borrayo G, et al. Clinical effectiveness of the cardiovascular polypill in a real-life setting in patients with cardiovascular risk: the SORS study. *Archives Med Res*. (2019) 50:31–40. doi: 10.1016/j.arcmed.2019.04.001
23. Liu H, Massi L, Laba TL, Peiris D, Usherwood T, Patel A, et al. Patients' and providers' perspectives of a polypill strategy to improve cardiovascular prevention in Australian primary health care: a qualitative study set within a pragmatic randomized, controlled trial. *Circ. Cardiovasc Quality Outcomes*. (2015) 8:301–8. doi: 10.1161/CIRCOUTCOMES.115.001483
24. Wald NJ, Luteijn JM, Morris JK, Taylor, D, Oppenheimer P. Cost-benefit analysis of the polypill in the primary prevention of myocardial infarction and stroke. *Europ J Epidemiol*. (2016) 31:415–26. doi: 10.1007/s10654-016-0122-1
25. Newman J, Grobman WA, Greenland P. Combination polypharmacy for cardiovascular disease prevention in men: a decision analysis and cost-effectiveness model. *Preventive Cardiol*. (2008) 11:36–41. doi: 10.1111/j.1520-037x.2007.06423.x
26. Lamy A, Lonn E, Tong W, Swaminathan B, Jung H, Gafni A, et al. The cost implication of primary prevention in the HOPE 3 trial. *Europ Heart J. Quality Care Clin Outcomes*. (2019) 5:266–71. doi: 10.1093/ehjqcco/qcz001
27. Karwalajtys T, Kaczorowski J. An integrated approach to preventing cardiovascular disease: community-based approaches, health system initiatives, and public health policy. *Risk Manag Healthcare Policy*. (2010) 3:39–48. doi: 10.2147/RMHP.S7528

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Nationwide Initiation of Cardiovascular Risk Treatments During the COVID-19 Pandemic in France: Women on a Slippery Slope?

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Objectives: This study examines the initiation of prescribed medication treatments for cardiovascular risk (antihypertensives, lipid-lowering drugs, oral anticoagulants in atrial fibrillation, and smoking cessation medications) during the COVID-19 pandemic in the French population.

Methods: For each year between 2017 and 2021, we used the French National Insurance Database to identify the number of people with at least one reimbursement for these medications but no reimbursement in the previous 12 months. We computed incidence rate ratios (IRRs) between 2017–2019 and, respectively 2020 and 2021 using Poisson regression adjusted for age and 2017–2019 time trends. We recorded the number of lipid profile blood tests, Holter electrocardiograms, and consultations with family physicians or cardiologists.

Results: In 2020, IRR significantly decreased for initiations of antihypertensives (−11.1%[CI95%, −11.4%;−10.8%]), lipid-lowering drugs (−5.2%[CI95%, −5.5%;−4.8%]), oral anticoagulants in atrial fibrillation (−8.6%[CI95%, −9.1%;−8.0%]), and smoking cessation medications (−50.9%[CI95%, −51.1%;−50.7%]) compared to 2017–2019. Larger decreases were found in women compared to men except for smoking cessation medications, with the sex difference increasing with age. Similar analyses comparing 2021 to 2017–2019 showed an increase in the initiation of lipid-lowering drugs (+ 11.6%[CI95%, 10.7%;12.5%]) but even lower rates for the other medications, particularly in women. In addition, the 2020 number of people visiting a family physician or cardiologist decreased by 8.4 and 7.4%. A higher decrease in these visits was observed in those over 65 years of age

compared to those under 65 years of age. A greater use of teleconsultation was found in women.

Conclusion: The COVID-19 pandemic heavily impacted the initiation of medication treatments for cardiovascular risk in France, particularly in women and people over 65 years.

Keywords: cardiovascular, medication, initiation, cardiovascular risk, COVID-19 pandemic

INTRODUCTION

Healthcare use has been challenged during the COVID-19 pandemic (1), particularly during the first epidemic wave and the first lockdown, which lasted from 17 March to 10 May 2020 in France (2, 3). Two subsequent lockdowns, although less restrictive than the first one, were implemented in France to contain the second epidemic wave- from 30 October to 15 December- and the third one – from 3 April to 2 May 2021. Furthermore, a curfew was in place between the second and third lockdowns because of a constant high circulation of SARS-CoV-2 in France. The dramatic decrease in medical visits during the first epidemic wave might have delayed and decreased the screening of arterial hypertension and other cardiovascular risk factors as well as hampered the initiation of related medication treatments as found in other studies (4, 5).

The main objective of this study was to analyze time-trends in the initiation of medication treatments for cardiovascular risk factors and diseases, such as antihypertensive and lipid-lowering treatments, smoking cessation medications and oral anticoagulants in patients with atrial fibrillation among the overall French population in 2020-2021 compared to 2017–2019. This first objective included the analysis of age and sex specific trends. A secondary objective was to analyze healthcare use during the same periods (family physician (general practitioner) and cardiologist visits, biological and clinical screening of cardiovascular risk factors).

MATERIALS AND METHODS

Data Sources

Data from the French National Insurance Databases ("Système National des Données de Santé"[SNDS]) were used. This database records reimbursements of health care expenditure for all persons with French health insurance coverage, which corresponds approximately to the overall French population, i.e., approximatively 66 millions of inhabitants (6). All persons born in France, French or foreign, and legal immigrants are covered by a universal health insurance. More specifically, this database contains individual details of all reimbursed medication treatments delivered outside of hospitals. All cardiovascular medications are reimbursed in France. Individual socio-demographic data are also available such as date of birth, sex, or whether the person is covered by the Complementary Universal Health Insurance (CMUc), which provides free access to healthcare to people with a low annual income (6). As all care might not be reimbursed at 100%, people living in France have to subscribe to a complementary insurance. For people with low income, an equivalent of these complementary insurance – the CMUc – is granted for free.

Population Selection and Cardiovascular Treatments

For each treatment of interest described below and for each year from 2017 to 2021, we selected all individuals in France (both metropolitan France and overseas territories) who had a first reimbursement for each medication treatment but no reimbursement in the past 12 months. As restriction measures were implemented in both metropolitan and overseas regions, the latter were included in the analysis and represented 3.2% of the study population. We used data until 23 May 2021 (week 20). Medication treatments for hypertension, dyslipidemia, smoking cessation and atrial fibrillation were considered, including antihypertensive, lipid-lowering agents (statins or others), smoking cessation products (nicotine replacement therapy (NRT) or varenicline), and oral anticoagulants when used for the prevention of thrombo-embolism in patients with atrial fibrillation (vitamin-K antagonist or direct oral anticoagulants). For antihypertensive medications, we first looked at the initiation of an antihypertensive medication whatever the class, and then according to the main classes of antihypertensive medications namely diuretics, betablockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). All these treatments were identified using "Anatomical Therapeutic Chemical Classification" (ATC) C02 except for C02CA02 (indoramin mainly used for migraine treatment), C03 (diuretics), C07 (betablocker), C08 (calcium channel blocker [CCB]), C09 (renin-angiotensin antagonist) for antihypertensives, N07BA (NRT, varenicline) for smoking cessation medications, C10 for lipid-lowering agents, B01AA (vitamin-K antagonist), B01AE07 (dabigatran), B01AF01 (rivaroxaban), and B01AF02 (Apixaban) for oral anticoagulant use in atrial fibrillation (edoxaban not yet commercialized in France). The use of oral anticoagulants in atrial fibrillation indication was determined using an algorithm described previously (7, 8). Briefly, the algorithm attributed the AF indication of oral anticoagulants regarding specific medical procedures, hospital diagnoses, delivery of other drugs and the presence of a competing cause (orthopedic surgery, venous thromboembolism, valvulopathy, etc. . .).

Some treatments, particularly antihypertensive medications, might not be prescribed for hypertension but in secondary

TABLE 1 | Numbers and characteristics of people who initiated a therapy of interest between 2017 and 2021, and corresponding age-standardized rates in France.

	Antihypertensive medication					Lipid-lowering treatment					Oral anticoagulants for atrial fibrillation					Smoking cessation medications				
	2017	**2018**	**2019**	**2020**	**2021[a]**	**2017**	**2018**	**2019**	**2020**	**2021[a]**	**2017**	**2018**	**2019**	**2020**	**2021[a]**	**2017**	**2018**	**2019**	**2020**	**2021[a]**
Number of persons initiating treatment																				
	1,491,569	1,513,627	1,642,450	1,518,686	NA	817,259	800,615	896,118	873,747	NA	224,756	229,956	243,213	227,409	NA	327,872	675,257	865,697	696,351	NA
Age-standardized[b] rates of persons initiating treatment																				
All sexes	2.2%	2.3%	2.4%	2.2%	NA	1.2%	1.2%	1.3%	1.3%	NA	313.2[c]	310.6[c]	318.8[c]	309.1[c]	NA	0.5%	1.0%	1.3%	1.0%	NA
Men	2.1%	2.1%	2.2%	2.1%	NA	1.4%	1.3%	1.4%	1.3%	NA	408.8[c]	399.5[c]	392.6[c]	401.8[c]	NA	0.5%	1.0%	1.3%	1.1%	NA
Women	2.3%	2.4%	2.6%	2.4%	NA	1.1%	1.1%	1.3%	1.2%	NA	238.3[c]	240.5[c]	259.5[c]	237.1[c]	NA	0.5%	1.0%	1.3%	1.0%	NA
Characteristics																				
Mean age, years	56.7	57.3	58.4	57.9	58.1	62.6	63.2	64.1	63.9	63.9	75.3	75.2	75.2	75.0	75.0	47.5	47.7	46.9	46.9	47.5
Age groups,%																				
<45	23.2	22.1	20.3	21.1	20.7	8.9	8.2	7.3	7.5	7.2	2.1	2.2	2.2	2.4	2.5	40.6	39.6	42.4	43.1	41.8
45–64	42.7	42.4	41.2	41.4	41.5	45.7	44.5	42.3	42.6	42.8	15.6	15.6	15.4	15.8	15.9	49.1	49.2	47.0	46.1	46.2
65–74	18.6	19.2	20.9	20.8	20.9	25.9	27.0	28.8	29.1	29.2	25.0	25.3	25.7	26.2	25.8	8.9	9.6	9.0	9.2	10.1
75–84	10.1	10.6	11.9	11.1	11.4	14.0	14.6	15.9	15.1	15.3	31.6	31.1	30.9	30.1	30.1	1.3	1.5	1.4	1.5	1.8
≥85	5.4	5.6	5.8	5.6	5.6	5.5	5.7	5.8	5.7	5.5	25.7	25.9	25.7	25.4	25.7	0.1	0.1	0.2	0.2	0.2
Women,%	55.5	55.9	58.2	56.3	55.1	48.7	48.7	52.0	51.0	50.5	45.2	45.5	47.3	46.0	45.6	50.4	50.0	49.7	49.5	49.2
History of cardiovascular diseases,%	24.1	24.7	24.7	25.1	23.5	42.0	43.8	42.0	42.3	39.2	81.7	79.6	76.1	73.7	69.3	19.7	19.9	19.2	19.9	20.4
CMUc,%	11.3	11.1	11.0	11.9	12.6	11.2	11.0	10.7	11.7	12.4	7.2	6.8	7.1	7.9	8.7	7.6	11.6	13.3	14.8	16.5
Nursing home,%	12.7	12.4	11.3	5.7	4.9	13.7	13.4	12.2	6.2	5.5	17.5	17.1	16.3	9.8	8.8	6.0	8.8	10.1	4.5	3.7

[a]*Up to week 20 (23 May 2021);* [b]*rates standardized based on the age structure of the 2017 French census population;* [c]*rates per 100,000 inhabitants.*
Italics: month of May incomplete for the year 2021.
NA: not applicable; CMUc: Complementary Universal Medical Coverage.

prevention after an ischemic event for instance. Therefore we conducted complementary analyses by dissociating initiation of these medications in people with a history of cardiovascular disease from people without such history.

Covariates

The following socio-demographics data were collected: age, sex, CMUc for people under 60 years, and whether the person lived in a nursing home. For those who initiated antihypertensive medication, lipid-lowering medication or smoking cessation medications, a history of cardiovascular disease was searched in the past 5 years according to the hospital diagnosis of cardiovascular disease or long-term disease status (LTD) using International Classification of Disease-10th revision (ICD-10) codes.

Healthcare Consumptions Related to the Initiation of Cardiovascular Risk Treatments

In 2019 and 2020, medical visits with family physicians or cardiologists were recorded, with a limit of one visit per week per person. The number of teleconsultations with a family physician or a cardiologist was also distinguished. In France, teleconsultation has been authorized since June 2018. However, its use remained very low until the COVID-19 pandemic. Then, a 100% reimbursement of teleconsultations was acted in March 2020, prolonged until 2022. Furthermore, a phone-only teleconsultation was eligible to full reimbursement from April to May 2020.

For the years 2017–2021, reimbursements for blood sample analysis for lipid profile were searched using codes from the Nomenclature of Procedures in Laboratory Medicine and the use of Holter electrocardiogram (ECG) using codes from the French Medical Classification for Clinical Procedures. Two different measures were computed: the number of patients with at least one procedure in the year and the overall number of these procedures per year.

Statistical Analysis

Using the national census population data provided by the National Institute of Statistics and Economic Studies, we calculated the rates of persons initiating the above-mentioned treatments of interest in France from 2017 to 2021. These rates were given by year, sex and age as national statistics gave us population census according to sex and age. Then, we estimated the annual incidence rate ratio (IRR) and weekly IRR between 2020–2021 and the previous time-period of 2017–2019 using Poisson regression adjusted for age and time trends from 2017 to 2019. In these regressions models, the census population was used as offset variable, and all were checked for over-dispersion. Models were stratified according to sex and age groups. We conducted a sensitivity analysis using an interrupted time series analysis to evaluate level changes introduced by the COVID-19 pandemic regarding the initiation of medication of interest. Results were detailed in **Supplementary Material**.

Statistical analyses were conducted using SAS Entreprise Guide 9.4.6.0.

Ethics Approval

In line with French governmental regulations and the National Ethics Committee, no patient consent was required. The databases used in the study contained pseudonymized patient information. Furthermore, full access to the SNDS is granted to the National Agency for Public Health (Santé Publique France) by decree (regulatory decision DE-2011-078).

RESULTS

Time Trends in the Initiation of Medical Treatment

In 2020, 1,518,686 persons initiated antihypertensive medication, 8,73,747 lipid-lowering medications, 2,27,409 oral anticoagulants in atrial fibrillation indication, and 6,96,351 smoking cessation medications (**Table 1** and **Supplementary Table 1**). These numbers and the corresponding age-standardized rates were lower in 2020 than in 2019 regardless of the treatment (**Table 1** and **Supplementary Table 1**). This observation was made for both men and women.

After accounting for age and 2017–2019 time trends, IRRs (**Figure 1** and **Supplementary Table 2**) showed an overall decrease in the initiation of antihypertensive medications (−11.1%[CI95%, −11.4%;−10.8%]), lipid-lowering medications (−5.2%[CI95%, −5.5%;−4.8%]), oral anticoagulants for atrial fibrillation (−8.6%[CI95%, −9.1%;−8.0%]), and smoking cessation medications (−50.9%[CI95%, −51.1%;−50.7%]) in 2020 compared to 2017–2019. Regarding antihypertensive medications, a greater decrease was recorded for diuretics (−19.6%[CI95%, −20.1%; −19.1%]) and angiotensin-receptor blockers (ARBs) (−18.7[CI95%, −19.2%; −18.1%]) (data not shown).

During the first lockdown of 2020, the initiation of the treatments of interest fell sharply down (−30% for antihypertensive therapy, −38% for lipid-lowering medications, −70% for oral anticoagulants in atrial fibrillation indication, and −69% for smoking cessation medications) (**Figure 1** and **Supplementary Table 2**). After the first lockdown, despite less marked decreases in the initiation of these treatments, the rates did not return to normal for the initiation of antihypertensive medications (−12%, respectively in weeks 20–43 and −3% in weeks 44–51 of 2020 compared to the same weeks in 2017–2019), oral anticoagulants in atrial fibrillation indication (−7% in weeks 20–43 and −3% in weeks 44–51) and smoking cessation medications (−50% for weeks 20–43 and 44–51). A significant increase in the initiation of lipid-lowering medications was nevertheless found for the second lockdown of 2020 (+ 8% compared to same weeks in 2017–2019) (**Figure 1** and **Supplementary Table 2**).

In early 2021, different time-trends were observed with a lower decrease in the initiation of antihypertensive therapy in 2021 (−3.8%[CI95%, −4.4%;−3.2%]) than in 2020

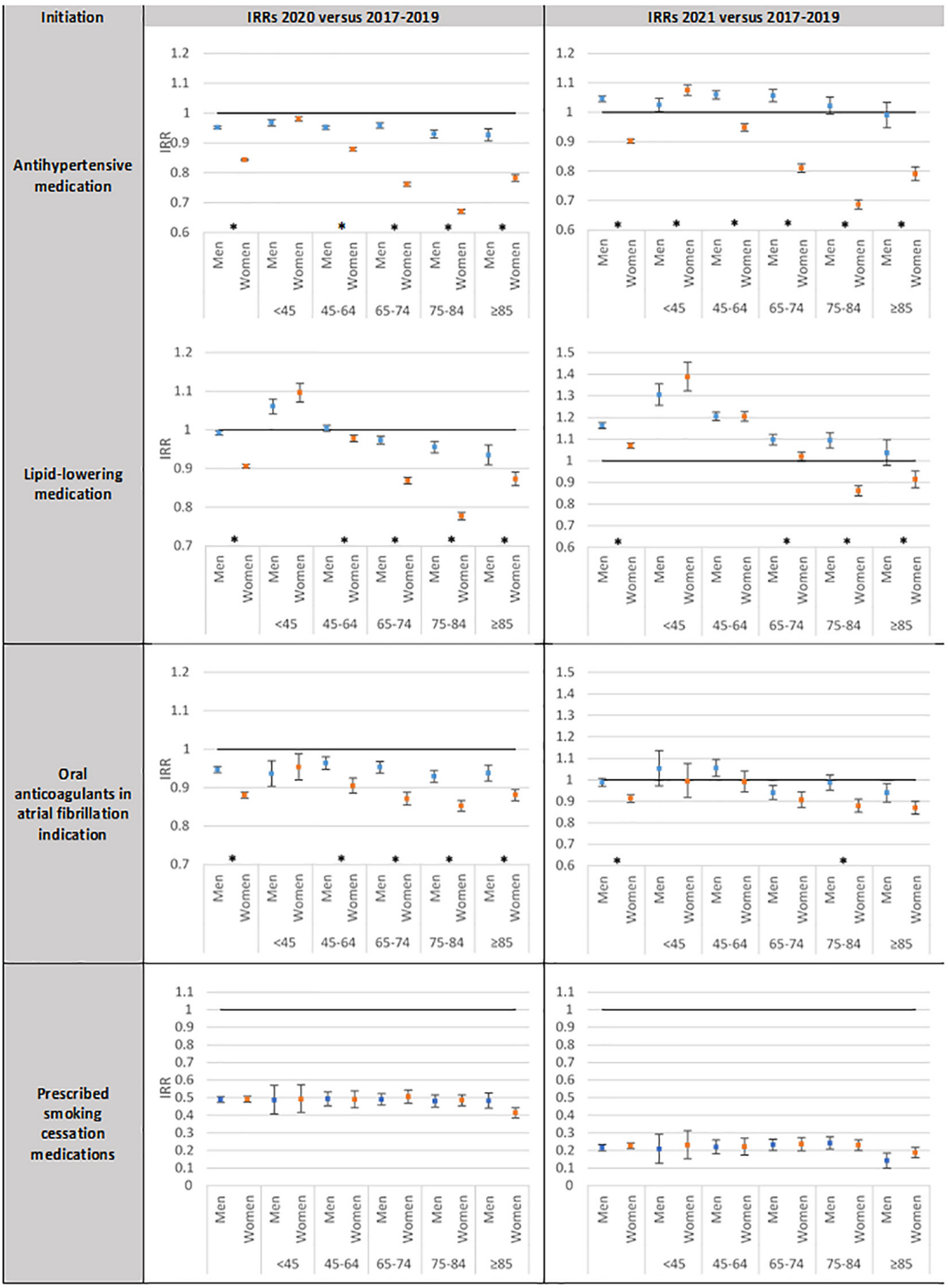

FIGURE 1 | Incidence rate ratio (IRR)[a] and 95% confidence intervals (95% CI) between the rates of treatment initiation, respectively in 2020 and 2021 compared to the rates of initiation in 2017–2019 according to lockdown/curfew time-periods. Gray: lockdown period; light gray: curfew period. [a]adjusted for age and 2017–2019 time trends; W: weeks.

(−11.1%[CI95%, −11.4%;−10.8%]) compared to 2017–2019 as well as for oral anticoagulant for atrial fibrillation (−4.9%[CI95%, −6.1%; −3.6%] in 2021 vs. −8.6%[CI95%, −9.1%;-−8.0%] in 2020) (**Figure 1** and **Supplementary Table 2**). An increase in the initiation of lipid-lowering medications (+ 11.6%[CI95%, 10.7%;12.5%]) was found in 2021 compared to 2017–2019 whereas initiation of smoking cessation medications continued to decrease in 2021, increasing the gap with previous time period in 2017–2019 (−77.8%[CI95%, −78.1%;−77.6%]) (**Figure 1** and **Supplementary Table 2**).

Differences According to Sex, Age, and History of Cardiovascular Diseases

When looking at the time trends in the initiation of the treatments of interest according to sex, age, and history of cardiovascular disease, substantial differences were observed (**Figure 2** and **Supplementary Figures 1–3**).

First, according to sex, greater decreases were registered in women compared to men regarding the initiation of antihypertensive medication (−15.6%[CI95%, −15.9%; −15.3%] vs. −4.8%[CI95%, −5.2%; −4.4%], $p < 0.0001$), lipid-lowering medications (−9.4%[CI95%, −9.9%; −8.9%] vs. −0.8%[CI95%, −1.3%; −2.4%], $p < 0.0001$), and oral anticoagulants for atrial fibrillation (−11.9%[CI95%, −12.7%;−11.2%] vs. −5.3%[CI95%, −6.1%; −4.5%], $p < 0.0001$) between 2020 and 2017–2019 (**Figure 2**). These differences persisted in 2021 according to sex: the time trends between 2017–2019 and 2021 were + 4.5%[CI95%, 3.5%;5.4%] vs. −9.8%[CI95%, −10.6%; −9.1%] ($p < 0.0001$) for the initiation of antihypertensive medication, + 16.3%[CI95%, 14.9%; 17.6%] vs. + 7.0%[CI95%, 5.7%; 8.2%] ($p < 0.0001$) for lipid-lowering medications initiation, and −1.1%[CI95%, −2.9%;−0.7%] vs. −8.7%[CI95%, −10.4%; −7.0%] ($p < 0.0001$) for oral anticoagulants in atrial fibrillation indication for men and women, respectively. On the contrary, no difference between men and women was found for the initiation of smoking cessation medications.

Second, except for prescribed smoking cessation medications, the decrease in the initiation of the other treatments of interest between 2017–2019 and 2020 intensified with age, with the highest decrease recorded in people aged 75−84 years with −24.0%[CI95%, −24.7%; −23.4%] for antihypertensive medications, −15.4%[CI95%, −16.2%; −14.5%] for lipid-lowering medications, and −11.1%[CI95%, −12.1%; −10.0%] for oral anticoagulants in atrial fibrillation indication (**Supplementary Figure 1**). The differences observed between men and women also varied with age with higher differences in the elderly (**Figure 2**).

Third, the sex and age differences highlighted above were accentuated when looking at the initiation of treatments in people without a history of cardiovascular disease (−1.6%[CI95%, −2.1%; −1.1%] and −15.6%[CI95%, −15.9%; −15.2%] in men and women, respectively ($p < 0.0001$), for antihypertensive medication, and + 4.0%[CI95%, 3.2%; 4.9%] and −12.8%[CI95%, −13.4%; −12.2%] for lipid-lowering treatment ($p < 0.0001$)) (**Supplementary Figure 2** and **Supplementary Table 3**).

Time Trends of Other Healthcare-Related Uses

In-Patients Visits vs. Teleconsultations

Family physician and cardiologist visits declined by 8.4 and 7.4%, respectively, between 2019 and 2020 (**Table 2**). The largest decreases were found in people under 65 years for family physicians (−9.6%) and those aged over 85 years for cardiologists (−8.7%). Except in the under 65 age group, a greater decrease in family physician visits was found in women compared to men (respectively −5.1 and −3.9% in 65–74 age group, −7.5 and −5.8% in the 75–84 age group, and −5.8 and −4.1% in ≥85 age group). Furthermore, teleconsultations increased more in women aged 65–74 years compared to men of the same age group, reaching 4.2% of family physician visits in women aged 65–74 years between 2019 and 2020 vs. 4.0% in men of the same age, and 4.4 and 4.1% of family physician visits in women and men aged 75–84 years old, respectively (**Table 2**). By contrast, in these age groups, the number of in-patient family physician visits decreased more in women (−9.1 and −11.6%) than in men (−7.8 and −9.7%). Regarding cardiologist visits, the decrease between 2019 and 2020 was only greater in women compared to men over 75 years.

Lipid Blood Tests

The rates of persons who had at least one reimbursement for lipid blood profiling decreased by −5.3%[CI95%, −5.4%; −5.3%] between 2017–2019 and 2021, similarly in men and women (**Table 3** and **Supplementary Table 4**). A larger decrease was observed among people aged under 45 years (−9.3%[CI95%, −9.5; −9.2%]) compared to the eldest age group over 85 years (−2.7%[CI95%, −3.0%; −2.4%]). In 2021, the rates were similar as compared to 2017–2019 in both men and women for all age groups.

Holter Electrocardiogram

The use of Holter ECG globally decreased by −3.0%[CI95%, −3.4%; −2.7%] in 2020 compared to 2017–2019, with a greater decrease among people aged under 45 years (−7.9%[CI95%, −8.7; −7.0%]) and an increase observed in those aged over 85 years (+ 10.4%[CI95%, 9.2; 11.6%]) (**Table 3** and **Supplementary Table 4**). The use of Holter ECG increased in 2021 compared to 2017–2019 (+ 6.8%[CI95%, 6.0%; 7.6%]).

DISCUSSION

A marked decrease in the initiation of cardiovascular risk main treatments was observed during the first year of the COVID-19 pandemic. Women and the oldest age groups seemed to be more impacted, particularly regarding the initiation of antihypertensive medication. Although a catch-up effect might be seen for lipid-lowering medications or in the youngest age groups in 2021, the initiation rates for other treatment of the cardiovascular risk remained generally lower in 2021 compared

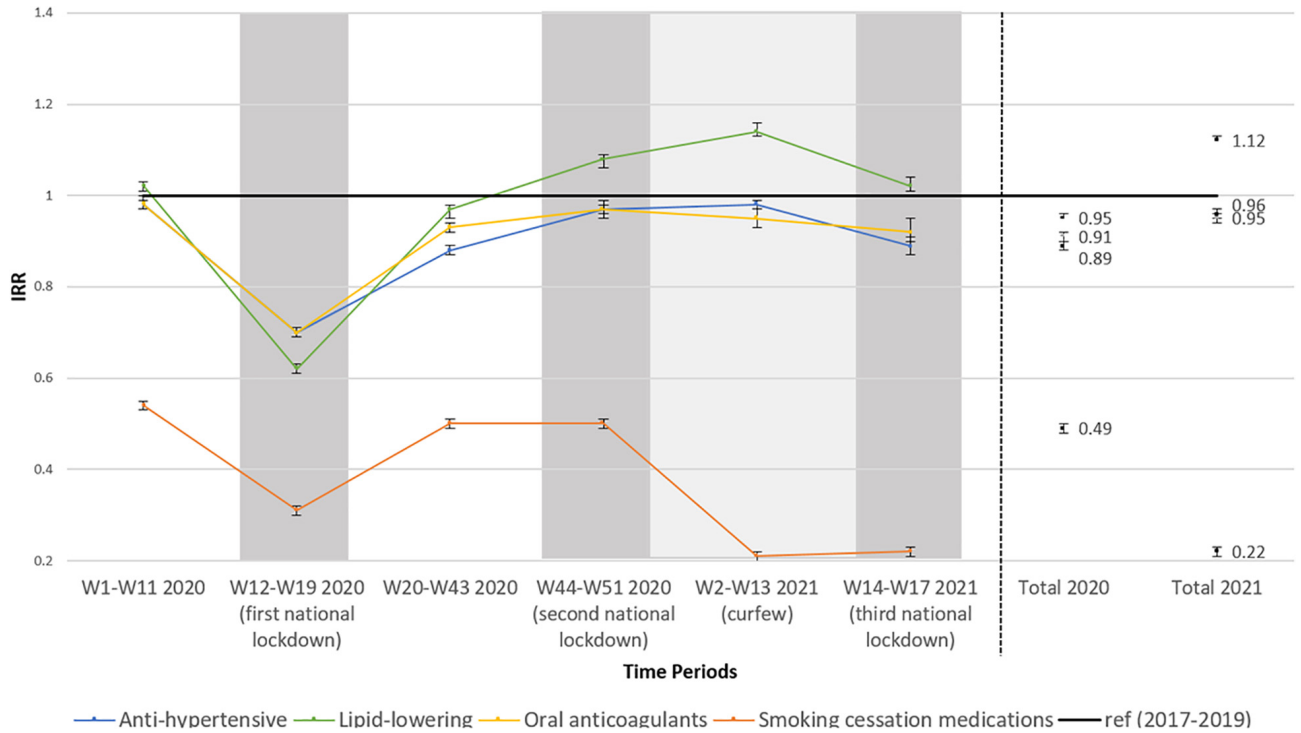

FIGURE 2 | Incidence rate ratio (IRR)[a] and 95% confidence intervals (95% CI) between rates of initiation of treatments, respectively in 2020 and 2021 compared to the rates of initiation in 2017–2019 according to sex by age group. [a]adjusted for age and 2017–2019 time trends; IRRs: Incidence rate ratios; Blue: men; Orange: women.

to time-period prior to the COVID-19 pandemic, especially in women. Concomitantly, a decrease in family physician and cardiologist visits along with a surge in teleconsultations was found with variations according to sex and age.

The implications of the COVID-19 pandemic regarding the incidence and management of cardiovascular diseases and their risk factors was predictable (5). Overall, this could be caused by a decrease in healthcare visits during the pandemic, leading to a decrease in the screening of hypertension, hypercholesterolemia and atrial fibrillation, and a less consideration of smoking. The initiation of antihypertensive medication and oral anticoagulants in atrial fibrillation was indeed the most impacted according to our results. Alexander et al. found the large decreases in blood pressure (−50.1%) and cholesterol level assessments (−36.9%) in 2020 compared to 2018–2019 in the United States, highlighting that these assessments were significantly less common during telemedicine than during in-person visits (9.6% vs. 69.7% for blood pressure; 13.5% vs. 21.6% for cholesterol) (4). Telehealth visits were associated with fewer new medication prescriptions in another American study examining how the pandemic impacted outpatient cardiology care (9). Although people could access telehealth consults instead of in-person visits with a more equitable access to healthcare, many patients did not visit a medical doctor at all. The increase in telehealth consultation during the COVID-19 pandemic did not compensate the decrease of in-person visits.

At the beginning of the pandemic, it was hypothesized that angiotensin-converting-enzyme (ACE) inhibitors and ARB medications was associated with a higher risk and severity of infection by SARS-CoV-2. Several studies thereafter showed the absence of an association or the lower risk or severity of SARS-CoV-2 infection in patients treated with these medications (10–13), including in France (14). Our results suggested no clear impact of this controversy on the initiation of ARB and ACE inhibitors medications that could be related to the quick denials of cardiology societies.

The lower rates for the initiation of oral anticoagulants for atrial fibrillation during the pandemic was observed elsewhere (15, 16) and was consistent with the decrease in both family physician and cardiology visits as well as the use of Holter ECG. The increased use of teleconsultations might have been particularly harmful for the opportunistic screening of asymptomatic hypertension or atrial fibrillation. Although teleconsultation was well accepted during the pandemic, it does not allow a proper clinical examination, with a risk of underdiagnosis and low rates of treatment initiation as reported elsewhere (17, 18). Regarding hypertension, no specific recommendation on the use of telehealth services for the screening was mentioned in the latest recommendations from the societies of Hypertension. Only an international consensus from the World Heart Federation was published (19). This position paper remained very general and reported telehealth experiences more in the management of already diagnosed hypertension

TABLE 2 | Numbers and 2019–2020 time trends (%) of family physician and cardiology visits according to sex, age, and type of visit (in-person visit or teleconsultations).

		All			Men			Women		
		2019	2020	Trends	2019	2020	Trends	2019	2020	Trends
All	Family physician visits	256902333	235339827	*−8.4%*	106959033	98152850	*−8.2%*	149943300	137186977	*−8.5%*
	Family physician teleconsultations	88054	13133132		31872	5036430		56182	8096702	
	In-person family physician visits	256814279	222206695	*−13.5%*	106927161	93116420	*−12.9%*	149887118	129090275	*−13.9%*
	Cardiologist visits	11665744	10803323	*−7.4%*	6246327	5784830	*−7.4%*	5419417	5018493	*−7.4%*
	Cardiologist teleconsultations	619	68984		321	37168		298	31816	
	In-person cardiologist visits	11665125	10734339	*−8.0%*	6246006	5747662	*−8.0%*	5419119	4986677	*−8.0%*
<65	Family physician visits	179511055	162188615	*−9.6%*	75636371	68265123	*−9.7%*	103874684	93923492	*−9.6%*
	Family physician teleconsultations	77451	9977869		27539	3790710		49912	6187159	
	In-person family physician visits	179433604	152210746	*−15.2%*	75608832	64474413	*−14.7%*	103824772	87736333	*−15.5%*
	Cardiologist visits	4811191	4432193	*−7.9%*	2619744	2398400	*−8.4%*	2191447	2033793	*−7.2%*
	Cardiologist teleconsultations	321	27377		188	14803		133	12574	
	In-person cardiologist visits	4810870	4404816	*−8.4%*	2619556	2383597	*−9.0%*	2191314	2021219	*−7.8%*
65–74	Family physician visits	36232730	34564327	*−4.6%*	16075597	15443282	*−3.9%*	20157133	19121045	*−5.1%*
	Family physician teleconsultations	4735	1411667		2307	615987		2428	795680	
	In-person family physician visits	36227995	33152660	*−8.5%*	16073290	14827295	*−7.8%*	20154705	18325365	*−9.1%*
	Cardiologist visits	3270387	3080580	*−5.8%*	1862606	1752099	*−5.9%*	1407781	1328481	*−5.6%*
	Cardiologist teleconsultations	94	19018		63	10988		31	8030	
	In-person cardiologist visits	3270293	3061562	*−6.4%*	1862543	1741111	*−6.5%*	1407750	1320451	*−6.2%*
75–84	Family physician visits	25525998	23781618	*−6.8%*	10411888	9807779	*−5.8%*	15114110	13973839	*−7.5%*
	Family physician teleconsultations	3047	1020489		1213	406943		1834	613546	
	In-person family physician visits	25522951	22761129	*−10.8%*	10410675	9400836	*−9.7%*	15112276	13360293	*−11.6%*
	Cardiologist visits	2508825	2309188	*−8.0%*	1302071	1206026	*−7.4%*	1206754	1103162	*−8.6%*
	Cardiologist teleconsultations	79	15313		37	8157		42	7156	
	In-person cardiologist visits	2508746	2293875	*−8.6%*	1302034	1197869	*−8.0%*	1206712	1096006	*−9.2%*
≥85	Family physician visits	15632550	14805267	*−5.3%*	4835177	4636666	*−4.1%*	10797373	10168601	*−5.8%*
	Family physician teleconsultations	2821	723107		813	222790		2008	500317	
	In-person family physician visits	15629729	14082160	*−9.9%*	4834364	4413876	*−8.7%*	10795365	9668284	*−10.4%*
	Cardiologist visits	1075341	981362	*−8.7%*	461906	428305	*−7.3%*	613435	553057	*−9.8%*
	Cardiologist teleconsultations	125	7276		33	3220		92	4056	
	In-person cardiologist visits	1075216	974086	*−9.4%*	461873	425085	*−8.0%*	613343	549001	*−10.5%*

than in the screening. Regarding AF, strategies of heart rate and rhythm monitoring through teleconsultation were spread in order to allow the screening of atrial fibrillation despite the COVID-19 pandemic, namely TeleCheck-AF (20, 21). An increase by 20% in the number of ECG with remote transmission was observed in 2020 compared to 2019 (data not shown). However, TeleCheck-AF approach was mainly developed to remotely detect AF episodes in patients who have been diagnosed for AF by ECG before.

A drop in the initiation of the use of prescribed smoking cessation medications was observed in our study with no rebound in 2021. The drop took into account the time-trend before the pandemic which showed almost a doubling in the initiation of prescribed smoking cessation medications between 2017 and 2019. Between 2017 and 2018, the doubling could be related to the national prevention campaign "Tobacco-Free Month" launched in October 2016 (22) with particularly substantial increase during the month of the campaign (data not shown). Between 2018 and 2019, the time-trend could also be related to a change in the reimbursement of these smoking cessation medications which have become fully reimbursed since, when prescribed by a physician. On the contrary the French Monitoring Centre for Drugs and Drug Addiction (OFDT) showed an increase by 4% of smoking cessation medications (delivered OTC or prescribed) in 2020 compared to 2019 (23). Therefore, our study showed a substantial impact of the pandemic on prescribed smoking cessation medication that could be related to the decrease in physician visits. This decrease might have been compensated by the increase in OTC smoking cessation medications. The effectiveness of NRT (the most sold of the smoking cessation medication) being higher when prescribed by a physician, the increase in OTC medication sales may be associated with a lower rate of effective smoking cessation in France in 2020. A British study carried out during the 2006–2018 period showed that the use of OTC NRTs was not related with self-reported tobacco abstinence, contrary to prescribed ones (24). Thus, the increase in OTC medication sales may be associated with a lower rate of effective smoking cessation in France in 2020. Several studies showed an increase in tobacco use among current smokers (25–27), including in France (28), and a decrease in the motivation

TABLE 3 | Incidence rate ratio (IRR)* and 95% confidence intervals (95% CI) for the rates of people with at least one lipid blood test and one Holter ECG in 2020 and 2021 compared to the rates in 2017–2019.

		Lipid blood test		Holter ECG	
		2020	2021 (W1-W20)	2020	2021 (W1-W20)
Total		0.94[0.94–0.94]	1.01[1.01–1.01]	0.97[0.97–0.98]	1.07[1.06–1.08]
Men		0.94[0.94–0.94]	0.99[0.99–0.99]	0.98[0.97–0.98]	1.06[1.05–1.07]
Women		0.95[0.94–0.95]	1.03[1.02–1.03]	0.97[0.97–0.98]	1.08[1.06–1.09]
<45		0.90[0.90–0.90]	1.00[1.00–1.00]	0.92[0.91–0.93]	1.03[1.01–1.05]
45–64		0.94[0.93–0.94]	1.03[1.03–1.03]	0.95[0.94–0.95]	1.07[1.05–1.08]
65–74		0.97[0.97–0.97]	0.99[0.99–1.00]	0.96[0.95–0.97]	1.04[1.02–1.05]
75–84		0.97[0.97–0.97]	1.01[1.01–1.02]	0.99[0.98–1.00]	1.08[1.07–1.10]
≥85		0.98[0.98–0.98]	0.99[0.98–1.00]	1.13[1.11–1.14]	1.17[1.14–1.19]
< 45	Men	0.88[0.87–0.88]	0.96[0.96–0.97]	0.93[0.92–0.95]	1.02[0.99–1.05]
	Women	0.91[0.91–0.92]	1.02[1.01–1.02]	0.91[0.90–0.93]	1.03[1.00–1.06]
45–64	Men	0.93[0.93–0.93]	1.01[1.01–1.01]	0.97[0.96–0.98]	1.09[1.07–1.11]
	Women	0.94[0.94–0.94]	1.05[1.04–1.05]	0.93[0.92–0.94]	1.05[1.03–1.07]
65–74	Men	0.97[0.97–0.97]	0.97[0.97–0.98]	0.97[0.96–0.98]	1.03[1.01–1.05]
	Women	0.97[0.97–0.98]	1.01[1.01–1.02]	0.96[0.95–0.97]	1.04[1.02–1.06]
75–84	Men	0.97[0.96–0.97]	1.00[0.99–1.00]	0.98[0.97–0.99]	1.05[1.03–1.08]
	Women	0.97[0.97–0.97]	1.03[1.02–1.03]	1.00[0.98–1.01]	1.11[1.09–1.14]
≥85	Men	0.97[0.97–0.98]	0.98[0.97–0.99]	1.08[1.06–1.10]	1.12[1.08–1.16]
	Women	0.98[0.98–0.99]	1.00[0.99–1.00]	1.16[1.14–1.18]	1.20[1.16–1.24]

** adjusted for age and 2017–2019 time trends.*

to quit (29). A US study also showed a dramatic decrease in the use of quit lines (30). Nevertheless, these changes mainly affected adults under 50 years of age in France (28). The polemic appeared in May 2020 around the potential protective effect of nicotine against SARS-CoV-2 infection and severity did not seem to have led to an increase in reimbursed smoking cessation medications. The government had limited the delivery of smoking cessation medications by fear of a rush to drugstore following this polemic. Finally, OFDT showed a massive increase in oral form of smoking cessation medications instead of nicotine patch.

The greater decrease in the initiation of treatments observed in older women aged 65–84 compared to men of the same age group between 2017–2019 and 2020 could relate to the larger decrease in family physician visits alongside the higher use of teleconsultations in women compared to men of this age group. This observation highlighted the different healthcare attendance and use of telemedicine during the pandemic according to age and sex. A study in the United States showed higher use of telemedicine among women during the pandemic compared to men (31). A decrease in gynecology visits has been observed in France in 2020 compared to 2019 and could be related to the higher decrease in women even in older age groups (data not shown).

Finally, we cannot exclude that the real incidence of cardiovascular risk factors decreased since the beginning of the pandemic due to change in people's behavior or diet and a reduction of professional and other stress. A study showed a decrease in blood pressure during the first lockdown in France (32). However, it seems less likely that these changes would have so quickly impacted blood pressure, lipid profile, or atrial fibrillation incidence. On the contrary, several studies showed an increase in sedentary behaviors, a decrease in physical activity and an increase in depression rates during the pandemic (33–36), which could lead to an increase in the incidence of cardiovascular risk factors (37), with the same limitations between the exposure to such behaviors and the incidence of arterial hypertension, hypercholesterolemia, or atrial fibrillation. Furthermore, studies on the impact of the COVID-19 pandemic on behavioral determinants of health revealed mitigated results (38–44) and were limited to the first epidemic wave, although the persistence of this impact has not been explored. We cannot also exclude that a decrease in the incidence of cardiovascular risk factors could be related to the death of patients at high cardiovascular risk because of SARS-CoV-2 infection. The decrease in overall cardiology procedures in 2020 vs. 2019 (data not shown) might indeed be due to a decrease in cardiovascular patients independently of the decrease in the number of cardiology visits.

A "catch-up" effect could be hypothesized for the initiation of lipid-lowering medications in the first months of 2021 although a lesser increase in lipid blood test rates was found. This could be also explained by the increase in visits to a cardiologist and an endocrinologist that has been found during the second lockdown whereas rates of visits to a family physician continue to decrease at that time (data not shown). The increase in rates of initiation of lipid-lowering medications in 2021 could also be related to constant increase in the use of these medications due to changes in the guidelines for circulating cholesterol concentrations achievement toward always reduced cholesterol levels. The latest guidelines dated from 2019 (23). Furthermore, no rush to visit a family physician or a cardiologist was observed

before the first lockdown in France on the contrary to a marked stock of medical treatments. No "catch-up" effect was found for the other medications. This might be explained by the continuous decrease in family physician visits. It also suggested that the "catch-up" effect for lipid-lowering medication might be related to the latest guidelines, a specific change for these medications only.

Clinical and Public Health Implications

These findings have important implications in the field of cardiovascular disease prevention. There could be a larger pool of patients at risk of cardiovascular diseases today compared to the pre-pandemic time period. The population was differentially impacted according to sex and age, which imply the need for sex-specific prevention. Women over 65 years old seemed to pay a high price during the COVID-19 pandemic, although this could be related to a decline in the screening of cardiovascular diseases in women. The Lancet commission on women and cardiovascular diseases alerts about "the stagnation on the overall reduction of cardiovascular disease burden for women in the past decade," as "cardiovascular disease in women remains understudied, under-recognized, underdiagnosed, and undertreated" (45). Greater attention should also be paid to people who used teleconsultations during the pandemic or had fewer medical visits.

Limitations

This study analyzed main treatments for cardiovascular risk and diseases, and therefore only the treated patients with arterial hypertension, hypercholesterolemia, or atrial fibrillation. The initiation of some antihypertensive medications could also be related to a cardiovascular event and not hypertension itself. To deal with this confusion, we studied the initiation of medications, respectively in people with a history of cardiovascular diseases and in people without such history. Almost all reimbursements of these treatments were recorded with the exception of treatments delivered in nursing homes with an in-house pharmacy. Nevertheless, only 21% of nursing homes have an in-house pharmacy in France, and a very small part of our treatment of interest was initiated when the patient was already in these healthcare structures (46). Furthermore, approximately 600,000 persons live in medical institutions in France, equivalent to less than 1% of the population. Regarding smoking cessation medications, these treatments are not exhaustively registered in our database as an unknown proportion is sold without prescription. Our analysis did not take into account OTC medications for hypertension, hypercholesterolemia or atrial fibrillation which are very rare in France for these conditions. OTC smoking cessation medications are on the contrary usually used in France. Therefore our study only reflected the impact of the COVID-19 pandemic on prescribed smoking cessation medications and therefore physician visits. Finally, antidiabetic medications were not included in our study despite diabetes put patients at high cardiovascular risk, because of a current study lead specifically for this treatment.

CONCLUSION

The pandemic had a major impact on the initiation of cardiovascular medication treatments and therefore the incidence and/or screening of cardiovascular risk factors, particularly in women, which could have consequences on the incidence of cardiovascular diseases in the near future. Lower rates of treatment initiations were found in 2021 compared to the period prior to the pandemic for antihypertensive medications and women aged over 65 years. The effect of the exponential use of teleconsultations on the screening and management of cardiovascular risk factors should be the focus of further research as well as the decrease in the overall number of physician visits which was not compensated after the first national lockdown.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AG directed the research, wrote the manuscript, and performed the statistical analyses. CGr, TL, VN-T, and RG contributed to statistical analyses, discussion and reviewed the manuscript. PT, CGu, JB, and VO directed the research, contributed to discussion and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.856689/full#supplementary-material

REFERENCES

1. Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, et al. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. *BMJ Open.* (2021) 11:e045343. doi: 10.1136/bmjopen-2020-045343
2. Davin-Casalena B, Jardin M, Guerrera H, Mabille J, Tréhard H, Lapalus D, et al. [The impact of the COVID-19 pandemic on first-line primary care in Southeastern France: feedback on the implementation of a real-time monitoring system based on regional health insurance data]. *Rev Epidemiol Sante Publique.* (2021) 69:105–15. doi: 10.1016/j.respe.2021.04.135
3. Lefrant JY, Fischer MO, Potier H, Degryse C, Jaber S, Muller L, et al. A national healthcare response to intensive care bed requirements during the COVID-19 outbreak in France. *Anaesth Crit Care Pain Med.* (2020) 39:709–15. doi: 10.1016/j.accpm.2020.09.007
4. Alexander GC, Tajanlangit M, Heyward J, Mansour O, Qato DM, Stafford RS. Use and content of primary care office-based vs telemedicine care visits during the COVID-19 pandemic in the US. *JAMA Netw Open.* (2020) 3:e2021476. doi: 10.1001/jamanetworkopen.2020.21476
5. Lau D, McAlister FA. Implications of the COVID-19 pandemic for cardiovascular disease and risk-factor management. *Can J Cardiol.* (2021) 37:722–32. doi: 10.1016/j.cjca.2020.11.001
6. Tuppin P, Rudant J, Constantinou P, Gastaldi-Menager C, Rachas A, de Roquefeuil L, et al. Value of a national administrative database to guide public decisions: from the systeme national d'information interregimes de l'assurance maladie (SNIIRAM) to the systeme national des donnees de sante (SNDS) in France. *Rev Epidemiol Sante Publique.* (2017) 65(Suppl. 4):S149–67. doi: 10.1016/j.respe.2017.05.004
7. Billionnet C, Alla F, Berigaud E, Pariente A, Maura G. Identifying atrial fibrillation in outpatients initiating oral anticoagulants based on medico-administrative data: results from the French national healthcare databases. *Pharmacoepidemiol Drug Saf.* (2017) 26:535–43. doi: 10.1002/pds.4192
8. Gabet A, Chatignoux E, Billionnet C, Maura G, Giroud M, Bejot Y, et al. Annual rate of newly treated atrial fibrillation by age and gender in France, 2010-2016. *Eur J Epidemiol.* (2019) 35:1139–47. doi: 10.1007/s10654-019-00594-3
9. Wosik J, Clowse MEB, Overton R, Adagarla B, Economou-Zavlanos N, Cavalier J, et al. Impact of the COVID-19 pandemic on patterns of outpatient cardiovascular care. *Am Heart J.* (2021) 231:1–5. doi: 10.1016/j.ahj.2020.10.074
10. Jia N, Zhang G, Sun X, Wang Y, Zhao S, Chi W, et al. Influence of angiotensin converting enzyme inhibitors/angiotensin receptor blockers on the risk of all-cause mortality and other clinical outcomes in patients with confirmed COVID-19: a systemic review and meta-analysis. *J Clin Hypertens (Greenwich).* (2021) 23:1651–63. doi: 10.1111/jch.14329
11. Asiimwe IG, Pushpakom S, Turner RM, Kolamunnage-Dona R, Jorgensen AL, Pirmohamed M. Cardiovascular drugs and COVID-19 clinical outcomes: a living systematic review and meta-analysis. *Br J Clin Pharmacol.* (2021) 87:4534–45. doi: 10.1111/bcp.14927
12. Bezabih YM, Bezabih A, Alamneh E, Peterson GM, Bezabhe W. Comparison of renin-angiotensin-aldosterone system inhibitors with other antihypertensives in association with coronavirus disease-19 clinical outcomes. *BMC Infect Dis.* (2021) 21:527. doi: 10.1186/s12879-021-06088-6
13. Baral R, Tsampasian V, Debski M, Moran B, Garg P, Clark A, et al. Association between renin-angiotensin-aldosterone system inhibitors and clinical outcomes in patients with COVID-19: a systematic review and meta-analysis. *JAMA Netw Open.* (2021) 4:e213594. doi: 10.1001/jamanetworkopen.2021.3594
14. Semenzato L, Botton J, Drouin J, Baricault B, Vabre C, Cuenot F, et al. Antihypertensive drugs and COVID-19 risk: a cohort study of 2 million hypertensive patients. *Hypertension.* (2021) 77:833–42. doi: 10.1161/hypertensionaha.120.16314
15. Onder G, Olimpieri PP, Celant S, Di Lenarda A, Ambrosio G, Reboldi G, et al. Under-prescription of direct oral anticoagulants for treatment of non-valvular atrial fibrillation and venous thromboembolism in the COVID-19 lockdown period. *Eur J Prev Cardiol.* (2021) 29:e149–52. doi: 10.1093/eurjpc/zwab096
16. Holt A, Gislason GH, Schou M, Zareini B, Biering-Sørensen T, Phelps M, et al. New-onset atrial fibrillation: incidence, characteristics, and related events following a national COVID-19 lockdown of 5.6 million people. *Eur Heart J.* (2020) 41:3072–9. doi: 10.1093/eurheartj/ehaa494
17. Schäfer I, Hansen H, Menzel A, Eisele M, Tajdar D, Lühmann D, et al. The effect of COVID-19 pandemic and lockdown on consultation numbers, consultation reasons and performed services in primary care: results of a longitudinal observational study. *BMC Fam Pract.* (2021) 22:125. doi: 10.1186/s12875-021-01471-3
18. Stephenson E, Butt DA, Gronsbell J, Ji C, O'Neill B, Crampton N, et al. Changes in the top 25 reasons for primary care visits during the COVID-19 pandemic in a high-COVID region of Canada. *PLoS One.* (2021) 16:e0255992. doi: 10.1371/journal.pone.0255992
19. Jeemon P, Séverin T, Amodeo C, Balabanova D, Campbell NRC, Gaita D, et al. World heart federation roadmap for hypertension – a 2021 update. *Glob Heart.* (2021) 16:63. doi: 10.5334/gh.1066
20. Pluymaekers NAHA, Hermans ANL, van der Velden RMJ, Gawałko M, den Uijl DW, Buskes S, et al. Implementation of an on-demand app-based heart rate and rhythm monitoring infrastructure for the management of atrial fibrillation through teleconsultation: teleCheck-AF. *EP Europace.* (2020) 23:345–52. doi: 10.1093/europace/euaa201
21. Gawałko M, Duncker D, Manninger M, van der Velden RMJ, Hermans ANL, Verhaert DVM, et al. The European telecheck-AF project on remote app-based management of atrial fibrillation during the COVID-19 pandemic: centre and patient experiences. *EP Europace.* (2021) 23:1003–15. doi: 10.1093/europace/euab050
22. Guignard R, Andler R, Richard JB, Pasquereau A, Quatremère G, Arwidson P, et al. Effectiveness of 'Mois sans tabac 2016': a French social marketing campaign against smoking. *Tob Induc Dis.* (2021) 19:60. doi: 10.18332/tid/139028
23. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the task force for the management of dyslipidaemias of the European society of cardiology (ESC) and European atherosclerosis society (EAS). *Eur Heart J.* (2019) 41:111–88. doi: 10.1093/eurheartj/ehz455
24. Jackson SE, Kotz D, West R, Brown J. Moderators of real-world effectiveness of smoking cessation aids: a population study. *Addiction.* (2019) 114:1627–38. doi: 10.1111/add.14656
25. Koopmann A, Georgiadou E, Reinhard I, Müller A, Lemenager T, Kiefer F, et al. The effects of the lockdown during the COVID-19 pandemic on alcohol and tobacco consumption behavior in Germany. *Eur Addict Res.* (2021) 27:242–56. doi: 10.1159/000515438
26. Carreras G, Lugo A, Stival C, Amerio A, Odone A, Pacifici R, et al. Impact of COVID-19 lockdown on smoking consumption in a large representative sample of Italian adults. *Tob Control.* (2021) 0:1–8. doi: 10.1136/tobaccocontrol-2020-056440
27. Gendall P, Hoek J, Stanley J, Jenkins M, Every-Palmer S. Changes in tobacco use during the 2020 COVID-19 lockdown in New Zealand. *Nicotine Tob Res.* (2021) 23:866–71. doi: 10.1093/ntr/ntaa257
28. Guignard R, Andler R, Quatremère G, Pasquereau A, du Roscoät E, Arwidson P, et al. Changes in smoking and alcohol consumption during COVID-19-related lockdown: a cross-sectional study in France. *Eur J Public Health.* (2021) 31:1076–83. doi: 10.1093/eurpub/ckab054
29. Klemperer EM, West JC, Peasley-Miklus C, Villanti AC. Change in tobacco and electronic cigarette use and motivation to quit in response to COVID-19. *Nicotine Tob Res.* (2020) 22:1662–3. doi: 10.1093/ntr/ntaa072
30. Jaklevic MC. COVID-19 and the "lost year" for smokers trying to quit. *JAMA.* (2021) 325:1929–30. doi: 10.1001/jama.2021.5601
31. Kakani P, Sorensen A, Quinton JK, Han M, Ong MK, Kamdar N, et al. Patient characteristics associated with telemedicine use at a large academic health system before and after COVID-19. *J Gen Intern Med.* (2021) 36:1166–8. doi: 10.1007/s11606-020-06544-0
32. Girerd N, Meune C, Duarte K, Vercamer V, Lopez-Sublet M, Mourad JJ. Evidence of a blood pressure reduction during the COVID-19 pandemic and associated lockdown period: insights from e-health data. *Telemed J E Health.* (2021) 28:266–70. doi: 10.1089/tmj.2021.0006
33. Lesser IA, Nienhuis CP. The impact of COVID-19 on physical activity behavior and well-being of Canadians. *Int J Environ Res Public Health.* (2020) 17:3899. doi: 10.3390/ijerph17113899

34. Stanton R, To QG, Khalesi S, Williams SL, Alley SJ, Thwaite TL, et al. Depression, anxiety and stress during COVID-19: associations with changes in physical activity, sleep, tobacco and alcohol use in Australian adults. *Int J Environ Res Public Health.* (2020) 17:4065. doi: 10.3390/ijerph17114065
35. Cénat JM, Blais-Rochette C, Kokou-Kpolou CK, Noorishad PG, Mukunzi JN, McIntee SE, et al. Prevalence of symptoms of depression, anxiety, insomnia, posttraumatic stress disorder, and psychological distress among populations affected by the COVID-19 pandemic: a systematic review and meta-analysis. *Psychiatry Res.* (2021) 295:113599. doi: 10.1016/j.psychres.2020.113599
36. Varga TV, Bu F, Dissing AS, Elsenburg LK, Bustamante JJH, Matta J, et al. Loneliness, worries, anxiety, and precautionary behaviours in response to the COVID-19 pandemic: a longitudinal analysis of 200,000 Western and Northern Europeans. *Lancet Reg Health Eur.* (2021) 2:100020. doi: 10.1016/j.lanepe.2020.100020
37. Hamieh NM, Meneton P, Wiernik E, Limosin F, Zins M, Goldberg M, et al. Depression, treatable cardiovascular risk factors and incident cardiac events in the Gazel cohort. *French J Psychiatry.* (2018) 1:S149. doi: 10.1016/S2590-2415(19)30388-5
38. Bann D, Villadsen A, Maddock J, Hughes A, Ploubidis GB, Silverwood R, et al. Changes in the behavioural determinants of health during the COVID-19 pandemic: gender, socioeconomic and ethnic inequalities in five British cohort studies. *J Epidemiol Commun Health.* (2021) 75:1136–42. doi: 10.1136/jech-2020-215664
39. Scarmozzino F, Visioli F. Covid-19 and the subsequent lockdown modified dietary habits of almost half the population in an italian sample. *Foods.* (2020) 9:675. doi: 10.3390/foods9050675
40. Rodríguez-Pérez C, Molina-Montes E, Verardo V, Artacho R, García-Villanova B, Guerra-Hernández EJ, et al. Changes in dietary behaviours during the COVID-19 outbreak confinement in the Spanish COVIDiet study. *Nutrients.* (2020) 12:1730. doi: 10.3390/nu12061730
41. Ding D, del Pozo Cruz B, Green MA, Bauman AE. Is the COVID-19 lockdown nudging people to be more active: a big data analysis. *Br J Sports Med.* (2020) 54:1183–4. doi: 10.1136/bjsports-2020-102575
42. Di Renzo L, Gualtieri P, Pivari F, Soldati L, Attinà A, Cinelli G, et al. Eating habits and lifestyle changes during COVID-19 lockdown: an Italian survey. *J Transl Med.* (2020) 18:229. doi: 10.1186/s12967-020-02399-5
43. Deschasaux-Tanguy M, Druesne-Pecollo N, Esseddik Y, de Edelenyi FS, Allès B, Andreeva VA, et al. Diet and physical activity during the coronavirus disease 2019 (COVID-19) lockdown (March-May 2020): results from the French nutrinet-Santé cohort study. *Am J Clin Nutr.* (2021) 113:924–38. doi: 10.1093/ajcn/nqaa336
44. Ammar A, Brach M, Trabelsi K, Chtourou H, Boukhris O, Masmoudi L, et al. Effects of COVID-19 home confinement on eating behaviour and physical activity: results of the ECLB-COVID19 international online survey. *Nutrients.* (2020) 12:1583. doi: 10.3390/nu12061583
45. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet.* (2021) 397:2385–438. doi: 10.1016/s0140-6736(21)00684-x
46. Atramont A, Bonnet-Zamponi D, Bourdel-Marchasson I, Tangre I, Fagot-Campagna A, Tuppin P. Health status and drug use 1 year before and 1 year after skilled nursing home admission during the first quarter of 2013 in France: a study based on the French national health insurance information system. *Eur J Clin Pharmacol.* (2018) 74:109–18. doi: 10.1007/s00228-017-2343-y

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Socioeconomic Status and Prognosis of Patients With ST-Elevation Myocardial Infarction Managed by the Emergency-Intervention "Codi IAM" Network

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Background: Despite the spread of ST-elevation myocardial infarction (STEMI) emergency intervention networks, inequalities in healthcare access still have a negative impact on cardiovascular prognosis. The Family Income Ratio of Barcelona (FIRB) is a socioeconomic status (SES) indicator that is annually calculated. Our aim was to evaluate whether SES had an effect on mortality and complications in patients managed by the "Codi IAM" network in Barcelona.

Methods: This is a cohort study with 3,322 consecutive patients with STEMI treated in Barcelona from 2010 to 2016. Collected data include treatment delays, clinical and risk factor characteristics, and SES. The patients were assigned to three SES groups according to FIRB score. A logistic regression analysis was conducted to estimate the adjusted effect of SES on 30-day mortality, 30-day composite cardiovascular end point, and 1-year mortality.

Results: The mean age of the patients was 65 ± 13% years, 25% were women, and 21% had diabetes mellitus. Patients with low SES were younger, more often hypertensive, diabetic, dyslipidemic ($p < 0.003$), had longer reperfusion delays ($p < 0.03$) compared to participants with higher SES. Low SES was not independently associated with 30-day mortality (OR: 0.95;9 5% CI: 0.7–1.3), 30-day cardiovascular composite end point (OR: 1.03; 95% CI: 0.84–1.26), or 1-year all-cause mortality (HR: 1.09; 95% CI: 0.76–1.56).

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Conclusion: Although the low-SES patients with STEMI in Barcelona city were younger, had worse clinical profiles, and had longer revascularization delays, their 30-day and 1-year outcomes were comparable to those of the higher-SES patients.

Keywords: ST-elevation myocardial infarction, reperfusion, primary percutaneous coronary intervention, mortality, inequalities

INTRODUCTION

Ischaemic heart disease is the leading component of cardiovascular disease (CVD), which is the first cause of mortality and morbidity worldwide (1, 2). Loss in quality-of-life and mortality due to cardiovascular disease has globally declined because of the implementation of evidence-based treatments and early and efficient management of acute coronary syndromes (ACSs), as well as appropriate drugs for secondary prevention and cardiac rehabilitation (3). Improvements in morbidity and survival after an ACS have spread unevenly throughout world regions, and they are more developed and implemented often in high-income countries (4). These differences may be partially explained by varying ACS emergency management modalities and population epidemiologic settings, including the influence of socioeconomic status (SES).

Multiple studies have shown that SES, measured by education level, occupation, or income, is associated with cardiovascular risk factors and outcomes after acute myocardial infarction (5–7). Even in high-income countries, poor socioeconomic circumstances may limit access to and increase delays in revascularization procedures, resulting in larger infarct size, lower compliance to secondary prevention drugs, and in general, poor application of and compliance with specialized state-of-the-art cardiac treatments (8, 9).

Implementation of coordinated and standardized treatment networks for acute ST-elevation myocardial infarction (STEMI) increases detection, decreases treatment times, and increases survival in all kinds of socioeconomic environments (6, 10).

The aim of this study was to analyze whether low SES determines more 30-day complications and 1-year all-cause mortality in patients with STEMI managed by the "Codi Infart Agut de Miocardi amb Elevació ST (Codi IAM)" emergency STEMI care network in Barcelona in a contemporary cohort from a European southern city.

MATERIALS AND METHODS

Population

In this retrospective cohort study, we included patients from the registry of the "Codi IAM" emergency management network diagnosed with STEMI from 2010 to 2016 who were residents of Barcelona. The registry includes, in addition, cardiac arrest or patients who died with an initial electrocardiogram showing ST-segment elevation or patients with a new left bundle-branch block. Barcelona patients were treated in other facilities outside Barcelona and non-residents were excluded.

The "Codi IAM" STEMI emergency management network was launched in 2010 in a region of 7.6 million inhabitants. The three main objectives of the network were (i) to increase the rate of reperfusion therapy among patients with STEMI, (ii) to achieve primary percutaneous coronary intervention (PPCI) in less than 120 min from the first contact with the health system (3), and (iii) to monitor the results of the network with a registry. The city of Barcelona was the first to be completely covered by the network because of its high-density population. Three PPCI hospitals that are open 24 h/7 days a week and one hospital with daytime PPCI cover the city's STEMI management needs. Updated operating details of the network have been recently published by our group (11). Basically, an emergency medical service (EMS) is responsible for detecting patients with STEMI and coordinates facilities (EMS ambulances and helicopters, with PPCI hospitals).

ST-elevation myocardial infarction was defined according to current guidelines (3). Fibrinolysis was only considered if expected delays in PPCI treatment were not acceptable and there were no contraindications. Percutaneous coronary intervention (PCI) post-fibrinolysis was initially only considered in the absence of effective reperfusion. The local health system provides universal health coverage; in addition, it provides a partial subsidy for medication costs depending on patients' income and working status.

The registry of the "Codi IAM" activity started in 2010 and includes demographic, clinical, therapeutic, and discharge data collected in an electronic form from patients with STEMI occurring within the previous 12 h. Epicardial coronary flow in the culprit STEMI artery is graded according to Thrombolysis in Myocardial Infarction (TIMI) flow grade (12), and reperfusion is considered optimal when TIMI 3 flow is obtained in the culprit lesion. Data collection was extended to new variables in 2012 (acute pulmonary edema, number of diseased vessels, and TIMI flow) and in 2015 (hypertension, dyslipidemia, smoking status, previous stroke, previous treatment, and type and number of stents). Bleeding was included only in cases requiring transfusion.

The Family Income Ratio of Barcelona (FIRB) is an indicator of the mean income ratio of inhabitants of the 73 districts in Barcelona city and shows imbalances relative to the mean value of the city, which is set at 100. The FIRB has been calculated annually since 2007 by the Technical Office of the Barcelona City Council, and it can be accessed online (13). This indicator combines five concepts: i) ratio of university

Abbreviations: ACS, Acute coronary syndrome; BMS, bare-metal stent; CHD, coronary heart disease; DES, drug-eluting stent; ECG, electrocardiogram; EMS, emergency medical system; FIRB, Family Income Ratio of Barcelona; OSs, onset of symptoms; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; SES, socioeconomic status; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

graduates, ii) ratio of unemployed to employable inhabitants, iii) the number of vehicles per inhabitant, iv) engine power of new vehicles acquired, and v) price of second-hand housing. FIRB was assigned to patients according to their address and district affiliation, and it has been used as a surrogate of socioeconomic status (SES) in this study. The patients were assigned to three SES classes according to the FIRB classification used by the Technical Office: low SES (low and very low SES corresponding to FIRB values below 80), mid SES (mid-low and mid-high corresponding to FIRB values from 81 to 125), and high SES (high and very high SES corresponding to FIRB values from 126 to 159) (13).

Mortality data of the patients were obtained from the National Mortality Registry. The quality of the data included in the registry is periodically verified by external audits.

End Points

Primary assessment end points were 30-day mortality, a 30-day composite end point including death, ventricular fibrillation, pulmonary edema, or cardiogenic shock during admission, and 1-year all-cause mortality in 30-day survivors.

Statistical Analysis

Categorical variables are shown as numbers and percentages; continuous variables are shown as mean and SD or as median and interquartile range, or as specified otherwise.

Patient characteristics and treatment times were compared according to each end point. Student's *t*-test or Mann-Whitney *U*-test was conducted for continuous variables and Chi-squared test, Fisher exact test, or ANOVA for categorical variables; *p*-tendency was used in all comparisons. A p-value < 0.05 was considered statistically significant. The association between SES and 30-day death or complications was evaluated with odds ratios (ORs) calculated using logistic regression models, and 1-year mortality in 30-day survivors was evaluated with hazard ratios (HRs) using Cox proportional-hazards regression models. The models were adjusted considering confounding variables associated with STEMI prognosis, which had $< 8\%$ missing values: age, sex, diabetes mellitus, recruitment year, type of initial care, place of treatment, time from electrocardiogram to PPCI, and Killip class. Kaplan Meier survival curves were fitted for the three SES categories, and log-ranked *p*-values were used for comparison.

The Patients were assigned to the hospital where they spent most of their hospital stay.

In order to calculate 1-year mortality, the mortality of patients admitted in 2016 was analyzed up to 2017. Analyses were performed using SPSS software version 24.0. This project was approved by the ethics committee of Hospital del Mar (2020/9056), and all data are anonymous. The project was approved by the Scientific Committee of "Codi IAM". Procedures and data collection complied with the Declaration of Helsinki and Spanish data protection laws.

RESULTS

The distribution of patients with STEMI treated in Barcelona city according to their SES is shown in **Figure 1**, in **Figure 1**: 43.4%

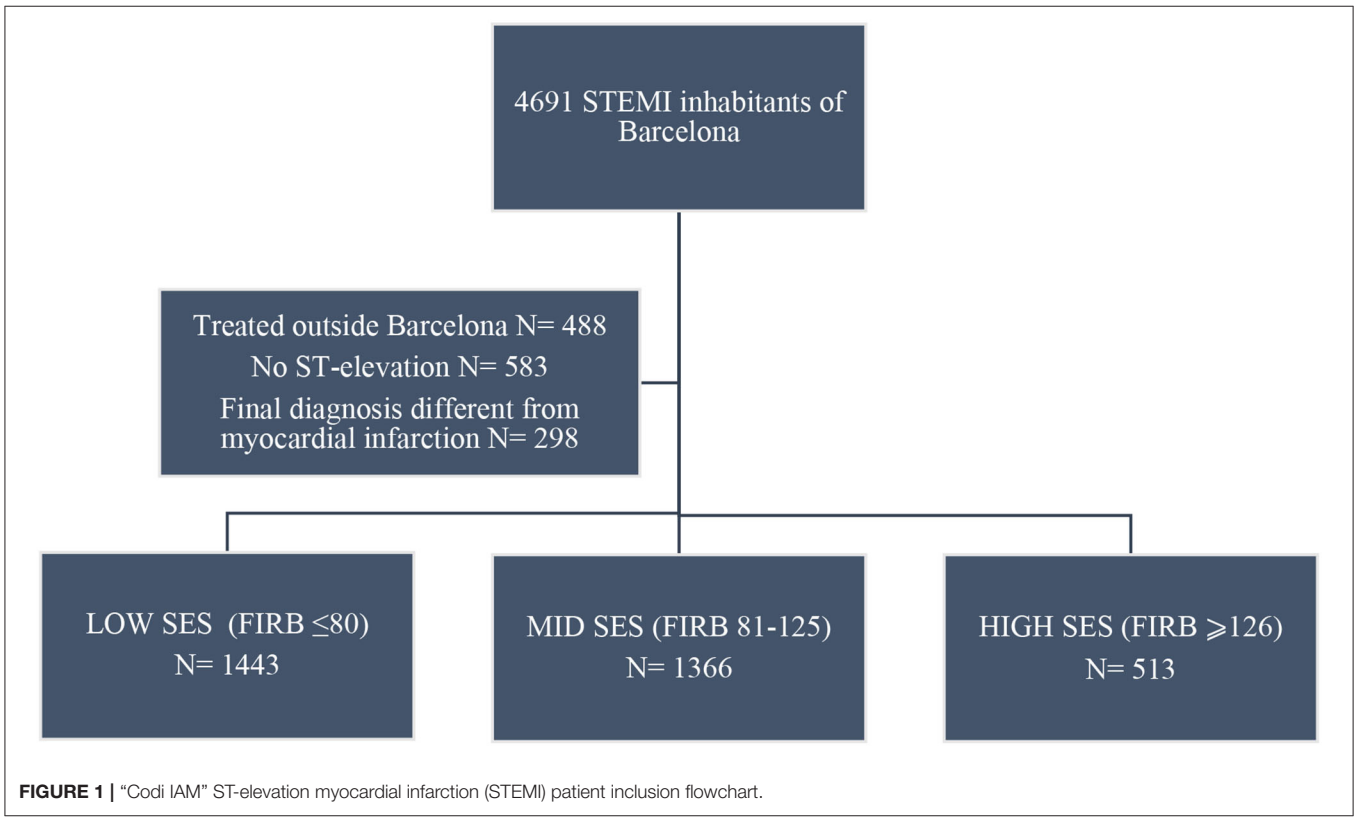

FIGURE 1 | "Codi IAM" ST-elevation myocardial infarction (STEMI) patient inclusion flowchart.

had low SES, 41.1% had mid SES, and 15.4% had high SES. The annual hospitalization rate of patients with STEMI is shown in **Supplementary Material 1**. The number of patients with STEMI treated from the lowest SES was higher than the mean rate during the 7 years of the study.

Patients with low SES were younger, had a higher prevalence of cardiovascular risk factors, and were more often initially cared for by general practitioners (**Table 1**). In addition, they had a more deleterious cardiovascular risk factor profile than patients with higher SES. There was no difference in Killip class at STEMI presentation by SES.

Patients received PPCI as the first treatment in more than 93% of the cases but with no significant differences according to SES. Patients with higher SES had significant epicardial coronary disease significantly less often than those with mid and low SES (**Table 2**). Patients with lower SES had a tendency to be less often treated with drug-eluting stents (DESs) than those with mid and higher SES (55.1 vs. 57.5 vs. 69%, respectively, $p < 0.35$). **Supplementary Material 2** shows differences in patients treated with DESs vs. bare-metal stents (BMS). DESs are significantly less used in the lower SES group; nevertheless, this difference is not greater than one unit.

Patients with lower SES had longer delays regarding time from symptom onset to diagnosis (first electrocardiogram) than those with highest SES (**Table 3**), and longer times from symptom onset to PPCI hospital than the mid and high SES groups. Electrocardiogram-to-open-artery times showed a decreasing trend with SES. Longer ischemic times were observed in patients with lower SES. Accordingly, ratios of PPCI in less than 120 min were higher in those patients with higher SES compared to those with lower SES.

In **Table 4**, we show that 30-day mortality, 30-day cardiovascular complications, and 1-year mortality did not differ between the SES groups after adjusting for confounding factors. There were no significant differences in survival curves at 1-year according to SES (**Figure 2**).

DISCUSSION

Low-SES patients with STEMI treated in Barcelona by the "Codi IAM" emergency network have a higher burden of cardiovascular risk factors and longer treatment delays than patients with higher SES. Despite this, they have similar mortality or cardiovascular complication rate at 30 days and similar 1-year mortality.

Recent STEMI guidelines have emphasized the importance of performing research addressing gaps in knowledge and the need for observational data and real-world evidence to ensure high-quality rapid and equal care for patients with STEMI in geographic areas (14). Previous studies from the late 1990s and early new century showed that SES was associated with both short- and long-term mortalities after ACS (15) and that an inverse trend in survival after myocardial infarction was also observed with SES levels in district-based studies (16, 17). However, these data come from heterogeneous studies, different time frames and may reflect inequalities in disease incidence, access to healthcare systems, and poor compliance with secondary prevention medications (18). Moreover, different SES indicators were used in previous studies: household income (14), highest educational level (15), geographical area (18),

TABLE 1 | Baseline clinical characteristics according to socioeconomic status (SES) classification.

	All $N = 3,322$	Low SES ≤80 $N = 1,443$	Mid SES 81–125 $N = 1,366$	High SES ≥126 $N = 513$	*P*-value
Age, years	65.3 ± 13.5	64.4 ± 13.9	65.8 ± 13.3	66.6 ± 13.0	0.002
Women,%	26.3	27.0	25.9	25.3	0.720
Smokers,%*	26.5	27.1	27.0	23.2	0.460
Hypertension,%*	40.8	43.0	41.8	30.4	0.024
Dyslipidemia,%*	32.1	35.2	31.9	22.5	0.008
Diabetes mellitus,%	20.7	23.3	20.2	14.4	<0.005
Previous stroke, %*	2.6	2.9	2.2	2.9	0.790
Oral anticoagulant,%*	1.9	2.5	1.0	2.9	0.720
Antiplatelet drugs, %*	8.0	9.6	5.9	8.7	0.280
		First contact			
General practitioner, %	15.1	18.9	13.4	9.0	<0.012
Emergency medical system, %	47.7	49.1	44.8	51.1	
		Complications			
Mechanical ventilation, %	6.3	5.2	7.5	6.0	0.150
Ventricular fibrillation, %	7.4	6.4	8.4	7.2	0.240
Atrial fibrillation, %	1.4	1.9	1.1	0.8	0.026
AV blockade, %	4.9	4.4	5.6	4.5	0.550
Pulmonary edema, %**	2.2	1.5	3.1	1.4	0.430
Cardiogenic shock, %	6.4	5.9	6.8	6.4	0.480

*AV Blockade, atrioventricular blockade. *Data since 2015, N = 991. **Data available since 2012. N = 2416.*

TABLE 2 | Primary reperfusion procedure in the "Codi IAM" network during the period 2010–2016 according to SES.

	All *N* = 3,322	Low SES ≤80 *N* = 1,443	Mid SES 81–125 *N* = 1,366	High SES ≥126 *N* = 513	*P*-value
Coronary angiogram without PCI, %	5.0	4.6	5.5	5.0	0.640
PPCI, %	93.4	94.2	92.7	92.5	
Thrombolysis, %	0.2	0.3	0.2	0.2	0.240
Initial TIMI 0, %*	68.3	66.3	69.0	72.2	0.035
Initial TIMI 3, %*	11.0	12.1	10.2	9.6	0.120
Final TIMI 0, %*	2.1	2.2	1.6	3.0	0.630
Final TIMI 3, %*	91.6	92.1	91.5	90.6	0.390
No significant epicardial coronary disease, %*	5.3	4.3	5.5	7.6	0.023
3-vessel disease, %*	15.0	15.2	15.1	14.0	0.670
Left main disease, %*	4.2	3.9	4.2	5.2	0.300
Stents used**					
Only BMS use, %	40.6	43.5	39.8	28.6	
Only DES use, %	57.7	55.1	57.5	69	0.353
Both BMS and DES use, %	1.93	1.45	2.65	2.38	
Anterior STEMI, %	41.8	42.4	40.6	43.1	0.890
Inferior STEMI, %	43.8	42.2	45.2	44.6	0.180
Bleeding with transfusion, %	0.6	0.7	0.3	1.0	0.920

**Data available since 2012. **Data available since 2015. PPCI, Primary percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction flow; BMS, bare metal stent; DES, drug-eluting stent; STEMI, ST-elevation myocardial infarction.*

TABLE 3 | Delays in initial medical care, diagnosis, and revascularization according to SES during the period 2010–2016.

	All *N* = 3,322	Low SES ≤80 *N* = 1,443	Mid SES 81–125 *N* = 1,366	High SES ≥126 *N* = 513	*P*-value
OS-ECG, min	82 [43–183]	85 [45–185]	85 [45–187]	75 [35–166]	0.003
ECG-Open Artery, min	85 [67–115]	87 [69–117]	83 [65–115]	81 [63–105]	<0.005
OS-Arrival to hospital, min	130 [82–240]	135 [85–240]	128 [80–254]	120 [75–225]	0.033
OS-Open Artery, min	184 [127–305]	190 [133–310]	180 [125–312]	165.5 [118–269]	0.003
PPCI <120 min from ECG, %	78.7	77.3	78.6	83.0	0.034
30-day mortality, %	7.7%	7.6%	8.3%	6.6%	0.430
30-day composite, %**	19.9%	19.4%	20.7%	19.1%	0.600
1-year mortality, %*	4.7%	5.2%	4.9%	5.1%	0.810

*OS, onset of symptoms; ECG, electrocardiogram; Min, minutes, median [interquartile range]. * in 30-day survivors; ** death, pulmonary edema, cardiogenic shock, or ventricular fibrillation.*

racial aspects (16), and various composite indexes (17, 19–21). Composite indexes can include varying combinations of household income, educational level, unemployment rate, vehicle ownership and engine power, prices of housing, the proportion of families with > 4 children, community services, environmental conditions, and crime level. These composites indexes reflect a multilevel stratum of social, educational, and economic data, which can give a better picture of concurring effects that determine health, acute and chronic treatments, and follow-up compared to strictly economic information.

Studies from various geographical areas have found that access to revascularization procedures is reduced in groups with lower SES (22). The population analyzed in this study represents a sample of homogeneously treated patients with STEMI: mostly (>93%) treated by PPCI in a public integrated medical system and features the inclusion of patients not treated with PPCI. The use of PPCI methods in patients with STEMI varies largely by region and can be explained by several factors such as supply factors, the number of physicians, and the number of available hospitalization beds for acute conditions, as well as constraining measures and "patient-level" factors (10). However, the standardization of treatments driven by new evidence-based medicine and consequent guidelines allows countries with different income levels to progressively organize emergency

TABLE 4 | Low-SES patients with ST-elevation myocardial infarction (STEMI) adjusted odds ratio (OR) of 30-day mortality (model 1); a 30-day composite end point (death, ventricular fibrillation, acute pulmonary edema, or cardiogenic shock) (model 2); and hazard ratio (HR) of 1-year mortality in 30-day survivors (model 3) in the "Codi IAM" network during the 2010-2016 period.

MODEL 1: 30-day mortality risk for STEMI patients in the whole cohort		
***N* = 3,078**	OR	95% CI
Low SES	0.95	0.70–1.30
MODEL 2: 30-day composite endpoint risk for STEMI patients in the whole cohort		
***N* = 3,078**	OR	95% CI
Low SES	1.03	0.84–1.26
MODEL 3: One-year mortality risk for STEMI patients in the whole cohort in 30-day survivors		
***N* = 2,720**	HR	95% CI
Low SES	1.09	0.76–1.56

Models 1 and 3 were adjusted for age, sex, diabetes mellitus, Killip III/IV vs. I/II, first medical care, coronary percutaneous intervention, hospital, year of treatment, time from electrocardiogram to coronary percutaneous intervention (>120 min), and type of initial medical care. Model 2 was adjusted for age, sex, diabetes mellitus, first medical care, coronary percutaneous intervention, hospital, year of treatment, time from electrocardiogram to coronary percutaneous intervention (>120 min), and type of initial medical care.

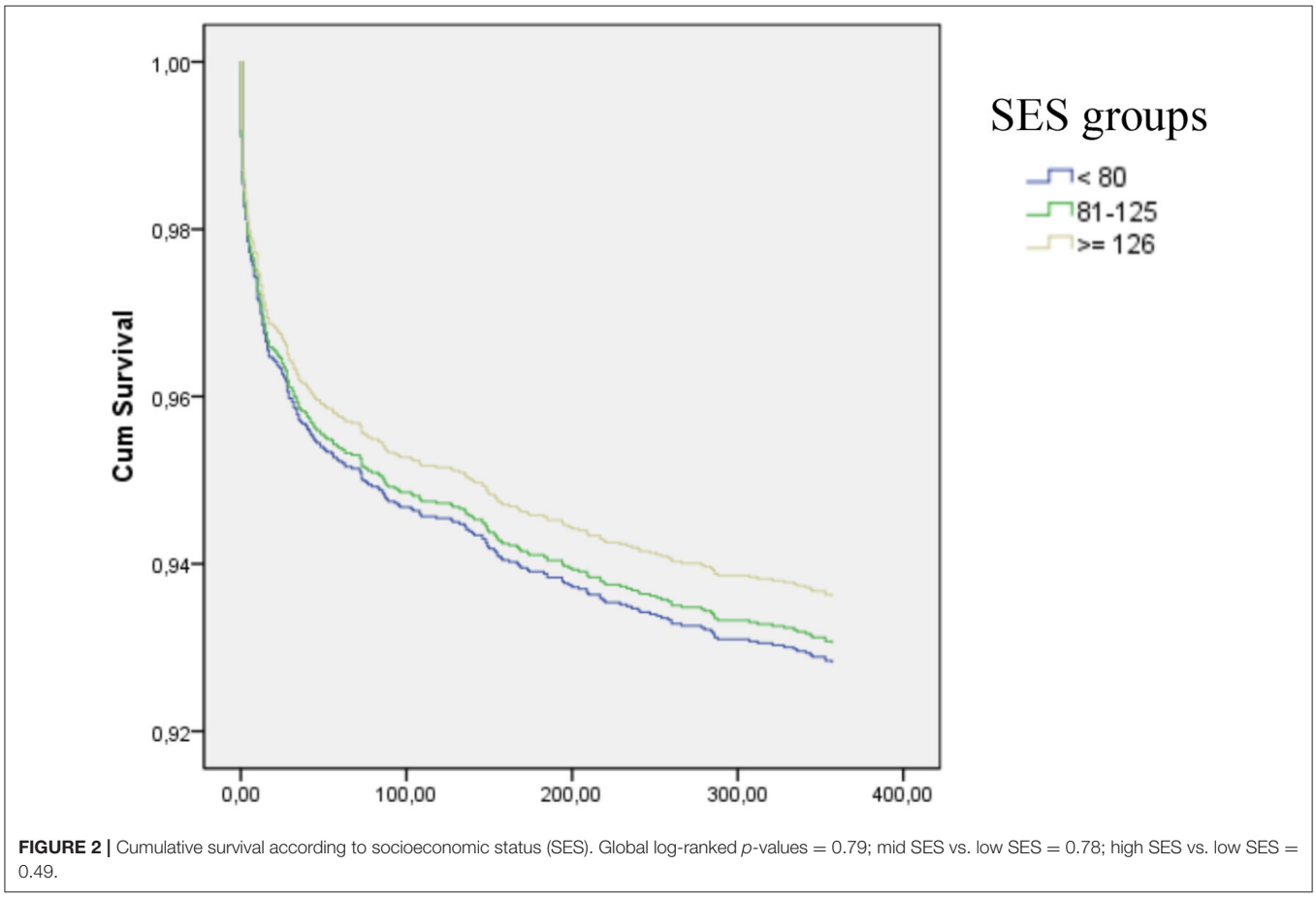

FIGURE 2 | Cumulative survival according to socioeconomic status (SES). Global log-ranked *p*-values = 0.79; mid SES vs. low SES = 0.78; high SES vs. low SES = 0.49.

networks for the early management of high-impact diseases in terms of incidence, hospitalization, and case fatality such as in STEMI (23, 24).

Network organization and public access to care and health may result in the neutralization of both higher incidence of the disease and adverse clinical baseline characteristics in low SES groups (25, 26). In our study, the low SES group had a worse cardiovascular profile, longer treatment delays, and different access routes to the health system, which did not, however, translate into worsened 30-day complications or 1-year mortality. Besides, when adjusting for potential confounders, SES data were not associated with either end points, suggesting that a robust healthcare system may flatten socioeconomic baseline disparity potential effect. Similar findings have been described in

international cohorts in different studies performed in a single-center fashion (22), in groups of hospitals within a geographical area (20, 26), or within a city (17). Those studies have in common the inclusion of patients with STEMI treated with PPCI as a standard treatment within a structural public STEMI network and showed no interaction of SES with mortality. However, most of these registries reported results from cohorts of patients before 2010. Other previous registries also included patients with other conditions such as non-ST-elevation myocardial infarction (21) or excluded patients treated with fibrinolysis (27). Exclusion of patients treated with fibrinolysis or patients who did not receive PPCI may, however, bias the results of any study aiming to clarify the importance of socioeconomic factors in STEMI prognosis because of the geographical gradient toward the periphery for lower-income groups and its relationship with the optimal timing of treatment for PPCI (17, 28, 29).

The lower tendency of use of DESs in the low-SES group observed in our study has also been reported in American cohorts (30–32), which is a "treatment-risk paradox" in which higher-risk patients are not treated with optimal or evidence-based strategies, and the use of mechanical support devices is reduced, and it may result in prognosis worsening (19, 33, 34). This finding may reflect the fact that differences in outcomes may not only be related to the use of a specific treatment/device in the acute period but to a whole standardized medical approach in which access to secondary prevention may be of utmost importance (35) and that the health system may override the burden of higher risk subsets.

Our study has several limitations. First, the data are derived from the first 7 years of implementation of a regional STEMI network, and its registry has evolved over the years and includes progressively more detailed data such as treated hypertension, treated dyslipidemia, smoking status, previous stroke, number and type of stents, and LV function. Moreover, there were no available records on the medical treatment administered during the index admission, at discharge, and/or regarding other therapies during follow-up such as cardiovascular rehabilitation. These treatments as well as the patients' adherence to prescriptions have been shown to have a direct impact on mortality (35, 36) and may also be related to socioeconomic conditions (21). Finally, the FIRB is a composite index that aggregates data from all inhabitants of a given district, so it does not allow analyzing effects of individual-level SES. However, the FIRB as a surrogate of SES by zip code results in a useful tool. Several prior studies have validated this approach of imputing individual SES in epidemiologic studies reflecting aggregate characteristics of a population and prevailing habits as well as its environmental attributes (such as available health resources) that impact its residents' health (37, 38).

CONCLUSION

Barcelona citizens with lower SES who are admitted with STEMI show more unfavorable clinical and cardiovascular risk factor features than citizens with higher SES. Nevertheless, the "Codi IAM" emergency network for STEMI management documented similar 30-day complications and 1-year mortality regardless of SES suggesting that a robust healthy system may override baseline adverse patients' characteristics.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the dataset belongs to Departament de Salut, Generalitat de Catalunya, and the researchers only have access to statistical analysis.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hospital del Mar Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HT-M: study management, data collection, interpretation of collected data, and preparation of the manuscript. BV: critical revisions of the manuscript. JM: participation in study management and acquisition of data and revision of the manuscript. RL, AA, and NF: critical revisions of the manuscript and data collection. XC: revision of the manuscript and data collection. JG-P, AR, MC, AC-V, XD, NR, and HC-G: revision of the manuscript. PP: extensive revision of the manuscript. JM: study management, interpretation of collected data, statistical analysis, and extensive revision of the manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol.* (2017) 70:1–25. doi: 10.1016/j.jacc.2017.04.052
2. Organization WH. *Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016.* In: Organization WH, editor. Geneva: World Health Organization.
3. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* (2018) 39:119–77. doi: 10.1093/eurheartj/ehx393
4. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJ, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. *Circulation.* (2014) 129:1483–92. doi: 10.1161/CIRCULATIONAHA.113.004042
5. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation.* (1993) 88:1973–98. doi: 10.1161/01.CIR.88.4.1973
6. Kampfer J, Yagensky A, Zdrojewski T, Windecker S, Meier B, Pavelko M, et al. Long-term outcomes after acute myocardial infarction in countries with different socioeconomic environments: an international prospective cohort study. *BMJ Open.* (2017) 7:e012715. doi: 10.1136/bmjopen-2016-012715
7. Rao SV, Schulman KA, Curtis LH, Gersh BJ, Jollis JG. Socioeconomic status and outcome following acute myocardial infarction in elderly patients. *Arch Intern Med.* (2004) 164:1128–33. doi: 10.1001/archinte.164.10.1128
8. Rosvall M, Chaix B, Lynch J, Lindstrom M, Merlo J. The association between socioeconomic position, use of revascularization procedures and five-year survival after recovery from acute myocardial infarction. *BMC Public Health.* (2008) 8:44. doi: 10.1186/1471-2458-8-44
9. Hawkins NM, Scholes S, Bajekal M, Love H, O'Flaherty M, Raine R, et al. The UK National Health Service: delivering equitable treatment across the spectrum of coronary disease. *Circ Cardiovasc Qual Outcomes.* (2013) 6:208–16. doi: 10.1161/CIRCOUTCOMES.111.000058
10. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med.* (2014) 371:818–27. doi: 10.1056/NEJMoa1311890
11. Tizon-Marcos H, Vaquerizo B, Marrugat J, Ariza A, Carrillo X, Munoz JF, et al. Differences in 30-day complications and 1-year mortality by sex in patients with a first STEMI managed by the Codi IAM network between 2010 and 2016. *Rev Esp Cardiol (Engl Ed).* (2020). doi: 10.1016/j.rec.2020.06.002
12. Group TS. The Thrombolysis in Myocardial Infarction (TIMI) trial. *Phase I findings N Engl J Med.* (1985) 312:932–6. doi: 10.1056/NEJM198504043121437
13. Barcelona Ad, Economia B. Any 2016 - Distribució Territorial de la Renda Familiar Disponible per Càpita a Barcelona- (Desembre de 2017) Any 2015 - Distribució Territorial de la Renda Familiar Disponible per Càpita a Barcelona- (Desembre de 2016) Any 2014 - Distribució Territorial de la Renda Familiar Disponible per Càpita a Barcelona- (Desembre de 2015) Any 2013 - Distribució Territorial de la Renda Familiar Disponible per Càpita a Barcelona - (Desembre de 2014) Any 2012 - Distribució Territorial de la Renda Familiar Disponible per Càpita a Barcelona - (Gener de 2014) Any 2011 - Barcelona Economia n.80 (nov. de 2012) Any 2010 - Barcelona Economia n.77 (nov. de 2011). In: *Programació Gtd, Programació DdEi,* editors. Barcelona: Ajuntament de Barcelona (2010-2016).
14. van Oeffelen AA, Agyemang C, Bots ML, Stronks K, Koopman C, van Rossem L, et al. The relation between socioeconomic status and short-term mortality after acute myocardial infarction persists in the elderly: results from a nationwide study. *Eur J Epidemiol.* (2012) 27:605–13. doi: 10.1007/s10654-012-9700-z
15. Igland J, Vollset SE, Nygard OK, Sulo G, Sulo E, Ebbing M, et al. Educational inequalities in 28 day and 1-year mortality after hospitalisation for incident acute myocardial infarction–a nationwide cohort study. *Int J Cardiol.* (2014) 177:874–80. doi: 10.1016/j.ijcard.2014.10.045
16. Bucholz EM, Ma S, Normand SL, Krumholz HM. Race, socioeconomic status, and life expectancy after acute myocardial infarction. *Circulation.* (2015) 132:1338–46. doi: 10.1161/CIRCULATIONAHA.115.017009
17. Biswas S, Andrianopoulos N, Duffy SJ, Lefkovits J, Brennan A, Walton A, et al. Impact of socioeconomic status on clinical outcomes in patients with st-segment-elevation myocardial infarction. *Circ Cardiovasc Qual Outcomes.* (2019) 12:e004979. doi: 10.1161/CIRCOUTCOMES.118.004979
18. Stirbu I, Looman C, Nijhof GJ, Reulings PG, Mackenbach JP. Income inequalities in case death of ischaemic heart disease in the Netherlands: a national record-linked study. *J Epidemiol Community Health.* (2012) 66:1159–66. doi: 10.1136/jech-2011-200924
19. Steele L, Palmer J, Lloyd A, Fotheringham J, Iqbal J, Grech ED. Impact of socioeconomic status on survival following ST-elevation myocardial infarction in a universal healthcare system. *Int J Cardiol.* (2019) 276:26–30. doi: 10.1016/j.ijcard.2018.11.111
20. Denvir MA, Lee AJ, Rysdale J, Walker A, Eteiba H, Starkey IR, et al. Influence of socioeconomic status on clinical outcomes and quality of life after percutaneous coronary intervention. *J Epidemiol Community Health.* (2006) 60:1085–8. doi: 10.1136/jech.2005.044255
21. Shimony A, Zahger D, Ilia R, Shalev A, Cafri C. Impact of the community's socioeconomic status on characteristics and outcomes of patients undergoing percutaneous coronary intervention. *Int J Cardiol.* (2010) 144:379–82. doi: 10.1016/j.ijcard.2009.04.033
22. Britton A, Shipley M, Marmot M, Hemingway H. Does access to cardiac investigation and treatment contribute to social and ethnic differences in coronary heart disease? Whitehall II prospective cohort study. *BMJ.* (2004) 329:318. doi: 10.1136/bmj.38156.690150.AE
23. Radovanovic D, Maurer L, Bertel O, Witassek F, Urban P, Stauffer JC, et al. Treatment and outcomes of patients with recurrent myocardial infarction: a prospective observational cohort study. *J Cardiol.* (2016) 68:498–503. doi: 10.1016/j.jjcc.2015.11.013
24. Galappatthy P, Bataduwaarachchi VR, Ranasinghe P, Galappatthy GKS, Wijayabandara M, Warapitiya DS, et al. Management, characteristics and outcomes of patients with acute coronary syndrome in Sri Lanka. *Heart.* (2018) 104:1424–31. doi: 10.1136/heartjnl-2017-312404
25. Agarwal S, Garg A, Parashar A, Jaber WA, Menon V. Outcomes and resource utilization in ST-elevation myocardial infarction in the United States: evidence for socioeconomic disparities. *J Am Heart Assoc.* (2014) 3:e001057. doi: 10.1161/JAHA.114.001057
26. Pancholy S, Patel G, Pancholy M, Nanavaty S, Coppola J, Kwan T, et al. Association between health insurance status and in-hospital outcomes after ST-segment elevation myocardial infarction. *Am J Cardiol.* (2017) 120:1049–54. doi: 10.1016/j.amjcard.2017.06.041
27. Fournier S, Muller O, Ludman AJ, Lauriers N, Eeckhout E. Influence of socioeconomic factors on delays, management and outcome amongst patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Swiss Med Wkly.* (2013) 143:w13817. doi: 10.4414/smw.2013.13817
28. Terkelsen CJ, Sorensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA.* (2010) 304:763–71. doi: 10.1001/jama.2010.1139
29. Kjaerulff TM, Bihrmann K, Andersen I, Gislason GH, Larsen ML, Ersboll AK. Geographical inequalities in acute myocardial infarction beyond neighbourhood-level and individual-level sociodemographic characteristics: a Danish 10-year nationwide population-based cohort study. *BMJ Open.* (2019) 9:e024207. doi: 10.1136/bmjopen-2018-024207
30. Hannan EL, Racz M, Walford G, Clark LT, Holmes DR, King SB, et al. Differences in utilization of drug-eluting stents by race and payer. *Am J Cardiol.* (2007) 100:1192–8. doi: 10.1016/j.amjcard.2007.05.039
31. Rao SV, Shaw RE, Brindis RG, Klein LW, Weintraub WS, Krone RJ, et al. Patterns and outcomes of drug-eluting coronary stent use in clinical practice. *Am Heart J.* (2006) 152:321–6. doi: 10.1016/j.ahj.2006.03.005
32. Yong CM, Abnousi F, Asch SM, Heidenreich PA. Socioeconomic inequalities in quality of care and outcomes among patients with acute coronary syndrome in the modern era of drug eluting stents. *J Am Heart Assoc.* (2014) 3:e001029. doi: 10.1161/JAHA.114.001029
33. Baumbach A, Heg D, Raber L, Ostoijc M, Brugaletta S, Strange JW, et al. Selective use of contemporary drug-eluting stents in primary angioplasty for ST-elevation myocardial infarction: pooled analysis of

COMFORTABLE AMI and EXAMINATION. *EuroIntervention.* (2017) 12:1577–86. doi: 10.4244/EIJ-D-15-00408

34. Brugaletta S, Gomez-Lara J, Ortega-Paz L, Jimenez-Diaz V, Jimenez M, Jimenez-Quevedo P, et al. 10-year follow-up of patients with everolimus-eluting versus bare-metal stents after ST-segment elevation myocardial infarction. *J Am Coll Cardiol.* (2021) 77:1165–78. doi: 10.1016/j.jacc.2020.12.059
35. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J.* (2017) 38:3056–65. doi: 10.1093/eurheartj/ehx515
36. Hermann M, Witassek F, Erne P, Rickli H, Radovanovic D. Impact of cardiac rehabilitation referral on one-year outcome after discharge of patients with acute myocardial infarction. *Eur J Prev Cardiol.* (2019) 26:138–44. doi: 10.1177/2047487318807766
37. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health.* (1992) 82:703–10. doi: 10.2105/AJPH.82.5.703
38. Smith GD, Hart C, Watt G, Hole D, Hawthorne V. Individual social class, area-based deprivation, cardiovascular disease risk factors, and mortality: the Renfrew and Paisley Study. *J Epidemiol Community Health.* (1998) 52:399–405. doi: 10.1136/jech.52.6.399

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Risk of Stroke Among Different Metabolic Obesity Phenotypes: A Systematic Review and Meta-Analysis

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Background and Purpose: Overweight/obesity is a modified risk factor for stroke. This systematic review and meta-analysis aimed to assess the impact of different obesity phenotypes on stroke risk in adults.

Methods: The PubMed, Embase, and Cochrane Library databases were searched from their inception to 7 March 2021 to identify the prospective cohort studies investigating stroke risk among different metabolic overweight/obesity phenotypes. The methodological quality of the included studies was evaluated using the Newcastle–Ottawa Scale. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using a random-effects model.

Results: A total of eleven prospective cohorts (n = 5,609,945 participants) were included in the systematic review, nine of which were included in the meta-analysis. All metabolically unhealthy phenotypes had a higher risk of stroke than the metabolically healthy normal-weight phenotypes, including metabolically unhealthy normal weight (HR = 1.63, 95% CI: 1.41–1.89, I^2 = 89.74%, n = 7 cohort studies, 1,042,542 participants), metabolically unhealthy overweight (HR = 1.94, 95% CI: 1.58–2.40, I^2 = 91.17%, n = 4 cohort studies, 676,166 participants), and metabolically unhealthy obese (HR = 1.99, 95% CI: 1.66–2.40, I^2 = 93.49%, n = 6 cohort studies, 1,035,420 participants) phenotypes. However, no risk of stroke was observed in the populations with metabolically healthy overweight (MHOW) (HR = 1.07, 95% CI: 1.00–1.14, I^2 = 69.50%, n = 5 studies, 4,171,943 participants) and metabolically healthy obese (MHO) (HR = 1.07, 95% CI: 0.99–1.16, I^2 = 54.82%, n = 8 studies, 5,333,485 participants) phenotypes. The subgroup analyses for the MHO studies suggested that the risk of stroke increased only when the MHO participants were mainly females, from North America, and when the World Health Organization standard was applied to define obesity. In the subgroup analysis of the risk of stroke in MHOW, a longer follow-up duration was also associated with a higher risk of stroke.

Conclusion: The risk of stroke increase for all metabolically unhealthy phenotypes irrespective of the body mass index (BMI). The associated risk of stroke with metabolic

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health but high BMI shows substantial heterogeneity, which requires future research considering the impact of sex and transition of the metabolic status on the risk of stroke.

Systematic Review Registration: The study protocol was prospectively registered in PROSPERO (No. CRD42021251021).

Keywords: obesity, stroke, risk factor, meta-analysis, metabolic health

INTRODUCTION

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 showed that stroke is the second leading cause of death globally, and the incidence and prevalence of stroke have grown substantially (1). The identification and control of risk factors could be an effective approach for preventing new stroke cases. Global evidence has shown that obesity is a modifiable risk factor for all types of stroke (2, 3). The GBD 2019 study revealed that obesity is the fastest-growing risk factor in high body mass index (BMI) (1). These findings have been included in clinical practice guidelines in either the West or the East, and weight reduction in overweight/obese individuals is recommended to reduce the risk of stroke (4, 5). However, obesity often coexists with other cardiometabolic risk factors such as hypertension, hyperglycemia, and dyslipidemia (6–9). A meta-analysis of 97 prospective cohorts found that the partial excess risk of overweight and obesity for stroke was mediated by metabolic factors, including high blood pressure, cholesterol, and glucose (10). Thus, co-controlling metabolic factors are gaining attention to achieve optimal body weight, compared with the previous goal of an appropriate BMI only (6–9).

In the last 15 years, a concept that classifies individuals into six phenotypes based on the BMI and metabolic health has been gradually developed and supported by animal and human studies: metabolically healthy normal weight (MHNW), metabolically healthy overweight (MHOW), metabolically healthy obese (MHO), metabolically unhealthy normal weight (MUNW), metabolically unhealthy overweight (MUOW), and metabolically unhealthy obese (MUO) (11).

Whether metabolically healthy overweight/obese increases the cardio-cerebrovascular risk is a substantial debate (12–15). A recent meta-analysis of eight prospective cohorts revealed that MHO is positively associated with an elevated risk of stroke (16). However, it only calculated the risk ratio at the end of the follow-up, which might have omitted the time-dependent effect. It did not perform a subgroup analysis considering the demographic factors and the coexisting health conditions of the participants. Recently, more prospective cohorts of the same interest have been published (17–19). We updated the literature search and conducted a meta-analysis to examine the causal relationship between the obesity phenotypes and stroke risk.

Abbreviations: BMI, body mass index; MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obese; IOTF, International Obesity Task Force; WGOC, Working Group on Obesity in China; WHO, World Health Organization.

MATERIALS AND METHODS

The systematic review and meta-analysis were conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (20). The study protocol was prospectively registered in PROSPERO (No. CRD42021251021).

Eligibility

Studies were included in the systematic review if they met the following criteria:

■ Type of study

Only the prospective cohort study was eligible as it is the most appropriate design for examining the causal relationship between exposure and risk of disease. A pilot search found that a considerable number of prospective cohorts were published.

■ Participants

The participants at baseline were adults (≥18 years old) without a preexisting stroke.

■ Exposure and control

The exposure group had one of the following phenotypes: MHOW, MHO, MUNW, MUOW, or MUO, and the reference group was MHNW. Overweight/obesity was defined by BMI in compliance with the standards from one of the following organizations: the International Obesity Task Force (IOTF), Working Group on Obesity in China (WGOC), and the World Health Organization (WHO). Currently, there is no consensus regarding the definition of metabolic health. We endorsed the methodology of the previous systematic reviews (16), and *"metabolic health was defined as individuals with less than two abnormal metabolic parameters."* This enabled a direct comparison between the previous evidence and our study.

■ Outcomes

The primary outcome was the first-ever stroke, which the participants could report—a clinical diagnosis confirmed by clinical signs/symptoms accompanied by brain images or a diagnosis in the medical records/national databases. The patients with ischemia, hemorrhage, or mixed stroke were eligible.

Studies were excluded if they were repeatedly published.

Search Strategy and Study Selection

We searched the PubMed, Embase, and the Cochrane Library databases from their inception to 7 March 2021. The search

strategy is presented in **Supplementary Table 1**. Two researchers (MMM and GYX) independently screened the literature by removing duplicates, reading the title/abstract, and reviewing the full text. We calculated the inter-rater agreement with the reference of kappa value, and the disagreements were resolved through discussion or consultation with a third researcher (NXJ).

Data Extraction

Two researchers (MMM and GYX) extracted the data using the double-entry method and were checked by a third researcher (NXJ). The data items included author, publication year, country, sample size, mean or range of age, sex, period of baseline data collection, follow-up duration, overweight/obesity definition, definition of (un)metabolic health, the confounding factors that were adjusted for in the multivariable analysis, and adjusted or non-adjusted effect sizes [hazard ratio (HR) and relative risk (RR)] with the corresponding 95% confidence intervals (CIs).

Methodological Quality Assessment

Two researchers (KZR, LLL) independently evaluated the methodological quality of the included studies using the Newcastle–Ottawa Scale (NOS), a tool for assessing the quality of observational studies in meta-analyses (21). It was composed of three domains (eight items): selection of the study groups, comparability, and ascertainment of the outcomes for the cohort study. The assessment outcomes ranged from zero stars up to nine stars. Studies with seven or more stars were considered high quality. We calculated the inter-rater agreement concerning the intraclass correlation coefficient (ICC), and any disagreement was resolved by discussion or consultation with a third researcher (MMM).

Statistical Analysis

Pooled HRs with 95% CIs were calculated using a random-effects model to assess the risk of stroke for MHOW, MHO, MUNW, MUOW, and MUO compared to MHNW. The heterogeneity was evaluated using Cochran's Q test and I^2 statistics. If the heterogeneity was considered significant ($p < 0.1$ or $I^2 > 50\%$), subgroup analyses were performed according to the duration of the follow-up, number of abnormal metabolic components, criteria for defining overweight/obesity, research sites, and proportion of females to explore the potential sources of heterogeneity. A sensitivity analysis was performed based on the methodological quality of the included studies and the leave-one-out method. The publication bias was evaluated by the visual inspection of asymmetry in the funnel plots and Egger's test for at least 10 studies. The statistical significance was set at $p < 0.05$. All data analyses were conducted using Stata/MP version 16.0.

RESULTS

Search Results

We initially identified 3,381 records from the database search and finally included 11 eligible cohort studies in the systematic review (13–15, 17–19, 22–26). The inter-examiner agreement between the two reviewers was good (kappa = 0.762, 95% CI: 0.5464–0.9776). The results from nine cohorts were quantitatively synthesized as two studies reported the relative ratio (RR) instead of HR (22, 25). A full flowchart of the study selection process is shown in **Figure 1**. A list of the excluded studies is shown in **Supplementary Data Sheet 1**.

Study Characteristics

The sample sizes of the included cohorts ranged from 5,171 to 3,495,777 participants. The included studies were conducted in different geographic locations: four studies were conducted in Europe (14, 15, 24, 25), two in North America (13, 26), and five in Asia (17–19, 22, 23). Female participants were enrolled in only three studies (13, 25, 26). The baseline information was collected between 1980 and 2018, and the duration of the follow-up ranged from 3 to 24 years. The BMI threshold for obesity varied, including BMI $\geq$ 25 kg/m^2 (International Obesity Task Force, IOTF) in two studies (17, 23), BMI $\geq$ 28 kg/m^2 (Working Group on Obesity in China, WGOC) in three studies (18, 19, 22), and BMI $\geq$ 30 kg/m^2 (World Health Organization, WHO) in six studies (13–15, 24–26). The definition of metabolic health was distinct, such as the Adult Treatment Panel III (ATP III) definition in three studies (14, 15, 26), the International Diabetes Federation (IDF) in one study (18), the Japanese diagnostic criteria in one study (17), modified harmonization and the Hammer's study in three studies (19, 22, 23). The stroke event was reported by the participants in another study (22), diagnosed according to the clinical signs/symptoms and brain images in four studies (13, 14, 23, 24), and was collected from the medical records and registration information in the national databases. The full details of the basic characteristics of the included cohorts are presented in **Table 1**.

Methodological Quality Assessment

The inter-examiner agreement was very good (ICC = 0.771, 95% CI: 0.3503–0.933). Regarding the methodological quality of the included studies, one study was awarded six stars (17), three studies evaluated eight stars (13, 15, 22), and seven studies achieved nine stars (14, 18, 19, 23–26). The average quality score was eight, suggesting that the methodological quality was generally moderate to high. The results of the quality assessments are presented in **Table 2**.

Results of the Meta-Analyses

Metabolically Healthy Overweight/Metabolically Healthy Obese and Risk of Stroke

Compared with the MHNW group, the risk of stroke was not significantly increased in the participants with MHOW (MHOW: HR = 1.07, 95% CI: 1.00–1.14, I^2 = 69.50%, n = 5 studies, 4,171,943 participants) (13, 18, 19, 24, 26) or MHO (HR = 1.07, 95% CI: 0.99–1.16, I^2 = 54.82%, n = 8 studies, 5,333,485 participants) (13, 14, 17–19, 23, 24, 26) (**Figure 2** and **Supplementary Table 2**). The subgroup analyses for the risk of stroke in the MHO were conducted in terms of the duration of the follow-up, the number of abnormal metabolic parameters, the definition of obesity, geographic locations, and proportion

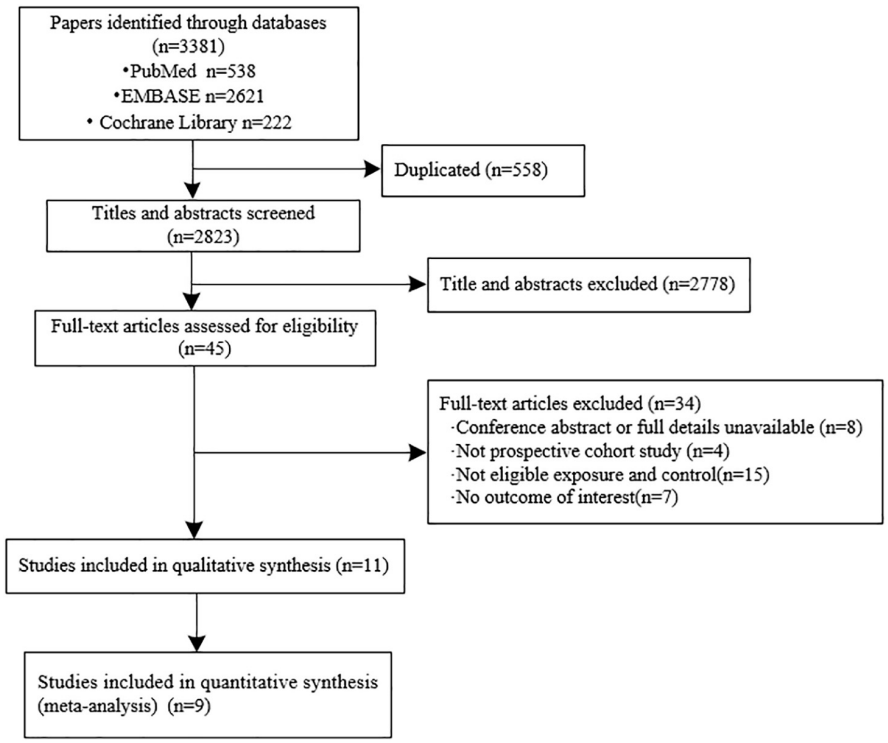

FIGURE 1 | Flow chart for the literature search, study selection, and reasons for exclusion.

of females (**Table 3** and **Supplementary Figures 1–5**), which revealed that the risk of stroke increased only when the MHO participants were mainly females, from North America, and when the WHO standard was applied in defining obesity, and these meta-analyses were of low heterogeneity. As for the subgroup analysis of the risk of stroke in the MHOW, a longer follow-up duration was also associated with a higher risk of stroke (**Table 3** and **Supplementary Figures 6–10**).

Metabolically Unhealthy Normal Weight and the Risk of Stroke

A higher risk of stroke was observed in the MUNW group than in the MHNW group (HR = 1.63, 95% CI: 1.41–1.89, I^2 = 89.74%, n = 7 cohort studies, 1,042,542 participants) (13–15, 18, 19, 23, 26) (**Figure 3** and **Supplementary Table 2**). The comprehensive subgroup analyses (**Table 3** and **Supplementary Figures 11–15**) suggested that the risk of stroke increased when the follow-up was over 15 years (HR = 2.18, 95% CI: 1.87–2.53, I^2 = 1.36%) than in those with a shorter follow-up duration, and this meta-analysis was quite homogeneous.

Metabolically Unhealthy Overweight/Metabolically Unhealthy Obese and the Risk of Stroke

Compared with the MHNW group, a higher risk of stroke was found in either the participants with MUOW (HR = 1.94, 95% CI: 1.58–2.40, I^2 = 91.17%, n = 4 cohort studies, 676,166 participants) (13, 18, 19, 26) or those with MUO (HR = 1.99, 95% CI: 1.66–2.40, I^2 = 93.49%, n = 6 cohort studies, 1,035,420 participants) (13, 14, 18, 19, 23, 26) (**Figure 4** and **Supplementary Table 2**). However, the subgroup analyses for the MUOW/MUO studies were substantially heterogeneous, except for the meta-analysis of MUOW only containing studies with a follow-up of more than 15 years, enrolling participants from North America, or studies with females accounting for most of the participants (**Table 3** and **Supplementary Figures 16–25**).

Sensitivity Analysis and Publication Bias

We performed a sensitivity analysis by omitting only one study with the lowest methodological quality of the NOS (17). An advanced risk of stroke was detected in the MHO participants compared to the MHNW participants (HR = 1.10, 95% CI: 1.03–1.18, I^2 = 42.18%, n = 7 cohort studies, 4,531,197 participants) (**Supplementary Figure 26**), which differed from the primary analysis. An additional sensitivity analysis excluding one study at a time is shown in **Supplementary Figure 27**. The publication bias was not assessed because fewer than ten included studies in each phenotype.

DISCUSSION

The Summary of the Main Findings and Strengths Compared With the Previous Studies

This systematic review and meta-analysis including nine prospective cohorts showed that metabolically unhealthy

TABLE 1 | Characteristics of the included studies.

Study	Country/Panel	Funding	Sample size	Age	Female (%)	Baseline collection period	Follow up	Definition of obesity	Definition of metabolic health	Adjusted variables in analyses
Hidetaka (17)	Japan/The Japan Medical Data Center (JMDC)	the Ministry of Health, Labour and Welfare, Japan and the Ministry of Education, Culture, Sports, Science and Technology, Japan	802288	42.8 ± 9.4	55.3%	2005∼2018	1126 ± 849 days	BMI ≥ 25 kg/m^{2}from the criteria by IOTF	Metabolic health was defined as none of the risk factors according to the Japanese diagnostic criteria.	Unadjusted
Zhou (18)	China/The Zhejiang Metabolic Syndrome cohort and the Kailuan cohort	the National Key Research and Development Program of China and Hangzhou Science and Technology Project	102037	51.5 ± 12.8	26.7%	Zhejiang: 2010∼2014 Kailuan: 2006∼2007	9.9 ± 2.0 years	BMI ≥ 28 kg/m^{2}from the criteria by WGOC	Metabolic health was defined as ≤1 of the risk factors according to IDF criteria.	age, sex, smoking, drinking, physical activity, family history of stroke
Gao (19)	China/The China Kadoorie Biobank cohort	the National Key R&D Program of China, the United Kingdom Wellcome Trust, National Natural Science Foundation of China and Chinese Ministry of Science and Technology	458246	50.9 ± 10.4	59.2%	2004∼2008	10.0 years	BMI ≥ 28 kg/m^{2}from the criteria by WGOC	Metabolic health was defined as ≤1 of the risk factors according to modified harmonization definition.	age, region, sex, education, household income, marital status, smoking, drinking, intakes of red meat, fresh fruits, and vegetables, physical activity, family history of heart attack or stroke
Li (22)	China/The China Health and Retirement Longitudinal Study (CHRLS)	the National Institute on Aging, the National Natural Science Foundation of China, the World Bank and Peking University	7849	59.88 ± 10.82	52.8%	2011∼2012	3.67 years	BMI ≥ 24 kg/m^2 (overweight/obesity) from the criteria by WGOC	Metabolic health was defined as ≤1 of the risk factors according to Hammer's study.	age, gender, residence, educational level, marital status, smoking, drinking, physical activity, history of arthritis, asthma and history of fall, physical impairments in ADL and IADL, and cognition score, total cholesterol, high-density cholesterol levels
Lee (23)	Korea/The Korean National Health Insurance Service–National Sample Cohort (NHIS-NSC)	the Seoul National University Hospital Research Fund, the National Research Foundation of Korea at Ministry of Education, Science and Technology and the Korean Healthcare Technology R&D project at the Ministry of Health and Welfare	354083	45.8 ± 14.2	47.3%	2004∼2008	7.43 ± 1.52 years	BMI ≥ 25 kg/m^{2}from the criteria by IOTF	Metabolic health was defined as none of the risk factors according to modified harmonization definition.	age, sex, income, area, smoking, drinking, exercise, history of ischemic heart disease, peripheral artery disease, congestive heart failure, transient ischemic attack, venous thromboembolism, chronic obstructive pulmonary disease, end-stage renal disease, liver cirrhosis, cancer, and cardiac surgery

(Continued)

TABLE 1 | (Continued)

Study	Country/Panel	Funding	Sample size	Age	Female (%)	Baseline collection period	Follow up	Definition of obesity	Definition of metabolic health	Adjusted variables in analyses
Nathalie (13)	United States/ The Nurses' Health Study (NHS)	the United States National Institutes of Health and the German Federal Ministry of Education and Research (BMBF)	90257	NA	100%	1980	24 years	BMI $\geq$ 30 kg/m^{2}from the criteria by WHO	Metabolic health was defined as none of the metabolic disorders (hypertension, diabetes, and hypercholesterolemia).	age, race, highest educational degree, alcohol consumption, smoking status, post-menopausal status, post-menopausal hormone use, physical examinations for screening purposes, aspirin use, family history of myocardial infarction and diabetes and physical activity
Caleyachetty (24)	United Kingdom/ The Health Improvement Network (THIN)	No mention	3495777	NA	54.5%	1995∼2015	5.4 years	BMI $\geq$ 30 kg/m^{2}from the criteria by WHO	Metabolic health was defined as none of the metabolic disorders (hypertension, diabetes, and hypercholesterolemia).	age, sex, smoking status and social deprivation
Laura (14)	Spain/The Vascular-Metabolic CUN cohort	No financial support	5171	men: 55.61 $\pm$ 13.68 women: 54.21 $\pm$ 12.87	38.1%	1997∼2002	Men: 9.18 years women: 8.97 years	BMI $\geq$ 30 kg/m^{2}from the criteria by WHO	Metabolic health was defined as $\leq$1 of the risk factors according to ATP III criteria.	age, sex, BMI, cigarette smoking, daily alcohol intake, lifestyle pattern, hypertension, coronary heart disease, type 2 diabetes, anti-aggregation therapy, HDL-cholesterol, LDL-cholesterol, and triglycerides
Hinnouho (15)	United Kingdom/The Whitehall II study	the United States National Institutes of Health, the United Kingdom Medical Research Council, the Economic and Social Research Council and the British Heart Foundation	7122	49.3	30.3%	1991∼1993	17.4 years	BMI $\geq$ 30 kg/m^{2}from the criteria by WHO	Metabolic health was defined as $\leq$1 of the risk factors according to ATP III criteria.	sex, socioeconomic status, marital status, ethnicity, physical activity, smoking, alcohol, fruits and vegetables consumption, CVD medication and procedures

(Continued)

TABLE 1 | (Continued)

Study	Country/Panel	Funding	Sample size	Age	Female (%)	Baseline collection period	Follow up	Definition of obesity	Definition of metabolic health	Adjusted variables in analyses
Andersen (25)	Denmark/Danish Medical Birth Register	the University of Copenhagen, Denmark, the Danish Agency of Science, Technology and Innovation and the Novo Nordisk Foundation	261489	30.5	100%	2004~2009	5.6 years	BMI ≥ 30 kg/m^2 from the criteria by WHO	Metabolic health was defined as none of the risk factors (any hypertensive disorder, any abnormality in glucose metabolism and dyslipidaemia).	age, calendar year and smoking
Song (26)	United States/The Women's Health Study	the National Institutes of Health, Bethesda, Maryland and an American Diabetes Association Career Development Award, Alexandria, Virginia	25626	NA	100%	1992~1995	10.2 years	BMI ≥ 30 kg/m^2 from the criteria by WHO	Metabolic health was defined as <2 of the risk factors according to ATP III criteria.	smoking, exercise, alcohol intake, total calorie intake, postmenopausal hormone use, multivitamin use and parental history of myocardial infarction at age <60 years

IOTF, International Obesity Task Force; WGOC, Working Group on Obesity in China; WHO, World Health Organization; ATP III, Adult Treatment Panel III; IDF, International Diabetes Federation; NA, not reported.

concurrent with either overweight or obesity resulted in an increased risk of stroke, which was not affected by the duration of the follow-up, the number of abnormal metabolic parameters, the definition of obesity, geographic locations, or the proportion of females. Although the primary meta-analysis supported the fact that overweight/obesity with metabolic health did not increase the risk of stroke, some subgroup analyses that only included a specific type of participant might present a different result. This study further examined the causal relationship between overweight/obesity and stroke-onset from the perspective of metabolism, which would assist with the stratified management of overweight/obesity and precision prevention for stroke. Compared with a previous study (16), our study had several strengths in terms of study design and data analyses. First, we included more recent cohorts by an updated search, which improved the precision of the estimated effect size; second, we calculated the HR instead of RR, which considered the time-dependent effect; third, we performed comprehensive subgroup analyses to explore the sources of heterogeneity and to test the robustness of the analysis models.

Explanations of the Results and Clinical Implications

We found that individuals with metabolically unhealthy phenotypes were at a higher risk of stroke, irrespective of the body weight, which was consistent with a previous systematic review (14, 16, 23). This suggests that multiple coexisting metabolic parameters play a leading role in the risk of incident stroke.

However, regarding the phenotypes of MHOW and MHO, our study suggested that the associated risk of stroke was not significantly increased, which differed from a previous systematic review (16). This was partially explained by the updates of the literature search and the different types of outcome data included in the meta-analysis. Furthermore, we observed additional findings when comprehensive subgroup analyses were performed. Concerning the participants with MHOW, a higher risk of stroke was identified by a longer duration of follow-up. This could be explained by the transition of the metabolic health status over long term. As studies have shown, MHOW is probably an unstable and intermediate condition, which could transfer to a metabolically unhealthy phenotype during the follow-up (28). Regarding the subgroup analysis of MHO, we found that MHO led to a higher risk of stroke only when the participants were all females and living in North America. This could be partially explained by the sex differences in the development of stroke. It has been well-recognized that the incidence of stroke is higher in women than in men after the menopausal period (29). The subgroup enrolled middle-aged female participants and continued the follow-up for incident stroke for more than 10 years immediately after their menopausal period. Another reason for the outstanding risk of stroke in the subgroup could be the high transition rate from metabolic health to unhealth in women. The Nurses' Health Study reported that 84% of the women with MHO and 68% with MHNW were converted to metabolically unhealthy

TABLE 2 | Quality evaluation of the included studies.

Study	Selection of the study groups				Comparability of the groups	Ascertainment of outcome			Sum	Overall quality
	1	2	3	4	5	6	7	8		
Hidetaka (17)	√	√	√	√		√		√	6	Moderate
Zhou (18)	√	√	√	√	√ √	√	√	√	9	High
Gao (19)	√	√	√	√	√ √	√	√	√	9	High
Li (22)	√	√	√	√	√ √	√		√	8	High
Lee (23)	√	√	√	√	√ √	√	√	√	9	High
Nathalie (13)		√	√	√	√ √	√	√	√	8	High
Caleyachetty (24)	√	√	√	√	√ √	√	√	√	9	High
Laura (14)	√	√	√	√	√ √	√	√	√	9	High
Hinnouho (15)		√	√	√	√ √	√	√	√	8	High
Andersen (25)	√	√	√	√	√ √	√	√	√	9	High
Song (26)	√	√	√	√	√ √	√	√	√	9	High

1: Representativeness of the exposed cohort; 2: Selection of the non-exposed cohort; 3: Ascertainment of exposure; 4: Demonstration that outcome of interest was not present at start of study; 5: Comparability of cohorts on the basis of the design or analysis; 6: Assessment of outcome; 7: Was follow-up long enough for outcomes to occur; 8: Adequacy of follow up of cohorts.

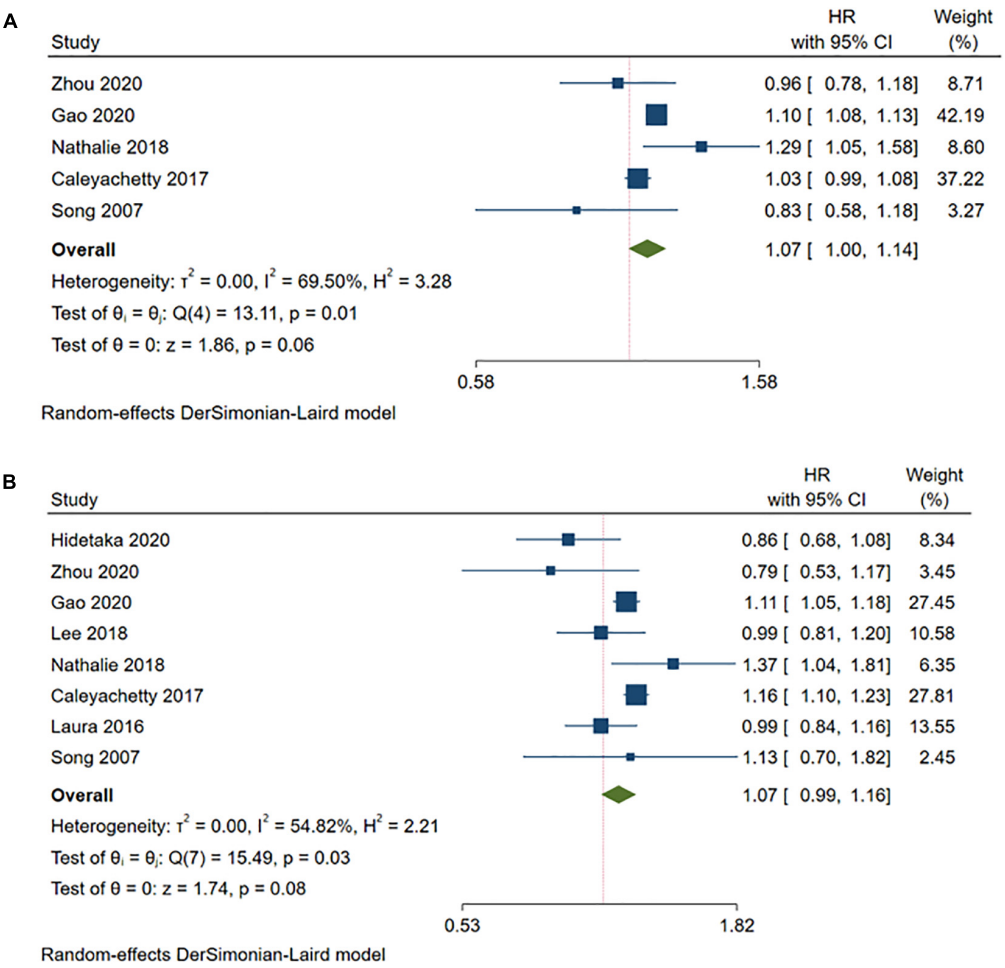

FIGURE 2 | Meta-analysis of the risk of stroke in the MHOW/MHO phenotypes compared with the MHNW phenotypes. **(A)** MHOW phenotypes; **(B)** MHO phenotypes. MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obese.

TABLE 3 | Subgroup analysis for the association between the metabolic phenotypes and risk of stroke.

Potential moderators	Subgroup	Number of studies	Number of participants	HR (95% CI)	I^2 (%)
MHOW					
Follow up	<9 years	1 (24)	3495777	1.03 (0.99–1.08)	/
	9∼15 years	3 (18, 19, 26)	585909	1.02 (0.89–1.18)	51.07
	>15 years	1 (13)	90257	1.29 (1.05–1.58)	/
Number of risk factors in metabolic health	0	2 (13, 24)	3586034	1.13 (0.91–1.40)	77.56
	≤1	2 (18, 19)	560283	1.07 (0.96–1.19)	41.53
	≤2	1 (26)	25626	0.83 (0.58–1.18)	/
Criteria for defining obesity	IOTF	0	0	/	/
	WGOC	2 (18, 19)	560283	1.07 (0.96–1.19)	41.53
	WHO	3 (13, 24, 26)	3611660	1.06 (0.89–1.28)	66.6
Region	Asia	2 (18, 19)	560283	1.07 (0.96–1.19)	41.53
	North America	2 (13, 26)	115883	1.06 (0.69–1.63)	77.53
	Europe	1 (24)	3495777	1.03 (0.99–1.08)	/
Proportion of female	<40%	1 (18)	102037	0.96 (0.78–1.18)	/
	40%∼90%	2 (19, 24)	3954023	1.07 (1.00–1.14)	85.24
	100%	2 (13, 26)	115883	1.06 (0.69–1.63)	77.53
MHO					
Follow up	<9 years	3 (17, 23, 24)	4652148	1.02 (0.85–1.23)	75.37
	9∼15 years	4 (14, 18, 19, 26)	591080	1.05 (0.95–1.17)	30.21
	>15 years	1 (13)	90257	1.37 (1.04–1.81)	/
Number of risk factors in metabolic health	0	4 (13, 17, 23, 24)	4742405	1.08 (0.92–1.27)	69.77
	≤1	3 (14, 18, 19)	565454	1.03 (0.90–1.18)	53.22
	≤2	1 (26)	25626	1.13 (0.07–1.82)	/
Criteria for defining obesity	IOTF	2 (17, 23)	1156371	0.93 (0.80–1.08)	0.00
	WGOC	2 (18, 19)	560283	0.99 (0.73–1.36)	63.95
	WHO	4 (13, 14, 24, 26)	3616831	1.13 (1.01–1.27)	39.21
Region	Asia	4 (17–19, 23)	1716654	0.98 (0.84–1.14)	61.91
	North America	2 (13, 26)	115883	1.31 (1.03–1.66)	0.00
	Europe	2 (14, 24)	3500948	1.09 (0.94–1.27)	69.77
Proportion of female	<40%	2 (14, 18)	107208	0.95 (0.81–1.12)	6.55
	40%∼90%	4 (17, 19, 24, 27)	5110394	1.08 (1.00–1.18)	63.89
	100%	2 (13, 26)	115883	1.31 (1.03–1.66)	0.00
MUNW					
Follow up	<9 years	1 (23)	354083	1.72 (1.55–1.90)	/
	9∼15 years	4 (14, 18, 19, 26)	591080	1.47 (1.23–1.76)	89.68
	>15 years	2 (13, 15)	97379	2.18 (1.87–2.53)	1.36
Number of risk factors in metabolic health	0	2 (13, 23)	444340	1.94 (1.51–2.49)	87.36
	≤1	4 (14, 15, 18, 19)	572576	1.50 (1.25–1.79)	89.58
	≤2	1 (26)	25626	1.24 (0.64–2.40)	/
Criteria for defining obesity	IOTF	1 (23)	354083	1.72 (1.55–1.90)	/
	WGOC	2 (18, 19)	560283	1.64 (1.41–1.91)	80.91
	WHO	4 (13–15, 26)	128176	1.55 (1.00–2.40)	93.62
Region	Asia	3 (18, 19, 27)	914366	1.66 (1.50–1.84)	75.99
	North America	2 (13, 26)	115883	1.82 (1.06–3.13)	65.06
	Europe	2 (14, 15)	12293	1.21 (1.10–1.33)	0.00
Proportion of female	<40%	3 (14, 15, 18)	114330	1.49 (1.06–2.11)	91.77
	40%∼90%	2 (19, 23)	812329	1.61 (1.45–1.79)	74.69
	100%	2 (13, 26)	115883	1.82 (1.06–3.13)	65.06
MUOW					
Follow up	<9 years	0	0	/	/
	9∼15 years	3 (18, 19, 26)	585909	1.83 (1.47–2.27)	87.32
	>15 years	1 (13)	90257	2.27 (1.96–2.62)	/
Number of risk factors in metabolic health	0	1 (13)	90257	2.27 (1.96–2.62)	/
	≤1	2 (18, 19)	560283	1.85 (1.44–2.36)	93.64

(Continued)

TABLE 3 | (Continued)

Potential moderators	Subgroup	Number of studies	Number of participants	HR (95% CI)	I^2 (%)
	≤2	1 (26)	25626	1.74 (1.05–2.88)	/
Criteria for defining obesity	IOTF	0	0	/	/
	WGOC	2 (18, 19)	560283	1.85 (1.44–2.36)	93.64
	WHO	2 (13, 26)	115883	2.22 (1.94–2.56)	0.00
Region	Asia	2 (18, 19)	560283	1.85 (1.44–2.36)	93.64
	North America	2 (13, 26)	115883	2.22 (1.94–2.56)	0.00
	Europe	0	0	/	/
Proportion of female	<40%	1 (18)	102037	2.11 (1.87–2.39)	/
	40%∼90%	1 (19)	458246	1.64 (1.61–1.68)	/
	100%	2 (13, 26)	115883	2.22 (1.94–2.56)	0.00
MUO					
Follow up	<9 years	1 (23)	354083	2.06 (1.86–2.29)	/
	9∼15 years	4 (14, 18, 19, 26)	591080	1.83 (1.42–2.36)	92.97
	>15 years	1 (13)	90257	2.58 (2.22–3.00)	/
Number of risk factors in metabolic health	0	2 (13, 23)	444340	2.29 (1.84–2.85)	82.74
	≤1	3 (14, 18, 19)	565454	1.88 (1.43–2.49)	95.28
	≤2	1 (26)	25626	1.49 (0.86–2.58)	/
Criteria for defining obesity	IOTF	1 (23)	354083	2.06 (1.86–2.29)	/
	WGOC	2 (18, 19)	560283	2.11 (1.38–3.22)	97.40
	WHO	3 (13, 14, 26)	121054	1.83 (1.18–2.86)	92.31
Region	Asia	3 (18, 19, 23)	914366	2.09 (1.64–2.66)	95.79
	North America	2 (13, 26)	115883	2.09 (1.24–3.53)	71.98
	Europe	1 (14)	5171	1.49 (1.28–1.74)	/
Proportion of female	<40%	2 (14, 18)	107208	1.98 (1.14–3.46)	96.68
	40%∼90%	2 (19, 23)	812329	1.86 (1.55–2.24)	91.16
	100%	2 (13, 26)	115883	2.09 (1.24–3.53)	71.98

IOTF, International Obesity Task Force; WGOC, Working Group on Obesity in China; WHO, World Health Organization; MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obese.

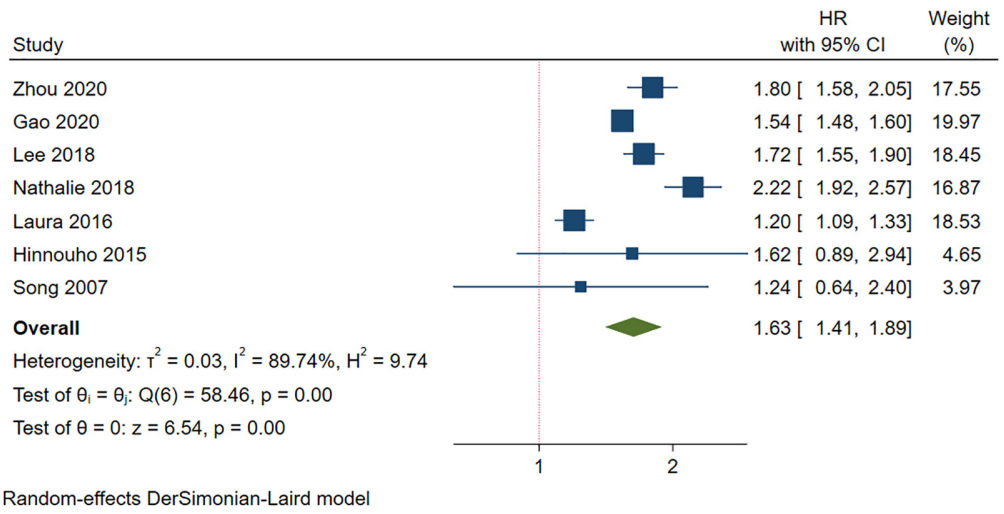

FIGURE 3 | Meta-analysis of the risk of stroke in the MUNW phenotypes compared with the MHNW phenotypes. MUNW, metabolically unhealthy normal weight; MHNW, metabolically healthy normal weight.

(13). The subgroup analysis also identified an associated risk of stroke for the MHO participants with obesity diagnosed based on the WHO criteria. This was not unexpected because the WHO defined obesity as a BMI of >30 kg/m^2 (30), which was higher than any other criteria, such as the IOTF and the WGOC standards.

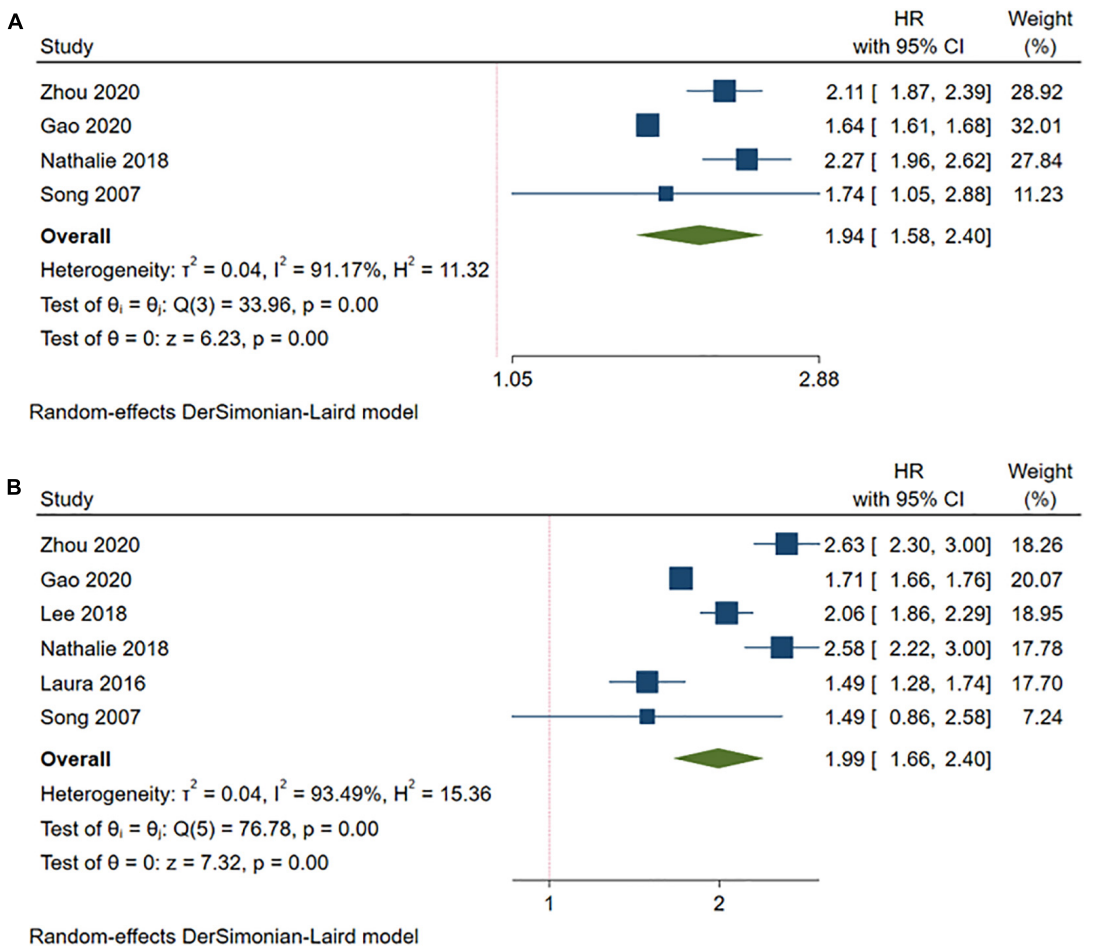

FIGURE 4 | Meta-analysis of the risk of stroke in the MUOW/MUO phenotypes compared with the MHNW phenotypes. **(A)** MUOW phenotypes; **(B)** MUO phenotypes. MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obese.

This study has several potential implications in clinical practice. First, metabolically unhealthy and elevated body weight had combined effects on increasing the risk of stroke. This suggests that when a strategy for stroke prevention is developed, monitoring metabolic parameters and achieving optimal body weight should be highlighted. Second, the potential long-term risk of stroke in individuals with metabolic health overweight/obesity should not be neglected, as the metabolic status might change over time, particularly in women. This suggests that maintaining metabolic health is also a goal for individuals with elevated body weight in the primary prevention of stroke. Third, as the homogeneous subgroup analysis showed, women appeared to have a higher risk of stroke when they had MHO, MUOW, and MUO. This suggests that the stroke prevention strategies tailored to female individuals with elevated body weight should be further studied and developed.

Limitations

This study has limitations. First, a few of the included cohorts performed multiple measurements of metabolic parameters during the follow-up, which might underestimate the impact of metabolic transitions on the risk of stroke. Second, our meta-analysis only calculated the risk of all stroke events, as most studies did not specify the type of stroke, and the confirmation method of the stroke events varied. This may not be sufficient to develop a precise prevention strategy for a specific type of stroke. Third, pooled HRs in this study were estimated by the random model to identify the average effect and the overall trend, therefore, although the statistical results potentially referred to a causal relationship of moderate-to-high strength, the HR value should not be considered as a typical risk effect (31, 32). Fourth, the definition of metabolic health varies, which may be changed alongside the ongoing studies. This suggests that an updated meta-analysis of the best available evidence is needed (33, 34). Finally, we only searched three representative English literature databases, which may have omitted some additional studies. However, methodological studies have suggested that restricting systematic reviews to English-language publications appears to have little impact on the effect estimates and conclusions of systematic reviews (35, 36).

CONCLUSION

The risk of stroke increases for all metabolically unhealthy phenotypes, irrespective of the BMI. The associated risk of stroke with metabolic health, but high BMI, is at substantial heterogeneity, which requires future research considering the impact of sex and transition of the metabolic status on the risk of stroke.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MM conceived the manuscript and analyzed the data. MM and YG searched the literature and collected the data. LL, ZK, and MM evaluated the methodological quality. XN and YC interpreted the results. XN designed the study, supervised the study implementation, validated the data, and wrote the manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.844550/full#supplementary-material

Supplementary Data Sheet 1 | The full list of excluded studies.

REFERENCES

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol.* (2021) 20:795–820. doi: 10.1016/S1474-4422(21)00252-0
2. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet (London, England).* (2016) 388:761–75. doi: 10.1016/s0140-6736(16)30506-2
3. Kim MS, Kim WJ, Khera AV, Kim JY, Yon DK, Lee SW, et al. Association between adiposity and cardiovascular outcomes: an umbrella review and meta-analysis of observational and Mendelian randomization studies. *Eur Heart J.* (2021) 42:3388–403. doi: 10.1093/eurheartj/ehab454
4. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2014) 45:3754–832. doi: 10.1161/str.0000000000000046
5. Chinese Society of Neurology [CSS]. Guidelines for the primary prevention of cerebrovascular diseases in China 2019. *Chin J Neurol.* (2019) 52:684–709. doi: 10.3760/cma.j.issn.1006-7876.2019.09.002
6. Zeng Q, Li N, Pan XF, Chen L, Pan A. Clinical management and treatment of obesity in China. *Lancet Diabetes Endocrinol.* (2021) 9:393–405. doi: 10.1016/s2213-8587(21)00047-4
7. Kim BY, Kang SM, Kang JH, Kang SY, Kim KK, Kim KB, et al. 2020 Korean society for the study of obesity guidelines for the management of obesity in Korea. *J Obesity Metab Synd.* (2021) 30:81–92. doi: 10.7570/jomes21022
8. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European guidelines for obesity management in adults. *Obesity Facts.* (2015) 8:402–24. doi: 10.1159/000442721
9. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, et al. American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrine Pract Off J Am College Endocrinol Am Assoc Clin Endocrinol.* (2016) 22(Suppl. 3):1–203. doi: 10.4158/ep161365.gl
10. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1·8 million participants. *Lancet (London, England).* (2014) 383:970–83. doi: 10.1016/s0140-6736(13)61836-x
11. Stefan N, Häring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. *Lancet Diabetes Endocrinol.* (2013) 1:152–62. doi: 10.1016/s2213-8587(13)70062-7
12. Mirzababaei A, Mozaffari H, Shab-Bidar S, Milajerdi A, Djafarian K. Risk of hypertension among different metabolic phenotypes: a systematic review and meta-analysis of prospective cohort studies. *J Hum Hypertens.* (2019) 33:365–77. doi: 10.1038/s41371-018-0146-y
13. Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. *Lancet Diabetes Endocrinol.* (2018) 6:714–24. doi: 10.1016/s2213-8587(18)30137-2
14. Sánchez-Iñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J, Martínez JA. Risk of incident ischemic stroke according to the metabolic health and obesity states in the Vascular-Metabolic CUN cohort. *Int J Stroke Off J Int Stroke Soc.* (2017) 12:187–91. doi: 10.1177/1747493016672083
15. Hinnouho GM, Czernichow S, Dugravot A, Nabi H, Brunner EJ, Kivimaki M, et al. Metabolically healthy obesity and the risk of cardiovascular disease and type 2 diabetes: the Whitehall II cohort study. *Eur Heart J.* (2015) 36:551–9. doi: 10.1093/eurheartj/ehu123
16. Ma LZ, Sun FR, Wang ZT, Tan L, Hou XH, Ou YN, et al. Metabolically healthy obesity and risk of stroke: a meta-analysis of prospective cohort studies. *Ann Transl. Med.* (2021) 9:197. doi: 10.21037/atm-20-4387
17. Itoh H, Kaneko H, Kiriyama H, Kamon T, Fujiu K, Morita K, et al. Metabolically healthy obesity and the risk of cardiovascular disease in the general population- analysis of a nationwide epidemiological database. *Circ J Off J Japanese Circ Soc.* (2021) 85:914–20. doi: 10.1253/circj.CJ-20-1040
18. Zhou Y, Zhang X, Zhang L, Li Z, Wu Q, Jin Z, et al. Increased stroke risk in metabolically abnormal normal weight: a 10-Year Follow-up of 102,037 participants in China. *Transl Stroke Res.* (2020) 12:725–34. doi: 10.1007/s12975-020-00866-1
19. Gao M, Lv J, Yu C, Guo Y, Bian Z, Yang R, et al. Metabolically healthy obesity, transition to unhealthy metabolic status, and vascular disease in Chinese adults: a cohort study. *PLoS Med.* (2020) 17:e1003351. doi: 10.1371/journal.pmed.1003351

20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ (Clinical Research Ed).* (2009) 339:b2535. doi: 10.1136/bmj.b2535
21. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. (2013). Available online at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed December 28, 2021).
22. Li H, He D, Zheng D, Amsalu E, Wang A, Tao L, et al. Metabolically healthy obese phenotype and risk of cardiovascular disease: results from the China Health and Retirement Longitudinal Study. *Arch Gerontol Geriatr.* (2019) 82:1–7. doi: 10.1016/j.archger.2019.01.004
23. Lee HJ, Choi EK, Lee SH, Kim YJ, Han KD, Oh S. Risk of ischemic stroke in metabolically healthy obesity: a nationwide population-based study. *PLoS One.* (2018) 13:e0195210. doi: 10.1371/journal.pone.0195210
24. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 Million Men and Women. *J Am College Cardiol.* (2017) 70:1429–37. doi: 10.1016/j.jacc.2017.07.763
25. Andersen SS, Andersson C, Berger SM, Jensen TB, Torp-Pedersen CT, Gislason GH, et al. Impact of metabolic disorders on the relation between overweight/obesity and incident myocardial infarction and ischaemic stroke in fertile women: a nationwide cohort study. *Clin Obesity.* (2015) 5:127–35. doi: 10.1111/cob.12096
26. Song Y, Manson JE, Meigs JB, Ridker PM, Buring JE, Liu S. Comparison of usefulness of body mass index versus metabolic risk factors in predicting 10-year risk of cardiovascular events in women. *Am J Cardiol.* (2007) 100:1654–8. doi: 10.1016/j.amjcard.2007.06.073
27. Lee MJ, Kim EH, Bae SJ, Choe J, Jung CH, Lee WJ, et al. Protective role of skeletal muscle mass against progression from metabolically healthy to unhealthy phenotype. *Clin Endocrinol.* (2019) 90:102–13. doi: 10.1111/cen.13874
28. Mongraw-Chaffin M, Foster MC, Anderson CAM, Burke GL, Haq N, Kalyani RR, et al. Metabolically healthy obesity, transition to metabolic syndrome, and cardiovascular risk. *J Am College Cardiol.* (2018) 71:1857–65. doi: 10.1016/j.jacc.2018.02.055
29. Bushnell CD, Chaturvedi S, Gage KR, Herson PS, Hurn PD, Jiménez MC, et al. Sex differences in stroke: challenges and opportunities. *J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab.* (2018) 38:2179–91. doi: 10.1177/0271678x18793324
30. World Health Organization [WHO]. *WHO Guidelines Approved by the Guidelines Review Committee. Guideline: Sugars Intake for Adults and Children*. Geneva: World Health Organization (2015).
31. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. editors. *Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (Updated February 2021)*. London: Cochrane (2021).
32. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol.* (2011) 64:1311–6. doi: 10.1016/j.jclinepi.2011.06.004
33. Smith GI, Mittendorfer B, Klein S. Metabolically healthy obesity: facts and fantasies. *J Clin Invest.* (2019) 129:3978–89. doi: 10.1172/JCI129186
34. Tsatsoulis A, Paschou SA. Metabolically healthy obesity: criteria, epidemiology, controversies, and consequences. *Curr Obes Rep.* (2020) 9:109–20. doi: 10.1007/s13679-020-00375-0
35. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care.* (2012) 28:138–44. doi: 10.1017/S0266462312000086
36. Dobrescu AI, Nussbaumer-Streit B, Klerings I, Wagner G, Persad E, Sommer I, et al. Restricting evidence syntheses of interventions to English-language publications is a viable methodological shortcut for most medical topics: a systematic review. *J Clin Epidemiol.* (2021) 137:209–17. doi: 10.1016/j.jclinepi.2021.04.012

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Genetically Determined Lifestyle and Cardiometabolic Risk Factors Mediate the Association of Genetically Predicted Age at Menarche With Genetic Predisposition to Myocardial Infarction: A Two-Step, Two-Sample Mendelian Randomization Study

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Background: Observational studies have shown an association between early age at menarche (AAM) and myocardial infarction (MI) with recorded cases. In this Mendelian randomization (MR) study, we used large amounts of summary data from genome-wide association studies (GWASs) to further estimate the association of genetically predicted AAM with genetically predicated risk of MI and investigate to what extent this association is mediated by genetically determined lifestyles, cardiometabolic factors, and estrogen exposure.

Methods: A two-step, two-sample MR study was performed by mediation analysis. Genetic variants identified by GWAS meta-analysis of reproductive genetics consortium (n = 182,416) were selected for genetically predicted AAM. Genetic variants identified by the Coronary ARtery DIsease Genome-wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics Consortium (n = 184,305) were selected for genetically predicted risk of MI. Genetic variants from other international GWAS summary data were selected for genetically determined mediators.

Results: This MR study showed that increase in genetically predicted AAM was associated with lower risk of genetically predicted MI (odds ratio 0.91, 95% confidence

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interval 0.84–0.98). Inverse variance weighted (IVW) MR analysis also showed that decrease in genetically predicted AAM was associated with higher genetically predicted alcohol intake frequency, current smoking behavior, higher waist-to-hip ratio, and higher levels of systolic blood pressure (SBP), fasting blood glucose, hemoglobin A1c (HbA1c), and triglycerides (TGs). Furthermore, increase in genetically predicted AAM was associated with genetically predicted longer sleep duration, higher levels of high-density lipoproteins, and older age at which hormone replacement therapy was started. The most essential mediators identified were genetically predicted current smoking behavior and levels of HbA1c, SBP, and TGs, which were estimated to genetically mediate 13.9, 12.2, 10.5, and 9.2%, respectively, with a combined mediation proportion of 37.5% in the association of genetically predicted AAM with genetically predicted increased risk of MI in an MR framework.

Conclusion: Our MR analysis showed that increase in genetically predicted AAM was associated with lower genetically predicted risk of MI, which was substantially mediated by genetically determined current smoking behavior and levels of HbA1c, SBP, and TGs. Intervening on the above mediators may reduce the risk of MI.

Keywords: age at menarche, cardiometabolic risk factors, myocardial infarction, Mendelian randomization, lifestyle, mediation analysis

INTRODUCTION

Cardiovascular disease (CVD), with myocardial infarction (MI) as one of the most acute and severe manifestations, continues to be the dominant cause of deaths worldwide and accounts for over 17 million deaths annually (1). Notably, women were reported to suffer a greater burden of ischemic symptoms caused by MI, with higher rates of functional disability and more adverse outcomes compared to men (2). However, conventional precautions against CVD demonstrate a persistent gap in effective recognition of gender-specific risk factors and understanding how these factors result in poorer outcomes for women (3). Thus, identifying gender-specific risk factors for adverse CVD events, especially MI, during women's lifetime could yield more timely prevention and improved clinical prognosis.

Menarche signifies the puberty and start of reproductive capacity, and is followed by the onset of cyclic ovarian function and increased secretion and exposure to endogenous estradiol. As a reproductive physiologic landmark of the female body, menarche is dependent on a tightly orchestrated process of neurohormonal alterations through the hypothalamus-pituitary-ovarian axis (4). Previous large-population cohort studies have reported that early age at menarche (AAM) was associated with increased risks of coronary heart disease (CHD) in both adolescent and adult women (5–11). Glucose intolerance, blood pressure, and serum lipids were reported to be increased in adolescent girls with early AAM, which might play an essential role in the development of ischemic heart disease (IHD) (12). Inconsistent results were obtained concerning the roles of smoking and estrogen exposure in mediating the association of AAM with IHD (6, 8, 9, 13, 14). As previous approaches for testing potential mediators in observational studies led to biased results by calculating the reduction in strength of the multivariable association between exposure variable and disease with adjustment for confounding factors (15, 16), it remains unclear whether the correlation of AAM with CHD is modified by diverse potential confounding factors, including lifestyles along with cardiometabolic factors, and the extent of their potential impacts.

Mendelian randomization (MR) has emerged as a new investigative approach that utilizes genetic variants as instrumental variables to investigate the association of an exposure of interest with an outcome. In brief, MR refers to a random combination of alleles in which DNA is transferred from parent to offspring as gametes formed during meiosis, a process known as Mendel's second law. This means that the inheritance of any particular genetic variant in an individual's DNA should be independent of other traits. Therefore, when individuals in a population are grouped by a specific genotype associated with biomarker differences, they should be similar in all aspects except for one group with genetically higher or lower biomarker levels. For this reason, MR has been described as "nature's randomized trial." MR is less prone to confounder bias, measurement error, and reverse causality; thus, it can provide more efficient and robust results that closely resemble those from randomized controlled studies (17–20). Based on the well-established MR framework, the two-step approach has higher sensitivity in evaluating potential mediators and is less likely to cause inherent bias compared with the traditional multivariable approach (21).

In this study, we aimed to estimate the association of genetically predicted AAM with genetic susceptibility of MI, and to further estimate whether and to what extent the association was mediated by lifestyles, anthropometric characteristics, cardiometabolic risk factors, and age at which hormone replacement therapy (HRT) was started.

MATERIALS AND METHODS

Overall Study Design

Large two-step, two-sample MR analyses involving over 647,920 participants selected from publicly available, summary-level genetic datasets were performed using a two-step strategy to investigate the association of genetically predicted AAM with genetically predicted risk of MI and whether this association could be mediated by lifestyles, conventional cardiometabolic risk factors, and age at which hormone replacement therapy was started. Two-sample MR analyses refer to the utilization of distinct data sets to ascertain the associations of same genetic variants with the exposure (e.g., AAM) and outcome (e.g., MI) of interest (22). The association of genetically predicted AAM with genetic disposition to MI was tested first, and the two-step approach was applied in mediation analyses. The two-step approach investigated the association of genetically predicted AAM with each genetically determined mediator in the first step. In the second step, the approach investigated the association of these genetically determined mediators with genetically predicted MI risk after adjusting for AAM. The proportion of mediation was also estimated for each mediator following the second step.

Data Sources

Selection of Genetic Instruments for Genetically Predicted Age at Menarche

Genetic association estimates for AAM were obtained from genome-wide association study (GWAS) meta-analysis derived from 182,416 participants of European ancestry that included 2,441,815 autosomal single nucleotide polymorphisms (SNPs) provided by the Reproductive Genetics (ReproGen) Consortium (23). A set of SNPs that reached GWAS significance ($p < 5 \times 10^{-8}$) in association with AAM were selected as genetic instruments. SNPs with linkage disequilibrium ($r^2 < 0.001$) were ruled out.

Selection of Genetic Instruments for Genetically Predicted Potential Mediators

We obtained SNPs for waist-to-hip ratio (WHR) from the Genetic Investigation of Anthropometric Traits (GIANT) consortium's 2015 GWAS meta-analysis including 2,542,447 SNPs from 210,088 participants of European descent (24). SNPs for fasting blood glucose (FBG) were extracted from Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC), which provided a GWAS meta-analysis of 2,445,760 SNPs from 46,186 participants of European descent in 2010 (25). SNPs for high-density lipoprotein (HDL) were obtained from a GWAS meta-analysis provided by Kettunen et al. (26) comprising 12,133,295 SNPs from 24,925 participants of European descent in 2016. SNPs for alcohol intake frequency, sleep duration, and age at which HRT was started were all acquired from an online public GWAS provided by Elsworth et al., and totaled 9,851,867 SNPs from participants of European descent in 2018. In addition, SNPs for current smoking behavior and systolic blood pressure (SBP) were selected from an online public GWAS provided by Neale et al., including 10,894,596 SNPs from participants of European descent in 2017. SNPs for hemoglobin A1c (HbA1c) were extracted from an online public GWAS provided by Neale et al. including 13,586,180 SNPs from participants of European descent in 2018. SNPs for triglycerides (TGs) were identified from an online public GWAS provided by Neale et al. comprised of 13,586,007 SNPs from participants of European descent in 2018. Detailed results of genetically predicted alcohol intake frequency, sleep duration, current smoking behavior, SBP, HbA1c, TGs, and age at which HRT was started could be obtained through online public GWAS database[1] using the R 4.0.3 software TwoSampleMR package. The SNPs were clumped, and those with linkage disequilibrium ($r^2 < 0.001$) were ruled out. SNPs that reached GWAS significance ($p < 5 \times 10^{-8}$) in association with potential mediators were selected as genetic instruments.

Selection of Genetic Instruments for Genetically Predicted Myocardial Infarction

For genetically predicted MI, we used genetic association estimates that were publicly available from the Coronary ARtery DIsease Genome wide Replication and Meta-analysis plus The Coronary Artery Disease Genetics Consortium (CARDIoGRAMplusC4D) 1000 Genomes-based GWAS meta-analysis of 123,504 controls and 60,801 cases including 8,600,000 SNPs (27). SNPs that reached GWAS significance ($p < 5 \times 10^{-8}$) in association with MI were selected as genetic instruments. The SNPs were clumped, and those with linkage disequilibrium ($r^2 < 0.001$) were ruled out.

Statistical Analysis

Association of Genetically Predicted Age at Menarche With Genetically Predicted Myocardial Infarction Risk

Two-sample MR analyses were performed to investigate the association of genetically predicted AAM with genetically predicted MI risk. We assumed that summarized GWAS data were available for multiple genetic variants that satisfied the following assumptions: (i) genetic variants were associated with exposure; (ii) genetic variants were independent of any confounder of the exposure-outcome association; (iii) genetic variants were independent of outcome and could only be associated with outcome through gene expression of exposure.

The genetic association of each effect allele with genetically predicted AAM was represented by X_k (k = 1, 2, 3...) with a standard error (SE) as σX_k. X_k (k = 1, 2, 3...) representing the effect size per allele of SNP_k (k = 1, 2, 3...) in AAM (in years). The data of X_k and σX_k were both extracted from beta value and SE in a relevant GWAS study with SNP characteristics (23), respectively, by applying the R 4.0.3 software TwoSampleMR package. The genetic association of each allele with genetically predicted MI was represented by Y_k (k = 1, 2, 3....) with an SE as σY_k. For a binary outcome as MI, Y_k (k = 1, 2, 3...) represented the effect size per allele of SNP_k (k = 1, 2, 3...) in the log-odds or the log probability of MI. The data of Y_k and σY_k were both extracted from OR and SE in a relevant GWAS study with SNP characteristics (27) and were harmonized, respectively,

[1] https://gwas-api.mrcieu.ac.uk/

by applying the R 4.0.3 software TwoSampleMR package. The ratio estimate of the association of genetically predicted AAM with genetically predicted MI could be calculated by formula Y_k/X_k (k = 1, 2, 3...). The SE of the ratio estimate could be approximated using the delta method, and the leading term is $\sigma Y_k/X_k$ (k = 1, 2, 3...) (28). To investigate the association of genetically predicted AAM with genetically predicted MI risk, an inverse variance weighted (IVW) meta-analysis using a fixed-effects model was implemented to pool estimates of MR as $\widehat{\beta}_{\mathrm{IVW}}$ across individual SNPs with the R 4.0.3 software (29). The calculation of $\widehat{\beta}_{\mathrm{IVW}}$ is shown by the following formula:

$$\widehat{\beta}_{\mathrm{IVW}} = \frac{\Sigma_k X_k Y_k \sigma_{Y_k}^{-2}}{\Sigma_{kX_k}^2 \sigma_{Y_k}^{-2}}$$

$se(\widehat{\beta}_{\mathrm{IVW}})$, the approximate standard error of the pooled estimates, was also calculated with the R 4.0.3 software using the following formula:

$$se(\widehat{\beta}_{\mathrm{IVW}}) = \sqrt{\frac{1}{\Sigma_k X_k^2 \sigma_{Y_k}^{-2}}}$$

Mediation With Genetically Predicted Lifestyles, Anthropometric and Cardiometabolic Parameters, and Age at Which Hormone Replacement Therapy Was Started

The genetic association of each effect allele with genetically determined potential mediators was represented by Z_k (k = 1, 2, 3....) with standard error (SE) σZ_k. Z_k (k = 1, 2, 3...) representing the effect size per allele of SNP_k (k = 1, 2, 3...) in potential mediators. The data of Z_k and σZ_k were extracted from beta value and SE in relevant GWAS studies on potential mediators with SNP characteristics as mentioned above in section "Materials and Methods" and were harmonized, by applying the R 4.0.3 software TwoSampleMR package. To investigate the association of genetically predicted AAM with each genetically determined potential mediator, the IVW meta-analysis, which used a fixed-effects model, was also implemented through the R 4.0.3 software to pool estimates of MR as $\widehat{\beta}_{\mathrm{IVW}*}$ across individual SNPs. The calculation of $\widehat{\beta}_{\mathrm{IVW}*}$ is shown by the following formula:

$$\widehat{\beta}_{\mathrm{IVW}*} = \frac{\Sigma_{kX_k Z_k} \sigma_{Z_k}^{-2}}{\Sigma_{kX_k}^2 \sigma_{Z_k}^{-2}}$$

$Se(\widehat{\beta}_{\mathrm{IVW}*})$, the approximate standard error of the above pooled estimates, was calculated with R 4.0.3 software using the following formula:

$$se(\widehat{\beta}_{\mathrm{IVW}*}) = \sqrt{\frac{1}{\Sigma_{kX_k}^2 \sigma_{Z_k}^{-2}}}$$

To determine the mediation of each factor, we multiplied coefficients of association of genetically predicted AAM with each mediator, and coefficients of association of each mediator with MI after adjusting for genetically predicted AAM. In order to estimate the association of t genetically determined potential mediators with genetically predicted risk of MI adjusting for influences from AAM, a regression-based MR was also conducted with the R 4.0.3 software (30).

Sensitivity Analyses

MR-Egger, MR-Egger intercept, and MR-PRESSO analyses were performed to estimate whether there was pleiotropy, which might affect the results of the MR analysis (30–32). The Robust Adjusted Profile Score (RAPS) was applied to test weak instrumental variables, and weighted median sensitivity analyses were conducted to estimate invalid instrumental variables (32).

Statistical Software

We carried out the two-step, two-sample MR analyses by utilizing R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria, 2008) and R studio version 1.3.1093 (Boston, MA, United States). We used the TwoSampleMR package for R to facilitate the MR analyses.

RESULTS

Association of Genetically Predicted Age at Menarche With Genetically Predicted Myocardial Infarction Risk

Characteristics of SNPs used as instrumental variables for AAM are listed in **Supplementary Table 1**. Genetic estimates for the association of genetically predicted AAM with genetically predicted MI are shown in **Supplementary Table 2**. **Figure 1** shows that increase in genetically predicted AAM was associated with lower risk of genetically predicted MI, with an odds ratio (OR) of 0.91 [95% confidence interval (CI) 0.84–0.98] in the main IVW MR analysis (also shown in **Supplementary Table 3**).

Association of Genetically Predicted Age at Menarche With Genetically Predicted Lifestyles, Anthropometric and Cardiometabolic Parameters, and Age at Which Hormone Replacement Therapy Was Started

Figure 2 indicates that increase in genetically predicted AAM was associated with lower genetically predicted alcohol intake frequency (OR: 0.95, 95% CI: 0.92–0.98, $p < 0.001$), current smoking behavior (OR: 0.99, 95% CI: 0.97–0.99, $p = 0.049$), WHR (OR: 0.95, 95% CI: 0.90–0.99, $p = 0.035$), FBG (OR: 0.97, 95% CI: 0.94–0.99, $p = 0.048$), HbA1c (OR: 0.75, 95% CI: 0.61–0.92, $p = 0.005$), SBP (OR: 0.97, 95% CI: 0.95–0.99, $p = 0.048$), and TGs (OR: 0.97, 95% CI: 0.94–0.99, $p = 0.041$) in the IVW MR analysis. **Figure 2** also shows that increase in genetically predicted AAM is associated with genetically predicted longer time of sleep duration (OR: 1.03, 95% CI: 1.01–1.05, $p = 0.001$), higher levels of HDL (OR: 1.08, 95% CI: 1.02–1.15, $p = 0.011$), and older age at which HRT was started (OR: 1.05, 95% CI: 1.01–1.09, $p = 0.008$) in the IVW MR analysis. The above potential genetically predicted mediators that were associated with genetically predicted AAM

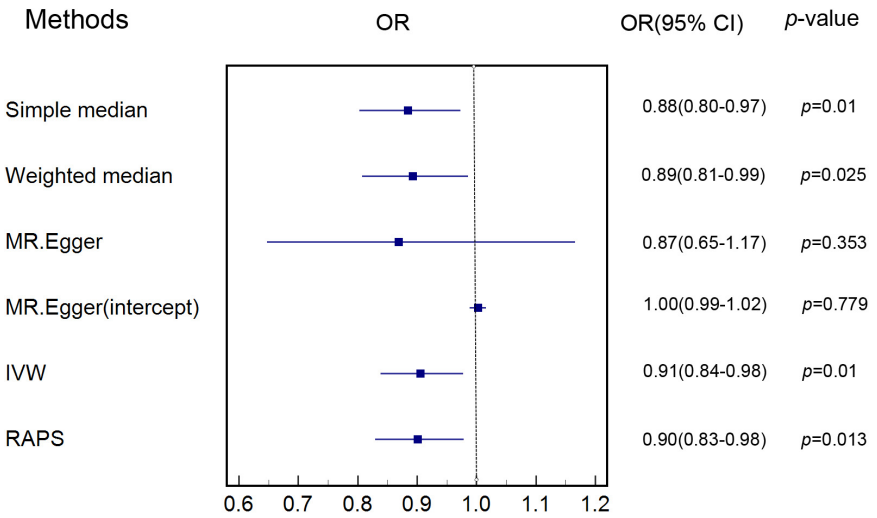

FIGURE 1 | Estimate of associations of genetically predicted AAM with genetically predicted MI. IVW was applied as main analysis for estimating the association of genetically predicted AAM with genetically predicted MI. AAM, age at menarche; MI, myocardial infarction; IVW, inverse variance weighted.

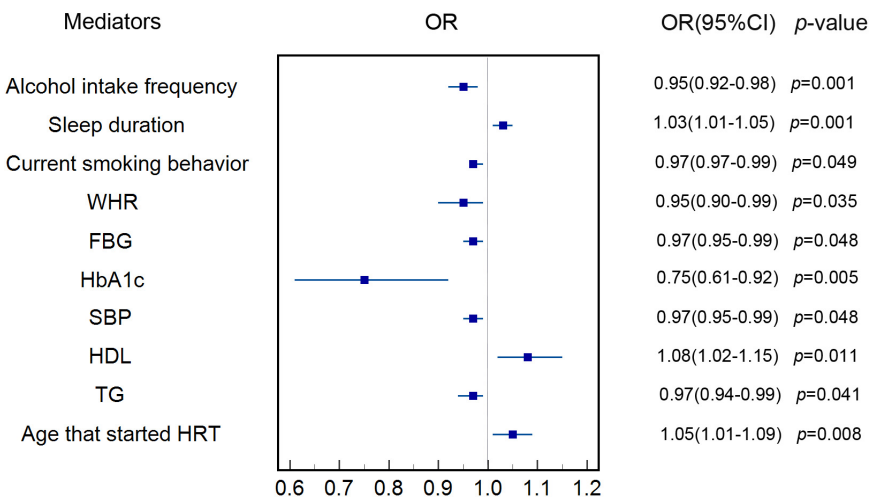

FIGURE 2 | Estimate of the association of genetically predicted AAM with each genetically determined potential mediator. IVW was applied as main analysis. The results showed that increase in genetically predicted AAM was associated with genetically determined longer sleep duration, higher levels of HDL and older at which HRT was started. The results also showed that increase in genetically predicted AAM was inversely associated genetically determined alcohol intake frequency, current smoking behavior, WHR, FBG, HbA1c, SBP, and TGs. AAM, age at menarche; IVW, inverse variance weighted; HDL, high-density lipoprotein; HRT, hormone replacement therapy; WHR, waist-hip-ratio; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; TG, triglycerides.

($p < 0.05$) were all involved in the MR analyses of association of each genetically predicted mediator with genetically predicted risk of MI. Characteristics of SNPs used as instrumental variables for genetically determined potential mediators are shown in **Supplementary Tables 4–13**. Genetic estimates for the association of genetically predicted AAM with genetically determined mediators can be seen in **Supplementary Tables 14–23**. MR estimates of associations of genetically predicted AAM with genetically determined risk factors are shown in **Supplementary Table 24**.

Association of Genetically Predicted Lifestyles, Anthropometric and Cardiometabolic Parameters, and Age at Which Hormone Replacement Therapy Was Started With Genetically Predicted Risk of Myocardial Infarction

Figure 3 shows that our MR analyses supported that genetically predicted increased risk of MI was associated with genetically predicted current smoking behavior (OR: 2.89, 95% CI: 1.37–

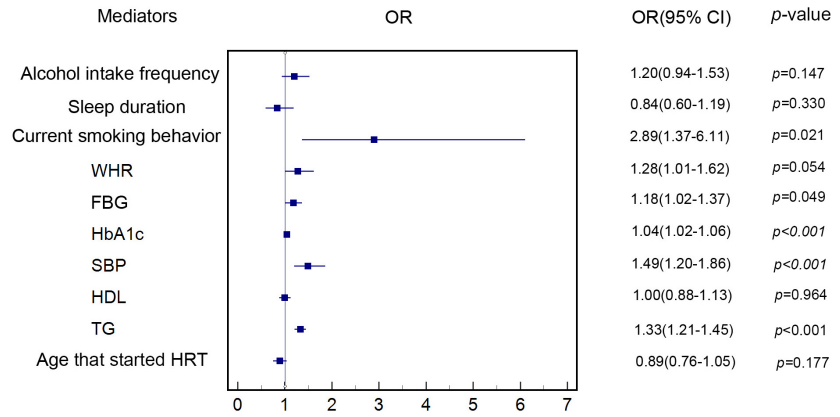

FIGURE 3 | Estimate of the association of each genetically determined potential mediator with genetically predicted MI. The association of genetically determined potential mediators with genetically predicted MI was estimated by linear regression-based MR method. MI, myocardial infarction; HDL, high-density lipoprotein; HRT, hormone replacement therapy; WHR, waist-hip-ratio; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; TG, triglycerides.

6.11, $p = 0.021$) and genetically predicted higher levels of FBG (OR: 1.18, 95% CI: 1.02–1.37, $p = 0.049$), HbA1c (OR: 1.04, 95% CI: 1.02–1.06, $p < 0.001$), SBP (OR: 1.49, 95% CI: 1.20–1.86, $p < 0.001$), and TGs (OR: 1.33, 95% CI: 1.21–1.45, $p < 0.001$) in the IVW MR analysis, after adjusting for genetically predicted AAM. Because there was no evidence of association of genetically predicted alcohol intake frequency, sleep duration, WHR, HDL, and age at which HRT was started with genetically predicted MI risk in the IVW MR analysis ($p > 0.05$), these potential mediators were excluded. Genetic estimates for the association of genetically determined mediators with genetically predicted MI after adjusting for genetically predicted AAM are shown in **Supplementary Tables 25–34**.

TABLE 1 | MR analyses of association of genetically predicted AAM with genetically predicted risk of MI and mediation explained by risk factors.

	Beta	Proportion (%)
Estimated association of AAM with MI	−0.0990	1.0
Estimated association of mediators with MI		
Current smoking behavior	−0.0138	13.9
HbA1c	−0.0121	12.2
SBP	−0.0104	10.5
TG	−0.0091	9.2
Total	−0.0370	37.5

MR, Mendelian randomization; AAM, age at menarche; MI, myocardial infarction; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; TG, triglycerides.

Mediation of Genetically Predicted Lifestyles and Cardiometabolic Parameters

The two-sample MR analyses showed that the percentage mediated by genetically predicted current smoking behavior and genetically predicted higher level of HbA1c, SBPs, and TGs was at a proportion of 13.9, 12.2, 10.5, and 9.2%, respectively (As is shown in **Table 1**). FBG was not involved in the final mediation analyses, because the mediation proportion of FBG was comparatively lower than the other four mediators, which indicated that it may not be a core mediator. The combined mediation proportion of the four risk factors accounted for 37.5% of the association of genetically predicted AAM with genetic predisposition to MI risk.

Sensitivity Analyses

Simple median ($p < 0.05$, **Supplementary Table 3**) and weighted median sensitivity analyses ($p < 0.05$, **Supplementary Table 3**) showed that our results were less likely to be biased with invalid instruments. RAPS ($p < 0.05$, **Supplementary Table 3**) indicated that weak instruments were unlikely to affect our results. Other sensitivity analyses including single SNP analysis (**Supplementary Table 35**) and leave-one-out analysis (**Supplementary Table 36**) provided results consistent with the main IVW MR analysis. MR-Egger ($p > 0.05$, **Supplementary Table 3**) and MR-PRESSO analysis ($p < 0.05$, **Supplementary Table 37**) also showed that our MR analysis was not significantly affected by pleiotropy.

DISCUSSION

The MR analyses conducted in this study provided strong evidence to support the association of genetically predicted AAM with genetically predicted risk of MI. This study also found that the association was mediated by genetically predicted current smoking behavior and levels of HbA1c, SBP, and TGs at a proportion of 13.9, 12.2, 10.5, and 9.2%, respectively. Together, all these genetically determined mediators account for more than one-third of the association of genetically predicted AAM with genetically predicted risk of MI.

Our findings are consistent with previous studies conducted in different settings (5, 9, 33, 34). A hospital-based case-control study conducted by La Vecchia et al. (33) enrolled 576 women (202 cases of acute MI) below 55 years of age from 1983 to

1986 in Northern Italy and found that women with menarcheal age of 12–14 years showed reduced risk of MI (relative risk: 0.49, 95% CI: 0.31–0.75) compared with women whose menarche occurred younger than 12 years old. Another population-based prospective study enrolled 15,807 women aged 40–79 years from 1993 to 1997 and evaluated them for CVD events for 10.6 years, showing an elevated risk of incident CHD [1.23 (1.06–1.43)] in women with early AAM (<12 years) compared with those with later menarche (5). Gallagher et al. conducted a cohort study in Shanghai, China from 1989 to 1991 involving 267,400 women textile workers who were followed up through 2000. Their results indicated that women with menarche at 13 years or earlier had an increased risk of IHD with a hazard ratio (HR) = 1.44 (95% CI: 1–2.05) adjusted for age compared with those with later menarche at 15 years (8). In addition, a prospective study with 34,022 Chinese females aged 45–74 at enrollment (1993–1998) found a significant inverse association between menarcheal age and risk for CHD mortality across different AAM categories. HRs for CHD mortality of different age groups (≤12, 13–14, 15–16, ≥17 years old) were 1.06 (0.80–1.34), 1 (referent), 0.76 (0.65–0.9), and 72 (0.58–0.88), respectively (p trend < 0.001) (9). Cooper et al. also reported that the risk of IHD decreased with increasing age of menarche onset (age-adjusted RR 0.76 per year, 95% CI: 0.6–0.95) in a cohort study involving 867 White college-educated women (34).

Given the progress shown in our understanding of the association between AAM and MI based on recorded cases, previous observational studies were still limited by relatively small sample sizes and bias due to adjustment of various factors, which might have influenced the association of AAM with MI risk. Several MR studies with relatively large sample sizes had been undertaken to further genetically estimate the association of AAM with cardiovascular risk factors and cardiometabolic diseases (35, 36). Our results are also in accordance with Cao and Cui, who observed that later AAM decreased the risk of CHD (OR: 0.92, 95% CI: 0.88–0.96). Early AAM was found to be associated with the rising trend of HDL but lower diastolic blood pressure (DBP) combined with lower levels of TGs, log fasting insulin, log homeostasis model assessment of insulin resistance (HOMA-IR), and log homeostasis model assessment of β cell function (HOMA-β) (36). Another MR analysis from the Guangzhou Biobank Cohort Study, which investigated the association between AAM and cardiovascular risk factors, revealed that AAM was inversely correlated with levels of FBG (35). However, none of the previous observational or MR studies examined which genetically determined mediators influenced the association of genetically predicted AAM with genetically predicted MI and to what extent in an MR framework.

Recent studies have indicated that early AAM might not be a simple independent determining factor of cardiovascular adverse events but might reflect negative metabolic imprinting during the pre-pubescence period, such as relatively high weight or body mass index (BMI) during childhood (37–40). There was, thus, an imperative need to investigate whether genetically predicted increased AAM is associated with genetically predicted lower risk of MI among women during puberty or later adulthood through lifestyles and cardiometabolic or other potential mediators as long-term impacts of metabolic imprinting.

Smoking

With regard to smoking behavior, Mueller et al. enrolled 34,022 Chinese women aged 45–74 years at baseline (1993–1998) and followed them prospectively throughout 2009. They found that increased AAM was associated with lower risk for CHD and CVD mortality among non-smoking females; HRs (95% CI) for CVD mortality in non-smoking females across different age categories of menarche (≤12, 13–14, 15–16, and ≥17 years old) were: 1.06 (0.87–1.29), 1 (referent), 0.89 (0.79–1), and 0.8 (0.69–0.93), respectively (p trend < 0.001), while for CHD mortality in non-smoking females the results were 1.06 (0.80–1.34), 1 (referent), 0.76 (0.65–0.9), and 0.72 (0.58–0.88), respectively (p trend < 0.001). However, no association was found between AAM and CHD or CVD mortality among smokers (9). Similarly, Gallagher et al. found that HRs (95% CI) for CVD mortality across different AAM groups (≤13, 14, 15, 16, and ≥17) were: 1.44 (1–2.05), 1.06 (0.76–1.47), 1 (referent), 1.09 (0.82–1.45), and 0.85 (0.65–1.12), respectively (p trend < 0.001) among non-smoking females vs. smokers (8).

The above results differ from the findings presented here, which showed that current smoking behavior might play a vital role in the association of genetically predicted AAM with genetically predicted MI. Consistent with our findings, Jacobsen made a similar point in his study, which suggested 1-year earlier AAM was associated with a mean 17.6% higher IHD mortality among women who smoked compared with 5.2% in women who never smoked (6). In addition, another cross-sectional study including 2,030 postmenopausal females 55–81 years old from England suggested that smoking behavior increased free estradiol significantly only in overweight postmenopausal females. These findings indicated that smoking-related increases in testosterone were translated into higher levels of estradiol through fat cells as an important peripheral conversion approach for postmenopausal overweight women. In the meantime, compared with lifetime smoking, current smoking behavior was found to significantly affect sex hormone levels; however, after a 1- to 2-year period of smoking cessation, sex hormone levels were the same as those of never smokers (41). Thus, relatively smaller sample size, low frequency of smoking among enrolled participants, lack of control of number of overweight women among enrolled participants, and inaccurate self-reported smoking time and cessation history might explain the different results between previous specific cohorts and our MR analyses. Given that sex hormone levels were associated with AAM, whether changes in current smoking behavior might modify CVD risks in a favorable direction through modification of endogenous sex hormones needs to be further investigated and results should be interpreted with caution.

SBP/HbA1c/TGs

Another clear finding to emerge from our MR analyses was that SBP, HbA1c, and TGs played vital roles in mediating the association of early genetically predicted AAM with genetically predicted MI, which was consistent with the results from

Remsberg et al., who found an inverse relationships among AAM and SBP (β estimates: −1.24, SE: 0.27), insulin (β estimates: −0.1, SE: 0.03), TGs (β estimates: −2.68, SE: 1.7) independent of fat-free mass and percent body fat during adolescence. Statistically significant associations were not found between AAM and glucose, total cholesterol, DBP, low-density lipoprotein, or HDL, which further supports the results from our MR analyses (12). In addition, another study that recruited 9,097 females aged 25–64 from China in 2004–2005 revealed that early AAM was associated with increased TGs, body fatness, and homeostasis model assessment of insulin resistance instead of FBG after adjusting for age (37). Lakshman et al. also reported that women with early AAM (<12 years) had a higher risk of hypertension [OR (95% CI):1.13 (1.02–1.24)] than those with later AAM in a prospective study that involved 15,807 females aged 40–79 years from 1993 to 1997 and followed for more than 10 years. Each 1-year delay of AAM was associated with 5% lower risk of hypertension (95% CI: 3–7%) in linear models, and hypertension risk could only be partially attenuated after adjusting for adult BMI and waist circumference (5).

The above studies support the finding that increased levels of HbA1c, which indicated that long-term hyperglycemia, in contrast to FBG, were more likely to mediate the association of early AAM with MI risk. Moreover, SBP may play a more crucial role in mediating the association of AAM with MI compared to DBP. Although both SBP and DBP could independently predict cardiovascular events, a cohort study involving 1.3 million adults from a general outpatient population suggested that SBP elevation (≥140 mmHg) had a greater effect on cardiovascular outcomes [HR (95% CI): 1.18 (1.17–1.18)] than DBP elevation [≥90 mmHg; HR (95% CI): 1.06 (1.06–1.07)], which further supported the findings of our MR analyses (42). Another interesting finding was that TGs, instead of other types of blood lipids, served a more essential role in mediation of the association of genetically predicted AAM with genetically predicted MI, which was further supported by results of the Newcastle Thousand Families Study, which recruited 1,142 children who were followed for 50 years. The study indicated that TGs were significantly associated with BMI at age 9 and were closely related with glucose metabolism in adult women after adjusting for adult percentage fat (43). Thus, the specific role of TGs and long-term impact on women need to be further investigated.

Potential Mechanism

Although the inverse association of AAM and MI was supported by a number of previous cohort studies, several other studies provided a J shape or U shape association between AAM and CVD or CHD (44–46). These inconsistent results indicated that early or late AAM might lead to increased cardiovascular risk by triggering different risk factors or mediators. Lee et al. reported that early AAM was more likely to be related to overnutrition, psychosocial stress, and metabolic syndrome, and late AAM is usually due to polycystic ovary syndrome, undernutrition, and excessive exercise, which might be related to hypercortisolism and hypoestrogenism (13). Thus, SBP, HbA1c, and TGs, which are closely related to metabolic syndrome, might mediate the association of genetically predicted AAM with genetically predicted MI through oxidative stress causing vascular damage and disruption of plaques by chronic inflammation. Simultaneously, early AAM may lead to female precocious puberty and early onset of smoking, which could result in insulin resistance of adipocytes, vessel damage, and oxidative stress in adolescent girls and significant changes in sex hormones through adipocytes in postmenopausal overweight women as a long-term effect (47, 48). Further studies with big data and experimental evidence might be necessary to delineate the above possible mechanisms.

Implications for Public Health and Clinical Management

Our study provides new insights from genetic estimates in an MR framework to further reveal the association of genetically predicted AAM with genetic predisposition to MI through a series of mediators that are closely related to metabolic syndrome. These innovative findings provided the potential targets for future pharmaceutical therapies and practical interventions such as lifestyle modifications on current smoking behavior and high-fat and high-sugar diets. Furthermore, our findings will also increase awareness of the importance of education for harmful habit cessation especially on girls during their early puberty to lower the MI risk by avoiding long duration of exposure to these cardiometabolic risk factors.

Innovations and Limitations

Our study made several remarkable advances. The major strength of our study is that it presented an MR framework to genetically assess the association of AAM with MI and genetically estimate the potential mediation proportion of different risk factors in mediating this relationship. This study provides more comprehensive and stronger evidence for further exploring the pathogenic mechanism of early AAM in MI. Moreover, more than 647,920 participants were involved in the two-sample MR analyses, which had a larger sample size than previous observational studies and MR analyses. The greater statistical power of this study also complements the imprecision that might arise in one-sample MR analyses when estimating mediation proportions. In addition, as genetic variants were immutable, naturally and randomly allocated at conception, MR analyses provide robust estimates to reduce bias. The genetic instruments that represented AAM and the mediators investigate the lifetime rather than short-term effects.

Note that our MR analyses also might be somewhat limited in some respect. Even though the results of our MR analyses were sufficiently robust to estimate the association of genetically predicted AAM with genetically predicted MI, we believe that conducting prospective cohort studies in the future will enable us to provide valuable information about the association of AAM with MI from more comprehensive perspectives and help future researchers formulate a broader view for making clinical decisions and public health policies. Additionally, not all aspects of the exposure (AAM) phenotype can necessarily be deduced

by these genetic variants. A notable example is that the genetic instruments for TG and SBP might capture average levels of TG and SBP but might not necessarily reflect the variability in serum lipid and blood pressure. The validity of our MR analyses relied on three key assumptions: (i) genetic variants were associated with AAM (exposure); (ii) genetic variants were independent of any confounder of AAM (exposure)-MI (outcome) association; (iii) genetic variants were only associated with MI (outcome) through gene expression instead of independent biological pathways (49). Because the second assumption was not easy to confirm because of potential unknown confounders, and the third assumption could be violated by pleiotropy, we performed various types of sensitivity analyses to further investigate whether the presence of pleiotropy, as well as weak instrumental variables and other invalid instrumental variables, influenced our results. The results of the sensitivity analysis were in accordance with those from our main IVW MR analysis. The analyses in this study were carried out on participants mostly of European descent, which may limit the generalizability of our findings to other ethnicities and populations.

CONCLUSION

Our MR analyses indicate that increase in genetically predicted AAM was associated with lower risk of genetically predicted MI, and that this association was found at least partially mediated through current smoking behaviors, SBP, and levels of HbA1c and TGs. In other words, early AAM might reflect adverse metabolic imprinting during the pre-pubertal phase. Given the increasing number of adolescent females globally who are currently challenged by earlier AAM currently as a result of social-economic progress, this study may help public health policymakers and doctors formulate more scalable and effective strategies to reduce the incidence of MI due to early AAM without political and social reforms. Further interventional studies should be performed to examine whether controlling for the above mediators in adolescent females is effective in reducing their increased MI risk, and to develop a clearer picture of other related mediators as well as the interplay among them.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

JZ and KC designed the study, performed the statistical analyses, and drafted the manuscript. Y-DT, TH, and ED participated in the design of the study, helped to perform the statistical analyses, and critically revised the manuscript. CS, PL, JW, WW, KZ, XM, XW, JG, YL, and JS helped to revise the manuscript in detail. All authors approved the final version of the manuscript and ensured that all aspects of the study are complete and accurate.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.821068/full#supplementary-material

REFERENCES

1. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol.* (2017) 70:1–25. doi: 10.1016/j.jacc.2017.04.052
2. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National registry of myocardial infarction 2 participants. *N Engl J Med.* (1999) 341:217–25. doi: 10.1056/NEJM199907223410401
3. Robertson RM. Women and cardiovascular disease: the risks of misperception and the need for action. *Circulation.* (2001) 103:2318–20. doi: 10.1161/01.cir.103.19.2318
4. DiVall SA, Radovick S. Pubertal development and menarche. *Ann N Y Acad Sci.* (2008) 1135:19–28. doi: 10.1196/annals.1429.026
5. Lakshman R, Forouhi NG, Sharp SJ, Luben R, Bingham SA, Khaw KT, et al. Early age at menarche associated with cardiovascular disease and mortality. *J Clin Endocrinol Metab.* (2009) 94:4953–60. doi: 10.1210/jc.2009-1789

6. Jacobsen BK, Oda K, Knutsen SF, Fraser GE. Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the adventist health study, 1976-88. *Int J Epidemiol.* (2009) 38:245–52. doi: 10.1093/ije/dyn251
7. Chang HS, Odongua N, Ohrr H, Sull JW, Nam CM. Reproductive risk factors for cardiovascular disease mortality among postmenopausal women in Korea: theKangwha cohort study, 1985-2005. *Menopause.* (2011) 18:1205–12. doi: 10.1097/gme.0b013e31821adb43
8. Gallagher LG, Davis LB, Ray RM, Psaty BM, Gao DL, Checkoway H, et al. Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai. *China. Int J Epidemiol.* (2011) 40:1510–8. doi: 10.1093/ije/dyr134
9. Mueller NT, Odegaard AO, Gross MD, Koh WP, Yuan J-M, Pereira MA. Age at menarche and cardiovascular disease mortality in Singaporean Chinese women: the Singapore Chinese health study. *Ann Epidemiol.* (2012) 22:717–22. doi: 10.1016/j.annepidem.2012.08.002
10. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. A prospective study of age at menarche, parity, age at first birth, and coronary heart disease in women. *Am J Epidemiol.* (1987) 126:861–70. doi: 10.1093/oxfordjournals.aje.a114723
11. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al. Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. *J Epidemiol.* (2006) 16:177–84. doi: 10.2188/jea.16.177
12. Remsberg KE, Demerath EW, Schubert CM, Chumlea WC, Sun SS, Siervogel RM. Early menarche and the development of cardiovascular disease risk factors in adolescent girls: the fels longitudinal study. *J Clin Endocrinol Metab.* (2005) 90:2718–24. doi: 10.1210/jc.2004-1991
13. Lee JJ, Cook-Wiens G, Johnson BD, Braunstein GD, Berga SL, Stanczyk FZ, et al. Age at menarche and risk of cardiovascular disease outcomes: findings from the National heart lung and blood institute-sponsored women's ischemia syndrome evaluation. *J Am Heart Assoc.* (2019) 8:e012406. doi: 10.1161/JAHA.119.012406
14. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med.* (2016) 374:1221–31. doi: 10.1056/NEJMoa1505241
15. Richmond RC, Hemani G, Tilling K, Davey Smith G, Relton CL. Challenges and novel approaches for investigating molecular mediation. *Hum Mol Genet.* (2016) 25:R149–56. doi: 10.1093/hmg/ddw197
16. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* (1986) 51:1173–82. doi: 10.1037//0022-3514.51.6.1173
17. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet.* (2017) 13:e1007081. doi: 10.1371/journal.pgen.1007081
18. Smith GD, Lawlor DA, Harbord R, Timpson N, Day I, Ebrahim S. Clustered environments and randomized genes: a fundamental distinction between conventional and genetic epidemiology. *PLoS Med.* (2007) 4:e352. doi: 10.1371/journal.pmed.0040352
19. Smith GD, Ebrahim S. "Mendelian randomization": can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol.* (2003) 32:1–22. doi: 10.1093/ije/dyg070
20. Lawlor DA, Harbord RM, Sterne JAC, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med.* (2008) 27:1133–63. doi: 10.1002/sim.3034
21. Relton CL, Davey Smith G. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. *Int J Epidemiol.* (2012) 41:161–76. doi: 10.1093/ije/dyr233
22. Marini S, Merino J, Montgomery BE, Malik R, Sudlow CL, Dichgans M, et al. Mendelian randomization study of obesity and cerebrovascular disease. *Ann Neurol.* (2020) 87:516–24. doi: 10.1002/ana.25686
23. Perry JR, Day F, Elks CE, Sulem P, Thompson DJ, Ferreira T, et al. Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche. *Nature.* (2014) 514:92–7. doi: 10.1038/nature13545
24. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Mägi R, et al. New genetic loci link adipose and insulin biology to body fat distribution. *Nature.* (2015) 518:187–96. doi: 10.1038/nature14132
25. Dupuis J, Langenberg C, Prokopenko I, Saxena R, Soranzo N, Jackson AU, et al. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet.* (2010) 42:105–16. doi: 10.1038/ng.520
26. Kettunen J, Demirkan A, Würtz P, Draisma HHM, Haller T, Rawal R, et al. Genome-wide study for circulating metabolites identifies 62 loci and reveals novel systemic effects of LPA. *Nat Commun.* (2016) 7:11122. doi: 10.1038/ncomms11122
27. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, et al. A comprehensive 1,000 genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet.* (2015) 47:1121–30. doi: 10.1038/ng.3396
28. Thompson JR, Minelli C, Del Greco MF. Mendelian randomization using public data from genetic consortia. *Int J Biostat.* (2016) 12:/j/ijb.2016. doi: 10.1515/ijb-2015-0074
29. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol.* (2013) 37:658–65. doi: 10.1002/gepi.21758
30. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through egger regression. *Int J Epidemiol.* (2015) 44:512–25. doi: 10.1093/ije/dyv080
31. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol.* (2016) 40:304–14. doi: 10.1002/gepi.21965
32. Freuer D, Meisinger C, Linseisen J. Causal relationship between dietary macronutrient composition and anthropometric measures: a bidirectional two-sample Mendelian randomization analysis. *Clin Nutr.* (2021) 40:4120–31. doi: 10.1016/j.clnu.2021.01.047
33. La Vecchia C, Decarli A, Franceschi S, Gentile A, Negri E, Parazzini F. Menstrual and reproductive factors and the risk of myocardial infarction in women under fifty-five years of age. *Am J Obstet Gynecol.* (1987) 157:1108–12. doi: 10.1016/s0002-9378(87)80271-5
34. Cooper GS, Ephross SA, Weinberg CR, Baird DD, Whelan EA, Sandler DP. Menstrual and reproductive risk factors for ischemic heart disease. *Epidemiology.* (1999) 10:255–9. doi: 10.1097/00001648-199905000-00008
35. Au Yeung SL, Jiang C, Cheng KK, Xu L, Zhang W, Lam TH, et al. Age at menarche and cardiovascular risk factors using mendelian randomization in the Guangzhou biobank cohort study. *Prev Med.* (2017) 101:142–8. doi: 10.1016/j.ypmed.2017.06.006
36. Cao M, Cui B. Negative effects of age at menarche on risk of cardiometabolic diseases in adulthood: a mendelian randomization study. *J Clin Endocrinol Metab.* (2020) 105:dgz071. doi: 10.1210/clinem/dgz071
37. Feng Y, Hong X, Wilker E, Li Z, Zhang W, Jin D, et al. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. *Atherosclerosis.* (2008) 196:590–7. doi: 10.1016/j.atherosclerosis.2007.06.016
38. Dunger DB, Ahmed ML, Ong KK. Effects of obesity on growth and puberty. *Best Pract Res Clin Endocrinol Metab.* (2005) 19:375–90. doi: 10.1016/j.beem.2005.04.005
39. Frisch RE. Body fat, menarche, fitness and fertility. *Hum Reprod.* (1987) 2:521–33. doi: 10.1093/oxfordjournals.humrep.a136582
40. Sloboda DM, Hart R, Doherty DA, Pennell CE, Hickey M. Age at menarche: influences of prenatal and postnatal growth. *J Clin Endocrinol Metab.* (2007) 92:46–50. doi: 10.1210/jc.2006-1378
41. Brand JS, Chan M-F, Dowsett M, Folkerd E, Wareham NJ, Luben RN, et al. Cigarette smoking and endogenous sex hormones in postmenopausal women. *J Clin Endocrinol Metab.* (2011) 96:3184–92. doi: 10.1210/jc.2011-1165
42. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, et al. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med.* (2019) 381:243–51. doi: 10.1056/NEJMoa1803180
43. Wright CM, Parker L, Lamont D, Craft AW. Implications of childhood obesity for adult health: findings from thousand families cohort study. *BMJ.* (2001) 323:1280–4. doi: 10.1136/bmj.323.7324.1280
44. Tamakoshi K, Yatsuya H, Tamakoshi A, Jacc Study Group. Early age at menarche associated with increased all-cause mortality. *Eur J Epidemiol.* (2011) 26:771–8. doi: 10.1007/s10654-011-9623-0
45. Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, et al. Age at menarche and risks of coronary heart and other vascular diseases in a large UK

cohort. *Circulation.* (2015) 131:237–44. doi: 10.1161/CIRCULATIONAHA.114.010070
46. Jung KJ, Kim M-R, Yun YD, Kim HC, Jee SH. Duration of ovarian hormone exposure and atherosclerotic cardiovascular disease in Korean women: the Korean heart study. *Menopause.* (2016) 23:60–6. doi: 10.1097/GME.0000000000000489
47. Maslov LN, Naryzhnaya NV, Boshchenko AA, Popov SV, Ivanov VV, Oeltgen PR. Is oxidative stress of adipocytes a cause or a consequence of the metabolic syndrome? *J Clin Transl Endocrinol.* (2019) 15:1–5. doi: 10.1016/j.jcte.2018.11.001
48. Oh SW, Yoon YS, Lee ES, Kim WK, Park C, Lee S, et al. Association between cigarette smoking and metabolic syndrome: the Korea National health and nutrition examination survey. *Diabetes Care.* (2005) 28:2064–6. doi: 10.2337/diacare.28.8.2064
49. Porcu E, Rüeger S, Lepik K, eQTLGen Consortium, Bios Consortium, Santoni FA, et al. Mendelian randomization integrating GWAS and eQTL data reveals genetic determinants of complex and clinical traits. *Nat Commun.* (2019) 10:3300. doi: 10.1038/s41467-019-10936-0

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The Nadir Oxygen-Specific Heart Rate Response in Sleep Apnea Links With the Occurrence of Acute Myocardial Infarction

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Background: Little is known regarding the quantification of sleep apnea- and hypoxemia-elicited heart rate (HR) response and its prognostic significance of the cardiovascular risk. We sought to explore the impact of HR response and variability specific to obstructive sleep apnea (OSA) on the occurrence of a common cardiovascular event – acute myocardial infarction (AMI).

Methods: Consecutive patients with suspected OSA were enrolled and underwent nocturnal respiratory study and electrocardiography monitoring. The minimal oxygen saturation ($minSpO_2$) was determined from the oxygen saturation curve under a subject-specific search window. Primary HR metrics such as maximal HR in response to $minSpO_2$ and respiratory event-specific HR variability were computed from the synchronized recordings. Multivariate regression analyses were conducted to analyze the associations between individualized HR metrics and the occurrence of AMI.

Results: Of 2,748 patients recruited, 39% (n = 1,071) had moderate-to-severe OSA (respiratory event index, REI $\geq$ 15), and 11.4% (n = 313) patients had AMI. Patients with AMI experienced severe OSA, severe $minSpO_2$, and greater HR reactions. Patients with $minSpO_2$ <90% had an adjusted odds ratio (OR) of 1.48 [95% confidence interval (CI): 1.09–2.00, p = 0.012) for AMI. Notably, $minSpO_2$-induced elevated mean HR response (HR_{mean} > 73 bpm) was significantly associated with AMI (OR 1.72, 95% CI: 1.32–2.23, $p < 0.001$). Patients with both severe $minSpO_2$ (<90%) and elevated HR_{mean} carried an additive OR of 2.65 (95% CI: 1.74–4.05, $p < 0.001$) for the risk of AMI after adjustment for potential confounders. A large total power spectrum specific to respiratory events was correlated with an adjusted OR of 0.61 for AMI risk.

Conclusion: Patients with substantial HR reactions to OSA-induced oxygen nadir and restricted cardiac cycle shifting to respiratory events were likely at increased risk of developing AMI. Detection of nocturnal HR response to hypoxemia may help improve cardiovascular risk stratification.

Keywords: sleep apnea, oxygen saturation, heart rate, myocardial infarction, cardiovascular risk

INTRODUCTION

The direct association with an augmented risk of cardiovascular (CV) morbidity and mortality has raised obstructive sleep apnea (OSA), a pervasive sleep-breathing disorder, as a critical public health problem (1, 2). Acute myocardial infarction (AMI), accounting for approximately 1.8 million deaths annually, remains the leading cause of CV morbidity and mortality worldwide (3). Previous clinic-based cohorts suggested that OSA is an independent risk factor for AMI (1, 4, 5). However, in a recent multi-center randomized study, moderate-to-severe OSA did not appear to impose an additional CV risk (6). Besides, OSA therapy with continuous positive airway pressure (CPAP) in recent randomized clinical trials (6–8) has failed to reduce CV events or mortality. These neutral findings may be partly related to the metrics used to evaluate OSA, and notably, the heterogeneity of CV risk across different phenotypes.

The conventional OSA severity measures simply focus on the frequency of apnea or hypopnea interruptions, while neglecting their immediate hypoxemic and autonomic consequences. A previous large-scale study found that minimal oxygen saturation ($minSpO_2$) <78%, but not apnea–hypopnea index (AHI), was independently correlated with an increased risk of sudden cardiac death (9). In patients with coronary artery disease, we reported that $minSpO_2$ was independently associated with left ventricular hypertrophy, a marker of CV risk (10). Hypoxemia in OSA is thus postulated as a primary factor preceding subclinical or overt CV damage (11). Besides, cyclical hypoxemia could also elicit a high cardiac variability or sympathetic activity, such as heart rate (HR) accelerations, and contribute to fatal CV events during sleep (1, 12). In this regard, it is plausible that a surge in HR to $minSpO_2$ or respiratory events could encapsulate the enormous sympathetic reactivity of OSA and may be one of the mediators of increased CV risk (13, 14).

However, to the best of our knowledge, no prior studies have addressed the HR response measures to $minSpO_2$ and heart rate variability (HRV) specific to respiratory events due to OSA and their effects on the occurrence of AMI. Therefore, in the present study, we sought to explore how $minSpO_2$-specific HR reactions and HRV parameters identify groups of individuals at particular risk of AMI in a large population with potential CV risk.

MATERIALS AND METHODS

Study Population

Consecutive patients with suspected sleep apnea between 2015 and 2020 at the Guangdong Cardiovascular Institute were enrolled. Patients were considered with suspected sleep apnea if they have the following characteristics: (1) risk factors, including overweight or obese, male gender, older age, postmenopausal state in women, enlarged upper airway soft tissues (e.g., tonsils, adenoids, and tongue), and craniofacial abnormalities (e.g., retrognathia and micrognathia), and (2) clinical symptoms and signs, including excessive sleepiness, fatigue, or unrefreshing sleep, snoring during sleep, witnessed breathing pauses, choking or gasping during sleep, nocturia, nocturnal gastroesophageal reflux, and morning headache. Patients who successfully underwent a cardiorespiratory sleep study and have not been previously diagnosed with OSA were included. Participants who met the following criteria were excluded: previous diagnosed OSA and received treatment with CPAP or other modalities; atrial fibrillation or other significant arrhythmias; and had implanted pacemakers or defibrillators. A total of 2,989 patients were screened for suspected sleep apnea by obtaining the above risk factors and clinical features *via* a detailed medical history taking and careful physical examination, as well as Epworth Sleepiness Scale (ESS) quantification. Among them, 151 patients with atrial fibrillation, nine patients with pacemakers or defibrillators, and six patients with previously diagnosed OSA were excluded. Of the remaining 2,823 patients who underwent nocturnal respiratory study and simultaneous electrocardiogram (ECG) recording, 75 patients whose monitoring data were of insufficient quality, which made proper interpretation difficult, were excluded. In total, 2,748 eligible patients were included in the final data analysis. The study was approved by the Clinical Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2018567), and written informed consent was obtained from all participants.

Clinical Data Acquisition

Demographics, anthropometrics, previous medical history, medications, and daytime ESS score were collected on admission. Blood samples were obtained immediately after admission using EDTA-containing tubes. The baseline estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft–Gault formula. Fasting blood samples were taken in the morning after admission to determine fasting glucose and serum lipids. Two-dimensional transthoracic echocardiography was performed to evaluate the left ventricular ejection fraction. The medical diagnoses were retrieved from the electronic recording system. The diagnosis of AMI was based on clinical manifestations, ECG findings, myocardial enzymes, echocardiography, and coronary angiography according to the criteria proposed by the Third Universal Definition of Myocardial Infarction (15). The diagnosis of AMI and OSA were confirmed at the same time when patients were admitted and hospitalized during the study period.

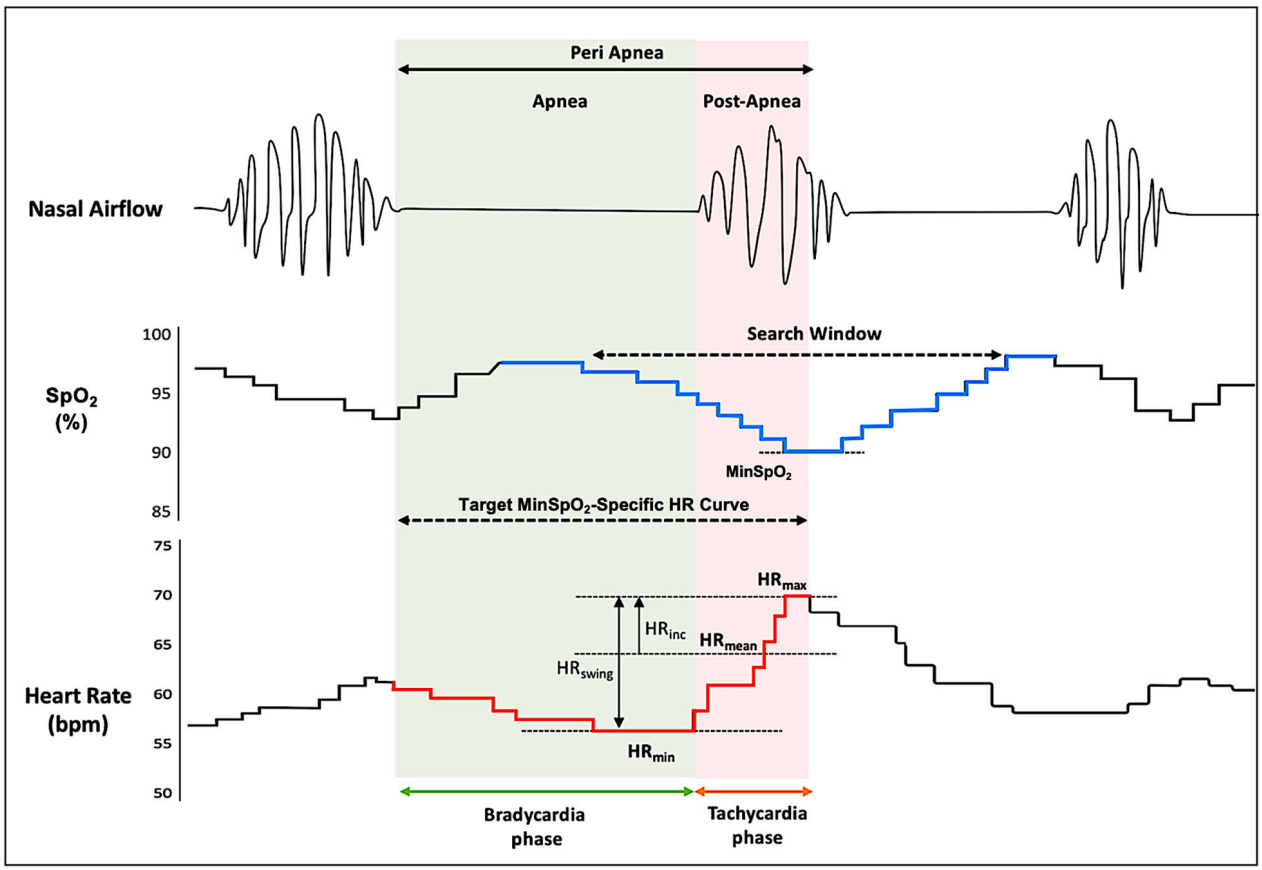

FIGURE 1 | Typical heart rate response during a sleep apneic event. The figure demonstrates a typical pattern of HR tracings (redline, lower) during the peri-apnea phase, with a synchronized timescale illustrating oxygen saturation (SpO_2) curve (blue line, middle) and nasal airflow (upper). The search window was yielded from overlaying respiratory event–associated oxygen desaturation curve (see section "Materials and Methods" for details). The $minSpO_2$ is identified based on subject-specific search window, and a corresponding target HR response curve is determined. HR, heart rate; HR_{min}, minimal HR during apnea phase that elicits a subsequent $minSpO_2$; HR_{max}, maximal HR in response to $minSpO_2$ during post-apnea phase; HR_{mean}, mean HR representing the average of the HR_{max} and the HR_{min}; HR_{swing}, HR swing indicative of the difference between HR_{max} and HR_{min}; HR_{inc}, the increment of HR from the HR_{mean} during the peri-apneic period; SpO_2, oxygen saturation.

Nocturnal Respiratory Study

All eligible patients with suspected sleep apnea underwent Type III nocturnal respiratory monitoring (Alice PDx, Philips 6 Investment Co., Shanghai, China) during the first 24–72 h after admission to evaluate the presence and severity of OSA. As for those with the presence of AMI, these patients were being admitted due to AMI and were evaluated for OSA within the same hospitalization period. Airflow was measured with a nasal pressure cannula, while respiratory efforts were measured utilizing respiratory inductance plethysmography. Apnea and hypopnea events were determined according to the criteria of the American Academy of Sleep Medicine (16). Apnea was defined as a ≥90% reduction of inspiratory airflow for ≥10 s while hypopnea was defined as ≥30% reduction in airflow associated with ≥3% desaturation for ≥10 s. The respiratory event index (REI) was calculated as the number of apnea and hypopnea episodes per recorded hour. The oxygen desaturation index (i.e., the number of ≥3% oxygen desaturations per recorded sleeping hour) was also recorded. A cut-off REI ≥5 events/h was used to define the existence of OSA. Patients with OSA were classified into mild ($5 \leq REI < 15$), moderate ($15 \leq REI < 30$), and severe ($REI \geq 30$) groups.

Nasal airflow and pulse oximetry were used to assess the severity of hypoxemic sequelae of OSA. The key indices analyzed in our study included: total duration of 3% oxygen desaturation, total duration of respiratory events, $minSpO_2$, mean SpO_2 levels, time spent with SpO_2 <90%, and nocturnal hypoxic burden (only ≥3% oxygen deoxygenation events considered) (10, 17, 18). All recordings were scored manually or calculated by an experienced sleep technician blinded to the clinical data.

Determination of Heart Rate Response to Minimal Oxygen Saturation and Respiratory Event

A single-lead ECG recording device (Shanghai YueGuang Technology Co. Ltd.) was attached to the patient's body simultaneously with the Type III portable monitoring device. The

TABLE 1 | Baseline characteristics.

Variables	Non-OSA *n* = 699	Mild OSA *n* = 978	Moderate OSA *n* = 589	Severe OSA *n* = 482	All *n* = 2,748	*p*-Value
Age, year	54.4 ± 13.0	58.1 ± 10.8	58.6 ± 10.8	56.7 ± 11.7	57.0 ± 11.7	<0.001
Male, *n* (%)	481 (68.8)	742 (75.9)	492 (83.5)	424 (88.0)	2,139 (77.8)	<0.001
BMI, kg/m^2	24.2 ± 3.1	25.3 ± 3.1	26.4 ± 3.2	27.3 ± 4.0	25.6 ± 3.5	<0.001
Diabetes mellitus, *n* (%)	133 (19.0)	230 (23.5)	173 (29.4)	144 (29.9)	680 (24.7)	<0.001
Dyslipidemia, *n* (%)	99 (14.2)	153 (15.6)	89 (15.1)	70 (14.5)	411 (15.0)	0.851
Hypertension, *n* (%)	339 (48.5)	568 (58.1)	371 (63.0)	341 (70.7)	1,619 (58.9)	<0.001
CAD, *n* (%)	372 (53.2)	602 (61.6)	371 (63.0)	278 (57.7)	1,623 (59.1)	<0.001
AMI, *n* (%)	65 (9.3)	115 (11.8)	73 (12.4)	60 (12.4)	313 (11.4)	<0.001
Total cholesterol, mmol/L	4.4 ± 1.1	4.5 ± 1.2	4.5 ± 1.3	4.6 ± 1.4	4.5 ± 1.2	0.440
LDL-C, mmol/L	2.9 ± 0.9	2.9 ± 0.9	3.0 ± 0.9	3.0 ± 0.9	2.9 ± 0.9	0.278
Triglycerides, mmol/L	1.6 ± 1.5	1.9 ± 1.9	1.8 ± 1.5	2.1 ± 2.3	1.8 ± 1.8	<0.001
FBG, mmol/L	5.1 ± 1.6	5.5 ± 2.0	5.7 ± 2.4	5.7 ± 2.2	5.5 ± 2.1	0.011
Creatinine, μmol/L	83.5 ± 58.5	87.2 ± 56.0	94.3 ± 79.2	109.4 ± 105.0	91.7 ± 73.1	<0.001
eGFR, ml/min	99.9 ± 29.8	93.8 ± 28.9	90.0 ± 28.0	85.4 ± 31.7	93.1 ± 30.0	<0.001
EF, %	62.3 ± 9.8	61.7 ± 10.0	60.0 ± 11.2	57.5 ± 14.1	60.7 ± 11.1	<0.001
ESS	5.6 ± 3.5	5.8 ± 3.7	6.2 ± 4.1	7.3 ± 4.5	6.1 ± 3.9	<0.001
TRT, h	7.99 (1.11)	8.00 (1.28)	8.05 (1.16)	8.20 (1.29)	8.04 (1.22)	0.013
REI, events/h	2.3 ± 1.2	9.0 ± 2.6	21.6 ± 4.1	43.7 ± 12.7	16.1 ± 15.5	<0.001
3% ODI, events/h	5.9 ± 4.6	14.7 ± 6.9	28.0 ± 8.9	48.8 ± 14.9	21.3 ± 17.2	<0.001
T90, min	1.21 ± 8.2	2.0 ± 7.2	4.8 ± 8.8	13.3 ± 14.3	4.4 ± 10.4	<0.001
Mean SpO_2, %	95.1 ± 1.6	94.3 ± 1.5	93.9 ± 1.5	92.8 ± 2.2	94.2 ± 1.8	<0.001
MinSpO_2, %	89.6 ± 2.8	85.9 ± 3.6	81.2 ± 5.6	75.0 ± 9.9	83.9 ± 7.5	<0.001

Values are given as the mean ± SD.
AMI, acute myocardial infarction; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; EF, ejection fraction; ESS, Epworth Sleepiness Scale; FBG, fasting blood glucose; LDL-C, low-density lipoprotein; minSpO_2, minimal oxygen saturation; REI, respiratory event index; 3% ODI, 3% oxygen desaturation index; OSA, obstructive sleep apnea; SpO_2, oxygen saturation recorded by pulse oximetry; TRT, total recording time of sleep; T90, time spent with SpO_2 lower than 90%.

TABLE 2 | Sleep respiratory parameters and minSpO_2-specific HR metrics among patients with and without AMI.

Variables	No AMI	AMI	All	*p*-Value
REI, events/h	15.9 ± 15.6	17.7 ± 15.4	16.1 ± 15.5	0.046
3% ODI, events/h	21.0 ± 17.1	23.6 ± 17.7	21.3 ± 17.2	0.013
T90, %	4.4 ± 10.5	4.4 ± 9.6	4.4 ± 10.4	0.982
Mean SpO_2, %	94.2 ± 1.8	94.1 ± 1.7	94.2 ± 1.8	0.333
MinSpO_2, %	84.7 ± 7.0	83.8 ± 7.5	83.9 ± 7.5	0.043
HR_{mean}, bpm	66.8 ± 10.7	70.0 ± 11.5	67.2 ± 10.9	<0.001
HR_{max}, bpm	87.0 ± 20.1	89.1 ± 18.4	87.2 ± 19.9	0.046
HR_{min}, bpm	52.1 ± 12.8	54.7 ± 15.5	52.4 ± 13.1	0.001
HR_{diff}, bpm	34.8 ± 23.5	34.4 ± 22.4	34.8 ± 23.3	0.772
HR_{inc}, bpm	20.2 ± 15.9	19.1 ± 14.6	20.1 ± 15.8	0.282

AMI, acute myocardial infarction; CI, confidence interval; HR, *heart rate;* HR_{min}, *minimal* HR *during apnea phase that elicits a subsequent minSpO_2;* HR_{max}, *maximal* HR *in response to minSpO_2 during post-apnea phase;* HR_{mean}, *mean* HR *representing the average of the* HR_{max} *and the* HR_{min}; HR_{swing}, HR *swing indicative of the difference between* HR_{max} *and* HR_{min}; HR_{inc}, *the increment of* HR *from the* HR_{mean} *during the peri-apneic period; minSpO_2, minimal oxygen saturation; OR, odds ratio; REI, respiratory event index; 3% ODI, 3% oxygen desaturation index; OSA, obstructive sleep apnea; SpO_2, oxygen saturation recorded by pulse oximetry; T90, time spent with SpO_2 lower than 90%.*

ECG signals were manually inspected, whereas noisy segments and other artifacts were excluded from the analysis due to the patient's movement. At every second, the HR was calculated from the R–R intervals of the raw ECG signals and was retro-graphed to configure an HR tracing curve with a wholly synchronized timescale with Type III portable monitoring channels. For each individually identified apnea or hypopnea, the SpO_2 signals were traced before and after the end of the obstructive respiratory event until two SpO_2 peaks on each side were identified. The average oxygen desaturation curve for each participant was determined by overlaying SpO_2 signals with respect to the end of events. This criterion yielded a search window for the determination of individual oxygen desaturation curves (17). Our target interest was the search window in which the nadir oxygen desaturation, that is, minSpO_2 throughout the night was located, and the corresponding HR curve was determined.

The primary minSpO_2-specific HR metrics during the peri-apneic period included HR_{min}, minimal HR during apnea phase that elicits a subsequent minSpO_2; HR_{max}, maximal HR in response to minSpO_2 during post-apnea phase; HR_{mean}, mean HR representing the average of the HR_{max} and the HR_{min}; HR_{swing}, HR_{swing} indicative of the difference between HR_{max} and HR_{min}; and HR_{inc}, the increment of HR from the HR_{mean} during the peri-apneic period (**Figure 1**). HRV measures specific to minSpO_2, and respiratory events were also computed based on R–R intervals. Fourier transformation was applied to calculate the frequency domains, among which low-frequency (LF) and high-frequency (HF) ratios were used to quantify the vago-sympathetic balance.

Statistical Analysis

Continuous variables were described as the mean ± standard deviation, and one-way ANOVA was used to compare differences between groups. The unpaired *t*-test was used for normally distributed variables, while the Mann–Whitney *U* test was used for continuous variables that were not normally distributed. Categorical variables were described by proportions, and Pearson's Chi-square test or Fisher's exact test was used to compare the differences between groups as appropriate. To determine the risk factors for the occurrence of AMI, both univariate and multivariate logistic regression analyses were conducted. Confounders included in the multivariate models were the ones that are correlated with AMI and clinically relevant factors. To assess the association between the $minSpO_2$-specific HR metrics and the composite variables of HR metrics and $minSpO_2$, and AMI prevalence, logistic regression analyses were applied to calculate the odds ratio (OR) and its associated 95% confidence intervals (CIs). Given the novelty of the $minSpO_2$–HR metrics, and uncertainty over the associations' linearity, preliminary associations between various quartiles and AMI were facilitated to determine the model structure and thresholds for individual HR metrics. A two-sided value of $p < 0.05$ was considered as statistically significant. Statistical analyses were performed using the R statistical software (R.3.6).

RESULTS

Baseline Characteristics

Of 2,748 studied participants (77.8% male, aged 57.0 ± 11.7 years), 699 (25%) had normal REI, whereas 978 (36%) had mild, 589 (21%) had moderate, and 482 (18%) had severe OSA quantified by REI, respectively. Most participants did not report excessive daytime sleepiness as assessed by the ESS Score. There was a high comorbidity of hypertension (58.9%), diabetes mellitus (24.7%), and dyslipidemia (15%) across populations with different severity of OSA. The prevalence of coronary artery disease reached approximately 59% (n = 1,623), whereas AMI accounted for 11.4% (n = 313) (**Table 1**). Moreover, patients with severe OSA quantified by REI, were heavier, male-predominant, had a higher prevalence of AMI, diabetes mellitus, hypertension, and had higher levels of triglycerides, lower eGFR, and lower ejection fraction (**Table 1**).

Comparison of Cardiorespiratory Parameters

Patients with AMI had a higher frequency of apneic or hypopneic episodes, that is, greater REI (17.7 vs. 15.9, $p = 0.046$), and greater 3% ODI (23.6 vs. 21.0, $p = 0.013$) compared to those without AMI. There was a significant difference in $minSpO_2$ between patients with and without AMI (83.8 vs. 84.7%, $p = 0.043$) among hypoxemic parameters. The resting HR (i.e., the average HR in the period excluding any respiratory events) was at a level of 66.01 ± 11.49 bpm, and no statistical difference was observed between AMI and non-AMI groups ($p = 0.437$). Further analyses on HR response to obstructive apnea followed by a $minSpO_2$, HR_{max}, HR_{mean}, and HR_{min} appeared significantly greater than resting HR and greater in patients with AMI (**Table 2**). No significant difference in other HR metrics, including HR_{swing}, HR_{inc}, and HR_{dur} was found between AMI groups.

Associations Between Minimal Oxygen Saturation-Specific Heart Rate Response and Acute Myocardial Infarction

Among various hypoxemic measures, $minSpO_2$ remained significantly associated with AMI risk after adjustment for potential confounders (**Supplementary Table 1**). The severity of $minSpO_2$ and the $minSpO_2$-specific HR_{max}, HR_{mean}, and HR_{min} were divided into two distinct groups, respectively, based on the preliminary logistic regression results (**Supplementary Tables 1**, **2**). As shown in **Table 3**, patients with $minSpO_2$ <90% had an OR of 1.48 (95% CI: 1.09–2.00, $p = 0.012$) for AMI risk after adjusting for possible confounders including age, gender, body mass index (BMI), hypertension, dyslipidemia, eGFR, and diabetes mellitus. Notably, substantial HR reactions to $minSpO_2$ were significantly associated with an increased likelihood of AMI (HR_{mean} > 73 bpm, OR 1.72, 95% CI: 1.32–2.23; HR_{max} > 83 bpm, OR: 1.31, 95% CI: 1.03–1.67; and HR_{min} > 60 bpm, OR: 1.94, 95% CI: 1.49–2.52; **Table 3**) even after adjusting for confounders.

We further examined whether associations between significant HR response and AMI risk would be more robust in patients with severe hypoxemia quantified by $minSpO_2$. The mixed groups with various magnitudes of HR metrics and $minSpO_2$ were analyzed to evaluate the synergistic effects on the estimated risk for AMI. Patients with severe $minSpO_2$ (i.e., <90%), if an elevated HR response was accompanied, would be at a ≥2-fold higher risk for developing AMI. For instance, patients with $minSpO_2$ <90% and an elevated $minSpO_2$-related HR_{mean} > 73 bpm had 2.65 times (95% CI: 1.74–4.05, $p < 0.001$) increased risk of AMI than those with $minSpO_2$ ≥90% and mild HR response ($HR_{mean} \leq 73$ bpm), as shown in **Table 4**.

Associations Between Sleep Apnea-Associated Heart Rate Variability Parameters and Acute Myocardial Infarction

HRV parameters were divided into quartiles and the first group was considered the reference group. Among $minSpO_2$ variables, the mean NN interval and LF spectral band showed a protective role in AMI risk (**Table 5**). The non-respiratory event-LF/HF was slightly higher in patients with AMI and severe OSA, than in non-AMI patients (0.80 vs. 0.77) and non-OSA patients (0.80 vs. 0.60), respectively. Patients with a higher LF/HF ratio would be at increased risk of AMI (OR = 1.34) after adjusting for age, gender, and BMI. Notably, respiratory event-associated total power (TP) spectral band, NN, and standard deviation of NN interval (SDNN) were related to decreased ORs of AMI incidence.

TABLE 3 | Relationship between $minSpO_2$ and $minSpO_2$-specific HR metrics with AMI.

	Unadjusted		Model 1		Model 2	
Items	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**
$MinSpO_2$, <90%	1.47 (1.10–1.96)	0.009	1.47 (1.08–1.98)	0.014	1.48 (1.09–2.00)	0.012
HR_{mean}, >73 bpm	1.78 (1.38–2.29)	<0.001	1.78 (1.37–2.30)	<0.001	1.72 (1.32–2.23)	<0.001
HR_{max}, >83 bpm	1.36 (1.08–1.73)	0.011	1.34 (1.06–1.70)	0.016	1.31 (1.03–1.67)	0.028
HR_{min}, >60 bpm	1.98 (1.53–2.53)	<0.001	2.02 (1.56–2.61)	<0.001	1.94 (1.49–2.52)	0.001

TABLE 4 | Associations of composite metrics of $minSpO_2$ and $minSpO_2$-specific HR metrics with AMI.

	Unadjusted		Model 1		Model 2	
Items	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**
$MinSpO_2$ + HR_{mean}						
Group 1	1.00		1.00		1.00	
Group 2	1.41 (0.83–2.39)	0.210	1.42 (0.83–2.43)	0.196	1.39 (0.81–2.37)	0.234
Group 3	1.35 (0.93–1.95)	0.114	1.36 (0.93–1.99)	0.113	1.38 (0.94–2.01)	0.103
Group 4	2.74 (1.82–4.13)	<0.001	2.74 (1.80–4.18)	<0.001	2.65 (1.74–4.05)	<0.001
$MinSpO_2$ + HR_{max}						
Group 1	1.00		1.00		1.00	
Group 2	1.55 (0.90–2.67)	0.114	1.53 (0.88–2.64)	0.130	1.54 (0.89–2.67)	0.124
Group 3	1.66 (1.02–2.68)	0.040	1.65 (1.01–2.68)	0.045	1.70 (1.04–2.77)	0.035
Group 4	2.33 (1.44–3.77)	0.001	2.26 (1.39–3.70)	0.002	2.25 (1.37–3.67)	0.002
$MinSpO_2$ + HR_{min}						
Group 1	1.00		1.00		1.00	
Group 2	1.32 (0.76–2.31)	0.329	1.40 (0.80–2.46)	0.239	1.35 (0.77–2.37)	0.304
Group 3	1.24 (0.87–1.77)	0.228	1.27 (0.88–1.83)	0.196	1.28 (0.89–1.85)	0.184
Group 4	2.79 (1.89–4.11)	<0.001	2.91 (1.94–4.36)	<0.001	2.81 (1.87–4.21)	<0.001

$MinSpO_2$ and HR *metrics (including* HR_{max}, HR_{mean}, *and* HR_{min}*) yield a total of four independent groups for individual* HR *response metric. Group 1 (Control) represents participants with $minSpO_2$ ≥90% and mild* HR *reaction (i.e.,* $HR_{mean} \leq 73$ *bpm,* $HR_{max} \leq 83$ *bpm, or* $HR_{min} \leq 60$ *bpm). Group 2 represents participants with $minSpO_2$ <90% and mild* HR *reaction. Group 3 represents participants with $minSpO_2$ ≥90% and substantial* HR *reaction (i.e.,* $HR_{max} > 83$ *bpm, or* $HR_{mean} > 73$ *bpm, or* $HR_{min} > 60$ *bpm). Group 4 represents participants with $minSpO_2$ <90% and substantial* HR *reaction. Each line represents a separate regression model. Model 1 adjusted for age, gender, and BMI. Model 2 adjusted for age, gender, BMI, hypertension, dyslipidemia, eGFR, and diabetes mellitus.*

AMI, acute myocardial infarction; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR*, heart rate; $minSpO_2$, minimal oxygen saturation.* HR_{min}*, minimal* HR *during apnea phase that elicits a subsequent $minSpO_2$;* HR_{max}*, maximal* HR *in response to $minSpO_2$ during post-apnea phase;* HR_{mean}*, mean* HR *representing the average of the* HR_{max} *and the* HR_{min}*; OR, odds ratio.*

TABLE 5 | Significant sleep apnea-specific heart rate variability parameters associated with AMI risk.

HRV variables*	Unadjusted		Model 1		Model 2	
	OR (95% CI)	***p*-Value**	**OR (95% CI)**	***p*-Value**	**OR (95% CI)**	***p*-Value**
$minSpO_2$-related						
LF > 77.2	0.69 (0.49–0.96)	0.028	0.62 (0.45–0.88)	0.007	0.64 (0.45–0.90)	0.011
NN > 1.02	0.50 (0.36–0.70)	<0.001	0.48 (0.34–0.67)	<0.001	0.49 (0.34–0.69)	<0.001
RE-related						
TP > 1570	0.62 (0.45–0.87)	0.006	0.57 (0.41–0.80)	0.002	0.61 (0.43–0.86)	0.005
NN > 1.02	0.49 (0.35–0.68)	<0.001	0.46 (0.33–0.64)	<0.001	0.49 (0.35–0.68)	<0.001
SDNN > 0.101	0.68 (0.49–0.96)	0.029	0.64 (0.45–0.90)	0.012	0.69 (0.48–0.98)	0.041
NRE-related						
LF/HF > 0.91	1.63 (1.17–2.27)	0.004	1.34 (0.95–1.88)	0.098	1.36 (0.96–1.92)	0.084

**The fourth quartiles were shown with the first quartile as the referenced group. Model 1 adjusted for age, gender, and BMI. Model 2 adjusted for age, gender, BMI, hypertension, dyslipidemia, eGFR, and diabetes mellitus.*

OR, odds ratio; $minSpO_2$, minimal oxygen saturation; RE, respiratory event; NRE, non-respiratory events; TP, total power; SDNN, standard deviation of NN interval; LF, low-frequency; HRV, heart rate variability.

DISCUSSION

The present study provides new insights into the quantification of HR response due to OSA and its capacity for AMI risk stratification. The novel and principal findings are that the hypoxemia measure—minSpO_2 that characterizes OSA-related hypoxemic severity correlated with incident AMI. Notably, patients with pronounced minSpO_2-specific HR reactions (specifically, HR_{max}, HR_{mean}, and HR_{min}) magnified AMI risk by nearly 1.3- to 1.9-fold compared to those with a mild HR response. This association appeared stronger among individuals with severe minSpO_2 <90%. Analysis of sleep apnea–specific HRV also supported the hidden role of enhanced sympathetic tone and restricted variations in cardiac cycle in the incidental occurrence of AMI.

The Role of Hypoxemia and Associated Heart Rate Surges

Recent literature has identified novel measures that may accurately quantify respiratory event-specific hypoxemia including the length of obstructive events (19) and the cumulative extent of oxygen desaturation (17, 20), which are postulated as new candidates for OSA-associated CV risk such as CV mortality, all-cause mortality (17, 21), and incident heart failure (22). Nevertheless, the above-mentioned studies paid less attention to the nadir oxygen saturation and its effects on CV risk. In contrast, in our study, the nadir oxygen desaturation, that is, minSpO_2, appears to be one of the strongest factors that correlate with AMI incidence, beyond REI, 3% ODI, and other hypoxemic measures. Similarly, we reported that minSpO_2 $\leq$ 80% could impose a two- to threefold higher odds on the development of left ventricular hypertrophy than those with minSpO_2 $\geq$ 90% in patients with coronary artery disease (10). These indicated that minSpO_2, representing the most severe dip of oxygen saturation, is likely to cause dysfunctional cardiac variability that may predispose patients to CV events. A previous large-scale longitudinal study showed that the minSpO_2 $\leq$ 78%, was independently associated with an increased risk of sudden cardiac death (9), suggesting that nadir oxygen desaturation is an essential element precipitating lethal ventricular arrhythmias. In this regard, characterizing minSpO_2-specific HR changes is an essential avenue to allow more target approaches to preventing CV events.

Triggering Effect of Periodic Respiratory Event-Specific Heart Rate Response and Variability

An increased sympathetic tone in OSA has been reported to be mostly responsible for the high prevalence of AMI (23) and CV events (1). To detect the rhythmic oscillation in OSA, previous studies used direct recordings of sympathetic fibers by invasive microneurographic techniques and an analysis of HRV (24, 25). Generally, HRV is derived from mathematical analyses of intervals between normal heartbeats, but a few limitations have been observed. The frequency domain analysis of HRV usually requires patients to be stationary and is limited to a fixed cut-point on the overnight graphical tracing of sleep (25). Such an HR measurement approach may be problematic since most OSA patients may not have significant event-free periods during sleep. OSA-induced necessary modifications of breathing patterns may also affect the HR oscillation and could not be distinguished by the HRV analysis (26). Similarly, Shimizu et al. developed a cyclic variation of HR score determined by Holter ECG and concluded that it was a useful screening tool for severe sleep-disordered breathing among patients with heart failure (13). However, the parameters used in that study did not consider the nadir hypoxic effect as minSpO_2-specific HR metrics did (13). Also, minSpO_2-specific HR reactions (either maximal, mean, or minimal HR), partly attributed to arousals from sleep (27–29), may reflect the substantive CV reactions to the extreme hypoxic effect.

The non-respiratory event–associated LF/HF in HRV analysis was slightly greater in patients with AMI as well as severe OSA, and as the ratio increased, the AMI risk increased by nearly 36%. This probably supported the link between enhanced sympathetic activity and AMI. In general, standard frequency-oriented OSA measures may serve as the substrate for CV morbidity, while the "hypoxic–sympathetic storm" is more likely to be a critical trigger of CV events. Also, we observed the protective role of a greater TP of spectral bands specific to respiratory events (namely, the square sum of cardiac cycle variations) in AMI risk. In other words, if hypoxemia is accompanied by restricted cardiac cycle shifting or mild HR swing amplitude, it might diminish coronary blood flow and precede individuals to myocardial infarction.

Proposed Mechanisms Linking Heart Rate Response, Variability, and Acute Myocardial Infarction Risk

The proposed mechanisms linking the minSpO_2 and specific HR response to it are explained separately for chronic and acute effects on the onset of AMI. Some reports show that OSA exhibits a peak with respect to the onset of CV diseases during sleeping to morning hours (30, 31). Presumably, traditional OSA parameters such as REI, 3% ODI, or hypoxemic duration may exert basal chronic pathophysiologic effects on the long-term development of CV damage. At the same time, the dramatic acute HR surge in response to minSpO_2 may be an acute trigger factor for AMI. In specific, regarding the chronic effects, long-term intermittent hypoxia and reoxygenation were shown to increase the myocardial infarct size (32). This hypoxemic mechanism is also thought to generate cardiac hyper-excitability by altering sympathovagal balance reflected by cyclical variations in HR (13), and as indicated by an increased basal LF/HF in patients with severe OSA and AMI. In terms of the acute impact, the rapid HR reactions may be associated with accelerated atherogenesis of the coronary artery initiated by endothelial dysfunction through mechanical and metabolic factors (33). If HR reacts dramatically to minSpO_2, there would be an augmented myocardial demand for oxygen and impaired

coronary perfusion due to a shorter diastolic filling duration. The myocardial ischemia will occur, and the infarct size will likely be expanded if accompanied by a high coronary plaque burden (34, 35). A high HR response *per se* has also been associated with coronary plaque disruption (36), rendering patients at a higher risk of suffering from acute AMI.

Practical Significance

The present study's findings may suggest the potential association between minSpO_2-elicited severe HR reactions, variability, and AMI risk in a large population with suspected OSA. This implied that abnormal cardiopulmonary interaction or sympathetic activation might play a potential role in AMI occurrence. The advantages of detecting such biological signals lie in their simplicity of operation, economic cost, non-invasiveness, remote accessibility, and portability. In clinical practice, apart from early recognition of OSA, additional investigation of nocturnal oxygen desaturation, especially minSpO_2 and HR response may discriminate the vulnerable phenotypes of patients at higher risk of AMI. However, these assumptions need to be further examined by future large-scale studies.

Study Strengths and Limitations

Our study's main strengths include first, a large sample size; and second, multi-dimensional analyses of cardiorespiratory measures. Most importantly, we conducted a compressive assessment of the HR metrics associated with minSpO_2, which has not been widely examined in previous literature. Nevertheless, this study has limitations. First, OSA was detected by portable cardiorespiratory monitoring rather than attended polysomnography (PSG). However, the cost-effective and user-friendly portable device has similar accuracy for OSA assessment compared with PSG (37). It also permits a more stable and actual assessment of the disease status because the first night effects could be largely reduced as fewer connecting devices are required. Second, multivariate models may not grant the complete elimination of the confounding factors for AMI. However, common risk factors for AMI such as dyslipidemia, diabetes mellitus, and hypertension were included in the multivariate models while avoiding overadjustment from other highly collinear variables. Finally, the nature of observational, cross-sectional research would not allow us to determine causality between HR metrics and AMI, which requires future prospective cohort studies.

CONCLUSION

In conclusion, increased HR reactions to OSA-induced minSpO_2 and several HRV indices were independently associated with a higher likelihood of AMI. Detection of nocturnal oxygen saturation and autonomic response to nadir hypoxemia may help improve CV risk stratification. Prospective large-scale randomized studies are warranted to evaluate the prognostic significance of OSA-specific HR metrics on CV outcomes across populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Clinical Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2018567). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZH contributed to the study design, data analysis, data interpretation, and manuscript drafting. YW, KH, and PC contributed to the data acquisition, analysis, and interpretation. JC and LW were responsible for the study design, analysis, interpretation of the data, and critical revision of the manuscript. All authors contributed substantially to the work and agreed to submit the manuscript for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.807436/full#supplementary-material

REFERENCES

1. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet.* (2005) 365:1046–53. doi: 10.1016/s0140-6736(05)71141-7
2. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med.* (2015) 3:310–8. doi: 10.1016/s2213-2600(15)00043-0
3. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J.* (2016) 37:3232–45. doi: 10.1093/eurheartj/ehw334
4. Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. *Eur Respir J.* (2006) 28:596–602. doi: 10.1183/09031936.06.00107805
5. Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. *Sleep Breath.* (2010) 14:131–6. doi: 10.1007/s11325-009-0298-7
6. Ánchez-de-la-Torre MS, Ánchez-de-la-Torre AS, Bertran S, Abad J, Duran-Cantolla J, Cabriada V, et al. Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med.* (2020) 8:359–67. doi: 10.1016/s2213-2600(19)30271-1
7. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med.* (2016) 375:919–31. doi: 10.1056/NEJMoa1606599
8. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med.* (2016) 194:613–20. doi: 10.1164/rccm.201601-0088OC
9. Gami AS, Olson EJ, Shen WK, Wright RS, Ballman KV, Hodge DO, et al. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. *J Am Coll Cardiol.* (2013) 62:610–6. doi: 10.1016/j.jacc.2013.04.080
10. Huang Z, Wang L, Liu Y, Huang K, Xu Y, Chen P, et al. Impact of obstructive sleep apnea on left ventricular mass index in men with coronary artery disease. *J Clin Sleep Med.* (2020) 16:1675–82. doi: 10.5664/jcsm.8642
11. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. *Chest.* (2015) 147:266–74. doi: 10.1378/chest.14-0500
12. Tverdal A, Hjellvik V, Selmer R. Heart rate and mortality from cardiovascular causes: a 12 year follow-up study of 379,843 men and women aged 40-45 years. *Eur Heart J.* (2008) 29:2772–81. doi: 10.1093/eurheartj/ehn435
13. Shimizu T, Yoshihisa A, Iwaya S, Abe S, Sato T, Suzuki S, et al. . Cyclic variation in heart rate score by holter electrocardiogram as screening for sleep-disordered breathing in subjects with heart failure. *Respir Care.* (2015) 60:72–80. doi: 10.4187/respcare.03341
14. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep apnea. Types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol.* (2017) 69:841–58. doi: 10.1016/j.jacc.2016.11.069
15. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Circulation.* (2012) 126:2020–35. doi: 10.1161/CIR.0b013e31826e1058
16. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American academy of sleep medicine. *J Clin Sleep Med.* (2012) 8:597–619. doi: 10.5664/jcsm.2172
17. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the osteoporotic fractures in men study and the sleep heart health study. *Eur Heart J.* (2019) 40:1149–57. doi: 10.1093/eurheartj/ehy624
18. Huang Z, Wang L, Liu Y, Li G, Chen J. Obstructive sleep apnea in coronary artery disease: the role of nocturnal hypoxic burden. *J Clin Sleep Med.* (2020) 17:359–60. doi: 10.5664/jcsm.9042
19. Cowie MR. Sleep-disordered breathing: how should we judge its severity? *Eur Heart J.* (2016) 37:1704–6. doi: 10.1093/eurheartj/ehv691
20. Oldenburg O, Wellmann B, Buchholz A, Bitter T, Fox H, Thiem U, et al. Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. *Eur Heart J.* (2016) 37:1695–703. doi: 10.1093/eurheartj/ehv624
21. Sankari A, Ravelo LA, Maresh S, Aljundi N, Alsabri B, Fawaz S, et al. Longitudinal effect of nocturnal R-R intervals changes on cardiovascular outcome in a community-based cohort. *BMJ Open.* (2019) 9:e030559. doi: 10.1136/bmjopen-2019-030559
22. Azarbarzin A, Sands SA, Taranto-Montemurro L, Vena D, Sofer T, Kim SW, et al. The sleep apnea-specific hypoxic burden predicts incident heart failure. *Chest.* (2020) 158:739–50. doi: 10.1016/j.chest.2020.03.053
23. Albert CM, Mittleman MA, Chae CU, Lee IM, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med.* (2000) 343:1355–61. doi: 10.1056/nejm200011093431902
24. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med.* (1993) 328:303–7. doi: 10.1056/nejm199302043280502
25. Montano N, Porta A, Cogliati C, Costantino G, Tobaldini E, Casali KR, et al. Heart rate variability explored in the frequency domain: a tool to investigate the link between heart and behavior. *Neurosci Biobehav Rev.* (2009) 33:71–80. doi: 10.1016/j.neubiorev.2008.07.006
26. Wang W, Tretriluxana S, Redline S, Surovec S, Gottlieb DJ, Khoo MC. Association of cardiac autonomic function measures with severity of sleep-disordered breathing in a community-based sample. *J Sleep Res.* (2008) 17:251–62. doi: 10.1111/j.1365-2869.2008.00652.x
27. Azarbarzin A, Ostrowski M, Moussavi Z, Hanly P, Younes M. Contribution of arousal from sleep to postevent tachycardia in patients with obstructive sleep apnea. *Sleep.* (2013) 36:881–9. doi: 10.5665/sleep.2716
28. Lachapelle P, Cascon J, Pamidi S, Kimoff RJ. Accuracy of portable devices in sleep apnea using oximetry-derived heart rate increases as a surrogate arousal marker. *Sleep Breath.* (2019) 23:483–92. doi: 10.1007/s11325-018-1708-5
29. Gao X, Azarbarzin A, Keenan BT, Ostrowski M, Pack FM, Staley B, et al. Heritability of heart rate response to arousals in twins. *Sleep.* (2017) 40:zsx055. doi: 10.1093/sleep/zsx055
30. Nakashima H, Henmi T, Minami K, Uchida Y, Shiraishi Y, Nunohiro T, et al. Obstructive sleep apnoea increases the incidence of morning peak of onset in acute myocardial infarction. *Eur Heart J Acute Cardiovasc Care.* (2013) 2:153–8. doi: 10.1177/2048872613478557
31. Ishibashi Y, Osada N, Sekiduka H, Izumo M, Shimozato T, Hayashi A, et al. Peak time of acute coronary syndrome in patients with sleep disordered breathing. *J Cardiol.* (2009) 53:164–70. doi: 10.1016/j.jjcc.2008.09.014
32. Belaidi E, Joyeux-Faure M, Ribuot C, Launois SH, Levy P, Godin-Ribuot D. Major role for hypoxia inducible factor-1 and the endothelin system in promoting myocardial infarction and hypertension in an animal model of obstructive sleep apnea. *J Am Coll Cardiol.* (2009) 53:1309–17. doi: 10.1016/j.jacc.2008.12.050
33. Giannoglou GD, Chatzizisis YS, Zamboulis C, Parcharidis GE, Mikhailidis DP, Louridas GE. Elevated heart rate and atherosclerosis: an overview of the pathogenetic mechanisms. *Int J Cardiol.* (2008) 126:302–12. doi: 10.1016/j.ijcard.2007.08.077
34. Buchner S, Satzl A, Debl K, Hetzenecker A, Luchner A, Husser O, et al. Impact of sleep-disordered breathing on myocardial salvage and infarct size in patients with acute myocardial infarction. *Eur Heart J.* (2014) 35:192–9. doi: 10.1093/eurheartj/eht450
35. Kent BD, Garvey JF, Ryan S, Nolan G, Dodd JD, McNicholas WT. Severity of obstructive sleep apnoea predicts coronary artery plaque burden: a coronary computed tomographic angiography study. *Eur Respir J.* (2013) 42:1263–70. doi: 10.1183/09031936.00094812

36. Heidland UE, Strauer BE. Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. *Circulation.* (2001) 104:1477–82. doi: 10.1161/hc3801.096325
37. de Oliveira ACT, Martinez D, Vasconcelos LFT, Cadaval Gonçalves S, do Carmo M, Lenz S, et al. Diagnosis of obstructive sleep apnea syndrome and its outcomes with home portable monitoring. *Chest.* (2009) 135:330–6. doi: 10.1378/chest.08-1859

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Dynamics of Emergency Cardiovascular Hospital Admissions and In-Hospital Mortality During the COVID-19 Pandemic: Time Series Analysis and Impact of Socioeconomic Factors

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Aims: This study aimed to evaluate the decline in urgent cardiovascular hospital admissions and in-hospital mortality during the COVID pandemic in two successive waves, and to evaluate differences by sex, age, and deprivation index subgroups.

Methods and Results: We obtained acute cardiovascular hospital episodes during the years 2019–2020 from region-wide data on public healthcare usage for the population of Catalonia (North-East Spain). We fitted time models to estimate the incidence rate ratios (IRRs) of the acute coronary syndrome (ACS) and acute heart failure (HF) admissions during the first pandemic wave, the between-waves period, and the second wave compared with the corresponding pre-COVID-19 periods and to test for the interaction with sex, age, and area-based socioeconomic level. We evaluated the effect of COVID-19 period on in-hospital mortality. ACS (n = 8,636) and HF (n = 27,566) episodes were defined using primary diagnostic ICD-10 codes. ACS and HF admissions decreased during the first wave (IRR = 0.66, 95%CI: 0.58–0.76 and IRR = 0.61, 95% CI: 0.55–0.68, respectively) and during the second wave (IRR = 0.80, 95%CI: 0.72–0.88 and IRR = 0.76, 95%CI: 0.69–0.84, respectively); acute HF admissions also decreased in the

period between waves (IRR: 0.81, 95%CI: 0.74–0.89). The impact was similar in all sex and socioeconomic subgroups and was higher in older patients with ACS. In-hospital mortality was higher than expected only during the first wave.

Conclusion: During the first wave of the COVID-19 pandemic, there was a marked decline in urgent cardiovascular hospital admissions that were attenuated during the second wave. Both the decline and the attenuation of the effect have been similar in all subgroups regardless of age, sex, or socioeconomic status. In-hospital mortality for ACS and HF episodes increased during the first wave, but not during the second wave.

Keywords: COVID-19, acute coronary syndrome, myocardial infarction, heart failure, time-series

INTRODUCTION

During the first pandemic wave (FW) of coronavirus disease 2019 (COVID-19) between March and April 2020, there was a marked decline in admissions for acute coronary syndrome (ACS) (1–11), heart failure (HF) (12–14), and other non-COVID health conditions (15–17).

While prioritization of healthcare services explains decreases in elective admissions, explanations for the decrease in the attention of emergent conditions remain conjectural (18). Possible reasons attributed to the steep decrease in hospital admissions for acute cardiovascular problems were patients' hesitation to refer to the hospital, missed diagnosis, and competing risk with COVID-19 mortality in the elderly and institutionalized patients (19). The analysis of differing trends of emergent cardiovascular admissions in successive waves periods and in the between-waves periods (BWP) might be useful to unravel the underlying mechanisms and to anticipate future trends. A few reports of results during the second pandemic wave (SW, between April and September 2020) indicate a second decline of unknown magnitude (20) despite information campaigns targeted at the affected populations.

Moreover, the COVID-19 pandemic has been shown to increase geographic, gender, and socioeconomic inequalities in access to healthcare (21). Age, gender, and deprivation level might influence behaviors in such ways that would imply a greater impact on more disadvantaged groups. Gender and age differences in admissions for acute myocardial infarction (MI) have been analyzed previously with differing results (22); but to the best of our knowledge, it has not been assessed in longer series (beyond the FW) considering socioeconomic indices. The potential influence of gender, age, and socioeconomic differences on the dynamic of admissions for acute HF decompensations has not been assessed so far.

Therefore, we aimed to evaluate the variations in ACS and acute HF hospital admissions during the COVID-19 pandemic period, including the FW and the SW, in comparison with the hospital admissions of the corresponding pre-COVID-19 pandemic periods. In addition, we aimed to assess whether age, gender, and socioeconomic status might have influenced these variations. Finally, we analyzed the predictors of in-hospital death.

MATERIALS AND METHODS

Population and Data Sources

We used region-wide data on public healthcare usage for the population of Catalonia, a North-East region in Spain with universal public healthcare coverage, with a reference population of more than 7 M and a hospital network of 11 reference tertiary hospitals performing percutaneous coronary intervention (PCI). Data were accessed through the Public Data Analysis for Health Research and Innovation Program (PADRIS). PADRIS allows access to information from different sources linked at the patient level with warranted accomplishment of ethical principles and the Spanish Law of data protection 3/2018.

Acute coronary syndrome and HF episodes from 31 December 2018 to 27 December 2020 were extracted from the Minimum Basic Data Set (MBD). Index admissions were identified with the International Classification of Diseases (ICD)-10 as the primary diagnostic (see diagnostic codes in **Supplementary Table 1**). We selected only emergency admissions.

Weekly COVID-19 cases were obtained from the Open Access Data Portal of the Catalan Government. Confirmed cases were defined as having a positive RT-PCR test or rapid antigen test for SARS-CoV-2.

For each episode, we extracted sex, age in 5 years' intervals, all diagnostic and procedure ICD-10 codes, region of residence, primary care service areas (PCSA), comorbidity status (AMG), and PCSA-based socioeconomic status (PCSA index).

Primary Care Service Areas Index

To strengthen territorial equity in the allocation of primary care resources, in 2015, the Catalan Health Department developed a socioeconomic deprivation indicator representative of the PCSA linked to adverse health outcomes. The indicator score ranges from 0 (less deprived) to 100 (more deprived) (23).

Comorbidity

The comorbidity index [Adjusted Morbidity Groups (AMGs)] score is a morbidity measure that enables assigning a weight based on the preexisting comorbidities (24). AMG explanatory value has been checked by comparing it with morbidity

measures such as the Charlson Index or the number of chronic diseases (24).

Statistical Analysis

Based on the visual representation of the weekly number of COVID-19 diagnostics, we defined the following periods of analysis: pre-COVID (from 31 December 2018 to 23 February 2020), FW (from 24 February 2020 to 27 April 2020), BWP (from 28 April 2020 to 20 September 2020), and SW (from 21 September 2020 to 27 December 2020). We considered the beginning of the FW as the date when the first case in the region was reported in the press (24 February 2020), although the COVID registry started later.

Patients' characteristics were compared between each COVID period and the corresponding pre-COVID period (same calendar period in 2019). Continuous variables were reported as mean (SD) or median (P25 to P75) and compared using Student's *t*-tests or Kruskal-Wallis tests. Categorical variables were reported as *n* (percentage) and compared using χ^2 tests.

Weekly admissions for ACS and HF were depicted from 31 December 2018 to 27 December 2020. Negative binomial regression was used to estimate the incidence rate ratios (IRRs) and their 95% confidence intervals for ACS and acute HF hospital admissions during the COVID-19 FW, during the BWP, and during the SW compared with the expected admissions, based on the pre-COVID-19 period. Using this approach, each IRR represents the ratio between the weekly number of admissions in each period and the weekly number of admissions in the reference period. First, we modeled the pre-COVID-19 time series to estimate the expected number of admissions in the COVID-19 periods by fitting sinusoidal functions to control seasonality and autocorrelation. Best-fitted models were selected on the basis of minimizing deviance of the model and then fitted to the whole series including COVID waves as indicators to calculate IRR. To show graphically the variations in ACS and HF hospital admissions attributable to the pandemic phases, we depicted the observed vs. the expected admissions estimated from the pre-COVID-19 model.

Finally, we fitted an additional set of models using fractional polynomial coefficients to parameterize in a flexible way the different descending and ascending slopes observed during the pandemic period. We used the parameters of the fitted models to estimate the instantaneous rate of change in the different periods and the absolute decrease in each wave.

Different effects of COVID periods [FW, BWP, and SW among sex, age ($<80/\geq80$), and PCSA index quartiles (first quartile/fourth quartile)] were estimated by including two-way interaction terms in regression models.

To assess whether changes in hospital mortality during the COVID-19 period were due to the distortion in healthcare during the pandemic or to changes in the risk profile of patients, we performed logistic mixed-effects regression with in-hospital mortality as the response variable and the pandemic periods together as a covariable. We adjusted the model by patients' characteristics [e.g., sex, age, comorbidity weight, type of ACS (in ACS model), PCSA index quartiles]. We used random slope models and non-structured covariance matrix for random effects to account for repeated episodes of individual patients and for the clustered structure of patients living in different PCSA (371 PCSA). All analyses were performed with R version 4.1.0.

RESULTS

After excluding elective admissions and patients younger than 20 years old, we analyzed a series of 36,202 episodes (corresponding to 34,575 patients) admitted for ACS (n = 8,424) or HF (26,151) between 31 December 2018 and 27 December 2020 (**Figure 1**).

Tables 1, **2** show the characteristics of patients attended for ACS and HF during each predefined COVID-19 period as compared with each corresponding pre-COVID-19 period: FW, BWP, and SW. The decline in admissions for every subgroup is presented as a% change. The description of the complete cohort is shown in **Supplementary Table 2**.

In general, patients admitted during the pandemic period had less comorbidities, as reflected by a consistently lower AMG score compared with the pre-COVID periods. In addition, in both conditions, the total hospital length of stay was significantly lower. Regarding ACS admissions (**Table 1**), the decline was significantly higher for patients aged 80 years or older admitted during the SW. Diagnostic episodes labeled as other AMI or other ACS increased in the whole COVID-19 period. As compared with the pre-COVID-19 period, the number of PCI remained virtually the same during the FW but decreased slightly during the BWP (−23%; p = 0.001) and during the SW (−32%; p = 0.01). In-hospital mortality increased during the FW [8.86% vs. 5.51% in the pre-COVID-19 period (p = 0.018)], and there were no statistically significant differences neither during the SW nor in the BWP.

Regarding acute HF admissions (**Table 2**), the proportion of older people admitted during the BWP was significantly lower, and in-hospital mortality was higher during the FW (7.41 vs. 9.26%; p = 0.022) but lower during the BWP (7.46 vs. 6.38%; p = 0.039) and during the SW (7.63% vs. 5.94%; p = 0.007).

Figure 2 shows the time series of ACS (**Figure 2A**) and HF (**Figure 2B**) weekly urgent hospital admissions and the distortion observed after the arrival of the pandemic wave. Both ACS and HF admissions series showed a significant seasonality, with lower admissions in summer weeks. After adjusting for seasonality and autocorrelation, there was a marked decrease in ACS episodes (**Supplementary Figure 1A**), reaching a maximum of 69.46% cases below the expected [IRR 0.43 (0.37–0.50), $p < 0.001$] coinciding with the highest peak of the FW. Then, after a recovery in the BWP, the number of admissions decreased again in a smoother way. Admissions for HF (**Supplementary Figure 1B**) also decreased steeply to a 72.83% less than expected [IRR 0.21 (0.17–0.26), $p < 0.001$] coinciding with the peak of the FW and then returned to normal levels to immediately decrease again to a sustained level about 30% below the expected.

The model parameters used to estimate IRRs and changes in the weekly number of admissions are shown in **Supplementary**

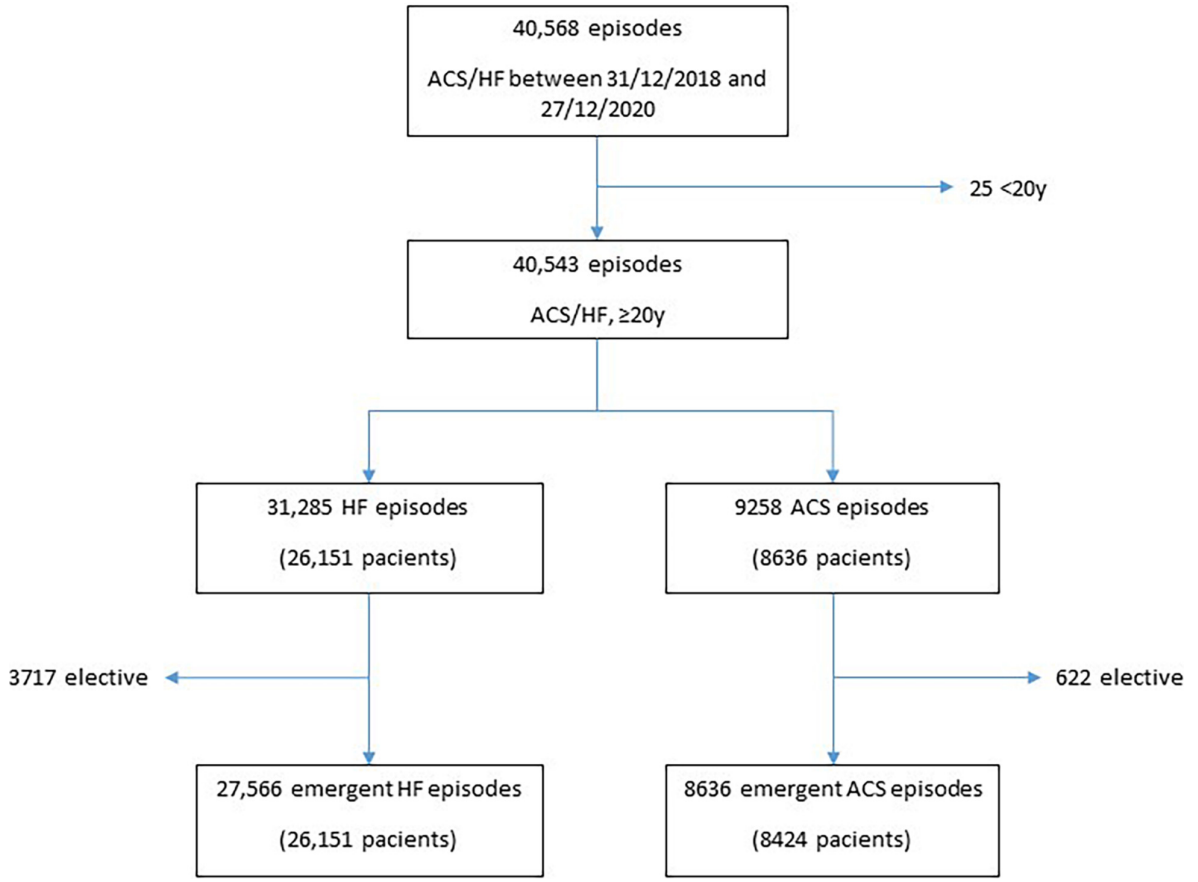

FIGURE 1 | Flowchart.

Tables 3–6. The IRRs of ACS admissions for the FW, the BWP, and the SW were 0.66 (0.58–0.76), 0.92 (0.84–1.00), and 0.80 (0.72–0.88), respectively. The IRRs of HF admissions for the FW, the BWP, and the SW were 0.61 (0.55–0.68), 0.81 (0.74–0.89), and 0.76 (0.69–0.84), respectively. **Supplementary Figures 2**, **3** show the results of the models with fractional polynomic coefficients for ACS and HF.

Supplementary Figures 4–15 show the separate time series according to gender, age, and area-level deprivation index. For the IRRs of ACS admissions, there was a significant interaction with age in the BWP and in the SW (**Figure 3**), when the relative reduction in the weekly number of admissions was higher for older people. Despite an apparent recovery in the admissions for ACS in the BWP [IRR 0.92 (0.84–1.00)], ACS admissions remained lower than expected among women, older, and in most deprived areas. Regarding HF, there was a significant decline of a similar magnitude in all subgroups (**Figure 4**), and HF admissions remained significantly lower than expected during the whole pandemic period.

Table 3 shows the association between the COVID-19 epidemic periods and in-hospital mortality adjusted for patient demographics, AMG score, type of ACS, and PCSA index. Mortality risk, compared with the corresponding pre-COVID-19 periods, was higher during the FW for both ACS (OR: 2.29; 95%CI: 1.6–3.27; $p < 0.001$) and HF episodes (OR: 1.33; 95% CI: 1.11–1.59; $p = 0.002$). In addition, ACS episodes labeled as other MI had the highest mortality risk (8.9; 95% CI 5.44–14.58; $p < 0.001$) as well as those episodes with a concomitant or recent diagnosis of coronavirus infection (OR: 4.1; 95% CI: 1.78–9.44; $p = 0.001$ and OR: 1.87; 95% CI: 1.22–2.86; $p = 0.004$ for ACS and HF, respectively).

DISCUSSION

This population-based time-trends analysis shows an important decrease in the number of emergent admissions for ACS and HF during the FW and during the SW compared with the corresponding pre-COVID-19 periods. This decrease was also present during the BWP, and it was similar among socioeconomic subgroups. However, there were less patients aged 80 years or older admitted for ACS during the BWP and the SW. Adjusted in-hospital mortality risk compared with the corresponding pre-COVID-19 periods was higher during the FW for both ACS and HF episodes despite a lower comorbidity weight and a similar rate of PCI.

Although the decrease in cardiovascular admissions was consistent during all the study periods, the impact of the SW

TABLE 1 | Characteristics of patients admitted to hospital for acute coronary syndrome (ACS) in each period compared with the reference pre-COVID-19 period.

	First wave period (24/02 to 27/04)				Between waves period (28/04 to 20/09)				Second wave period (21/09 to 27/12)			
	Pre-COVID-19	**COVID-19**	**% change**	***P*-value**	**Pre-COVID-19**	**COVID-19**	**% change**	***P*-value**	**Pre-COVID-19**	**COVID-19**	**% change**	***P*-value**
N	817	519	−36		1788	1308	−12		1308	1001	−23	
Women	250 (30.60)	171 (32.95)	−32	0.368	617 (34.51)	505 (32.21)	−18	0.159	449 (34.33)	331 (33.07)	−26	0.526
Men	567 (69.40)	348 (67.05)	−39		1171 (65.49)	1063 (67.79)	−9		859 (65.67)	670 (66.93)	−22	
Age				0.638				0.352				0.001
< 80	579 (70.87)	374 (72.06)	−35		1288 (72.04)	1152 (73.47)	−11		883 (67.51)	738 (73.73)	−16	
≥ 80	238 (29.13)	145 (27.94)	−39		500 (27.96)	416 (26.53)	−17		425 (32.49)	263 (26.27)	−38	
Type of ACS				< 0.001				< 0.001				< 0.001
Unstable angina	143 (17.50)	84 (16.18)	−41		272 (15.21)	274 (17.47)	1		167 (12.77)	167 (16.68)	0	
NSTEMI	560 (68.54)	325 (62.62)	−42		1249 (69.58)	997 (63.58)	−20		944 (72.17)	671 (67.03)	−29	
STEMI	97 (11.87)	57 (10.98)	−41		228 (12.75)	95 (6.06)	−58		173 (13.23)	63 (6.29)	−64	
Other MI	8 (0.98)	43 (8.29)	438		14 (0.78)	161 (10.27)	1050		10 (0.76)	75 (7.49)	650	
Other ACS	9 (1.10)	10 (1.93)	11		25 (1.4)	41 (2.61)	64		14 (1.07)	25 (2.50)	79	
AMG weight, mean (SD)	32.92 (17.46)	20.44 (16.29)	−38	<0.001	31.82 (16.47)	18.61 (14.44)	−41	<0.001	31.19 (16.27)	17.16 (13.85)	−45	<0.001
PCSA index, mean (SD)	42.11 (15.27)	42.68 (15.00)	1	0.514	42.20 (14.62)	41.24 (15.10)	−2	0.064	41.79 (14.56)	42.05 (14.56)	1	0.680
Quantiles of PCSA index				0.084				0.799				0.414
1st	202 (24.72)	116 (22.35)	−43		422 (23.60)	394 (25.13)	−7		324 (24.77)	221 (22.08)	−32	
2nd	188 (23.01)	113 (21.77)	−40		428 (23.94)	376 (23.98)	−12		306 (23.39)	262 (26.17)	−14	
3rd	187 (22.89)	139 (26.78)	−26		432 (24.16)	370 (23.60)	−14		305 (23.32)	236 (23.58)	−23	
4th	215 (26.32)	145 (27.94)	−33		472 (26.40)	389 (24.80)	−18		335 (25.61)	249 (24.88)	−26	
PCI during hospitalization	353 (43.21)	242 (46.63)	−31	0.220	826 (46.20)	633 (40.37)	−23	0.001	619 (47.32)	420 (41.96)	−32	0.010
In−hospital mortality	45 (5.51)	46 (8.86)	2	0.018	69 (3.86)	73 (4.66)	6	0.253	60 (4.59)	48 (4.80)	−20	0.814
Hospital length of stay (days), mean (SD); median (p25 to p75)	9.41 (8.03); 7 (5 to 11)	7.11 (6.34); 5 (3 to 9)	−24	<0.001	8.88 (7.71); 7 (4 to 11)	8.29 (7.21); 6 (4 to 10)	−7	<0.001	9.47 (9.63); 7 (4 to 11)	8.03 (6.97); 6 (4 to 10)	−15	<0.001

Numbers indicate n (%) except if otherwise stated.

TABLE 2 | Characteristics of patients admitted to hospital for acute heart failure (HF) in each period compared with the reference pre-COVID-19 period.

	First wave period (24/02 to 27/04)				Between waves period (28/04 to 20/09)				Second wave period (21/09 to 27/112)			
	Pre-COVID-19	**COVID-19**	**% change**	***P*-value**	**Pre-COVID-19**	**COVID-19**	**% change**	***P*-value**	**Pre-COVID-19**	**COVID-19**	**% change**	***P*-value**
N	3,200	1,749	−45		5,641	4,026	−29		4,090	2795	−32	
Women	1,741 (54.41)	946 (54.09)	−46	0.830	3130 (55.49)	2,200 (54.16)	−30	0.195	2,315 (56.60)	1,525 (54.56)	−34	0.094
Men	1,459 (45.59)	803 (45.91)	−45		2,511 (44.51)	1,862 (45.84)	−26		1,775 (43.40)	1,270 (45.44)	−28	
Age				0.107				0.001				0.061
<80	1,246 (38.94)	722 (41.28)	−42		2,106 (37.33)	1,651 (40.65)	−22		1,517 (37.09)	1,099 (39.32)	−28	
≥80	1,954 (61.06)	1,027 (58.72)	−47		3,535 (62.67)	2,411 (59.35)	−32		2,573 (62.91)	1,696 (60.68)	−34	
AMGweight, mean (SD)	48.33 (15.39)	33.86 (18.22)	−30	<0.001	48.74 (15.86)	31.18 (17.69)	−36	<0.001	46.40 (15.73)	28.08 (15.59)	−39	<0.001
PCSA index, mean (SD)	41.03 (15.08)	41.76 (14.66)	2	0.108	40.76 (15.27)	41.73(15.15)	2	0.002	40.73 (15.33)	40.96 (14.99)	1	0.556
Quantiles of PCSA index				0.166				0.110				0.751
1st	836 (26.13)	426 (24.36)	−49		1,534 (27.19)	1,008 (24.82)	−34		1,137 (27.80)	754 (26.98)	−34	
2nd	790 (24.69)	408 (23.33)	−48		1349 (23.91)	989 (24.35)	−27		995 (24.33)	681 (24.36)	−32	
3rd	681 (21.28)	419 (23.96)	−38		1,220 (21.63)	929 (22.87)	−24		861 (21.05)	573 (20.50)	−33	
4th	790 (24.69)	445 (25.44)	−44		1,370 (24.29)	1,006 (24.77)	−27		986 (24.11)	712 (25.47)	−28	
In−hospital mortality	237 (7.41)	162 (9.26)	−32	0.022	421 (7.46)	259 (6.38)	−38	0.039	312 (7.63)	166 (5.94)	−47	0.007
Hospital length of stay (days), mean (SD); median (p25 to p75)	10.33 (10.04); 8 (4 to 13)	8.64 (7.32); 7 (4 to 11)	−16	<0.001	9.59 (8.66); 7 (4 to 12)	8.98 (7.75); 7 (4 to 11)	−6	0.017	9.77 (9.34); 7 (4 to 12)	8.47 (7.13); 6 (3 to 11)	−13	<0.001

Numbers indicate n (%) except if otherwise stated.

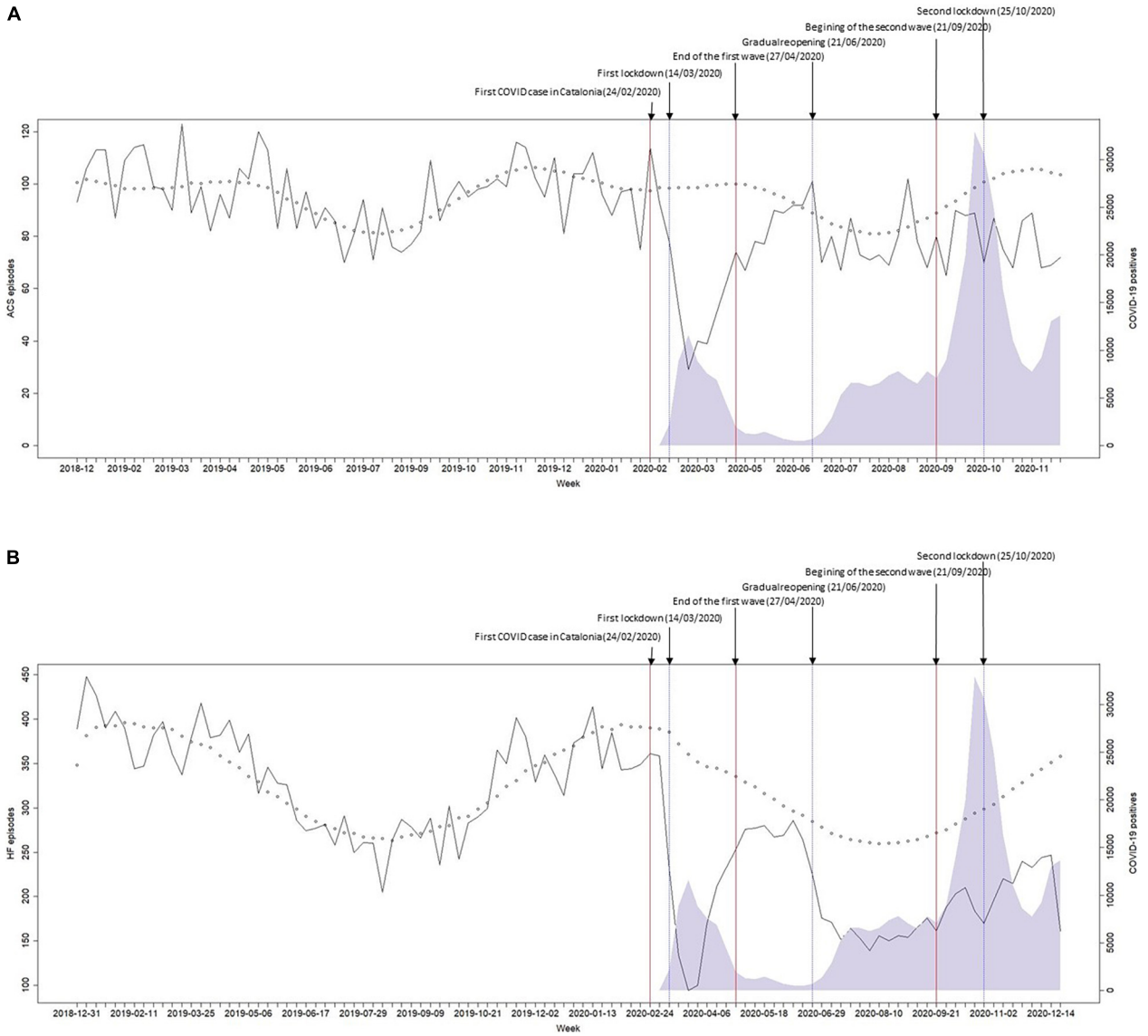

FIGURE 2 | Weekly number of hospital admissions for **(A)** acute coronary syndrome and **(B)** heart failure, between 31 December 2018 and 27 December 2020. Black line: observed hospital admissions; shaded area: number of COVID-19 cases; red lines: predefined period limits: pre-pandemic, first wave, period between waves, and second wave; small circles: negative binomial model estimated values (pre-COVID-19).

was clearly different from the impact of the FW. The impact of the SW was quite attenuated, probably due to the rapid reaction of hospitals to increase their intensive care capacity and to the information campaigns launched to raise awareness of the need to contact the emergency services when experiencing symptoms compatible with MI.

There were also remarkable differences between ACS episodes and acute HF episodes. While the number of ACS admissions gradually returned to the expected levels in the BWP, admissions for acute HF remained low for almost the whole observed pandemic period studied. Whether the number of admissions has recovered to usual values or has decreased again to similar levels in the successive waves needs to be further addressed. Besides patients' hesitation to go to the hospital, this sustained decrease might be related in part to the fact that HF symptoms are closer to COVID-19 symptoms. Since the primary focus of health professionals has been a rapid COVID-19 diagnosis, it might have led to underdiagnoses of HF cases. In addition, acute HF hospitalizations might have been lower because patients were preferably attended to in the primary care setting or due to the increased use of telemedicine, which is less practicable in the setting of the acute ischemic heart disease.

It has been speculated that lifestyle changes occurring during the lockdown periods might have influenced acute coronary disease incidence (25). However, the observations, as in other contexts (8), that the decline in admissions preceded the

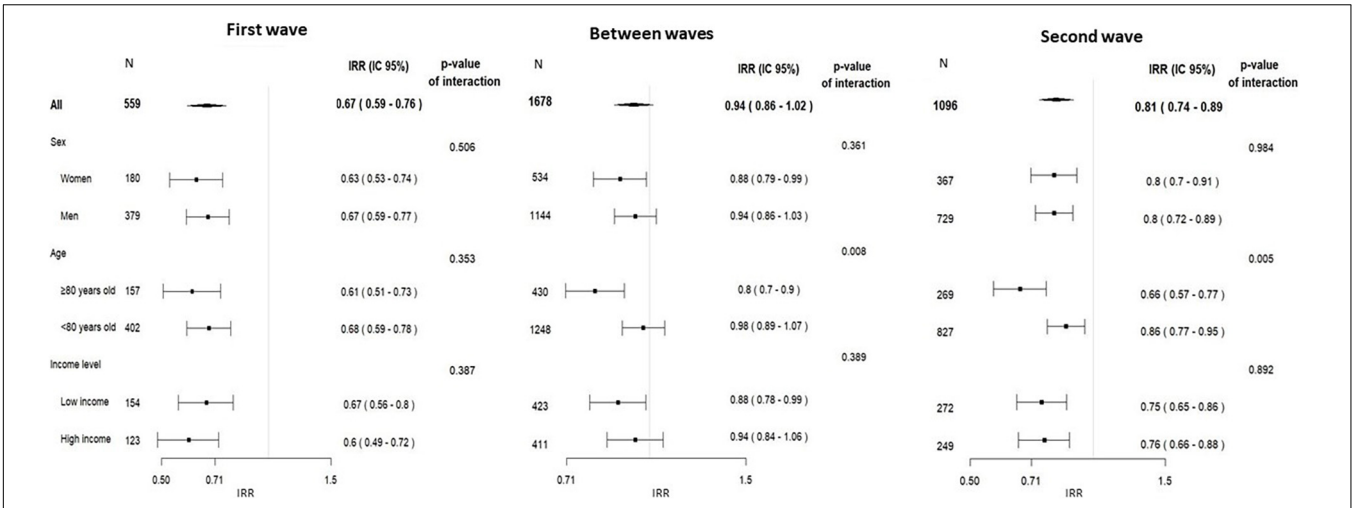

FIGURE 3 | Incidence rate ratios of acute coronary syndrome admissions, in the three predefined pandemic period vs. the corresponding pre-pandemic period (2019) by subgroups of socioeconomic factors, and the *p*-value for the interaction between period and each socioeconomic factor.

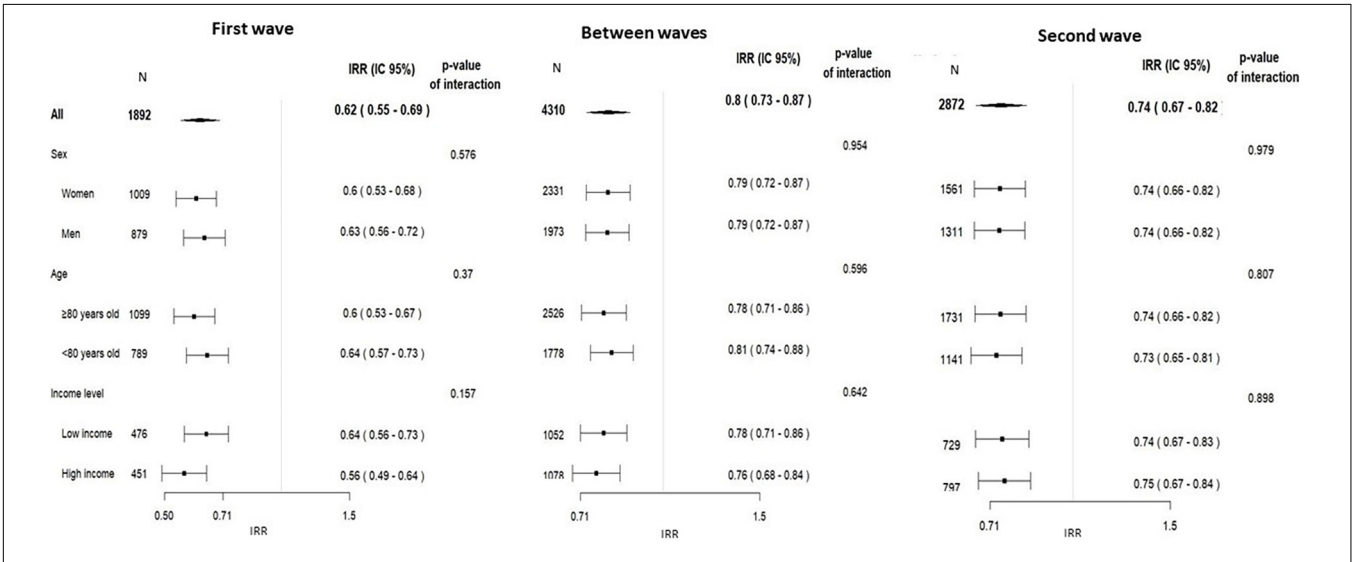

FIGURE 4 | Incidence rate ratios of acute heart failure admissions, in the three predefined pandemic period vs. the corresponding pre-pandemic period (2019) by subgroups of socioeconomic factors, and the *p*-value for the interaction between period and each socioeconomic factor.

lockdown and that the return to "normal" levels preceded the reopening suggest that environmental changes, decreased physical activity, or diminished stress are unlikely to be major contributors to these trends.

Some changes in the characteristics of patients attended to during the successive COVID-19 periods compared with the corresponding pre-COVID-19 periods might give some hints for the interpretation of trends. Overall, patients admitted during the COVID-19 period had much lower comorbidity weight assessed by AMG score. This suggests that those patients with more comorbidities and higher risk who had a cardiovascular event did not seek care or that the healthcare system collapsed at some point and could not hospitalize these more fragile patients. Another possibility is a certain degree of competitive risk between COVID-19 disease and cardiovascular events, which could result in a lower rate of cardiovascular events in the population with a higher rate of severe COVID-19 disease, which was precisely the elderly and the more fragile population, especially during the FW. The stronger decrease in admissions of patients aged 80 years or older in the BWP and during the SW supports the hypothesis of competitive risk with the high COVID-19-related mortality during the FW.

Another indirect finding that suggests the burden of the healthcare facilities during certain periods was the hospital length of stay. It declined steadily during the epidemic waves and, to a lesser extent, during the BWP. In the future, it will become clear whether this indicates a simple trend in a complex context or a

TABLE 3 | Association of patient characteristics and COVID-19 periods with in-hospital mortality for acute coronary syndrome (ACS) and heart failure (HF).

	ACS valid (*n** = 8,622)		HF valid (*n*** = 27,531)	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Women	0.93 (0.75 to 1.15)	0.487	0.86 (0.78 to 0.95)	0.002
Age (for 5 years increase)	1.44 (1.36 to 1.52)	<0.001	1.30 (1.26 to 1.34)	<0.001
AMG weight	1.02 (1.01 to 1.02)	<0.001	1.01 (1.00 to 1.01)	<0.001
Type of ACS				
Unstable angina (ref)	1		-	
Other ACS	2.81 (1.32 to 5.99)	0.007		
NSTEMI	2.22 (1.51 to 3.26)	<0.001	-	
STEMI	6.13 (4.03 to 9.35)	<0.001	-	
Other MI	8.67 (5.32 to 14.13)	<0.001	-	
Quartiles of PCSA index				
1st	1		1	
2nd	1.00 (0.75 to 1.33)	0.993	1.05 (0.90 to 1.23)	0.501
3rd	1.19 (0.90 to 1.57)	0.223	1.10 (0.94 to 1.28)	0.245
4th	1.09 (0.83 to 1.44)	0.525	1.05 (0.90 to 1.22)	0.553
COVID19 period				
1st wave	2.14 (1.50 to 3.05)	<0.001	1.36 (1.14 to 1.62)	0.001
Between waves	1.20 (0.90 to 1.62)	0.217	0.94 (0.82 to 1.09)	0.432
2nd wave	1.37 (0.97 to 1.93)	0.072	0.86 (0.72 to 1.03)	0.094

**14 missing values for PCSA; **35 missing values for PCSA.*
ACS, acute coronary syndrome; HF, heart failure; OR, odds ratio; AMG, adjusted morbidity groups; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; MI, myocardial infarction; PCSA, primary care service areas.

real change in the efficiency of the health system for managing these cardiovascular events. In any case, it indicates the effort of the healthcare professionals to minimize the overload of the system and the awareness of the risk of infection during admission by professionals and by the patients and their families.

The increase in the number of diagnoses labeled as other ACS or other MI, present in only few cases, might be due to codification problems during the overwhelming working conditions of the professionals responsible for codification during the pandemic peaks. This fact prevents us to draw conclusions about the differential changes by type of ACS.

The analysis of mortality determinants reveals that, unlike the results observed in other series (26), there was a significantly increased risk of in-hospital mortality after ACS and acute HF episodes in the FW but not in the SW. The increase in mortality was independent of case mix and despite a lower comorbidity weight and a similar rate of PCI compared with the pre-COVID-19 period. This probably reflects, on the one hand, the delay in patients seeking care increasing symptoms-to-balloon time (2), together with a more important healthcare overload during the FW and, on the other hand, a certain learning curve effect that benefited the second and subsequent waves.

Our results are consistent with those observed in other contexts. The study by Bodilsen et al. (16), in Denmark, highlighted HF as one of the health conditions not returning to baseline levels, together with respiratory and nervous system diseases, cancer, acute exacerbations of chronic pulmonary disease, sepsis, and pneumonia.

Although female sex and older age have been linked to increased delay before seeking healthcare (27), the COVID-19 pandemic does not seem to have affected differently the pattern of admission for ACS and HF in male and female patients (**Figures 3**, **4**). This suggests that the potential different behavior of men and women for seeking care shown in other studies is attenuated in a context such as COVID-19 pandemic. However, we observed that the decline in hospital admissions was higher in older patients, but only after the FW. Huynh et al. (28) found a higher reduction of acute MI in women $\geq$70 years old during the COVID-19 pandemic in a Swedish healthcare region without lockdown.

To the best of our knowledge, this is the largest study showing the effects of the COVID-19 pandemic on acute cardiovascular disease admissions during a sufficiently large time window to include two successive waves. Previous reports have observed lower hospital admission rates for MI (5, 6, 11, 29, 30) and HF (13, 14, 31, 32) during the FW that are comparable with our study; however, reports of further declines in successive waves are scarce. In this sense, Wu et al. (20) reported a second decline of a similar magnitude (41% for HF and 34% for MI) during the SW in the United Kingdom.

Limitations

Despite the use of large region-wide administrative databases that offer clear advantages, disadvantages include the following: Lack of detail in clinical severity, comorbidities, out-of-hospital mortality and causes of mortality, lower data quality, and higher risk of misclassification. In the case of HF, it would have been informative to merge hospital admissions to primary care emergent admissions and telecare attentions. Adoption of telecare programs as a response to the pandemic might have influenced the rate of hospital admissions. Finally, we used related ICD-10 diagnostic codes to label cases with concomitant COVID-19, as we did not have access to data for laboratory-proven SARS-Cov-2 infection. However, the proportion of patients with a diagnosis of both cardiovascular disease and COVID-19 infection was low, and its impact on overall outcomes might not be very relevant. Finally, the depiction of the COVID wave does not correspond with the real cases, especially during the FW, when fewer RT-PCR tests or rapid antigen tests for SARS-CoV-2 were performed, and specific diagnostic codes for COVID-19 were not available.

CONCLUSION AND PRACTICAL IMPLICATIONS

The decline in hospital admissions for ACS and acute HF during the FW of the COVID-19 pandemic was marked and striking. We provide evidence that the decline was attenuated but still observed in the SW and that the impact has been similar in all age, sex, and socioeconomic subgroups in the

Catalan healthcare system. In addition, the adjusted in-hospital mortality risk comparing the corresponding pre-COVID-19 periods shows a clearly higher risk during the FW for both ACS and HF episodes but not during the SW, which indicates the difficulty of the healthcare system to adapt to new and stressful pandemic conditions.

The impact of COVID-19 in Spain was among the strongest reported worldwide, and its indirect impact on other non-COVID health conditions should be surveilled by health authorities. Numerous efforts have been made to forecast health resources needs for COVID-19 but not for other health problems that have been strongly impacted by the pandemic. Extending our temporal series to longer time frames, and including other contextual factors that might influence the rate of ACS or HF admissions, can serve to anticipate future distortions and prepare the health services to improve the attention of non-COVID health problems.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors upon request with the permission of AQuAS. Requests to access these datasets should be directed to https://aquas.gencat.cat/ca/ambits/analitica-dades/padris/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committee Vall d'Hebron. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AR, AA-S, and IF-G conceived the study. AR received funds for the study. AR, JM, RL, and CÁ-M obtained the data. AR, CÁ-M, JRM, and SP-H performed the data management and statistical analysis. AR and IF-G have drafted the manuscript. All authors participated in the study design, contributed to the interpretation of the results, revised it critically for important intellectual content, and gave the final approval.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.827212/full#supplementary-material

REFERENCES

1. Romaguera R, Ribera A, Güell-Viaplana F, Tomás-Querol C, Muñoz-Camacho JF, Agudelo V. Decrease in ST-segment elevation myocardial infarction admissions in Catalonia during the COVID-19 pandemic. *Rev Esp Cardiol.* (2020) 73:778–80. doi: 10.1016/j.rec.2020.06.001
2. Rodríguez-Leor O, Cid-Álvarez B, Pérez de Prado A, Rossello X, Ojeda S, Serrador A, et al. Impact of COVID-19 on ST-segment elevation myocardial infarction care. The Spanish experience. *Rev Esp Cardiol.* (2020) 73:994–1002.
3. Mesnier J, Cottin Y, Coste P, Ferrari E, Schiele F, Lemesle G, et al. Hospital admissions for acute myocardial infarction before and after lockdown according to regional prevalence of COVID-19 and patient profile in France: a registry study. *Lancet Public Health.* (2020) 5:536–42. doi: 10.1016/S2468-2667(20)30188-2
4. Tam CCF, Cheung KS, Lam S, Wong A, Yung A, Sze M, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment-elevation myocardial infarction care in Hong Kong, China. *Circ Cardiovasc Qual Outcomes.* (2020) 13:e006631. doi: 10.1161/CIRCOUTCOMES.120.006631
5. De Filippo O, D'Ascenzo F, Angelini F, Bocchino PP, Conrotto F, Saglietto A, et al. Reduced rate of hospital admissions for ACS during Covid-19 outbreak in Northern Italy. *N Engl J Med.* (2020) 383:88–9. doi: 10.1056/NEJMc2009166
6. Garcia S, Albaghdadi M, Meraj P, Schmidt C, Garberich R, Jaffer FA, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. *J Am Coll Cardiol.* (2020) 75:2871–2. doi: 10.1016/j.jacc.2020.04.011
7. Woolf SH, Chapman DA, Sabo RT, Weinberger DM, Hill L. Excess deaths from covid-19 and other causes, March-April 2020. *JAMA.* (2020) 324:510–3. doi: 10.1001/jama.2020.11787
8. Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet.* (2020) 396:381–9. doi: 10.1016/S0140-6736(20)31356-8
9. Gluckman TJ, Wilson MA, Chiu ST, Penny BW, Chepuri VB, Waggoner JW, et al. Case rates, treatment approaches, and outcomes in acute myocardial infarction during the coronavirus disease 2019 pandemic. *JAMA Cardiol.* (2020) 5:1419–24. doi: 10.1001/jamacardio.2020.3629
10. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. *Eur Heart J.* (2020) 41:1852–3. doi: 10.1093/eurheartj/ehaa314
11. Solomon MD, McNulty EJ, Rana JS, Leong TK, Lee C, Sung SH, et al. The covid-19 pandemic and the incidence of acute myocardial infarction. *N Engl J Med.* (2020) 383:691–3.
12. Reza N, DeFilippis EM, Jessup M. Secondary impact of the COVID-19 pandemic on patients with heart failure. *Circ Heart Fail.* (2020) 13:e007219. doi: 10.1161/CIRCHEARTFAILURE.120.007219
13. König S, Hohenstein S, Meier-Hellmann A, Kuhlen R, Hindricks G, Bollmann A, et al. In-hospital care in acute heart failure during the COVID-19 pandemic:

insights from the German-wide Helios hospital network. *Eur J Heart Fail.* (2020) 22:2190–201. doi: 10.1002/ejhf.2044
14. Shoaib A, Van Spall HGC, Wu J, Cleland JGF, McDonagh TA, Rashid M, et al. Substantial decline in hospital admissions for heart failure accompanied by increased community mortality during COVID-19 pandemic. *Eur Hear J Qual Care Clin Outcomes.* (2021) 7:378–87. doi: 10.1093/ehjqcco/qcab040
15. Rosenbaum L. The untold toll - the pandemic's effects on patients without Covid-19. *N Engl J Med.* (2020) 382:2368–71. doi: 10.1056/NEJMms2009984
16. Bodilsen J, Nielsen PB, Søgaard M, Dalager-Pedersen M, Speiser LOZ, Yndigegn T, et al. Hospital admission and mortality rates for non-covid diseases in Denmark during covid-19 pandemic: nationwide population based cohort study. *BMJ.* (2021) 373:n1135. doi: 10.1136/BMJ.N1135
17. Ullrich A, Schranz M, Rexroth U, Hamouda O, Schaade L, Diercke M, et al. Impact of the COVID-19 pandemic and associated non-pharmaceutical interventions on other notifiable infectious diseases in Germany: an analysis of national surveillance data during week 1–2016 – week 32–2020. *Lancet Reg Health Eur.* (2021) 6:100103. doi: 10.1016/j.lanepe.2021.100103
18. Mercier G, Arquizan C, Roubille F. Understanding the effects of COVID-19 on health care and systems. *Lancet Public Health.* (2020) 5:e524. doi: 10.1016/S2468-2667(20)30213-9
19. Cameli M, Pastore MC, Mandoli GE, D'Ascenzi F, Focardi M, Biagioni G, et al. COVID-19 and acute coronary syndromes: current data and future implications. *Front Cardiovasc Med.* (2021) 7:593496. doi: 10.3389/fcvm.2020.593496
20. Wu J, Mamas MA, de Belder MA, Deanfield JE, Gale CP. Second decline in admissions with heart failure and myocardial infarction during the COVID-19 pandemic. *J Am Coll Cardiol.* (2021) 77:1141–3. doi: 10.1016/j.jacc.2020.12.039
21. Abrams E, Szefler S. COVID-19 and the impact of social determinants of health. *Lancet Respir Med.* (2020) 8:659–61. doi: 10.1016/S2213-2600(20)30234-4
22. Moreno R, Alonso JJ, Caballero R, Del Corral E, Elízaga J, Asenjo RM, et al. Age and gender influence on time of arrival for STEMI patients during Covid-19 pandemic. *Am J Emerg Med.* (2021) 42:244–5. doi: 10.1016/j.ajem.2020.06.013
23. Colls C, Mias M, García-Altés A. Un índice de privación para reformar el modelo de financiación de la atención primaria en Cataluña. *Gac Sanit.* (2020) 4:44–50. doi: 10.1016/j.gaceta.2018.07.015
24. Monterde D, Vela E, Clèries M. Adjusted morbidity groups: a new multiple morbidity measurement of use in Primary Care. *Aten Primaria.* (2016) 48:674–82. doi: 10.1016/j.aprim.2016.06.003
25. Tsigkas G, Koufou EE, Katsanos K, Patrinos P, Moulias A, Miliordos I, et al. Potential relationship between lifestyle changes and incidence of hospital admissions for acute coronary syndrome during the covid-19 lockdown. *Front Cardiovasc Med.* (2021) 8:604374. doi: 10.3389/fcvm.2021.604374
26. Scalise M, Bossone E, Mannelli MP, Ranieri B, Franzese M, Castaldo R, et al. STEMI-PCI incidence rates and outcomes during COVID-19 pandemic: insights from Cardarelli Hospital, Naples, Southern Italy. *Eur J Prev Cardiol.* (2021). [Online ahead of print]. doi: 10.1093/EURJPC/ZWAB165
27. Moser DK, McKinley S, Dracup K, Chung ML. Gender differences in reasons patients delay in seeking treatment for acute myocardial infarction symptoms. *Patient Educ Couns.* (2005) 56:45–54. doi: 10.1016/j.pec.2003.11.011
28. Huynh J, Barmano N, Karlsson J-E, Stomby A. Sex and age differences in the incidence of acute myocardial infarction during the COVID-19 pandemic in a Swedish health-care region without lockdown: a retrospective cohort study. *Lancet Healthy Longev.* (2021) 2:e283–9. doi: 10.1016/s2666-7568(21)00085-4
29. De Rosa S, Spaccarotella C, Basso C, Calabrò MP, Curcio A, Filardi PP, et al. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *Eur Heart J.* (2020) 41:2083–8.
30. Campo G, Fortuna D, Berti E, De Palma R, Di Pasquale G, Galvani M, et al. In- and out-of-hospital mortality for myocardial infarction during the first wave of the COVID-19 pandemic in Emilia-Romagna, Italy: a population-based observational study. *Lancet Reg Health Eur.* (2021) 3:100055. doi: 10.1016/j.lanepe.2021.100055
31. Blecker S, Jones SA, Petrilli CM, Admon AJ, Weerahandi H, Francois F, et al. Hospitalizations for chronic disease and acute conditions in the time of COVID-19. *JAMA Intern Med.* (2021) 181:269–71. doi: 10.1001/jamainternmed.2020.3978
32. Sokolski M, Gajewski P, Zymliński R, Biegus J, Berg JMT, Bor W, et al. Impact of coronavirus disease 2019 (COVID-19) outbreak on acute admissions at the emergency and cardiology departments across europe. *Am J Med.* (2021) 134:482–9. doi: 10.1016/j.amjmed.2020.08.043

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Epidemiology of Congenital Heart Disease in Jinan, China From 2005 to 2020: A Time Trend Analysis

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Background: Although congenital heart defect (CHD) was the dominating birth defect, the time trend analysis of CHD was largely unknown. In our study, the time trend analysis of CHD from 2005 to 2020 in Jinan was conducted, aimed to reveal the epidemiological characteristics in a city and provided the data basis for the government to make a policy intervention.

Methods: A multi-institutional and retrospective review of CHD for all births from January 1, 2005 to December 31, 2020 was performed. Proportioner prevalence was used to describe the distribution of CHD. Comparisons of CHD characteristics among different groups were assessed with Chi-squares tests. Cochran-Armitage tests (CAT) were used to track changes in CHD prevalence.

Results: About 322,374 births and 5,180 CHD in Jinan were included from 2005 to 2020, and the total CHD prevalence was 3.92 per 1,000 births. The CHD prevalence showed an upward trend, with a total increase of 227.66% from 2005 to 2020. The CHD prevalence in urban areas was 34.17% higher than that in rural areas, but the gap was narrowing. Atrial septal defect (3.07 per 1,000 births), patent ductus arteriosus (1.62 per 1,000 births), ventricular septal defect (1.18 per 1,000 births), tetralogy of Fallot (0.62 per 1,000 births), and atrioventricular septal defect (0.47 per 1,000 births) were the 5 most common subtypes.

Conclusion: The prevalence of CHD in Jinan was gradually on the rise, which needs to be highly focused on by the health management department. Older pregnant women and women in rural areas should be concerned, and targeted measures need to be introduced.

Keywords: epidemiology, congenital heart disease, prevalence, time trend analysis, causes analysis

INTRODUCTION

Congenital heart disease (CHD) was defined as clinically significant structural heart and/or great vessels disease present at birth (1). It was estimated that the global average prevalence of CHD was 9.4 per 1,000 live births in 2010–2017 (2). CHD accounts for 28% of all birth defects, which was the most common birth defect (3). In China, 90–150 thousand new births with CHD were diagnosed every year, and infant mortality due to CHD reached 3.91 per 1,000 births in 2018 (4). Although child mortality caused by CHD has declined, the burden of disease caused by CHD was still serious in developing countries (5). CHD was also an important cause of disability in children (6). Infants with CHD frequently required early surgical treatment after birth to improve outcomes (7, 8), which always caused serious economic burden. The annual healthcare costs associated with CHD were estimated to be $5.6 billion, accounting for 15.1% of total pediatric hospitalization costs (9). In China, the total economic burden of CHD exceeded 12.6 billion RMB every year (10). In view of the heavy disease burden and serious health damage caused by CHD, the comprehensive prevention and control of CHD had become a public health issue. Therefore, the reliable epidemiological characteristics of CHD were important in order to have a better insight into its etiology and a finding of high-risk population.

Many studies in China have reported the prevalence of CHD. However, the period for identifying CHD in most studies was from 28 gestation weeks to 7 days after births. In fact, as with the large-scale use of ultrasound in obstetrics, more and more CHDs were diagnosed before 28 gestation weeks. So, that monitoring period cannot reflect the real level of CHD.

Jinan is the most representative city in eastern China for its geographic character, economic figure, and composition of population. In 2005, Jinan established a birth defect monitoring network, covering all medical institutions in the city. In 2011, all maternal and newborn information, including information on CHD, was reported through the web-based reporting system, and accurate and reliable data were available.

In this study, we extended the monitoring period of CHD, from 12 gestation weeks to 7 days after birth. We also performed a trend analysis and a difference test on the characteristics and subtypes of CHD, and the causes of these results were also analyzed. We believe that our study would provide suggestions for the government to formulate scientific policies and serve as a model for some developing cities to prevent CHD.

METHODS

Study Population

A multi-institutional and retrospective review of CHD for all births from January 1, 2005 to December 31, 2020 was performed. The study population involved all the pregnant women and fetus/neonates in hospitals of Jinan. The period of identifying CHD was from 12 gestation weeks to 7 days after births, during which CHD diagnosed for the first time was required to report. CHD was coded according to the International Classification of Diseases (10th edition) (11).

Data Collection

Data collection was based on the three-level network of the Maternal and Child Healthcare Institutions (MCH), including hospitals, county-level MCH, and city-level MCH (12). The doctors in hospitals reported the information of pregnant women and fetus/neonates to county-level MCH. The submitted data were verified by the staff in county-level MCH and reported to the city-level MCH every month. Ultimately, 52 hospitals, including 1,322,374 births and 5,180 CHD, were included in the study.

Variables such as the diagnosis gestation week of CHD, the gender of CHD, the maternal age of CHD, the subtype of CHD, and the other demographic characteristics were collected and analyzed.

Data Quality Management

In order to keep high-quality data, a series of standard operating procedures, including data collection, data abstraction, data evaluation, were developed. To ensure accuracy and completeness of CHD, quality control was routinely performed, and 10% normal findings and all abnormal findings were reviewed by cardiologists.

In the process of quality control, the related variables of CHD, such as the gestation week, the CHD subtype, the maternal age, and so on, were the key check contents.

Statistical Analysis

Demographic and clinical characteristics of CHD were expressed as proportion or prevalence. Cochran-Armitage tests (CATs) were used to track changes of the prevalence of CHD in rural and urban areas, the proportion of CHD before and after 28 gestation weeks, and the prevalence of CHD subtypes. The prevalence of CHD according to different maternal characteristics was assessed with Chi-squares tests. Cochran-Armitage tests (CATs) were used to track changes of the CHD prevalence. R version 3.5.1 (the Comprehensive R Archive Network) was used for the data analysis, with a significance level at $p < 0.05$.

RESULTS

The Prevalence of CHD in Jinan From 2005 to 2020

We counted 1,322,374 births and 5,180 CHD from 2005 to 2020, and the prevalence was 3.92 per 1,000 births. Time trend analysis showed that the prevalence of total CHD was increased, from 1.52 per 1,000 births in 2005 to 4.99 per 1,000 births in 2020, with a total increase of 227.66% and an annual increase of 14.23%.

Overall, during the study period, an "S" shape curve can be found in the time trend of CHD prevalence. The first stage was from 2005 to 2010, during which the CHD prevalence was about 2.46 per 1,000 births. The second stage was from 2011 to 2015, during which the CHD prevalence was about 3.58 per 1,000 births. The third stage was from 2016 to 2020, during which the CHD prevalence was about 5.21 per 1,000 births (**Table 1**, **Figure 1**).

TABLE 1 | The prevalence of CHD between urban areas and rural areas from 2005 to 2020.

Year	Urban*			Rural[&]			Total[#]			Extent%Δ[$]
	Births	CHD	PRE	Births	CHD	PRE	Births	CHD	PRE	
2005	19,467	43	2.21	27,835	29	1.04	47,302	72	1.52	52.83
2006	18,957	58	3.06	3,1007	53	1.71	49,964	111	2.22	44.13
2007	25,889	84	3.24	35,782	69	1.93	61,671	153	2.48	40.57
2008	24,475	85	3.47	35,329	73	2.07	59,804	158	2.64	40.50
2009	26,593	90	3.38	40,145	76	1.89	66,738	166	2.49	44.06
2010	36,732	142	3.87	44,228	100	2.26	80,960	242	2.99	41.51
2011	36,700	149	4.06	44,722	115	2.57	81,422	264	3.24	36.66
2012	39,763	195	4.90	49,291	158	3.21	89,054	353	3.96	34.64
2013	35,551	178	5.01	41,907	132	3.15	77,458	310	4.00	37.09
2014	50,363	208	4.13	58,848	152	2.58	10,9211	360	3.30	37.46
2015	35,959	154	4.28	40,481	113	2.79	76,440	267	3.49	34.82
2016	62,281	420	6.74	69,238	326	4.71	131,519	746	5.67	30.18
2017	49,217	300	6.10	53,464	230	4.30	102,681	530	5.16	29.42
2018	49,853	300	6.02	52,224	250	4.79	102,077	550	5.39	20.45
2019	49,134	259	5.27	53,128	221	4.16	102,262	480	4.69	21.09
2020	40,445	230	5.69	43,366	188	4.34	83,811	418	4.99	23.77
Total	60,1379	2,895	4.81	72,0995	2,285	3.17	132,2374	5,180	3.92	34.17

**Cochran-Armitage trend (CAT) $P < 0.05$.*
[$] Cochran-Armitage trend (CAT) $P < 0.05$.
[&] Cochran-Armitage trend (CAT) $P < 0.05$.
[#] Cochran-Armitage trend (CAT) $P < 0.05$.
Extent%Δ = (the CHD prevalence in urban areas- the CHD prevalence in rural areas)/ the CHD prevalence in urban areas×100%.

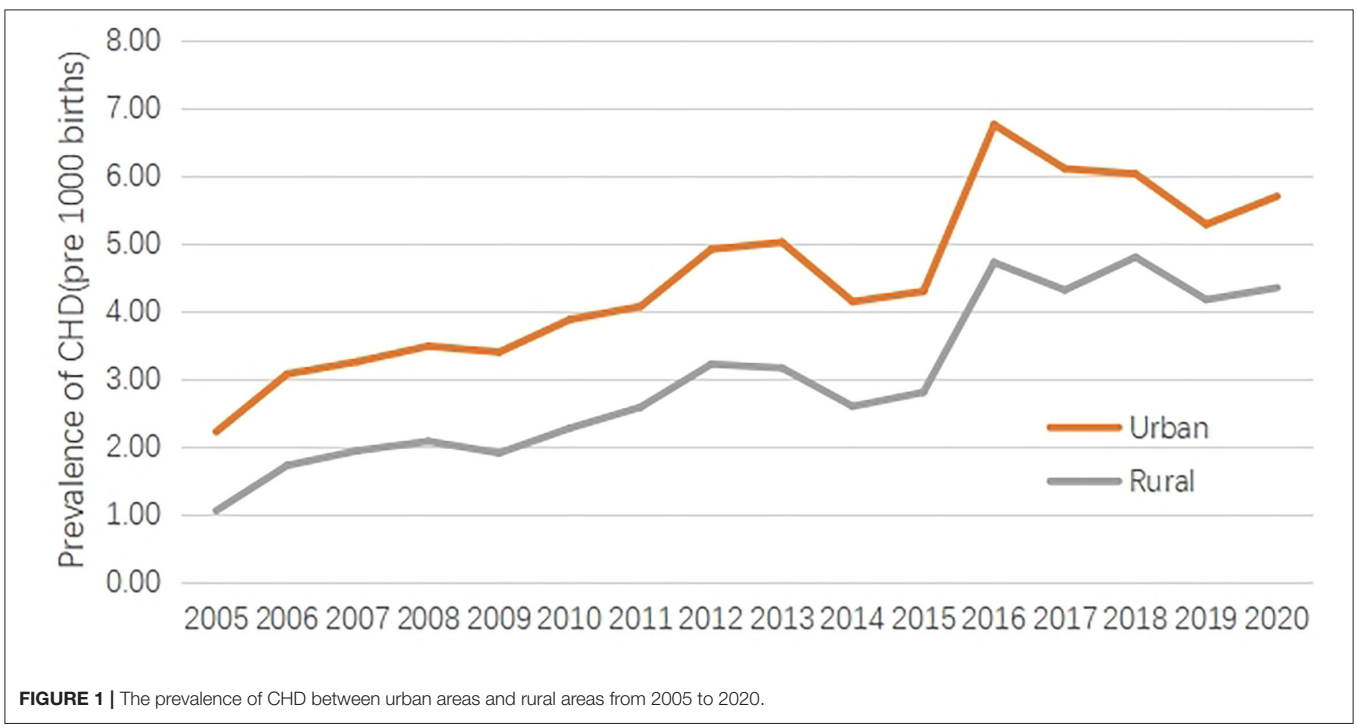

FIGURE 1 | The prevalence of CHD between urban areas and rural areas from 2005 to 2020.

The Prevalence of CHD Between Urban Areas and Rural Areas in Jinan From 2005 to 2020

From 2005 to 2020, the CHD prevalence was 4.81 per 1,000 births in urban areas and 3.17 per 1,000 births in rural areas. Time trend analysis showed an upward trend of the CHD prevalence in urban and rural areas, and respectively increased by 157.45% and 316.03% in 2020 compared with 2005. Obviously, the increasing range in rural areas was larger than that in urban areas.

The gap of CHD prevalence between urban and rural areas was analyzed. Overall, the CHD prevalence in urban areas was 34.17% higher than that in rural areas, but the gap, gradually, was narrowed, from 52.83% in 2005 to 23.77% in 2020 (**Table 1**, **Figure 1**).

The Proportion of CHD Before 28 Gestation Weeks and After 28 Gestation Weeks in Jinan From 2005 to 2020

Between 2005 and 2020, the proportion of CHD was 31.20% before 28 gestation weeks and 68.80% after 28 gestation weeks. Time trend analysis showed an upward trend of the CHD proportion before 28 gestation weeks and increased by 192.82% in 2020 compared with 2005. On the contrary, a downward trend of the CHD proportion was found after 28 gestation weeks, which decreased by 31.11% in 2020 compared with 2005.

Overall, the gap of the CHD proportion between before 28 gestation weeks and after 28 gestation weeks gradually narrowed, from 520% in 2005 to 45.88% in 2020 (**Table 2**, **Figure 2**).

The Difference of CHD Prevalence in Jinan According to Different Maternal Characteristics

Firstly, the CHD prevalence of male births was 17.92% higher than that of female births, and this difference was statistically significant ($p < 0.05$). Secondly, the CHD prevalence of maternal delivery season was highest in autumn (4.73 per 1,000 births) and least in spring (3.49 per 1,000 births), and the difference was statistically significant ($p < 0.05$). Besides, significant differences were also found in different maternal age groups. The highest CHD prevalence was found in over 35 years old (7.18 per 1,000 births), followed by under 20 years old (5.52 per 1,000 births) (**Table 3**, **Figure 3**).

The Prevalence of the 5 Most Common CHD Subtypes in Jinan From 2005 to 2020

Overall, atrial septal defect (ASD), patent ductus arteriosus (PDA), ventricular septal defect (VSD), tetralogy of Fallot (TOF), and atrioventricular septal (AVSD) were the 5 most common subtypes. The prevalence of these CHD subtypes was 3.07 per 1,000 births, 1.62 per 1,000 births, 1.18 per 1,000 births, 0.62 per 1,000 births, and 0.47 per 1,000 births, respectively.

Time trend analysis showed that the total CHD prevalence in different subtypes increased over time. Compared with 2005, the 5 most common CHD subtypes, respectively, increased by 251.51, 162.74, 109.23, 33.08, and 15.32%. Obviously, the increasing range of ASD was largest among the 5 most common CHD subtypes. Besides, we also found that ASD, PDA, VSD, and TOF had the highest prevalence in 2016 from 2005 to 2020 (**Table 4**).

DISCUSSION

The total CHD prevalence in Jinan was 3.92 per 1,000 births from 2005 to 2020 and 5.61 per 1,000 births from 2016 to 2020, which were roughly equivalent to the CHD prevalence in China (13) over the same period but were higher than that in Changzhou (14), and lower than that in Zhejiang (15), in Asia, and in the world (2). We speculated that there may be several reasons for this difference. Firstly, it might be due to the different monitored periods. The monitored period, in our study, was from 12 gestation weeks to 7 days after births, but that in Asia or in the world was from birth to 6 years old, and that in Changzhou was from 28 gestation weeks to 7 days after births. Secondly, various screening approaches also played an important role. In our study, B-ultrasound was the main screening method for CHD in Jinan. However, in the study in Zhejiang, in addition to B-ultrasound examination, the pulse oximetry was used for CHD screening after birth.

In our study, 5 epidemiological characteristics of congenital heart disease in Jinan were found.

TABLE 2 | The propotion of CHD before 28 gestation weeks and after 28 gestation weeks from 2005 to 2020.

Year	Births	Before 28 gestation weeks*		After 28 gestation weeks#		Extent%Δ$
		CHD	Propotion (%)	CHD	Propotion (%)	
2005	47,302	10	13.89	62	86.11	520.00
2006	49,964	14	12.61	97	87.39	592.86
2007	61,671	26	16.99	127	83.01	388.46
2008	59,804	30	18.99	128	81.01	326.67
2009	66,738	30	18.07	136	81.93	353.33
2010	80,960	38	15.70	204	84.30	436.84
2011	81,422	43	16.29	221	83.71	413.95
2012	89,054	72	20.40	281	79.60	290.28
2013	77,458	74	23.87	236	76.13	218.92
2014	109,211	107	29.72	253	70.28	136.45
2015	76,440	77	28.84	190	71.16	146.75
2016	131,519	305	40.88	441	59.12	44.59
2017	102,681	210	39.62	320	60.38	52.38
2018	102,077	220	40.00	330	60.00	50.00
2019	102,262	190	39.58	290	60.42	52.63
2020	83,811	170	40.67	248	59.33	45.88
Total	132,2374	1,616	31.20	3,564	68.80	120.54

*Cochran-Armitage trend (CAT) $P < 0.05$.
#Cochran-Armitage trend (CAT) $P < 0.05$.
$Cochran-Armitage trend (CAT) $P < 0.05$.
Extent%Δ =(the CHD propotion after 28 gestation weeks- the CHD propotion before 28 gestation weeks)/ the CHD propotion after 28 gestation weeks×100%.

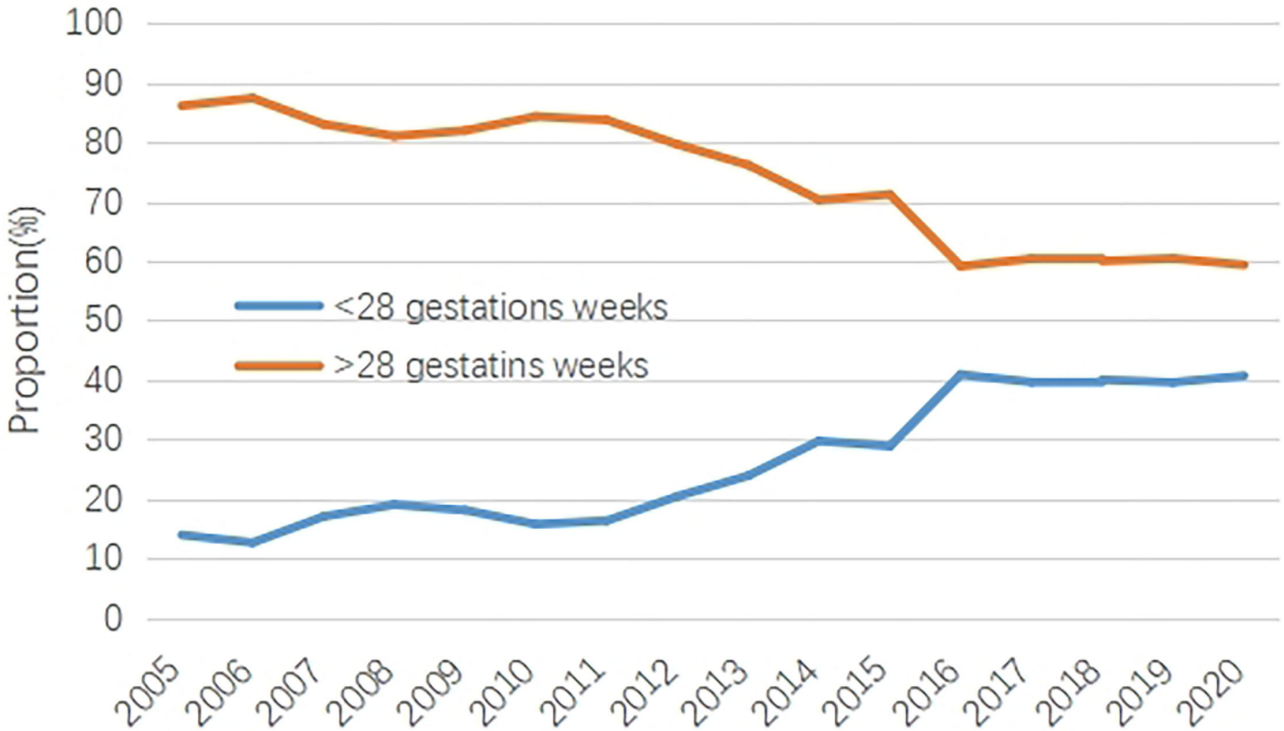

FIGURE 2 | The proportion of CHD before 28 gestation weeks and after 28 gestation weeks from 2005 to 2020.

TABLE 3 | The prevalence of CHD from 2005 to 2020 in Jinan according to different characteristics.

Variable	Births	CHD	Prevalence	*P* value
Infant gender				<0.001
Male	695,665	2,978	4.28	
Female	626,709	2,202	3.51	
Season				<0.001
Spring (March, April, May)	320,421	1,117	3.49	
Summer (June,July,August)	320,452	1,134	3.54	
Autumn (September, October, November)	326,300	1,544	4.73	
Winter (December,January,February)	355,201	1,385	3.90	
Maternal age				<0.001
<20	17,204	95	5.52	
20–24	235,339	736	3.13	
25–29	519,356	1,730	3.33	
30–34	388,498	1,456	3.75	
35-	161,977	1,163	7.18	

Firstly, the total CHD prevalence increased significantly over time in Jinan; the upward trend was also found in other studies in China (16, 17). We found an "S" shape in the time trend of the CHD prevalence, and 2011 and 2016 were two obvious growth inflection points. In particular, the prevalence of atrial septal defect (ASD) and ventricular septal defect (VSD) reached their highest levels in 2016 in nearly 15 years. The phenomenon was explained by the following two reasons. On the one hand, it might be attributed to the established information systems. Jinan Maternal and Child Health Information System was an information system based on case collection. Since 2011, every examination of pregnant women throughout pregnancy, especially ultrasound examination, can be found in the information system. However, previous information collections were aggregated data, and information omissions or misdiagnosis of CHD existed. On the other hand, the comprehensive two-child policy implemented in 2016 had a significant impact on the increase in the prevalence of CHD (18, 19). After the implementation of the policy, women over 35 years old in Jinan increased by 45% (20), which undoubtedly increased the prevalence of CHD.

Secondly, we found that the proportion of CHD before 28 gestation weeks increased gradually. This phenomenon was also found in other studies on the CHD diagnosis gestational weeks (21). Large-scale B-ultrasound examination was an important reason for this phenomenon. After 2016, free prenatal ultrasound was included in public health projects in Jinan. Every pregnant woman can obtain a free prenatal ultrasound examination at about 24 gestation weeks, and more and more CHD can be found in the perinatal period, resulting in increasing prevalence.

Thirdly, significant differences across gender, maternal delivery season, and maternal age were found. (i) The CHD prevalence in male births was higher than that in female births, which was consistent with some previous studies (22, 23). This difference may be explained by the higher susceptibility of Y

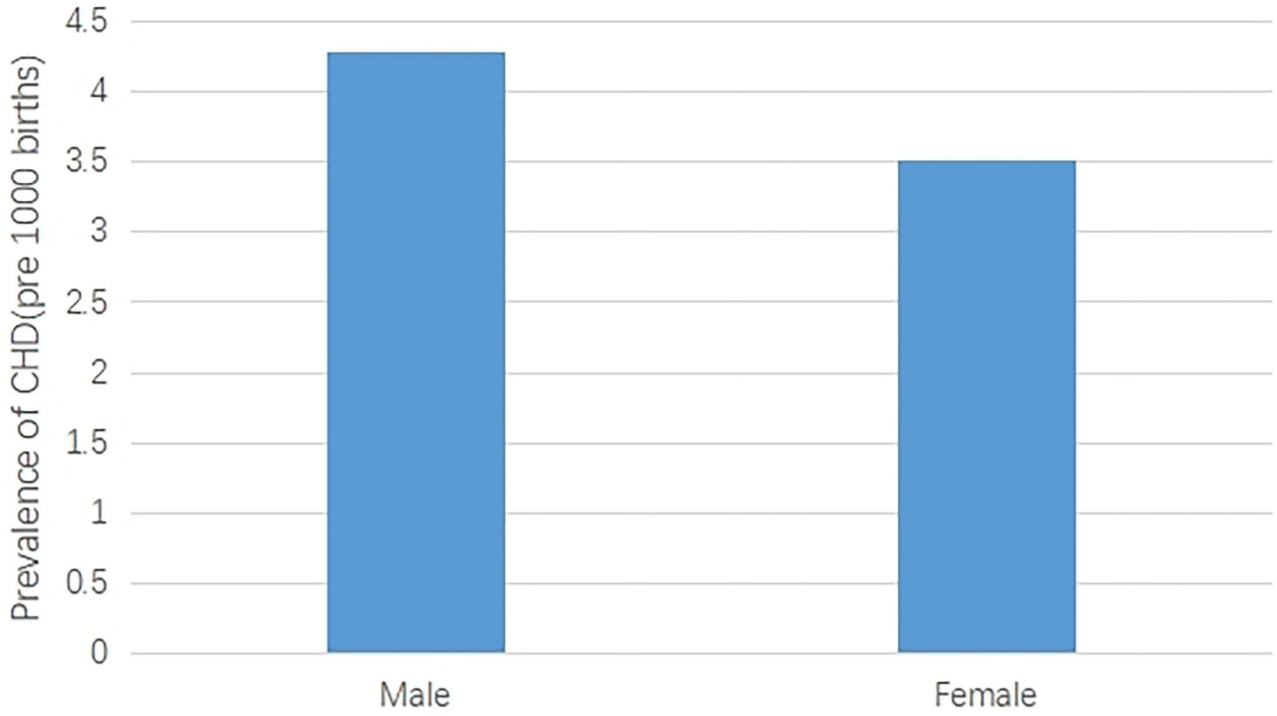

FIGURE 3 | The prevalence of CHD between male births and female births.

TABLE 4 | The prevalence of the the 5 most common CHD subtypes in Jinan from 2005 to 2020.

Year	Atrial septal defect*		Patent ductus arteriosus#		Ventricular septal defect&		Tetralogy of Fallot$		Atrioventricular septal@	
	CHD	PRE	CHD	PRE	CHD	PRE	CHD	PRE	CHD	PRE
2005	17	0.87	12	0.62	11	0.57	9	0.46	8	0.41
2006	28	1.48	11	0.58	20	1.06	9	0.47	10	0.53
2007	35	1.35	17	0.66	27	1.04	12	0.46	11	0.42
2008	42	1.72	19	0.78	35	1.43	14	0.57	8	0.33
2009	41	1.54	21	0.79	34	1.28	13	0.49	10	0.38
2010	79	2.15	43	1.17	33	0.90	21	0.57	19	0.52
2011	100	2.72	57	1.55	40	1.09	20	0.54	20	0.54
2012	114	2.87	75	1.89	41	1.03	26	0.65	21	0.53
2013	107	3.01	57	1.60	42	1.18	21	0.59	19	0.53
2014	135	2.68	77	1.53	43	0.85	25	0.50	16	0.32
2015	98	2.73	65	1.81	25	0.70	20	0.56	13	0.36
2016	292	4.69	167	2.68	99	1.59	51	0.82	34	0.55
2017	205	4.17	95	1.93	71	1.44	31	0.63	25	0.51
2018	211	4.23	98	1.97	62	1.24	33	0.66	21	0.42
2019	192	3.91	85	1.73	65	1.32	35	0.71	22	0.45
2020	150	3.71	75	1.85	63	1.56	30	0.74	28	0.69
Total	1846	3.07	974	1.62	711	1.18	370	0.62	285	0.47

*Cochran-Armitage trend (CAT) $P < 0.05$.
#Cochran-Armitage trend (CAT) $P < 0.05$.
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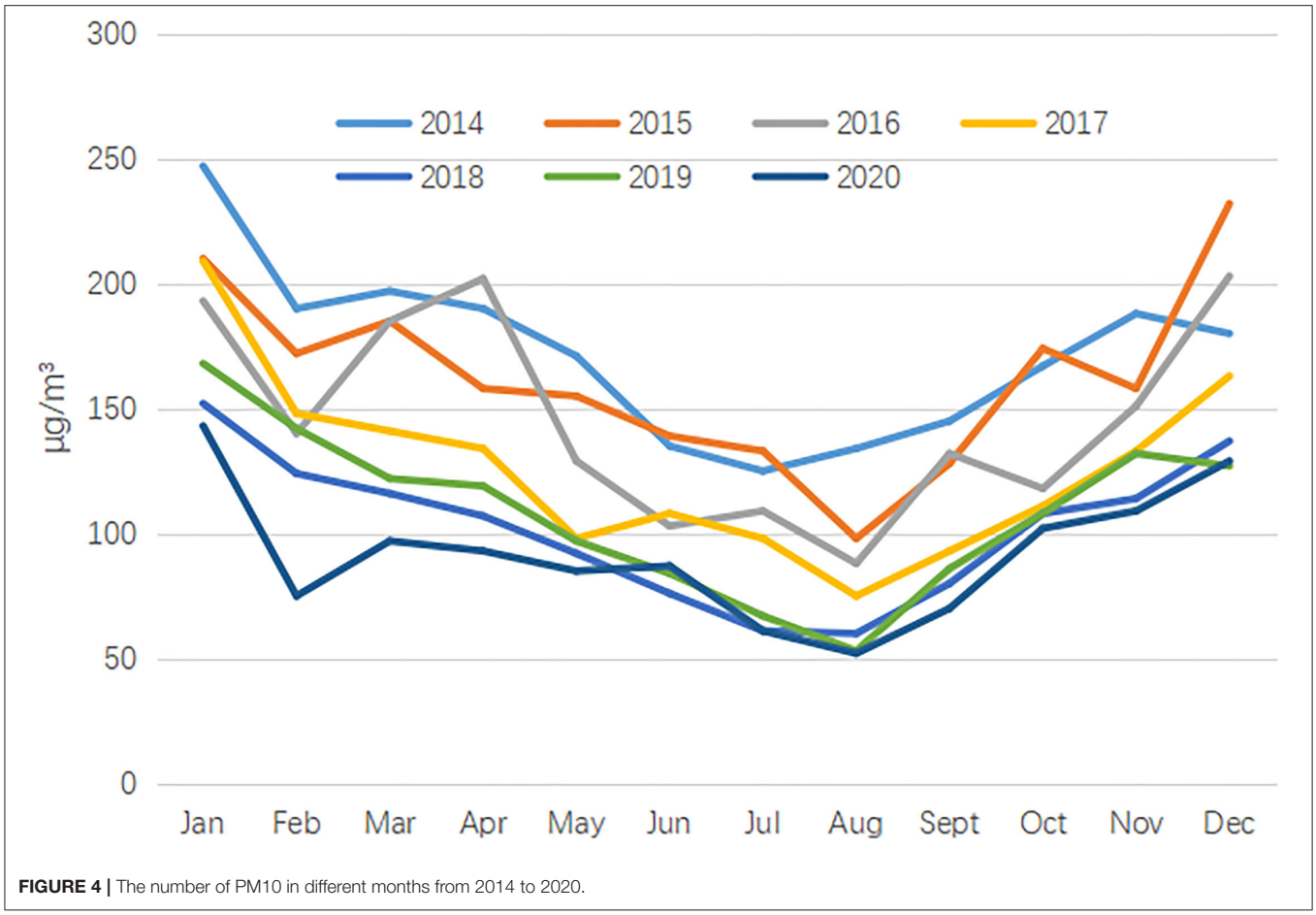

FIGURE 4 | The number of PM10 in different months from 2014 to 2020.

chromosome than X chromosome (24). (ii) The CHD prevalence in autumn was highest. As we all know, the critical period of fetal heart and embryo development was 3–8 gestation weeks. In our study, the CHD prevalence in autumn was highest, which indicated that early maternal exposure was in winter. In Jinan, air pollution was relatively serious in winter, especially PM10 (**Figures 4**, **5**). Some studies have pointed out that PM2.5 or PM10 was an important risk factor in birth defects (25, 26). (iii) Like other studies, we also found high CHD prevalence in elderly pregnant women (27–29). As more and more women delay their childbearing age, the government should attach great importance to the above issue. It is estimated that the maternal age has delayed from 26.12 years old in 2005 to 31.26 years old in 2020.

Fourthly, the total CHD prevalence in urban areas was higher than that in rural areas, which was also reported in many other pieces of literature (30, 31). Perhaps, the stronger overall health awareness, the wider use of prenatal diagnosis techniques, more accessibility, and reporting practices in urban areas can be used to explain the phenomenon (32). Interestingly, the gap of the CHD prevalence between urban areas and rural areas was getting smaller and smaller. Several reasons can be used to explain this phenomenon. (i) After 2011, with the advancement of public health projects, the use of prenatal diagnostic techniques became more widespread in rural areas, allowing a large number of congenital heart diseases to be detected prenatally. (ii) An important reason for the phenomenon was changes in environmental exposures. In recent years, the environmental protection measures implemented in urban areas of Jinan have become more and more strict, and the environmental quality has become better and better. On the contrary, the environmental quality in rural areas has not been greatly improved. Especially during the Spring Festival, due to the use of firecrackers, the environmental quality in rural areas was very poor (33). National Environmental Monitoring Center reports that more than 60% cities in rural areas have excessive air pollution during the Spring Festival holiday (34), and the data in our study also showed the poor air quality in January, each year during the Spring Festival from 2014 to 2018.

Fifthly, in Jinan, the reported CHD was dominated by mild lesions (84.31%), such as VSD, ASD, and PDA. The finding also was confirmed in other studies (35). The following reasons can explain this phenomenon. Firstly, comprehensive use of echocardiography and improved echocardiographic techniques were likely to account substantially for the increased prevalence of mild lesions. With the improvement of health awareness, more and more pregnant women were checked fetal health by B-ultrasound. In 2020, the proportion of fetal

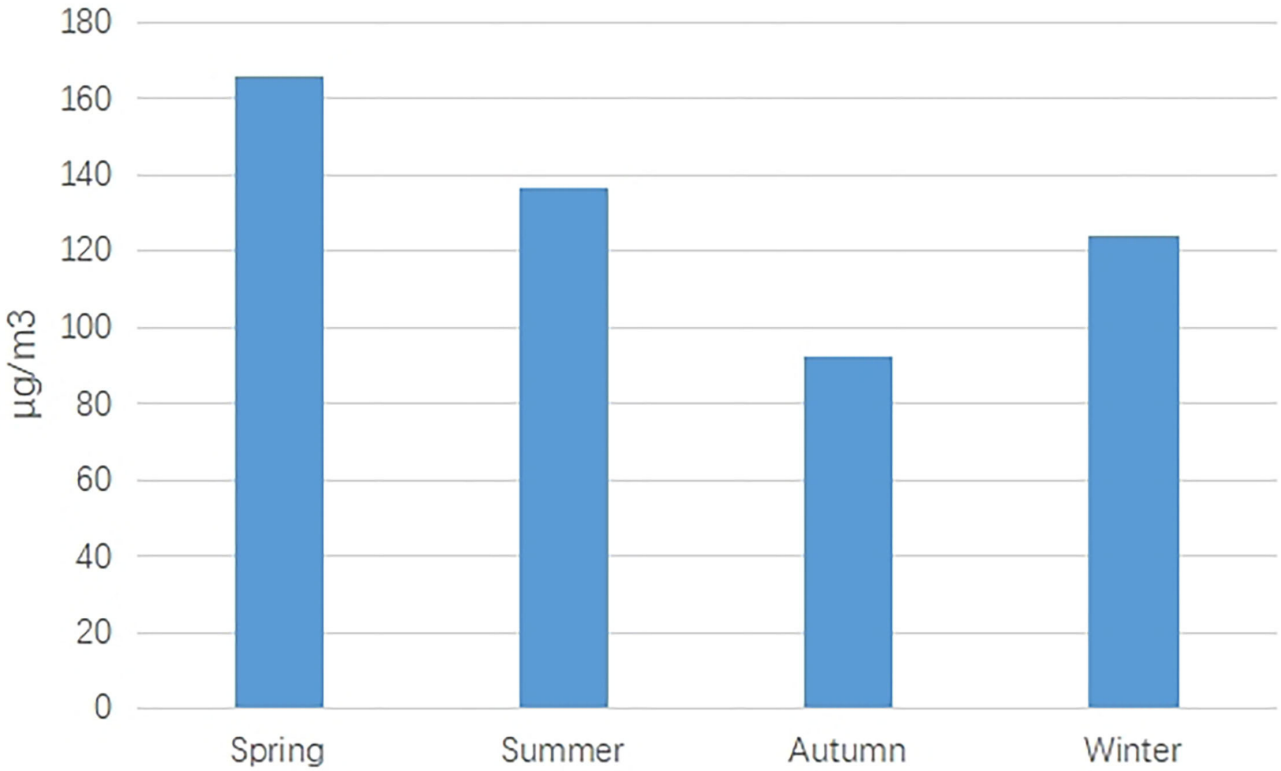

FIGURE 5 | The number of PM10 in different seasons.

cardiac ultrasound examination reached 92.13%. So, many previous mild lesions were reported in the prenatal period. The second reason should be attributed to air pollution. The terrain in Jinan belonged to a basin bottom structure, which made the air pollutants, especially PM10, unable to be dissipated in time. Some epidemiologic studies have suggested the possible association of maternal exposure to PM10 during the first trimester of gestation with VSD, ASD, and PDA (25, 36).

Limitation

Firstly, the prevalence of CHD in our study was based on hospitals; births with CHD given out of hospital would be missed. Therefore, the actual prevalence of CHD might be underestimated. Secondly, as a cross-sectional study, some risk factors of CHD, such as the natural environment or other maternal complications, were not considered because of limited data.

CONCLUSION

The CHD prevalence was increased in Jinan from 2005 to 2020. The CHD prevalence in urban areas and before 28 gestation weeks was increased faster. Mild lesions, such as VSD, ASD, and PDA, were the dominating subtypes. Elderly pregnant women and women in rural areas should be focused.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Jinan Maternity and Child Care Hospital Affiliated to Shandong First Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LZ, BL, and HL participated in data collection. ZL conceived the idea, participated in data analysis, and drafted the manuscript. CW and SY participated in the design and

implementation of the study. All authors read and approved the final manuscript.

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REFERENCES

1. Mitchell SC, Korones SCSB, Berendes HWW. Congenital Heart Disease in 56,109 Births Incidence and Natural History. *Circulation.* (1971) 43:323–32. doi: 10.1161/01.CIR.43.3.323
2. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol.* (2019) 48:1–9. doi: 10.1093/ije/dyz009
3. Linde D, Koningsc E, Slagerc M, Witsenburg M, Helbing WA, Takkenberg JJM, et al. Birth Prevalence of Congenital Heart Disease Worldwide. *J Am Coll Cardiol.* (2011) 58:2241–7. doi: 10.1016/j.jacc.2011.08.025
4. Manchen G, Fengwen Z, Xiangbin P. Interpretation of the section of congenital heart diseases in Annual Report on Cardiovascular Health and Diseases in China (2019). *Chin J Clin Thorac Cardiovasc Surg.* (2021) 28:384–7. doi: 10.1097/CD9.0000000000000040
5. Collaborators GCHD. Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Child Adolesc Health.* (2020) 4:185–200. doi: 10.1016/S2352-4642(19)30402-X
6. Teun V, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder B. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol.* (2011) 8:50–60. doi: 10.1038/nrcardio.2010.166
7. Bakker MK, Bergman J, Krikov S, Amar E, Botto LD. Prenatal diagnosis and prevalence of critical congenital heart defects: an international retrospective cohort study. *BMJ Open.* (2019) 9:e028139. doi: 10.1136/bmjopen-2018-028139
8. Colaco SM, Karande T, Bobhate PR, Jiyani R, Kulkarni S. Neonates with critical congenital heart defects: Impact of fetal diagnosis on immediate and short-term outcomes. *Ann Pediatr Cardiol.* (2017) 10:126. doi: 10.4103/apc.APC_125_16
9. Simeone RM, Oster ME, Cassell CH, Armour BS, Gray DT, Honein MA. Pediatric inpatient hospital resource use for congenital heart defects. *Birth Defects Res A Clin Mol Teratol.* (2014) 100:934–43. doi: 10.1002/bdra.23262
10. Huaijin Q, Zhu J. *Birth Defect Prevention Report 2012.* Beijing: People's Sanitary Publishing Press (2013).
11. WHO Organization. ICD-10: international statistical classification of diseases and related health problems: tenth revision. *Acta Chirurgica Iugoslavica.* (2010) 56:65–9. doi: 10.2298/ACI0903065V.
12. Dai L, Zhu J, Liang J, Wang YP, Wang H, Mao M. Birth defects surveillance in China. *World J Pediatr.* (2011) 7:302–10. doi: 10.1007/s12519-011-0326-0
13. Zhao L, Chen L, Yang T, Wang T, Qin J. Birth prevalence of congenital heart disease in China, 1980–2019: a systematic review and meta-analysis of 617 studies. *Eur J Epidemiol.* (2020) 35:1–12. doi: 10.1007/s10654-020-00653-0
14. Zhou Y, Mao X, Zhou H, Qin Z, Yu B. Epidemiology of birth defects based on a birth defect surveillance system in Southern Jiangsu, China, 2014–2018. *J Matern Fetal Neonatal Med.* (2020) 7:1–7. doi: 10.3389/fpubh.2020.00378
15. Zhang X, Sun Y, Zhu J, Zhu Y, Qiu L. Epidemiology, prenatal diagnosis, and neonatal outcomes of congenital heart defects in eastern China: a hospital-based multicenter study. *BMC Pediatr.* (2020) 20:1–8. doi: 10.1186/s12887-020-02313-4
16. Sun PF, Ding GC, Zhang MY, He SN, Gao Y, Wang JH. Prevalence of Congenital Heart Disease among Infants from 2012 to 2014 in Langfang, China. *Chin Med J.* (2017) 130:1069–73. doi: 10.4103/0366-6999.204923
17. Qu Y, Liu X, Zhuang J, Chen G, Mai J, Guo X, et al. Incidence of Congenital Heart Disease: The 9-Year Experience of the Guangdong Registry of Congenital Heart Disease, China. *PLoS ONE.* (2016) 11:e0159257. doi: 10.1371/journal.pone.0159257
18. Hesketh T, Zhou X, Wang Y. The End of the One-Child Policy: Lasting Implications for China. *JAMA.* (2015) 314:2349–50. doi: 10.1001/jama.2015.16279
19. Zeng Y, Hesketh T. The effects of China's universal two-child policy. *Lancet.* (2016) 388:1930–8. doi: 10.1016/S0140-6736(16)31405-2
20. Yu D, Zhang L, Yang S, Chen Q, Li Z. Trends, causes and solutions of maternal mortality in <city>Jinan</city>, China: the epidemiology of the MMR in 1991-2020. *BMC Public Health.* (2021) 21:1792. doi: 10.1186/s12889-021-11816-3
21. Xie D, Fang J, Liu Z, Wang H, Yang T, Sun Z, et al. Epidemiology and major subtypes of congenital heart defects in Hunan Province, China. *Medicine.* (2018) 97:1–11. doi: 10.1097/MD.0000000000011770
22. Li JJ, Liu Y, Xie SY, Zhao GD, Dai T, Chen H, et al. Newborn screening for congenital heart disease using echocardiography and follow-up at high altitude in China. *Int J Cardiol.* (2019) 274:106–112. doi: 10.1016/j.ijcard.2018.08.102
23. Li S, Hong SX, Wang TM. A population-based surveillance system on birth defects and its application. *Chin J Epidemiol.* (2001) 22:172–5.
24. Sokal R, Tata LJ, Fleming KM. Sex prevalence of major congenital anomalies in the United Kingdom: a national population-based study and international comparison meta-analysis. *Birth Defects Res A Clin Mol Teratol.* (2014) 100:79–91. doi: 10.1002/bdra.23218
25. Zhang B, Liang S, Zhao J, Qian Z, Bassig BA, Yang R, et al. Maternal exposure to air pollutant PM2.5 and PM10 during pregnancy and risk of congenital heart defects. *J Expo Sci Environ Epidemiol.* (2016) 26:422–7. doi: 10.1038/jes.2016.1
26. Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Nieuwenhuijsen RM. Ambient Air Pollution and Risk of Congenital Anomalies: a Systematic Review and Meta-analysis. *Environ Health Perspect.* (2011) 119:598–606. doi: 10.1289/ehp.1002946
27. Miller A, Riehle-Colarusso T, Siffel C, Frías JL, Correa A. Maternal age and prevalence of isolated congenital heart defects in an urban area of the United States. *Am J Med Genet A.* (2011) 155A:2137–45. doi: 10.1002/ajmg.a.34130
28. Luo YL, Cheng YL, Gao XH, Tan SQ, Li JM, Wang W, et al. Maternal age, parity and isolated birth defects: a population-based case-control study in Shenzhen, China. *PLoS ONE.* (2017) 8:1–11. doi: 10.1371/journal.pone.0081369
29. Baird PA, Sadovnick AD, Yee IM. Maternal Age and birth defects: a population study. *Lancet.* (1991) 337:527–530. doi: 10.1016/0140-6736(91)91306-F
30. Pei L, Kang Y, Zhao Y, Yan H. Prevalence and risk factors of congenital heart defects among live births: a population-based cross-sectional survey in Shaanxi province, Northwestern China. *BMC Pediatr.* (2017) 17:18. doi: 10.1186/s12887-017-0784-1
31. Zhang X, Su L, Wu S, Hao X, Guo S, Kota S, et al. Prevalence of birth defects and risk-factor analysis from a population-based survey in Inner Mongolia, China. *BMC Pediatr.* (2012) 12:125. doi: 10.1186/1471-2431-12-125
32. Tang S, Meng Q, Chen L, Bekedam H, Whitehead M. Tackling the challenges to health equity in China. *Lancet.* (2008) 372:1493–501. doi: 10.1016/S0140-6736(08)61364-1
33. Xiao-Hui MA, Sun ZB, Ding HY, Zi-Ming LI. Effect of fireworks and meteorological conditions on air quality during Spring Festival in Beijing. *J Meteorol Environ.* (2015) 31:50–5.

34. Pan BF, Li-Na LI. The influence of burning fireworks on the air quality in major cities during the spring festival in chin. *Environ Eng.* (2016) 34:34–7. doi: 10.13205/j.hjgc.201601016
35. Morris JK, Springett AL, Greenlees R, Loane M, Addor MC, Arriola L, et al. Trends in congenital anomalies in Europe from 1980 to 2012. *PLoS ONE.* (2018) 13:1–18. doi: 10.1371/journal.pone.0194986
36. Baldacci S, Gorini F, Minichilli F, Pierini A, Santoro M, Bianchi F. Review of epidemiological studies on individual and environmental risk factors in the aetiology of congenital heart defects. *Epidemiol Prev.* (2016) 40:185–96. doi: 10.19191/EP16.3-4.P185.085

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Association of Neighborhood Alcohol Environment With Alcohol Intake and Cardiovascular Risk Factors in India: Cross-Sectional Evidence From APCAPS

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There are more and more proofs about the impact of neighborhood alcohol environment on alcohol-associated events. The relationship between the neighborhood availability and accessibility of alcohol outlet with individual level of alcohol consumption along with 11 cardiovascular risk factors was explored for the first time in India using data from the 3rd follow-up of the Andhra Pradesh children and parents study (APCAPS) (n = 6156, for liquor intake and 5,641 for heart and blood vessel risk elements). In fully adjusted models, volunteers in the lowest tertile performed worse than volunteers in the highest tertile of distance to the closest alcohol outlet were more probably to exhibit less alcohol consumption (−14.40 g/day, 95% *CI*: −26.21, −2.59). A unit per km^2 rise in alcohol outlet density in 400 m buffering area was related to a rise in waist circumference (1.45 mm, 95% *CI*: 0.13, 2.77), SBP (0.29 mmHg, 95% *CI*: 0.09, 0.49), and DBP (0.19 mmHg, 95% *CI*: 0.03, 0.35). A unit per 100 m rise in distance to the closest alcohol outlet was related to a rise in waist circumference (−2.39 mm, 95% *CI*: −4.18, −0.59), SBP (−0.41 mmHg, 95% *CI*: −0.68, −0.15), and DBP (−0.29 mmHg, 95% *CI*: −0.51, −0.07). Neighborhood availability of alcohol outlets within immediate locality of participants' households had a closer relationship with cardiovascular risk factors than that within the whole village. Public health policies designed to limit neighborhood availability and accessibility of alcohol outlets ought to be advocated in southern India.

Keywords: alcohol environment, availability, accessibility, alcohol intake, cardiovascular risk, APCAPS

INTRODUCTION

Cardiovascular disease (CVD) causes huge disease burden and deaths worldwide (1). In India, it contributed 28.1% of the total deaths and 14.1% of the total disability-adjusted life-years in 2016 (2). Alcohol use is a key modifiable risk factor for acute and chronic diseases globally, causing 2.8 million deaths in 2016 (3). Heavy drinking is associated with an increased risk of initial presentation

of several symptomatic manifestations of CVD, such as coronary death, heart failure, cardiac arrest, transient ischemic attack, ischemic stroke, intracerebral hemorrhage, and peripheral arterial disease (4). In India, alcohol attributable deaths would lead to a loss of 258 million life years between 2011 and 2,050, causing significant negative health impact and economic burden (5).

Data from multiple countries indicate a close connection between the neighborhood alcohol environment, especially the availability and accessibility of alcohol (on and/or off-premises), and the individual alcohol consumption (6). However, most of the existing studies have been conducted in high-income countries and have focused on the association between alcohol environment and drinking behaviors and beliefs among adolescents or young adults (7–9). Very few studies have been carried out in low- and middle-income countries. Ibitoye et al. found that high density of alcohol-selling outlets and outdoor advertisements increased alcohol use among adolescents in Tanzania (10). Study from rural South Africa found that density of alcohol outlets was associated with problematic drinking among young men (11).

Further, there is increasing evidence about the impact of neighborhood alcohol environment on alcohol-related events including experienced violence, injuries, and drunk-driving fatalities (12–14). Higher alcohol outlet density was also shown to be associated with non-injury health outcomes such as liver problems, mental health, sexually transmitted infections, and total deaths (15–17). By now, to the best of our knowledge, no study has addressed the association between the availability and accessibility of alcohol with individual level of alcohol consumption and cardiovascular risk factors in general population in low- and middle-income countries.

In order to inform policies for the control of local alcohol use and disease burden of CVD in low- and middle- income countries, further evidence on the effect of alcohol environment on individual alcohol use as well as cardiovascular risk is urgently needed. Therefore, we carried out data analysis from a peri-household cohort study in southern India here to investigate whether access to and availability of alcohol outlets in the local neighborhood is related with alcohol consumption and cardiovascular risk factors.

MATERIALS AND METHODS

Study Participants

The Andhra Pradesh children and parents study (APCAPS) study has been explained previously (18, 19). In short, it's an inter-generation cohort in south India, which started with the follow-up of the participants of the Hyderabad Nutrition Trial (HNT) conducted from 1987 to 1990. It was conducted in 29 villages close to Hyderabad in Ranga Reddy district, Andhra Pradesh. The data used in this cross-sectional analysis are from the 3rd follow-up where the index participants of HNT and their family members were enrolled. Between 2010 and 2012, data on sociodemographic features, lifestyle-related factors, anthropometric measurements, and heart and blood vessel biomarkers of study participants was collected (20–22). Of the 6,659 participants from 3rd follow-up, current analysis is based on data from 6,156 participants after removing 503 participants with missing information on household address, sociodemographic features, or drinking quantity. For analysis of association between alcohol environment and cardiovascular risk factors, data from n = 5,641 participants was considered after removing participants with diagnosed heart disease and/or missing data on lifestyle risk factors.

Global Positioning System-Dependent Surveys of Alcohol Environment

In 2016, geographic coordinates (latitude and longitude) of all the alcohol outlets in study villages were captured by Global Positioning System (GPS). Both availability and accessibility were examined to measure neighborhood alcohol environment. Availability of alcohol outlets was measured near the participants' households and in the entire village by determining density of outlets in two buffering regions of participants' households, 400 and 1,600 m, respectively. The degree of accessibility of an alcohol outlet was measured as the distance from a household to the closest outlet. The R software 3.5.1 was adopted to obtain the geography exposures.

Alcohol Intake and Cardiovascular Risk Factors

Data on alcohol intake were collected through questionnaire by well-experienced researchers in the 3rd follow-up. Fasting glucose, insulin, body mass index (BMI), waist circumference, waist-hip-ratio (WHR), blood pressure, serum triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were analyzed as cardiovascular risk factors herein. Fasting blood specimens were collected and prepared for physiological measurements and biochemical assays in the 3rd follow-up (19). Glucose level was estimated *via* the glucose oxidase/peroxidase-4-aminophenazone-phenol procedure. Insulin level was estimated using an electrochemiluminescence immunoassay. Concentrations of triglycerides and cholesterols (HDL, total) were measured using enzymatic calorimetric method (23, 24). LDL-C level was calculated by standard Friedewald–Fredrickson equation (25). The anthropometry evaluations included weight (identified to the nearest 0.1 kg by digitalized SECA scale), height (nearest 1 mm by portable plastic stadiometer), as well as waist circumference and hip circumference (nearest 1 mm by portable plastic stadiometer). The BMI was calculated by dividing weight in kilograms by the square of height in meters. The WHR was calculated by dividing waist circumference by hip circumference. The blood pressure was measured at the right arm in the seated posture *via* an oscillometry equipment (Omron M5-I). Three results were recorded and the average value was considered for these measurements.

Covariates

The data on sociodemographic and lifestyle variables such as age, gender, educational level (illiterate, primary school,

middle school, and above), occupation (unskilled, skilled, and others), Standard of Living Index (SLI) (low, middle, and high), smoking (never, former, and current), drinking (gram/day), and physical activity (extremely inactive, sedentary, moderately active, and vigorously active) were collected using standardized questionnaires by practiced researchers. The SLI was adopted to measure the family socioeconomic conditions (20). The data on diet intake (in the last year) and physical activities (in the last week) were gathered by semi-quantitation questionnaires (19).

Statistical Analysis

Considering the possible clustering of neighborhood alcohol environment, three-level mixed-effects linear regression was employed to evaluate the relationship between the densities and distances of alcohol outlets (exposures) with individual level of alcohol consumption (outcome 1) and cardiovascular risk factors (outcome 2). In the analysis of alcohol consumption, age (continuous, year), and gender [categorical, (male and female)] were adjusted in model 1; education level [categorical, (illiterate, primary school, and middle school and above)], occupation [categorical, (unskilled, skilled, and others)], and SLI [categorical, (low, middle, and high)] were further adjusted in model 2. In the analysis of cardiovascular risk factors, we adjusted for same variables in model 1 and 2; we further included tobacco use [categorical, (never, former, and current)], physical activity [categorical, (extremely inactive, sedentary, moderately active, and vigorously active)], and daily energy intake (continuous, kcal/day) in model 3. To account for the effect of disease diagnosis on behaviors, we performed a sensitivity analysis by excluding participants with diagnosed high blood pressure and/or diabetic disease to account for the effect of disease diagnosis on behaviors.

Stata software 15.1 was used for statistical analyses. PASS software 15.0 was used for power analysis in linear regression. Take SBP for example, a sample size of 5,641 achieves 99% power to detect a change in slope from 0.00 under the null hypothesis to 0.31 under the alternative hypothesis when the standard deviation of the alcohol outlet density (units/km^2) within 400 m buffering area is 2.96, the standard deviation of SBP (mmHg) is 15.89, and the two-sided significance level is 0.05.

RESULTS

Baseline Characteristics

Our data set for the analysis of the association between alcohol environment and cardiovascular risk factors included 5,641 individuals (3,244 men and 2,397 women) residing in 29 villages with median age of 29.1 years. **Table 1** presents the sociodemographic characteristics of participants, densities and distances of alcohol outlets, and measures of alcohol intake and cardiovascular risk factors. The median intake of alcohol was 29.1 gram (interquartile range: 68.6 gram) per day and the densities of alcohol outlets (on and/or off-premise) within 400 m were higher than that within 1,600 m.

TABLE 1 | Socio-demographic, food environment, and biological characteristics of APCAPS participants.

Characteristics (*N* = 5,641)	All	
	Median	**P5-P95**
Socio-demographic factors		
Age (years)	29.1	16.2–60.0
Sex (%)		
Male	57.5	
Female	42.5	
Education (%)		
Illiterate	35.7	
Primary school	23.3	
Middle school and above	41.0	
Occupation (%)		
Unskilled	41.32	
Skilled	27.83	
Others	30.85	
Standard of living index (%)		
Low	27.3	
Middle	37.6	
High	35.2	
Alcohol drinking (g/day)	29.1	0–373.6
Energy intake (kcal/day)	2117.3	1106.2–3987.4
Smoking status (%)		
Never	74.8	
Former	1.1	
Current	24.1	
Physical activity (%)		
Extremely inactive	15.2	
Sedentary	54.7	
Moderately active	25.1	
Vigorously active	5.0	
Alcohol environment		
Alcoholoutlet density (units/km^2)		
≤400 m	4.0	0–9.9
≤1,600 m	0.4	0.1–1.0
Distance to the nearest outlet(m)	159.8	31.0–505.8
Biological characteristics		
BMI (Kg/m^2)	20.0	15.3–27.4
Waist circumference (mm)	705.0	563.0–905.5
WHR	0.8	0.7–1.0
Systolic blood pressure (mmHg)	117.3	99.7–150.0
Diastolic blood pressure (mmHg)	76.7	59.3–101.3
Fasting glucose (mg/dl)	90.9	75.5–118.1
Insulin (Uu/ml)	5.2	1.1–16.4
Triglycerides (mmol/L)	1.2	0.6–3.1
Total cholesterol (mmol/L)	4.2	2.8–6.04
HDL cholesterol (mmol/L)	1.1	0.7–1.7
LDL cholesterol (mmol/L)	2.4	1.3–3.9

P5, 5th percentile; P95, 95th percentile.

Alcohol Outlet and Alcohol Consumption

Table 2 presents associations between availability and accessibility of alcohol outlets and individual level of alcohol

TABLE 2 | Association between alcohol availability and accessibility with individual level of alcohol intake in APCAPS participants (n = 6,156).

	Model 1			Model 2		
	β	95% *CI*	*p*	β	95% *CI*	*p*
Outlet density in 400 m buffer (units/km^2)						
Linear, per 1- units/km^2 increment	0.06	−1.97, 2.09	0.956	0.14	−1.87, 2.14	0.893
Tertile 1	Reference			Reference		
Tertile 2	6.72	−8.76, 22.21	0.395	8.13	−7.16, 23.43	0.297
Tertile 3	4.26	−13.20, 21.71	0.633	5.50	−11.77, 22.76	0.533
Outlet density in 1,600 m buffer (units/km^2)						
Linear, per 1- units/km^2 increment	−25.19	−56.15, 5.77	0.111	−23.76	−54.30, 6.77	0.127
Tertile 1	Reference			Reference		
Tertile 2	1.85	−21.11, 24.80	0.875	3.21	−19.41, 25.82	0.781
Tertile 3	−11.73	−32.06, 8.60	0.258	−10.69	−30.73, 9.35	0.296
Distance to the nearest outlet						
Linear, per 100 m increment	−0.75	−3.35, 1.86	0.574	−0.91	−3.48, 1.67	0.490
Tertile 1	Reference			Reference		
Tertile 2	−5.01	−15.88, 5.85	0.366	−4.23	−14.95, 6.50	0.440
Tertile 3	**−14.07**	**−26.02,−2.12**	**0.021**	**−14.40**	**−26.21,−2.59**	**0.017**

Model 1 is adjusted for age and sex. Model 2 is adjusted for model 1 + education, occupation, and Standard of Living Index.
Bold number indicates that the estimates reach statistical significance.

consumption. In model 1, compared with participants at the lowest tertile, those at the highest tertile of distance to the nearest alcohol outlet were more likely to have lower level of alcohol consumption [−14.07 g/day, 95% *CI*: −26.02, −2.12]. The association stayed robust in fully adjusted model 2 (−14.40 g/day, 95% *CI*: −26.21, −2.59). There was no association between density of alcohol outlet within 400 m buffering area or 1,600 m buffering area with daily alcohol intake.

Alcohol Outlet and Cardiovascular Risk Factors

The association between availability and accessibility of alcohol outlets and cardiovascular risk factors is presented in **Table 3**. In fully adjusted models, a unit per km^2 increase in alcohol outlets' density within 400 m buffering area was associated with an increase in waist circumference (1.45 mm, 95% *CI*: 0.13, 2.77), systolic blood pressure (SBP) (0.29 mmHg, 95% *CI*: 0.09, 0.49), and diastolic blood pressure (DBP) (0.19 mmHg, 95% *CI*: 0.03, 0.35). There was no association between densities of alcohol outlets within 1,600 m buffering area with cardiovascular risk factors.

In fully adjusted models, a unit per 100 m increase in distance to the closest alcohol outlet was associated with a decrease in waist circumference (−2.39 mm, 95% *CI*: −4.18, −0.59), SBP (−0.41 mmHg, 95% *CI*: −0.68, −0.15), and DBP (−0.29 mmHg, 95% *CI*: −0.51, −0.07). Association between density and distance of alcohol outlet with other cardiovascular risk factors was weak and inconsistent across different models.

Sensitivity Analysis

Supplementary Table 1 presents associations between availability and accessibility of alcohol outlets and cardiovascular risk factors after excluding participants with high blood pressure and diabetic disease (n = 5,294). The results were largely unchanged except the association between alcohol outlets density within 400 m buffering area and waist circumference. The significant association disappeared in fully adjusted model (1.15 mm, 95% *CI*: −0.12, 2.43).

DISCUSSION

We examined associations between neighborhood alcohol environment with individual level alcohol intake and cardiovascular risk factors in data from the 3rd wave of follow-up of APCAPS. Greater distance to the nearest alcohol outlet was associated with a lower daily alcohol intake, waist circumference and blood pressure. Higher density of alcohol outlets within 400 m buffering area was associated with higher waist circumference and blood pressure. There was no link found between alcohol outlets within 1,600 m buffering zone and daily alcohol intake and cardiovascular risk factors. To the best of our knowledge, this is the first study to examine both availability and accessibility of alcohol outlets in the local neighborhood in relation to both alcohol intake and multiple cardiovascular risk factors in India.

Previous studies have indicated that density of alcohol outlets is significantly associated with increased alcohol consumption in developed countries (26–28). Few studies have been reported from the low- and middle-income countries. A study carried out in rural South Africa found that alcohol outlet density was not associated with prevalence of heavy drinking (11), which was in accordance with our results. We found no association between density of alcohol outlets within 400 m buffering area or 1,600 m buffering area with daily alcohol intake. Azar et al. found significant association between density

TABLE 3 | Association between alcohol availability and accessibility with cardiovascular risk factors in APCAPS participants (n = 5,641).

	Model 1			Model 2			Model 3		
	β	95% *CI*	*p*	β	95% *CI*	*p*	B	95% *CI*	*p*
Glucose									
Alcohol outlet density (units/km^2)									
≤400 m	0.09	−0.20, 0.37	0.557	0.05	−0.24, 0.34	0.741	0.06	−0.22, 0.34	0.684
≤1600 m	2.46	−1.74, 6.67	0.251	2.29	−1.90, 6.47	0.284	2.36	−1.67, 6.38	0.251
Distanceto the nearest outlet (100 m)	−0.18	−0.57, 0.21	0.372	−0.14	−0.53, 0.25	0.472	−0.15	−0.54, 0.24	0.454
Insulin									
Alcohol outlet density (units/km^2)									
≤400 m	0.08	−0.01, 0.18	0.095	0.05	−0.05, 0.14	0.328	0.04	−0.05, 0.14	0.380
≤1600 m	1.05	−0.38, 2.49	0.151	0.91	−0.52, 2.33	0.213	0.90	−0.54, 2.34	0.220
Distance to the nearest outlet (100 m)	−0.73	−1.63, 0.16	0.109	−0.47	−1.36, 0.41	0.296	−0.46	−1.34, 0.43	0.312
BMI									
Alcohol outlet density (units/km^2)									
≤400 m	**0.06**	**0.01, 0.11**	**0.025**	0.04	−0.01, 0.09	0.096	0.04	−0.01, 0.09	0.130
≤1600 m	0.48	−0.21, 1.18	0.171	0.47	−0.20, 1.15	0.171	0.46	−0.24, 1.15	0.197
Distance to the nearest outlet (100 m)	**−0.08**	**−0.16,−0.01**	**0.021**	−0.07	−0.14, 0.00	0.067	−0.06	−0.13, 0.01	0.076
Waist circumference									
Alcohol outlet density (units/km^2)									
≤400 m	**2.03**	**0.68, 3.38**	**0.003**	**1.53**	**0.23, 2.84**	**0.021**	**1.45**	**0.13, 2.77**	**0.031**
≤1,600 m	13.92	−4.50, 32.35	0.139	14.50	−3.15, 32.14	0.107	13.91	−4.20, 32.02	0.132
Distance to the nearest outlet (100 m)	**−2.92**	**−4.77,−1.08**	**0.002**	**−2.44**	**−4.23,−0.64**	**0.008**	**−2.39**	**−4.18,−0.59**	**0.009**
WHR*									
Alcohol outlet density (units/km^2)									
≤400 m	0.61	−0.22, 1.45	0.152	0.51	−0.31, 1.34	0.223	0.48	−0.34, 1.31	0.251
≤1,600 m	10.87	−1.52, 23.27	0.086	11.27	−0.84, 23.38	0.068	11.20	−0.99, 23.40	0.072
Distance to the nearest outlet (100 m)	−0.68	−1.81, 0.44	0.232	−0.68	−1.78, 0.43	0.230	−0.66	−1.76, 0.44	0.241
Systolic blood pressure									
Alcohol outlet density (units/km^2)									
≤400 m	**0.31**	**0.11, 0.51**	**0.002**	**0.29**	**0.09, 0.49**	**0.004**	**0.29**	**0.09, 0.49**	**0.005**
≤1600 m	2.74	−0.26, 5.74	0.074	2.75	−0.23, 5.74	0.071	2.76	−0.24, 5.75	0.071
Distanceto the nearest outlet (100 m)	**−0.44**	**−0.71,−0.17**	**0.001**	**−0.42**	**−0.68,−0.15**	**0.002**	**−0.41**	**−0.68,−0.15**	**0.002**
Diastolic blood pressure									
Alcohol outlet density (units/km^2)									
≤400 m	**0.22**	**0.05, 0.38**	**0.009**	**0.20**	**0.03, 0.36**	**0.018**	**0.19**	**0.03, 0.35**	**0.020**
≤1,600 m	2.20	−0.20, 4.59	0.072	2.27	−0.12, 4.67	0.063	2.28	−0.12, 4.68	0.063
Distanceto the nearest outlet (100 m)	**−0.31**	**−0.53,−0.09**	**0.006**	**−0.29**	**−0.51,−0.07**	**0.009**	**−0.29**	**−0.51,−0.07**	**0.010**
Triglycerides									
Alcohol outlet density (units/km^2)									
≤400 m	−0.00	−0.01, 0.01	0.757	−0.00	−0.02, 0.01	0.658	−0.00	−0.02, 0.01	0.618
≤1,600 m	0.02	−0.14, 0.19	0.780	0.04	−0.13, 0.21	0.674	0.04	−0.13, 0.21	0.679
Distanceto the nearest outlet (100 m)	0.00	−0.01, 0.02	0.719	0.00	−0.01, 0.02	0.725	0.00	−0.01, 0.02	0.711
Total cholesterol									
Alcohol outlet density (units/km^2)									
≤400 m	−0.01	−0.02, 0.01	0.292	−0.01	−0.03, 0.00	0.174	−0.01	−0.03, 0.00	0.154
≤1,600 m	−0.03	−0.26, 0.21	0.835	−0.02	−0.26, 0.21	0.842	−0.02	−0.26, 0.21	0.849
Distanceto the nearest outlet (100 m)	−0.00	−0.02, 0.01	0.664	−0.00	−0.02, 0.02	0.792	−0.00	−0.02, 0.02	0.809
HDL cholesterol									
Alcohol outlet density (units/km^2)									
≤400 m	−0.00	−0.01, 0.00	0.716	−0.00	−0.01, 0.00	0.878	−0.00	−0.01, 0.00	0.886
≤1,600 m	−0.07	−0.15, 0.02	0.118	−0.07	−0.15, 0.02	0.110	−0.07	−0.15, 0.02	0.110
Distanceto the nearest outlet (100 m)	0.00	−0.00, 0.01	0.497	0.00	−0.01, 0.01	0.701	0.00	−0.01, 0.01	0.704
LDL cholesterol									
Alcohol outlet density (units/km^2)									
≤400 m	−0.00	−0.02, 0.01	0.599	−0.01	−0.02, 0.01	0.354	−0.01	−0.02, 0.01	0.326
≤1600 m	0.03	−0.16, 0.22	0.766	0.03	−0.16, 0.22	0.775	0.03	−0.16, 0.22	0.777
Distanceto the nearest outlet (100 m)	−0.01	−0.02, 0.01	0.334	−0.01	−0.02, 0.01	0.523	−0.01	−0.02, 0.01	0.535

**Independent variable multiplies 1,000 to show more information. Model 1 is adjusted for age, sex. Model 2 is adjusted for model 1 + education, occupation, and Standard of Living Index. Model 3 is adjusted for model 2 + tobacco, physical activity, and energy.*
Bold number indicates that the estimates reach statistical significance.

of alcohol outlets and clubs with risky drinking only existed among residents in urban communities but not in rural areas of Australia (29). On the other hand, a systematic review found that density measures are far more frequently examined than distance measures in studies on alcohol environment and alcohol consumption (30). No significant association was found between the physical distance from an individual's home to their nearest alcohol outlet with frequency and quantity of alcohol consumption in both urban and mixed communities of developed countries (31–33). However, a study carried out in Tanzania found that close distance to alcohol outlets may facilitate and increase adolescent alcohol use (10). In the current study, greater distance to the nearest alcohol outlet was associated with a decrease in daily alcohol consumption. The relationship between neighborhood alcohol outlet density and distance with alcohol consumption is complex and may vary due to differences in neighborhood design, travel patterns, local alcohol control policies, and enforcement, as well as drinking norms (34).

In a previous study carried out in south India, Li et al. found that higher density of unhealthy food vendors was associated with increased prevalence of obesity-related outcomes and blood pressure (35). Immoderate consumption of alcohol, like unhealthy food, is associated with serious health problems (36). To our knowledge, no study has been reported to assess the association between densities or physical distance of alcohol outlets with individual levels of cardiovascular risk factors, such as adiposity measures, glucose-insulin, blood pressure, and lipid profile. We found that not only density of alcohol outlets but also distance to the nearest alcohol outlet were associated with waist circumference and blood pressure. Annual gain in waist circumference was associated with increased consumption of alcoholic beverages in the PREDIMED trial (37). A systematic review and meta-analysis found that a reduction in alcohol intake was associated with increased blood pressure reduction in people who drank more than two drinks per day (38). Higher density and lower physical distance may increase the frequency of cues related to drinking and make alcohol more accessible, thus increasing the risk of obesity and high blood pressure through immoderate alcohol consumption.

Some limitations of this study must be acknowledged. One thing is that the coordinates of alcohol outlets were derived in 2016, which was 4 years after the third wave of follow-up in APCAPS. The temporal association between alcohol environment with higher levels of waist circumference and blood pressure cannot be ascertained in the present study. Awareness of having CVDs may change the behavior of alcohol access and alcohol drinking in participants and generate bias (39). Thus, we conducted sensitivity analysis in dataset after excluding participants with diagnosed hypertension and diabetes. The results were largely unchanged. Other limitations should also be mentioned. We only assessed the physical availability and accessibility of alcohol outlets. The available data did not allow us to look into other alcohol environment factors such as travel patterns, local alcohol control policies, or drinking norms, which could also influence alcohol consumption as well as cardiovascular risk factors. Moreover, the resulting data on alcohol use was self-reported through semi-quantitative questionnaires, which may have resulted in under-reporting by respondents (40).

CONCLUSION

Despite limitations, our study is the first to examine the association between neighborhood availability and accessibility of alcohol outlets with alcohol consumption as well as cardiovascular risk factors in south India. Shorter distance to the nearest alcohol outlet was associated with increased alcohol consumption. Higher waist circumference and blood pressure were associated with a shorter distance to the nearest alcohol outlet as well as a higher density of alcohol outlets. Neighborhood availability of alcohol outlets within immediate locality of participants' households had a closer relationship with cardiovascular risk factors than that within the whole village. Public health policies designed to limit neighborhood availability and accessibility of alcohol outlets should be encouraged in south India.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YL and PM: study conception and study design. AA, BK, and SK: data analysis. YL, PM, and AA: manuscript drafting. All authors have approved the submitted version and agreed to publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.844086/full#supplementary-material

REFERENCES

1. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* (2017) 390:1151–210. doi: 10.1016/S0140-6736(17)32152-9
2. India State-Level Disease Burden Initiative CVD Collaborators. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990-2016. *Lancet Glob Health.* (2018) 6:e1339–51. doi: 10.1016/S2214-109X(18)30407-8
3. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet.* (2018) 392:1015–35.
4. Bell S, Daskalopoulou M, Rapsomaniki E, George J, Britton A, Bobak M, et al. Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records. *BMJ.* (2017) 356:j909. doi: 10.1136/bmj.j909
5. Jyani G, Prinja S, Ambekar A, Bahuguna P, Kumar R. Health impact and economic burden of alcohol consumption in India. *Int J Drug Policy.* (2019) 69:34–42. doi: 10.1016/j.drugpo.2019.04.005
6. Popova S, Giesbrecht N, Bekmuradov D, Patra J. Hours and days of sale and density of alcohol outlets: impacts on alcohol consumption and damage: a systematic review. *Alcohol Alcohol.* (2009) 44:500–16.
7. Chen MJ, Grube JW, Gruenewald PJ. Community alcohol outlet density and underage drinking. *Addiction.* (2010) 105:270–8. doi: 10.1111/j.1360-0443.2009.02772.x
8. Paschall MJ, Lipperman-Kreda S, Grube JW. Effects of the local alcohol environment on adolescents' drinking behaviors and beliefs. *Addiction.* (2014) 109:407–16. doi: 10.1111/add.12397
9. Morrison CN, Byrnes HF, Miller BA, Wiehe SE, Ponicki WR, Wiebe DJ. Exposure to alcohol outlets, alcohol access, and alcohol consumption among adolescents. *Drug Alcohol Depend.* (2019) 205:107622. doi: 10.1016/j.drugalcdep.2019.107622
10. Ibitoye M, Kaaya S, Parker R, Likindikoki S, Ngongi L, Sommer M. The influence of alcohol outlet density and advertising on youth drinking in urban Tanzania. *Health Place.* (2019) 58:102141. doi: 10.1016/j.healthplace.2019.05.019
11. Leslie HH, Ahern J, Pettifor AE, Twine R, Kahn K, Gomez-Olive FX, et al. Collective efficacy, alcohol outlet density, and young men's alcohol use in rural South Africa. *Health Place.* (2015) 34:190–8. doi: 10.1016/j.healthplace.2015.05.014
12. Treno AJ, Johnson FW, Remer LG, Gruenewald PJ. The impact of outlet densities on alcohol-related crashes: a spatial panel approach. *Accid Anal Prev.* (2007) 39:894–901. doi: 10.1016/j.aap.2006.12.011
13. Anderson P, Chisholm D, Fuhr DC. Effectiveness and cost-effectiveness of policies and programmes to reduce the harm caused by alcohol. *Lancet.* (2009) 373:2234–46. doi: 10.1016/S0140-6736(09)60744-3
14. Nesoff ED, Milam AJ, Pollack KM, Curriero FC, Bowie JV, Knowlton AR, et al. Neighbourhood alcohol environment and injury risk: a spatial analysis of pedestrian injury in Baltimore City. *Inj Prev.* (2019) 25:350–6. doi: 10.1136/injuryprev-2018-042736
15. Theall KP, Scribner R, Cohen D, Bluthenthal RN, Schonlau M, Lynch S, et al. The neighborhood alcohol environment and alcohol-related morbidity. *Alcohol.* (2009) 44:491–9. doi: 10.1093/alcalc/agp042
16. Richardson EA, Hill SE, Mitchell R, Pearce J, Shortt NK. Is local alcohol outlet density related to alcohol-related morbidity and mortality in Scottish cities? *Health Place.* (2015) 33:172–80. doi: 10.1016/j.healthplace.2015.02.014
17. Theall KP, Wallace M, Felker-Kantor E, Madkour AS, Brashear M, Ferguson T, et al. Neighborhood alcohol environment: differential effects on hazardous drinking and mental health by sex in persons living with HIV (PLWH). *AIDS Behav.* (2019) 23:3237–46. doi: 10.1007/s10461-019-02632-3
18. Kinra S, Rameshwar Sarma KV, Ghafoorunissa, Mendu VV, Ravikumar R, Mohan V, et al. Effect of integration of supplemental nutrition with public health programmes in pregnancy and early childhood on cardiovascular risk in rural Indian adolescents: long term follow-up of Hyderabad nutrition trial. *BMJ.* (2008) 337:a605. doi: 10.1136/bmj.a605
19. Kinra S, Radha Krishna KV, Kuper H, Rameshwar Sarma KV, Prabhakaran P, Gupta V, et al. Cohort profile: Andhra Pradesh Children and Parents Study (APCAPS). *Int J Epidemiol.* (2014) 43:1417–24. doi: 10.1093/ije/dyt128
20. Ebrahim S, Kinra S, Bowen L, Andersen E, Ben-Shlomo Y, Lyngdoh T, et al. The effect of rural-to-urban migration on obesity and diabetes in India: a cross-sectional study. *PLoS Med.* (2010) 7:e1000268. doi: 10.1371/journal.pmed.1000268
21. Kinra S, Johnson M, Kulkarni B, Rameshwar Sarma KV, Ben-Shlomo Y, Smith GD. Socio-economic position and cardiovascular risk in rural Indian adolescents: evidence from the Andhra Pradesh children and parents study (APCAPS). *Public Health.* (2014) 128:852–9. doi: 10.1016/j.puhe.2014.06.005
22. Matsuzaki M, Sullivan R, Ekelund U, Krishna KVR, Kulkarni B, Collier T, et al. Development and evaluation of the Andhra pradesh children and parent study physical activity questionnaire (APCAPS-PAQ): a cross-sectional study. *BMC Public Health.* (2016) 16:48. doi: 10.1186/s12889-016-2706-9
23. Roeschlau P, Bernt E, Gruber W. Enzymatic determination of total cholesterol in serum. *Z Klin Chem Klin Biochem.* (1974) 12:226.
24. Siedel J, Schiefer S, Rosseneu M, Bergeaud R, De Keersgieter W, Pautz B, et al. Immunoturbidimetric method for routine determinations of apolipoproteins A-I, A-II, and B in normo- and hyperlipemic sera compared with immunonephelometry. *Clin Chem.* (1988) 34:1821–5. doi: 10.1093/clinchem/34.9.1816
25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* (1972) 18:499–502. doi: 10.1093/clinchem/18.6.499
26. Brenner AB, Borrell LN, Barrientos-Gutierrez T, Diez Roux AV. Longitudinal associations of neighborhood socioeconomic characteristics and alcohol availability on drinking: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Soc Sci Med.* (2015) 145:17–25. doi: 10.1016/j.socscimed.2015.09.030
27. Foster S, Hooper P, Knuiman M, Lester L, Trapp G. Associations between proposed local government liquor store size classifications and alcohol consumption in young adults. *Health Place.* (2018) 52:170–3. doi: 10.1016/j.healthplace.2018.06.001
28. Slutske WS, Deutsch AR, Piasecki TM. Neighborhood alcohol outlet density and genetic influences on alcohol use: evidence for gene-environment interaction. *Psychol Med.* (2019) 49:474–82. doi: 10.1017/S0033291718001095
29. Azar D, White V, Coomber K, Faulkner A, Livingston M, Chikritzhs T, et al. The association between alcohol outlet density and alcohol use among urban and regional Australian adolescents. *Addiction.* (2016) 111:65–72. doi: 10.1111/add.13143
30. Shih RA, Mullins L, Ewing BA, Miyashiro L, Tucker JS, Pedersen ER, et al. Associations between neighborhood alcohol availability and young adolescent alcohol use. *Psychol Addict Behav.* (2015) 29:950–9. doi: 10.1037/adb0000081
31. Abbey A, Scott RO, Smith MJ. Physical, subjective, and social availability: their relationship to alcohol consumption in rural and urban areas. *Addiction.* (1993) 88:489–99. doi: 10.1111/j.1360-0443.1993.tb02055.x
32. Scribner RA, Cohen DA, Fisher W. Evidence of a structural effect for alcohol outlet density: a multilevel analysis. *Alcohol Clin Exp Res.* (2000) 24:188–95. doi: 10.1111/j.1530-0277.2000.tb04590.x
33. Young R, Macdonald L, Ellaway A. Associations between proximity and density of local alcohol outlets and alcohol use among Scottish adolescents. *Health Place.* (2013) 19:124–30. doi: 10.1016/j.healthplace.2012.10.004
34. Schonlau M, Scribner R, Farley TA, Theall K, Bluthenthal RN, Scott M, et al. Alcohol outlet density and alcohol consumption in Los Angeles county and southern Louisiana. *Geospat Health.* (2008) 3:91–101. doi: 10.4081/gh.2008.235
35. Li Y, Mallinson PAC, Bhan N, Turner C, Bhogadi S, Sharma C, et al. Neighborhood physical food environment and cardiovascular risk factors in India: cross-sectional evidence from APCAPS. *Environ Int.* (2019) 132:105108. doi: 10.1016/j.envint.2019.105108
36. Cohen D, Rabinovich L. Addressing the proximal causes of obesity: the relevance of alcohol control policies. *Prev Chronic Dis.* (2012) 9:E94. doi: 10.5888/pcd9.110274
37. Konieczna J, Romaguera D, Pereira V, Fiol M, Razquin C, Estruch R, et al. Longitudinal association of changes in diet with changes in body weight and waist circumference in subjects at high cardiovascular risk: the PREDIMED trial. *Int J Behav Nutr Phys Act.* (2019) 16:139. doi: 10.1186/s12966-019-0893-3
38. Roerecke M, Kaczorowski J, Tobe SW, Gmel G, Hasan OSM, Rehm J. The effect of a reduction in alcohol consumption on blood pressure: a systematic

review and meta-analysis. *Lancet Public Health.* (2017) 2:e108–20. doi: 10.1016/S2468-2667(17)30003-8

39. Eames S, Hoffmann TC, Phillips NF. Evaluating stroke patients' awareness of risk factors and readiness to change stroke risk-related behaviors in a randomized controlled trial. *Top Stroke Rehabil.* (2014) 21(Suppl. 1):S52–62. doi: 10.1310/tsr21S1-S52
40. Bowen L, Bharathi AV, Kinra S, Destavola B, Ness A, Ebrahim S. Development and evaluation of a semi-quantitative food frequency questionnaire for use in urban and rural India. *Asia Pac J Clin Nutr.* (2012) 21:355–60.

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Predictors of Rehabilitation Referral Among Cardiovascular Surgical Patients

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Objective: Cardiovascular disease (CVD) continues to be the leading cause of mortality globally. Cardiac rehabilitation (CR) programs act by modifying the evolution of CVD and mortality; however, CR programs are under-used. The aim was to determine the profile of patients that received rehabilitation after cardiac surgery.

Patients and Methods: A retrospective observational study was conducted from January 2017 to December 2017 at a single center. The study sample was chosen among patients admitted to the Intensive Care Unit of the Hospital Gregorio Marañón/Gregorio Marañón General University Hospital. Socio-demographic and clinical variables were collected.

Results: In the present study, 336 patients underwent cardiac surgery of which 63.8% were men and 87.1% had ≥1 cardiovascular risk factors. Of the total cohort, 24.7% were operated for ischemic heart disease, 47.9% valvulopathy, 11% underwent combined surgery, 3.6% cardiac transplantation, 6.5% aneurysms, and 3.9% congenital disease. In-hospital respiratory rehabilitation was prescribed to all patients. Only 4.8% of the patients received motor rehabilitation and 13.8% were referred to CR. We found higher referral rates among patients with more cardiovascular risk factors, <65 years of age, and those undergoing coronary surgery and heart transplantation. Age, ischemic heart disease, and overweight were independent predictors of CR referral.

Conclusion: The benefit of CR programs after cardiac surgery is widely described; however, the referral rate to CR remains low. It is crucial to optimize referral protocols for these patients.

Keywords: cardiovascular rehabilitation, cardiovascular disease, cardiac surgical procedures, secondary prevention, referral and consultation

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INTRODUCTION

According to the latest report of the National Institute of Statistics regarding the causes of death in Spain in 2017, cardiovascular diseases (CVDs) continue to be the most prominent cause of death, representing 28.8% of total deaths (1). Further, ischemic heart disease is the leading cause of premature death in Spain. According to the Cardiovascular Surgery Registry in Spain (2), about

35,576 procedures are performed per year, of which 22,201 are major surgeries (3). Our hospital is one of the points of reference for this type of surgery, including heart transplantation.

Cardiac rehabilitation (CR) programs act by modifying the evolution of disease, controlling cardiovascular risk factors, and reducing morbidity and mortality (4). As a result, CR programs are currently considered as a Class IA indication in the treatment of heart disease (5). In clinical practice guidelines, CR is recommended for patients with CVD (6), heart failure (7), undergoing revascularization (8), and stable coronary heart disease (9). Similarly, these CR programs are indicated after heart valve disease (HVD) (10), heart transplant (HT) (11), and atrial fibrillation (12). Importantly, CR programs added to respiratory rehabilitation during and after admission, are cost-effective in these patients (13). To this point, in patients undergoing cardiac surgery, CR and respiratory rehabilitation during admission favor a faster recovery, reduce postoperative complications, and shorten hospital stay (14). Despite this, the implementation of CR programs is extremely low in many countries, including ours, with less than 10% of patients being rehabilitated (15). Therefore, it is critical to identify characteristics that predict CR referral in these surgical patients so that targeted interventions can be developed to improve CR referral.

There are reviews in the literature that suggest that CR programs are not available in more than 60% of countries around the world (16). In a recent study that analyzed the characteristics of different CR programs around the world, it was concluded that only 54.7% of the countries offered some type of CR program (17).

The objective of our study was to determine the socio-demographic factors and percentage of patients undergoing cardiac surgery, who performed an in-hospital respiratory rehabilitation program and outpatient CR program in order to identify patient characteristics that predict referral to CR programs.

MATERIALS AND METHODS

This retrospective observational study was approved by the Research Ethics Committee of the Gregorio Marañón Health Research Institute on July 2, 2018. The inclusion criteria for this study included: admission to the Intensive Care Unit of the Hospital Gregorio Marañón/Gregorio Marañón General University Hospital from January 2017 to December 2017 after cardiac surgery, not deceased during the post-operative period, not suffering from significant cognitive or severe physical impairment that hinders the rehabilitative treatment, having been assessed by the rehabilitation service during their admission, and living in Madrid.

In our hospital, the program starts from admission, beginning in the immediate postoperative phase (phase I) through supervised teaching of respiratory physiotherapy exercises, postural recommendations, mobility exercises, and stimulation of activities in a progressive way. After hospital discharge, the patient is referred as a candidate for the outpatient CR program (phase II), which consists of a supervised program of aerobic and strength exercises. It also includes psychological care and education for the control of cardiovascular risk factors and medication management. In this program, the objectives are improving functional capacity and offer the necessary knowledge for the safe practice of exercise and healthy lifestyle once the program is finished, continuing at home (phase III).

Information was collected from the electronic medical records, including socio-demographic data such as sex, age, and reference hospital as well as clinical data including cardiovascular risk factors, personal history of diseases (heart, respiratory, neurological, musculoskeletal, psychiatric diseases, or others), and the cause of surgery (ischemic heart disease, valve heart disease, heart transplant, aneurysm, congenital heart disease, and others). A body mass index greater than 25 was considered overweight.

In addition, the date of admission and hospital discharge, the date of surgery and whether there were post-surgical complications was collected. Information on the rehabilitation performed was collected that included respiratory, motor, and/or CR. Among those referred to CR, the date of CR referral, the referring department (i.e., cardiology or rehabilitation), the follow-up phase in which they were referred (i.e., during admission or in outpatient consultations), enrollment status into the CR program, and the start date of the program was also collected. It is important to note that regarding the referral to the CR program, we refer to the phase II of CR, performed outside the hospital in a center that belongs to the same health complex (outpatient CR program). Being a retrospective study, the data were collected months after cardiac surgery, and after the period for carrying out the CR program had elapsed, which allowed the data listed above to be collected. All data were collected manually through electronic medical records. As it was an observational study, the ethics committee of our center accepted the exemption of informed consent.

This data was stored on an Excel data collection sheet (Microsoft Office for Windows XP) and then statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0. The results of the numerical variables were presented using their mean and standard deviation. For categorical variables, the results were shown in frequencies and percentages. The numerical variables with non-normal distribution were presented by means of their median and interquartile range (25th percentile; 75th percentile). The normality analysis was assessed with the Kolmogorov–Smirnov test. To compare differences between two or more groups, non-parametric tests were applied. The association between variables was analyzed using the Pearson Chi-square test. Regression models were created to evaluate the association between patient characteristics and CR referral, univariate modeling was performed adjusting for age and sex, and predictors that were significant were included for final multivariate modeling. Findings are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Model assumptions were assessed graphically, and missing data were omitted. In all cases, two-tailed p-values < 0.05 were considered statistically significant.

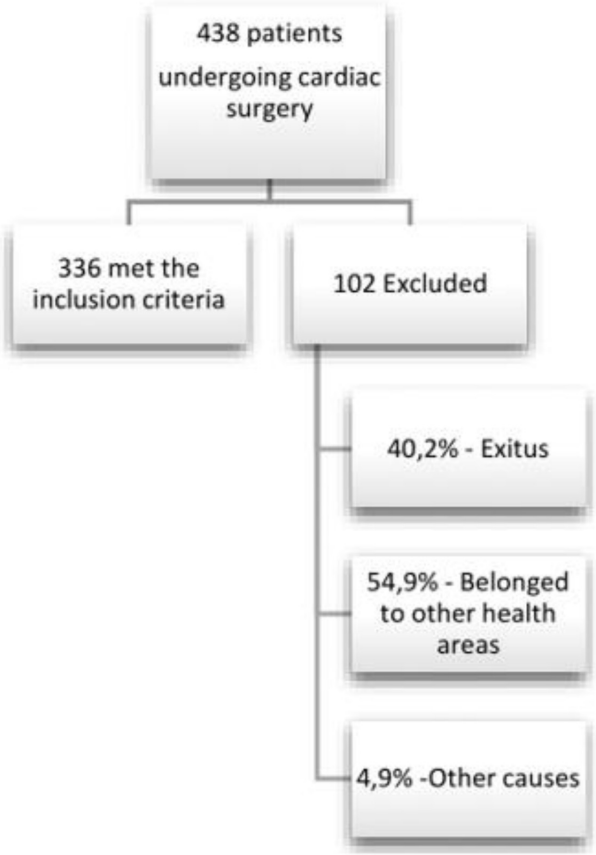

FIGURE 1 | Flow chart of study design.

RESULTS

As shown in **Figure 1**, 438 patients underwent cardiac surgery in 2017 in our hospital. Of these patients, 102 patients were excluded: 40.2% ($N = 41$) due to exits, 54.9% ($N = 56$) for belonging to other health areas, and 4.9% ($N = 5$) for other causes (e.g., not assessed by the rehabilitating physician). There were 336 patients that met the inclusion criteria in the study. Of the patients included, 63.8% ($N = 213$) of these patients were men. The average age of the cohort was 64.16 years (SD = ±12.96) and 87.1% ($N = 291$) had at least one cardiovascular risk factor. The most frequent cardiovascular risk factors were hypertension (66.8%, $N = 223$), dyslipidemia (57.1%, $N = 190$), and smoking (36.9%, $N = 122$). Additionally, 29.1% ($N = 97$) suffered from diabetes mellitus, 10.6% ($N = 35$) were overweight or obese, and 0.6% ($N = 2$) consumed alcohol abusively. Only one of them used other illicit drugs (**Table 1**).

Approximately 72.5% ($N = 242$) of the patients had suffered CVD before the surgical intervention. Of these, 19.8% ($N = 66$) had suffered heart failure, 1.8% ($N = 6$) congenital heart disease, 22.8% ($N = 76$) ischemic heart disease, 5.1% ($N = 17$) any cardiomyopathy, 5.4% ($N = 18$) had a pacemaker or an implantable automatic defibrillator, 46.8% ($N = 156$) heart valve

TABLE 1 | Sociodemographic and clinical data of the total sample.

Variable	
Sex female (%)	36.2% (*N* = 121)
Age (%)	Average 64.16 (SD 12.96)
<65	48.5 (*N* = 162)
≥65	51.5 (*N* = 174)
Healthcare area (% of patients)	–
Our hospital	28.2 (*N* = 94)
Hospital from the area	54.4 (*N* = 181)
Hospital from a different area	17.1 (*N* = 57)
CVRF (%)	87.1
HTA	66.8 (*N* = 223)
DL	57.1 (*N* = 190)
DM	29.1 (*N* = 97)
Overweight/obesity	10.6 (*N* = 35)
Tobacco	36.9 (*N* = 122)
Alcohol	0.6 (*N* = 2)
Other drugs	0.3 (*N* = 1)
Previous CV comorbidities (%)	72.5
HF	19.8 (*N* = 66)
CHD	1.8 (*N* = 66)
IHD	22.8 (*N* = 76)
Myocardiopathy	5.1 (*N* = 17)
Pacemarker/ICD	5.4 (*N* = 18)
HVD	46.8 (*N* = 156)
Arrhythmia	29 (*N* = 97)
Other comorbidities (%)	78.4
Pulmonary disease	18.3 (*N* = 61)
Neurological disease	19.5 (*N* = 65)
Musculoskeletal disease	17.8 (*N* = 59)
Psychiatric disease	7.2 (*N* = 24)
Other disease	68 (*N* = 227)
Diagnosis to surgery (%)	–
IHD	24.7 (*N* = 83)
HVD	47.9 (*N* = 161)
IHD + HVD	11 (*N* = 37)
HT	3.6 (*N* = 12)
Aneurysms	6.5 (*N* = 22)
CHD	3.9 (*N* = 13)
Others	10.4 (*N* = 35)
Complications after surgery (%)	53.3 (*N* = 180)
Performed RR (%)	100 (*N* = 336)
Performed MR (%)	4.8 (*N* = 16)
Contraindications for CRP (%)	3 (*N* = 10)
Hospital length stay (days)	Average 23.34 (min 2, max 235)
Referred to CRP (%)	13 (*N* = 46)
Referred by ambulatory cardiology	10.2
Referred by ambulatory rehabilitation	4
Referred by hospital cardiology	5
Referred by hospital rehabilitation	3
Started CRP (%)	12.2 (*N* = 41)
Waiting days to start the program	Average 136.1 (SD 98.03, max 473, min 9)

CVRF, cardiovascular risk factors; HTA, hypertension; DL, dyslipidemia; DM, diabetes mellitus; CV, cardiovascular; HF, heart failure; CHD, congenital heart disease; IHD, ischemic heart disease; ICD, implantable cardioverter defibrillator; HVD, heart valve disease; HT, heart transplant; RR, respiratory rehabilitation; MR, motor rehabilitation; CRP, cardiac rehabilitation program.

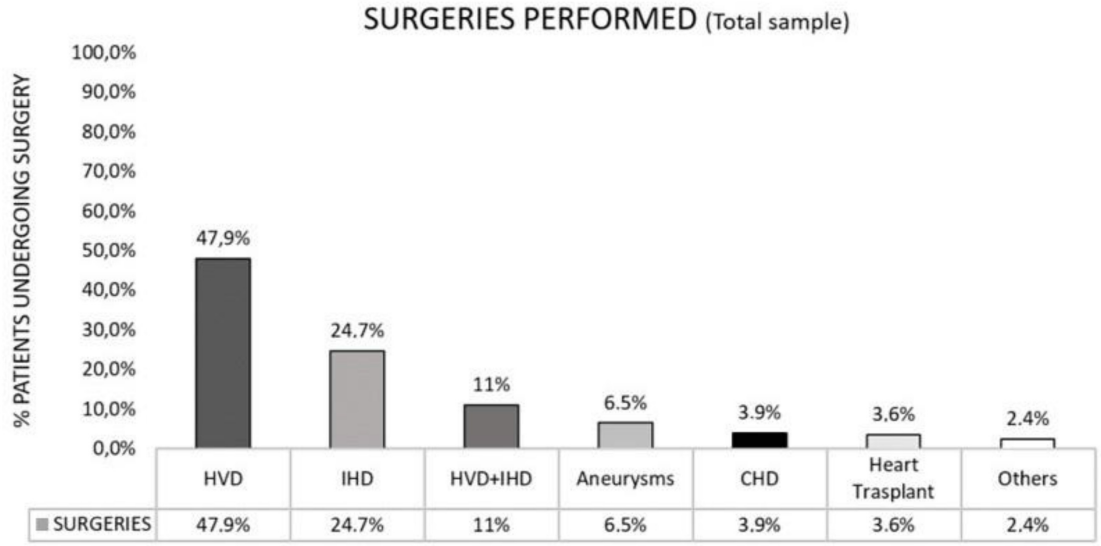

FIGURE 2 | Surgeries performed among the study population.

disease, and 29% ($N = 97$) by some arrhythmia (e.g., AF, extrasystoles). Furthermore, 78.4% ($N = 262$) had suffered another type of CVD not mentioned above (**Table 1**).

In relation to previous medical history of non-CVD, 18.3% ($N = 61$) had a history of respiratory diseases (e.g., SAS, COPD, or others), 19.5% ($N = 65$) neurological diseases (previous stroke or others), 17.8% ($N = 59$) suffered from musculoskeletal pathology (e.g., joint prostheses, low back pain, cervical pain), 7.2% ($N = 24$) had a history of psychiatric illness (e.g., depression, anxiety, psychosis) and 68% ($N = 227$) had other comorbidities not included in the previous categories (**Table 1**). Regarding the surgeries performed, 47.9% ($N = 161$) of the patients were operated for heart valve disease (HVD), 24.7% ($N = 83$) for isolated ischemic heart disease, 11% ($N = 37$) underwent combined surgery (heart valve and coronary surgery), 6.5% ($N = 22$) for aneurysm repair, 3.9% ($N = 13$) for congenital heart disease and 3.6% ($N = 12$) for heart transplant transplantation (**Figure 2**).

All patients were holistically evaluated by the medical rehabilitation team and received respiratory rehabilitation during their hospitalization (**Figure 3**). The average length of stay at the hospital was 24 days (SD ± 25.9) and 53.3% ($N = 180$) of the patients suffered some complications during the immediate post-operative period (**Table 1**).

Of the total of patients referred to CR ($N = 46$), most of them started the program [(90% $N = 41$)] and the average time from the referral to the beginning of phase II CR was 136 days (SD ± 98.03). Regarding the profile of patients referred to the phase II CR, there was a clear prevalence of men [71.7% ($N = 33$)] compared to women, although this did not reach statistical significance ($p = 0.229$) (**Tables 2**, **3**). Those with more complications and longer admission received motor rehabilitation [4.8% ($N = 16$)] and at discharge, only 13.8% ($N = 46$) were referred to CR (**Figure 3**). Of those admitted, only 3% ($N = 10$) presented absolute contraindications for referral to CPR. Most patients were referred by the Cardiology Department: 10.9% ($N = 5$) were referred by the cardiologist at the time of hospital discharge and 73.9% ($N = 34$) were referred by the cardiologist from external consultations area in the first control after hospital discharge. The rest of the patients were referred to the program by the rehabilitation department; 6.52% ($N = 3$) were referred at the time of hospital discharge and 8.7% ($N = 4$) were derived from external rehabilitation consultations in the first control after hospital discharge.

A higher referral rate was observed in patients <65 years of age (69.56% $N = 32$) ($p = 0.001$). Regarding the reason for surgery, 50% ($N = 23$) underwent coronary surgery, 15.2% ($N = 7$) underwent heart valve surgery, 13% ($N = 6$) underwent combined surgery (heart valve and coronary surgery), 15.2% ($N = 7$) received a heart transplant, 2.1% ($N = 1$) underwent aneurysms repair surgery and only two patients

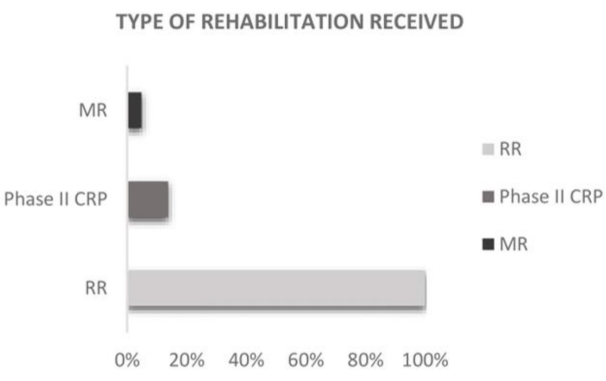

FIGURE 3 | Type of rehabilitation received among the study population.

TABLE 2 | Characteristics of patients referred to the phase II CRP.

Variable	
Sex female (%)	28.3 (*N* = 13)
Age (%)	Average 60.8
<65	69.5 (*N* = 32)
≥65	30.4 (*N* = 14)
Healthcare area (% of patients)	–
Our hospital	43.48 (*N* = 20)
Hospital from the area	45.65 (*N* = 21)
Hospital from a different area	10.87 (*N* = 5)
CVRF (%)	89.13 (*N* = 41)
HTA	63
DL	67.4
DM	37
Overweight/obesity	19.56
Tobacco	47.8
Alcohol	2.17
Other drugs	0
Previous CV comorbidities (%)	58.7 (*N* = 27)
HF	8.7
CHD	4.3
IHD	30.4
Myocardiopathy	6.5
Pacemarker/ICD	10.9
HVD	28.3
Arrhythmia	17.4
Other comorbidities (%)	76.1 (*N* = 35)
Pulmonary disease	17.4
Neurological disease	17.4
Musculoskeletal disease	15.2
Psychiatric disease	8.7
Other disease	65.2
Diagnosis to surgery (%)	–
IHD	50 (*N* = 23)
HVD	15.2 (*N* = 7)
IHD + HVD	13 (*N* = 6)
HT	15.21 (*N* = 7)
Aneurysms	2.1 (*N* = 1)
CHD	4.3 (*N* = 2)
Others	0
Complications after surgery (%)	65.21 (*N* = 30)
Performed RR (%)	100 (*N* = 46)
Performed MR (%)	0
Hospital length stay (days)	Average 28.09 (min 8, max 131)
CVRF (%)	–
0 CVRF	8.7
1 CVRF	19.6
2 CVRF	28.3
3 CVRF	21.7
4 CVRF	19.6
5 CVRF	2.1

N = 46 (13.8%).

CRP, cardiac rehabilitation program; CVRF, cardiovascular risk factors; HTA, hypertension; DL, dyslipidemia; DM, diabetes mellitus; CV, cardiovascular; HF, heart failure; CHD, congenital heart disease; IHD, ischemic heart disease; ICD, implantable cardioverter defibrillator; HVD, heart valve disease; HT, heart transplant; RR, respiratory rehabilitation; MR, motor rehabilitation; CRP, cardiac rehabilitation program.

(4.3%) underwent surgery for some type of congenital heart disease (**Figure 4**). Patients who underwent coronary surgery and heart transplantation had a greater CR referral rate ($p = 0.001$) than other surgical subpopulations (**Tables 2**, **3**). In addition, the analysis showed that the patients with more than three cardiovascular risk factors was associated with a higher referral to CR ($p = 0.0313$) and within these, being overweight was a predictor of increased referral ($p = 0.0172$). The average hospital stay among the referred patients was 28.09 days (SD ± 26.20) and 65.21% of them ($N = 30$) suffered some complication in the immediate postoperative period. Both parameters were not significant for the referral to phase II CR.

Multivariate analysis identified age (<65 years), ischemic heart disease diagnoses, and overweight/obesity as significant independent predictors of CR referral. We did not observe an association or interaction with sex, suggesting no differences in our sample (**Table 3**).

DISCUSSION

Early rehabilitation after surgery, beginning in the intensive care unit, reduces complications in the postoperative period. The incidence of cardiopulmonary, cognitive and neuro-orthopedic complications is lower with the early onset of rehabilitation (18). Specifically, the benefits of rehabilitation in patients with CVD have been widely described. It is presumed that these improvements are the result of exercise training, psychological counseling, and education in preventive strategies (e.g., medication adherence, improved cardiovascular risk factor control) (4, 5). Despite the scientific evidence to date, the levels of referral and use of these programs are low worldwide (16, 17).

In our study, we have focused on analyzing the referral to CR programs of patients undergoing cardiac surgery. We found low levels of referral from our center in 2017 (13.8%), with rates similar to other studies. For example, the Spanish Registry of CR Units (R-EUReCa), states that "The implementation of a CRP in many countries, among which is the ours, is extremely low rehabilitating less than 10% of the candidate patients" (15). The European CR Inventory Survey shows an even lower referral in our country (<3%) (19).

The patients most frequently referred were those who underwent revascularization surgery because of ischemic heart disease. These patients are the ones who benefit most frequently from CR programs. In this pathology, CR has shown clear benefits and is strongly recommended in clinical guidelines (8). Heart transplant was the second most frequent cause of surgery among patients who were referred to our CR program. In this type of surgery, CR has also demonstrated clear benefits (11). Other frequent surgeries such as heart valve replacement or aneurysm repair also benefit from post-operative CR (10).

In the present study, regarding the predictors of CR referral in surgical patients, we found that those under 65 years had a higher referral rate. This is similar to other studies and can be explained by various personal, clinical, and social factors (20). Older adults generally have a lower perception that exercise improves health, less family support, greater risk of social isolation, and also tend

TABLE 3 | Predictors of phase II cardiac rehabilitation program following cardiac surgery.

	Univariate			Age and sex adjusted			Multivariate		
Variable	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**	**OR**	**95% CI**	***p*-Value**
Sex (female)	0.67	0.3424–1.2933	0.2296	0.73	0.3702–1.4257	0.2529	1.01	0.5077–2.1754	0.2251
Age >65	0.4	0.2116–0.7619	0.0052	0.41	0.185–0.4325	<0.0001	0.32	0.1561–0.6517	0.0055
IHD surgery	3.81	2.0253–7.1752	<1e−04	4.76	2.4182–9.3669	<0.0001	3.57	1.7242–7.566	0.001
HVD surgery	0.25	0.1304–0.4819	<1e−04	0.28	0.1431–0.5406	0.0002	0.46	0.2175–0.9372	0.0241
Overweight/obesity	2.67	1.19–5.9758	0.0172	2.65	1.1591–6.0771	0.0209	2.52	1.0144–5.9889	0.0467
HT surgery	6.51	2.0084–21.1118	0.0018	4.56	1.3579–15.281	0.041			
Aneurysms surgery	0.92	0.2617–3.2339	0.8964	0.8	0.2236–2.8805	0.736			
CHD surgery	1.07	0.2293–4.9707	0.9335	0.83	0.1709–4.053	0.8202			
Other surgery	0.33	0.0757–1.4059	0.1329	0.28	0.0649–1.2346	0.093			
CVRF									
HTA	0.83	0.4437–1.5685	0.5736	1.04	0.5318–2.0313	0.9101			
DL	1.87	0.9778–3.593	0.0585	2.4	1.2165–4.7486	0.0116			
DM	1.51	0.8015–2.8602	0.2012	1.85	0.9537–3.6076	0.0687			
Tabaco	1.64	0.8879–3.0165	0.1144	1.39	0.7428–2.6111	0.3017			
>1 CVRF	0.98	0.4857–1.9861	0.9599						
>2 CVRF	1.04	0.5134–2.1058	0.9138						
>3 CVRF	2.25	1.0757–4.7155	0.0313						
Previous CV comorbidities	0.58	0.3063–1.1049	0.0979						
HF	0.66	0.2804–1.5386	0.3332						
CHD	3.01	0.5363–16.9011	0.2105						
IHD	1.68	0.8556–3.2854	0.1322						
Myocardiopathy	1.3	0.3579–4.6876	0.6934						
Pacemarker/ICD	2.44	0.8289–7.1931	0.1053						
HVD	0.52	0.2721–0.9855	0.045	0.54	0.2834–1.0456	0.0678			
Arrhythmia	0.44	0.1991–0.9846	0.0457	0.52	0.2297–1.1791	0.1176			
Other comorbidities	0.91	0.4394–1.8926	0.8045						
Pulmonary disease	0.88	0.389–1.9875	0.7571	0.95	0.4138–2.1846	0.9054			
Neurological disease	0.94	0.432–2.0616	0.8844	1	0.452–2.2209	0.9962			
Musculoskeletal disease	1.08	0.4919–2.3713	0.8479	1.19	0.5319–2.6589	0.6729			
Psychiatric disease	1.21	0.3945–3.7053	0.7397	1.18	0.3756–3.6759	0.7816			
Others	0.84	0.4406–1.5912	0.5878	0.99	0.5103–1.92	0.9758			

IHD, ischemic heart disease; HVD, heart valve disease; HT, heart transplant; CHD, congenital heart disease; CVRF, cardiovascular risk factors; HTA, hypertension; DL, dyslipidemia; DM, diabetes mellitus; CV, cardiovascular; HF, heart failure; CHD, congenital heart disease; IHD, ischemic heart disease; ICD, implantable cardioverter defibrillator; HVD, heart valve disease.

to present more comorbidities. In our study, no differences were found regarding referral in patients who presented complications during the postoperative period. These patients had a longer hospital stay (more days of admission) and this variable (days of admission) also showed no differences in referral to CR programs. In contrast, patients with more cardiovascular risk factors before surgery (more specifically those patients with overweight or obesity) were more likely to be referred to CR. This may be due to the prescribing physician of CR perceiving a greater sense of illness and that these patients may be the ones who could potentially benefit most from the program.

Regarding sex, the existence of an imbalance in participation in CR programs between men and women has been documented and several studies have shown differences in attitudes toward treatment depending on the patient's sex (21–23). In our study there was a clear tendency to lower CR referral in women, however, these differences were not statistically significant. A possible explanation contributing to this is that women are more likely to live longer than men. Specifically, ischemic heart disease in women occurs at more advanced ages, with a higher rate of acute renal failure, arrhythmias, shock, complicated diabetes, heart failure, and cerebrovascular disease. For these reasons, the low CR referral rate in these patients may be related to clinical characteristics (e.g., greater comorbidity and older age) instead of sex bias (21, 22).

Our study has several clinical implications. Although CR is a safe and effective therapy for patients after cardiovascular surgery, the design of well-defined effective strategies for the implementation of CR continues to pose a challenge in clinical practice. The success of a CR program begins with the referral of candidate patients by health professionals who manage these patients in hospitalization settings (24). Our study highlights a significant gap in clinical practice with respect to this key step. Recent studies have shown that one of the most important

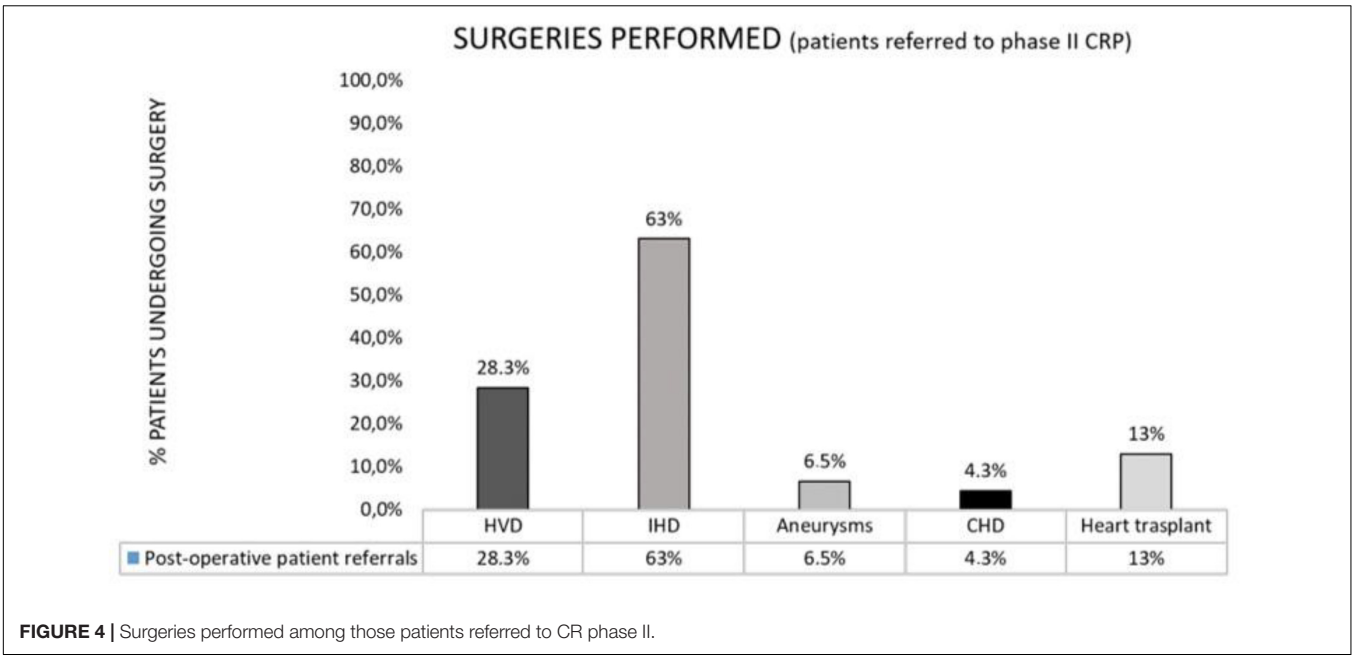

FIGURE 4 | Surgeries performed among those patients referred to CR phase II.

factors that influenced the referral to CR programs was the benefit perceived by the doctor (25). These rehabilitation units are underused, in part, due to the lack of knowledge of the prescribing professional and the concern about the safety of exercise training in these patients. We must look for solutions to increase the referral and the role of health professionals is very important.

Referral of hospitalized patients at the time of the discharge is one of the most accurate predictors that patients will being enrolled in a CR programs. Other factors are demographic factors, advanced age, low socioeconomic and cultural level, and distance to the center of CR, greater burden of morbidity (COPD, AIT, and cognitive dysfunction) (26). Additionally, the creation of referral protocols, as the one that already exists in our hospital for ischemic heart diseases, in coordination with all the professionals involved and their systematic application could improve and increase referral to CR programs (27). Added to this, coordination between hospitals must also be improved (since sometimes the patients are operated in a center different to their reference hospital) and between outpatient centers (28).

For the management of a chronic disease, it is necessary for patients to take a more active role in the daily decisions about the management of their disease. For this, the association and communication between the patient and health professionals is essential. The incorporation of trained nurses in the care system to support physicians has proven to be effective in improving the management of chronic diseases. Models like this can be implemented to improve the efficacy and adherence to these programs, resulting in better control of the patient's disease and increasing their satisfaction (29).

While the present study provides evidence of the factors that might affect the referral rate of cardiac surgical patients to CR, caution is needed when interpreting these results. This study is retrospective, and some other factors beyond the clinical characteristics of the patients could affect CR referral rate.

CONCLUSION

The benefit of CR in patients undergoing cardiac surgery has been described extensively. The beginning of rehabilitation in the early postoperative period, extends this benefit. Despite this, the level of referral to CR programs remains low. The results of this study will be part of a quality improvement project, in order to create protocols and measures that help to improve and optimize the referral of candidate patients to CRPs. The future trend should be to greater referral and participation, with special emphasis on the most affected patient groups, such as women and the elderly. PRM physicians might play a key role, in a multidisciplinary team, in order to ensure the optimal management of these complex cardiac patients. Further studies with multi-centric, larger sample size and including other socio-demographic and clinical data should be conducted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Gregorio Maranon Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MS and MA-R: conceptualization. LG: formal analysis and writing – original draft preparation. MS: writing – review, editing, and supervision. JM-I, JS, and FL-J: writing – review and editing. ML and MM: data curation. MA-R: supervision. All authors have read and agreed to the final version of the manuscript and gave final approval and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

REFERENCES

1. Instituto Nacional de Estadística. *Defunciones Según la Causa de Muerte Disponible en*. (2016). Available online at: https://www.ine.es/prensa/edcm_2017.pdf (accessed October 23, 2020).
2. Situación de la cardiopatía isquémica en España. *En: Estrategia en Cardiopatía Isquémica Del Sistema Nacional de Salud*. Madrid: Centro de Publicaciones (2006). p. 25–31.
3. López Menéndez J, Polo López L, Silva Guisasola J, Centella Hernández T. Cirugía cardiovascular en España en el año 2016. Registro de intervenciones de la Sociedad Española de cirugía torácica-cardiovascular. *Cir Cardiov.* (2017) 24:381–97. doi: 10.1016/j.circv.2017.09.005
4. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *J Am Coll Cardiol.* (2016) 67:1–12. doi: 10.1016/j.jacc.2015.10.044
5. Heran BS, Chen JM, Ebrahim S, Moxham T, Oldridge N, Rees K, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev.* (2011) 6:CD001800. doi: 10.1002/14651858.CD001800.pub2
6. Smith SC, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF guideline AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update a guideline from the American heart association and American college. *Circulation.* (2011) 124:2458–73. doi: 10.1161/cir.0b013e318235eb4d
7. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev.* (2019) 1:CD003331. doi: 10.1002/14651858.CD003331.pub5
8. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. ACCF/AHA/SCAI guideline for percutaneous coronary intervention. *Circulation.* (2011) 124:574–651. doi: 0.1161/CIR.0b013e31823ba622
9. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European society of cardiology. *Eur Heart J.* (2013) 34:2949–3003. doi: 10.1093/eurheartj/eht296
10. Sibilitz KL, Berg SK, Tang LH, Risom SS, Gluud C, Lindschou J, et al. Exercise-based cardiac rehabilitation for adults after heart valve surgery. *Cochrane Database Syst Rev.* (2016) 3:CD010876. doi: 10.1002/14651858.CD010876.pub2
11. Anderson L, Nguyen TT, Dall CH, Burgess L, Bridges C, Taylor RS. Exercise-based cardiac rehabilitation in heart transplant recipients. *Cochrane Database Syst Rev.* (2017) 4:CD012264. doi: 10.1002/14651858.CD012264.pub2
12. Risom SS, Zwisler A-D, Johansen PP, Sibilitz KL, Lindschou J, Gluud C, et al. Exercise-based cardiac rehabilitation for adults with atrial fibrillation. *Cochrane Database Syst Rev.* (2017) 2:CD011197. doi: 10.1002/14651858.CD011197.pub2
13. Shields GE, Wells A, Doherty P, Heagerty A, Buck D, Davies LM. Cost-effectiveness of cardiac rehabilitation: a systematic review. *Heart.* (2018) 104:1403–10. doi: 10.1136/heartjnl-2017-312809
14. Chen JO, Liu JF, Liu YQ, Chen YM, Tu ML, Yu HR, et al. Effectiveness of a perioperative pulmonary rehabilitation program following coronary artery bypass graft surgery in patients with and without COPD. *Int J Chron Obstruct Pulmon Dis.* (2018) 13:1591–7. doi: 10.2147/COPD.S157967
15. De Pablo C. *Registro Español de Unidades de Rehabilitación Cardiaca 'R-EUReCa'. Coordinadora R-EUReCa. Grupo de Trabajo de la Sección de Riesgo Vascular y RehabilitaciónCardiaca*. Madrid: Sociedad Española de Cardiología (2014–2015).
16. Turk-Adawi K, Sarrafzadegan N, Grace SL. Global availability of cardiac rehabilitation. *Nat Rev Cardiol.* (2014) 11:586–96. doi: 10.1038/nrcardio.2014.98
17. Supervia M, Turk-Adawi K, Lopez-Jimenez F, Pesah E, Ding R, Britto R, et al. Nature of cardiac rehabilitation around the globe. *EClinicalMedicine.* (2019) 13:46–56. doi: 10.1016/j.eclinm.2019.06.006
18. Parker A, Sricharoenchai T, Needham DM. Early rehabilitation in the intensive care unit: preventing physical and mental health impairments. *Curr Phys Med Rehabil Rep.* (2013) 1:307–14. doi: 10.1007/s40141-013-0027-9
19. Bjarnason-Wehrens B, McGee H, Zwisler AD, Piepoli MF, Benzer W, Schmid JP, et al. Cardiac rehabilitation in Europe: results from the European cardiac rehabilitation inventory survey. *Eur J Cardiovasc Prev Rehabil.* (2010) 17:410–8. doi: 10.1097/HJR.0b013e328334f42d
20. Schopfer DW, Forman DE. Cardiac rehabilitation in older adults. *Can J Cardiol.* (2016) 32:1088–96. doi: 10.1016/j.cjca.2016.03.003
21. Jegier B, Pietka I, Wojtczak-Soska K, Jaszewski R, Lelonek M. Cardiac rehabilitation after cardiac surgery is limited by gender and length of hospitalisation. *Kardiol Pol.* (2011) 69:42–6.
22. Supervía M, Medina-Inojosa JR, Yeung C, Lopez-Jimenez F, Squires RW, Pérez-Terzic CM, et al. Cardiac rehabilitation for women: a systematic review of barriers and solutions. *Mayo Clin Proc.* (2017) 92:565–77. doi: 10.1016/j.mayocp.2017.01.002
23. Hyun K, Negrone A, Redfern J, Atkins E, Chow C, Kilian J, et al. Gender difference in secondary prevention of cardiovascular disease and outcomes following the survival of acute coronary syndrome. *Heart Lung Circ.* (2021) 30:121–7. doi: 10.1016/j.hlc.2020.06.026
24. Thomas RJ. The gap in cardiac rehabilitation referral: a system-based problem with system-based solutions. *J Am Coll Cardiol.* (2015) 65:2089–90. doi: 10.1016/j.jacc.2015.03.521
25. Gallagher R, Neubeck L, Du H, Astley C, Berry NM, Hill MN, et al. Facilitating or getting in the way? The effect of clinicians' knowledge, values and beliefs on referral and participation. *Eur J Prev Cardiol.* (2016) 23:1141–50. doi: 10.1177/2047487316630085
26. Aragam KG, Dai D, Neely ML, Bhatt DL, Roe MT, Rumsfeld JS, et al. Gaps in referral to cardiac rehabilitation of patients undergoing percutaneous coronary intervention in the United States. *J Am Coll Cardiol.* (2015) 65:2079–88. doi: 10.1016/j.jacc.2015.02.063
27. Grace SL, Russell KL, Reid RD, Oh P, Anand S, Rush J, et al. Effect of cardiac rehabilitation referral strategies on utilization rates a prospective, controlled study. *Arch Intern Med.* (2011) 171:235–41. doi: 10.1001/archinternmed.2010.501
28. Redfern J, Hyun K, Chew DP, Astley C, Chow C, Aliprandi-Costa B, et al. Prescription of secondary prevention medications, lifestyle advice and referral to rehabilitation among acute coronary syndrome (ACS) inpatients: results from a large prospective audit in Australia and New Zealand. *Heart.* (2014) 100:1281–8. doi: 10.1136/heartjnl-2013-305296
29. Ciccone MM, Aquilino A, Cortese F, Scicchitano P, Sassara M, Mola E. Feasibility and effectiveness of a disease and care management model in the primary health care system for patients with heart failure and diabetes (Project

Leonardo). *Vasc Health Risk Manag.* (2010) 6:297–305. doi: 10.2147/vhrm.s9252

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Development and Validation of Predictive Model—HASBLAD Score—For Major Adverse Cardiovascular Events During Perioperative Period of Non-cardiac Surgery: A Single Center Experience in China

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Background: Major adverse cardiovascular events (MACEs) represent a significant reason of morbidity and mortality in non-cardiac surgery during perioperative period. The prevention of perioperative MACEs has always been one of the hotspots in the research field. Current existing models have not been validated in Chinese population, and have become increasingly unable to adapt to current clinical needs.

Objectives: To establish and validate several simple bedside tools for predicting MACEs during perioperative period of non-cardiac surgery in Chinese hospitalized patients.

Design: We used a nested case-control study to establish our prediction models. A nomogram along with a risk score were developed using logistic regression analysis. An internal cohort was used to evaluate the performance of discrimination and calibration of these predictive models including the revised cardiac risk index (RCRI) score recommended by current guidelines.

Setting: Peking University Third Hospital between January 2010 and December 2020.

Patients: Two hundred and fifty three patients with MACEs and 1,012 patients without were included in the training set from January 2010 to December 2019 while 38,897 patients were included in the validation set from January 2020 and December 2020, of whom 112 patients had MACEs.

Main Outcome Measures: The MACEs included the composite outcomes of cardiac death, non-fatal myocardial infarction, non-fatal congestive cardiac failure or hemodynamically significant ventricular arrhythmia, and Takotsubo cardiomyopathy.

Results: Seven predictors, including **H**emoglobin, C**A**RDIAC diseases, Aspartate aminotransferase (A**S**T), high **B**lood pressure, **L**eukocyte count, general **A**nesthesia, and **D**iabetes mellitus (HASBLAD), were selected in the final model. The nomogram

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and HASBLAD score all achieved satisfactory prediction performance in the training set (*C* statistic, 0.781 vs. 0.768) and the validation set (*C* statistic, 0.865 vs. 0.843). Good calibration was observed for the probability of MACEs in the training set and the validation set. The two predictive models both had excellent discrimination that performed better than RCRI in the validation set (*C* statistic, 0.660, $P < 0.05$ vs. nomogram and HASBLAD score).

Conclusion: The nomogram and HASBLAD score could be useful bedside tools for predicting perioperative MACEs of non-cardiac surgery in Chinese hospitalized patients.

Keywords: non-cardiac surgery, major adverse cardiovascular events, prediction model, Takotsubo cardiomyopathy, nomogram, risk score

INTRODUCTION

With the continuous improvement of human life expectancy, increasing number of elderly patients underwent surgery (1). A considerable proportion of these patients present with cardiovascular risk factors or suffer from cardiovascular comorbidities, leading to an increased risk of perioperative cardiovascular complications. Major adverse cardiovascular events (MACEs) represented a significant source of perioperative morbidity and mortality (2). Up to 42% of perioperative deaths were due to cardiac complications, such as myocardial infarction (MI), cardiac arrest, and congestive heart failure (HF) (3), and the incidence of these complications was likely to rise in the aging population (4). The prevention of perioperative cardiac complications has been one of the hotspots in the research field, which requires comprehensive preoperative risk assessment and postoperative monitoring of patients at risk.

Current guidelines highly recommended the use of predictive models to assess the risk of perioperative MACEs (1, 5–7), including the revised cardiac risk index (RCRI) (8), and the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) risk model (9). RCRI was the most widely validated and used model. However, as an index that has existed for over two decades, it has limitations to meet the clinical requirement, including the underestimation of the cardiac risk (10), and inadequate representation of high-risk subgroups (8). With respect to the NSQIP model, although the internal validation showed excellent predictive ability, with a *C*-statistic of 0.895 for predicting cardiovascular complications, none of the NSQIP-derived calculators have been robustly externally validated. Moreover, it was too complicated to use at the bedside (11).

In China, its huge and aging population, expanding economy, and lifestyle changes have created a tremendous demand for perioperative healthcare services. Nearly 20 million elderly patients-−25% of all patients—need surgery in China each year (12).

However, there was no predictive model based on Chinese data, and the predictive models recommended by the guidelines have not been validated in the Chinese population.

Therefore, we sought to establish and validate an effective risk predictive model based on the Chinese population, hoping to provide convenient bedside tools for predicting perioperative MACEs with satisfactory performance in non-cardiac surgeries.

MATERIALS AND METHODS

Study Design

This is a single-center, observational study conducted in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement (13). The selection of the training set was based on a nested case-control study, while the selection of the validation set was based on a cohort study.

Study Population and Data Collection

We conducted a retrospective review of all patients who underwent in-hospital non-cardiac surgeries with age over 18 years by a medical record system in the Peking University Third Hospital between January 2010 and December 2019. We selected surgical types proposed in the 2014 ESC guidelines (**Supplementary Table 1**). Non-cardiac surgeries contained the operations conducted on organs except for the heart and its appendages (the details were showed in **Supplementary Table 1**). The operation risk level of surgical operation ranged from low to high. Then we matched the patients with the same age who underwent the same type of surgery at the same time (1 month before or after the operation of patients with MACEs) who had no MACEs, as the control group, according to the ratio of 1:4 (**Figure 1**). With respect to the validation set, we prospectively selected patients who underwent non-cardiac surgery with age over 18 years from January 2020 to December 2020. Since all of patients who suffered perioperative MACEs would need to apply for multidisciplinary consultation including cardiology, the information of application records, diagnosis and treatment experience could be recorded. Through the multidisciplinary consultation system, we could monitor the situation for perioperative complications of patients timely and collect the exact number of patients broken out the cardiovascular events without obvious omissions. At the same time, the number of

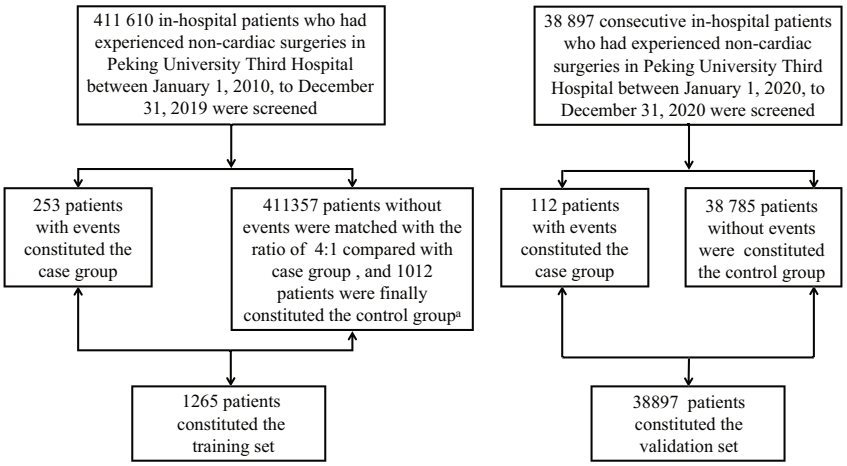

FIGURE 1 | Patients screening process of training set and validation set. a: The patients were matched according to the type of operation, operative time and age with the ratio of 4:1 between non-events group and events group. The matched patients belonged to one same operation type which was demonstrated in **Supplementary Table 1** in **Supplemental Appendix**, while they were randomly selected in patients who had operation one month before or after the patients in events group.

surgeries for the whole year of 2020 was extracted from the medical record system.

The International Classification of Diseases, Tenth Revision (ICD-10) has been used to extract the target population. Subsequently, trained clinical reviewers collected clinical data from the medical chart, operative archives, anesthesia records, and progress notes with the surgical attending. Then, we collected demographic data, co-morbidities, laboratory results, inspection status, and procedure-related data, including the type of surgery, procedure risk, and length of stay for each patient. Cardiac diseases included acute and chronic HF, chronic coronary disease, acute coronary syndrome, severe aortic stenosis, severe aortic regurgitation, severe mitral valve stenosis, severe mitral valve regurgitation, atrial fibrillation, ventricular tachyarrhythmias, and patients with pacemaker/implantable cardioverter defibrillator. Venous blood samples were drawn in the fasting condition to test leukocyte, hemoglobin (HGB), platelet (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, potassium, and fibrinogen.

This study was conducted in accordance with the Declaration of Helsinki and with approval from the ethics committee of Peking University Third Hospital (No. M2018258).

Study Outcomes

The MACEs included the composite outcomes of cardiac death, non-fatal MI, non-fatal congestive cardiac failure, hemodynamically significant ventricular arrhythmia, and Takotsubo cardiomyopathy of patients who underwent non-cardiac surgeries during hospitalization. Cardiac death was defined as sudden death or death secondary to MI, arrhythmia, or HF. MI was defined according to the Fourth universal definition of ESC guideline (14). Hemodynamically significant ventricular arrhythmia included ventricular tachycardia, ventricular flutter, and fibrillation that could affect hemodynamics apparently. Takotsubo cardiomyopathy was defined based on diagnosis criteria of Mayo Clinic (15).

Statistical Analysis

Statistical analysis was performed using R 4.0.3. We first classified the patients with MACEs in the training set according to the operation types (a total of 30) proposed in the 2014 ESC guidelines (**Supplementary Tables 1, 2**). Then, among the patients without MACEs in the training set, the process of matching was conducted using propensity score matching (PSM). One patient with MACE matched 4 patients without MACEs using operation type (showed in **Supplementary Table 1**), age, and operation time (particular year of operation). Continuous variables conformed to the normal distribution were expressed as the mean ± standard deviation, and *t*-test was used for comparison between two groups. While medians (Interquartile range) and Wilcoxon tests were used for continuous variables not conformed to normal distribution. Categorical variables were presented as percentages with Chi-squared test or Fisher's exact test for comparison between two groups. We used univariable logistics regression to select variables firstly entering to the regression model with P-value < 0.1. Then multivariable logistic regression analysis was conducted by a backward stepwise method to choose variables ultimately be included in the model. The

TABLE 1 | Baseline characteristics of the training set.

Variables	MACEs ($n = 253$)	Non-MACEs ($n = 1012$)	*P*-value
Age (years)	71 (58, 78)	70.5 (58, 78)	0.497
≤70	124 (49%)	506 (50%)	
>70	129 (51%)	506 (50%)	
Sex (males)	111 (43.9%)	481 (47.5%)	0.331
Endoscopic operation	46 (18.2%)	321 (31.7%)	<0.001
General anesthesia	183 (72.3%)	657 (64.9%)	0.031
Length of stay (days)	14 (9, 22)	9 (5,15)	<0.001
Cardiac disease	89 (35.2%)	122 (12.1%)	<0.001
HT	140 (55.3%)	374 (37%)	<0.001
DM	74 (29.2%)	115 (11.4%)	<0.001
CKD	14 (5.5%)	19 (1.9%)	0.002
Leukocyte (×109 l−1)	7.8 (6.23, 10.79)	6.48 (5.35, 8.1)	<0.001
HGB (g l−1)	120 (102, 136)	131 (118, 143)	<0.001
PLT (×109 l−1)	191 (150, 245)	206 (172.75, 255)	0.001
ALT (U l−1)	24 (15, 39)	16 (12, 24)	<0.001
AST (U l−1)	24 (17, 40)	21 (17, 25)	<0.001
Scr (mmol l−1)	81 (66, 108)	74 (63, 88)	<0.001
Potassium (mmol l−1)	4.08 (3.8, 4.42)	4.05 (3.81, 4.3)	0.258
Fibrinogen (g l−1)	3.43 (2.79, 4)	3.14 (2.69, 3.71)	0.001

HT, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; HGB, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine.

TABLE 2 | The proportion of MACEs in both training set and validation set.

MACEs	Training set ($n = 253$)	Validation set ($n = 112$)
Cardiac death	81 (31.7%)	10 (8.9%)
HF	78 (31.0%)	69 (61.6%)
Non-fatal MI	71 (28.2%)	21 (18.8%)
Hemodynamically arrhythmia	14 (5.6%)	3 (2.7%)
Stress cardiomyopathy	9 (3.5%)	9 (8.0%)

MACEs, major adverse cardiovascular events; HF, heart failure; MI, myocardial infarction.

variables included in the model were used to construct the nomogram using the package "rms." To construct a risk score, restricted cubic spline (RCS) was used to help finding the best cut-off values of continuous variables. The multivariable logistic regression model was performed with all variables which were categorical. We used odds ratio (OR) as the weight to assign a value to each variable. The area under the curve (AUC) for the receiver operating characteristic (ROC) curve was used to validate the discrimination efficiency of the model and a fifth quantile calibration curve was used to assess the model's calibration (16). The Delong test was used to evaluate whether the difference between the two ROC curves was statistically significant. The local institutional review board approved this analysis.

TABLE 3 | Results of univariate logistic regression analysis.

Variables	OR	95% CI	*P*-value
Age	1.002	0.994-1.011	0.566
Sex (vs. female)	1.159	0.878-1.529	0.297
Endoscopic operation	0.478	0.339-0.676	<0.001
General anesthesia	1.413	1.042-1.915	0.026
Length of stay	1.048	1.035-1.061	<0.001
Cardiac disease	3.959	2.875-5.452	<0.001
HT	2.113	1.599-2.793	<0.001
DM	3.225	2.311-4.500	<0.001
CKD	3.061	1.513-6.194	0.002
Leukocyte	1.163	1.119-1.210	<0.001
HGB	0.976	0.969-0.982	<0.001
PLT	0.998	0.996-1.000	0.081
ALT	1.01	1.005-1.014	<0.001
AST	1.01	1.006-1.015	<0.001
Scr	1.001	1.000-1.002	0.105
Potassium	1.2	0.890-1.619	0.231
Fibrinogen	1.231	1.084-1.398	0.001

OR, odds ratio; CI, confidence interval; HT, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; HGB, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine.

RESULTS

Study Population and Baseline Characteristics

After the screening period, there were 1,265 patients (MACEs group: 253; non-MACEs group: 1,012) in the training set and 38,897 patients (MACEs group: 112; non-MACEs: 38,785) in the validation set. The specific screening process was shown in **Figure 1**.

In the training set, patients with the age older than 70 years accounted for 51.5% (129 patients). There was no significant difference in age (median age: 71 vs. 70.5 years, $P = 0.497$) and sex (males, 43.9 vs. 47.5%, $P = 0.331$) between the two groups. The prevalence of cardiac diseases (35.2 vs. 12.1%, $P < 0.001$), hypertension (HT) (55.3 vs. 37%, $P < 0.001$), diabetes mellitus (DM) (29.2 vs. 11.4%, $P < 0.001$), chronic kidney disease (CKD) (5.5 vs. 1.9%, $P = 0.002$), and general anesthesia (72.3 vs. 64.9%, $P = 0.031$) was significantly higher in patients with MACEs. There were less endoscopic surgeries in MACEs group (18.2 vs. 31.7%, $P < 0.001$). Leukocyte, ALT, AST, and fibrinogen levels were significantly higher in MACEs group, whereas HGB and PLT levels were significantly lower. Baseline characteristics of the training set were presented in **Table 1**.

Major Adverse Cardiovascular Events

Two hundred and fifty three patients in the training set suffered MACEs during the perioperative period. The composition of cardiovascular outcomes was as follows: cardiac death (81; 31.7%), nonfatal HF (78; 31%), nonfatal MI (71; 28.2%),

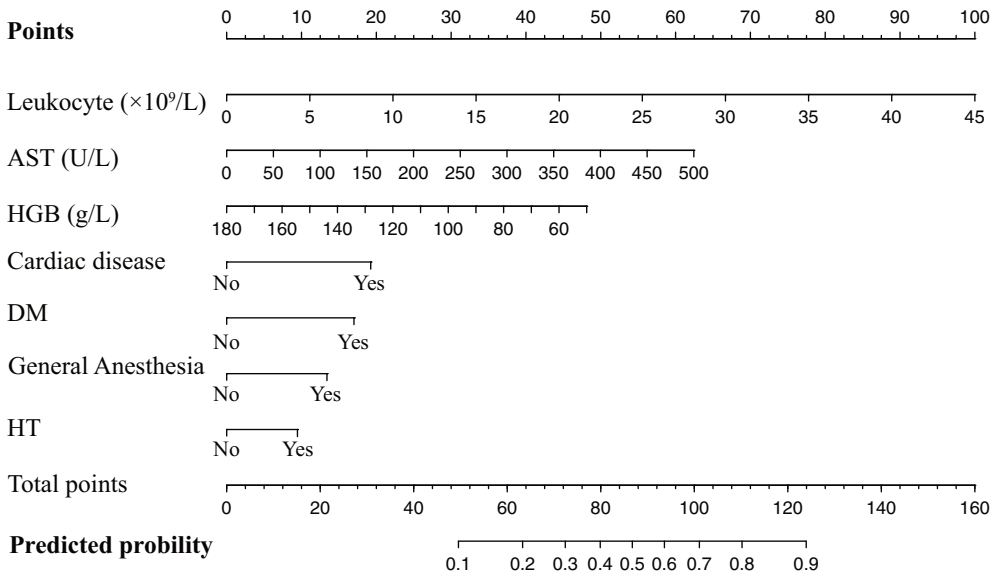

FIGURE 2 | Nomogram of the training set used to predict the MACEs risk. AST, aspartate aminotransferase; HGB, hemoglobin; DM, diabetes mellitus; HT, hypertension.

TABLE 4 | Results of multivariate logistic regression analysis in the training set.

Variables	Model 1 (nomogram)		Variables	Model 2	
	β	OR (95% CI)		*β*	OR (95% CI)
DM			DM		
No		Reference	No		Reference
Yes	1.005	2.732 (1.855-4.025)	Yes	1.025	2.788 (1.889-4.115)
Cardiac disease			Cardiac disease		
No		Reference	No		Reference
Yes	1.138	3.119 (2.171-4.482)	Yes	1.143	3.135 (2.179-4.511)
HT			HT		
No		Reference	No		Reference
Yes	0.559	1.749 (1.260-2.426)	Yes	0.564	1.757(1.265-2.441)
Leukocyte	0.131	1.140 (1.094-1.189)	Leukocyte		
			$\leq 10\times10^9$ l^{-1}		Reference
			$>10\times10^9$ l^{-1}	0.620	1.858 (1.281-2.696)
HGB	−0.022	0.978 (0.971-0.986)	HGB		
			≥110 g l^{-1}		Reference
			<110 g l^{-1}	0.961	2.615 (1.828-3.739)
AST	0.007	1.007 (1.003-1.011)	AST		
			≤40 U l^{-1}		Reference
			>40 U l^{-1}	1.677	5.352 (3.424-8.365)
General anesthesia			General anesthesia		
No		Reference	No		Reference
Yes	0.792	1.207 (1.538-3.168)	Yes	0.696	2.006 (1.398-2.879)

OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; HT, hypertension; HGB, hemoglobin; AST, aspartate aminotransferase.

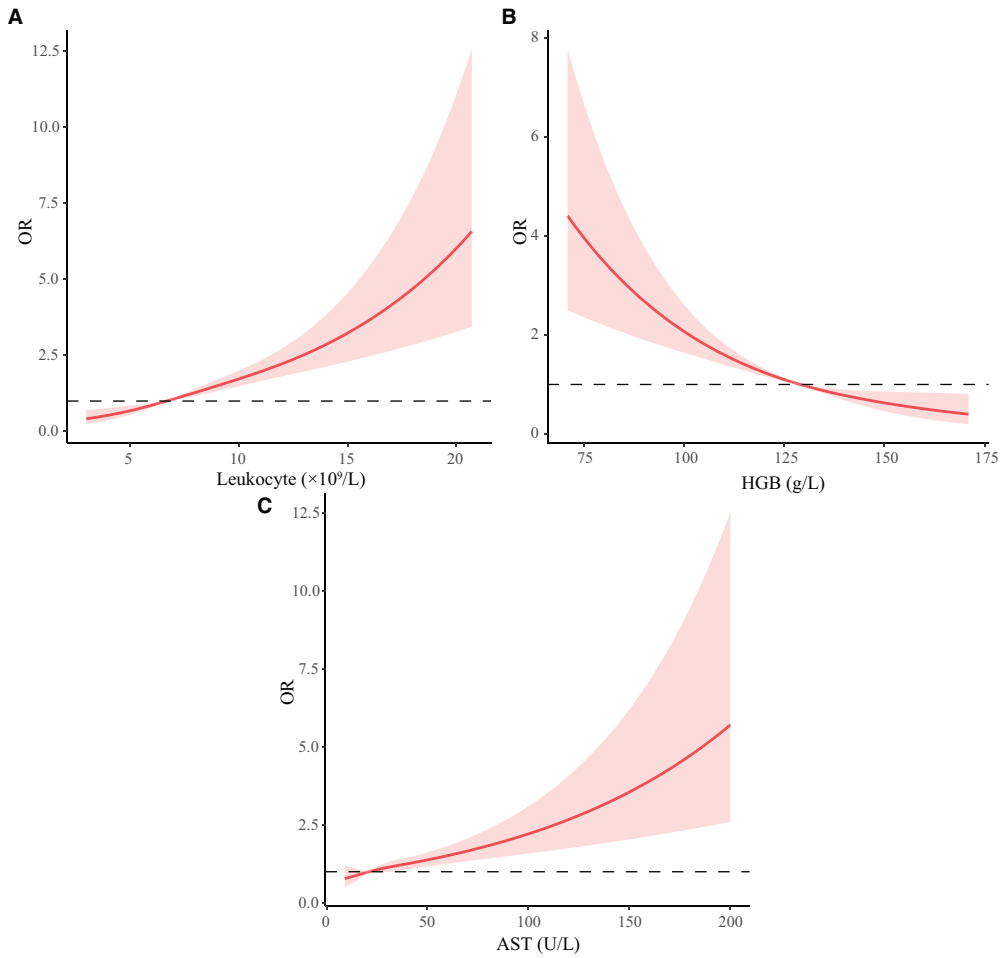

FIGURE 3 | Restricted cubic spline curve of continuous variables. HGB, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase. **(A-C)** Represents the changing trend of risk of MACEs with leukocyte, HGB, and AST.

hemodynamically arrhythmia (14; 5.6%), and Takotsubo cardiomyopathy (9; 3.5%). There were 112 patients suffered MACEs in the validation set, with the proportion of MACEs as follows: cardiac death (10; 8.9%), HF (69; 61.6%), nonfatal MI (21; 18.8%), hemodynamically arrhythmia (3; 2.7%), and Takotsubo cardiomyopathy (9; 8.0%). Details were illustrated in **Table 2**.

Development of the Prediction Model of Nomogram

The results of the univariate logistic regression analysis were shown in **Table 3**. Cardiac disease, HT, DM, CKD, endoscopic operation, length of hospital stay, general anesthesia, leukocyte, HGB, PLT, ALT, AST, and fibrinogen were significantly associated with perioperative MACEs with the preset standard of $P < 0.1$, which would be included in multivariate analysis preliminarily. After considering the clinical practice and results of logistic regression, we finally selected seven factors for Model 1, including cardiac diseases, HT, DM, general anesthesia, leukocyte, HGB, and AST. We also illustrated the Model 1 in the form of a nomogram for more convenient use in clinical work. In the nomogram, the score assigned to each variable was proportional to its risk contribution to MACEs. The total score on the risk axis represented the probability of MACEs risk. The higher the score, the higher the risk of developing MACEs in the perioperative period. Details were showed in **Table 3** and **Figure 2**.

Converting Continuous Variables to Categorical Ones

We used RCS curves to evaluate the relationship between continuous variables, including leukocyte, HGB and AST, and MACEs. Leukocyte and AST were positively correlated with MACEs, while HGB was negatively correlated with MACEs. Combined with clinical experience and the results of statistical analysis, we take 10×10^9 /L, 110 g/L, and 40 U/L as cut-off points of leukocyte, HGB, and AST respectively, converting them to categorical variables. Details were illustrated in **Table 4** and **Figure 3**.

TABLE 5 | Score assignment of model variables.

Variables	OR	Points assigned
HGB (<110 vs. ≥110 g l^{-1})	2.615	2
CARDIAC disease (yes vs. no)	3.135	2
AST (>40 vs. ≤40 U l^{-1})	5.352	2
Blood pressure (HT, yes vs. no)	1.757	1
Leukocyte (>10 vs. ≤10 × 10^9 l^{-1})	1.858	1
General anesthesia (yes vs. no)	2.006	2
DM (yes vs. no)	2.788	2

DM, diabetes mellitus; HT, hypertension; AST, aspartate aminotransferase; HGB, hemoglobin.

Construction of Risk Score

We then built Model 2 with the same seven risk factors in the training set, after converting leukocyte, HGB, and AST to categorical variables. Using OR of model 2 for the weights of assigning scores, we defined OR ≥ 2 as an independent high-risk factor and assigned 2 points, including cardiac diseases, general anesthesia, DM, AST (> 40 U/L), and HGB (<110 g/L). For risk factors with OR < 2, 1 point shall be assigned including leukocyte (>10 × 10^9/L) and HT, constructing the HASBLAD score. If there were no above risk factors, 0 points will be assigned. The complete scoring table was shown in **Table 5**.

Evaluation of Model Discrimination and Calibration in the Training Set

According to the ROC analysis, we draw a preliminary conclusion that both Model 1 (the nomogram; *C* statistic, 0.781; 95% CI: 0.748-0.813) and Model 3 (HASBLAD score; *C* statistic, 0.768; 95% CI: 0.735-0.802) performed well in predicting MACEs in the training set. Calibration curves reflected the extent to which a model correctly estimates the absolute risk (whether the values predicted by the model agree with the observed values). The results showed that both Model 1 (the nomogram) and Model 3 (HASBLAD score) predicted the probability of MACEs accurately (**Figures 4**, **5**).

Baseline Characteristics of the Validation Set

Consistent with training set, cardiac diseases, HT, DM, leukocyte, HGB, AST and general anesthesia still showed a significant difference between MACEs and non-MACEs groups. The age of patients in MACEs group was significantly higher than patients without MACEs (mean age: 67.56 vs. 47.59 years, $P < 0.001$). Details were showed in **Table 6**.

Internal Validation of the Prediction Model and the Comparison With RCRI

With respect to discrimination in the validation set, Model 1 (the nomogram; *C* statistic, 0.865; 95% CI: 0.829-0.901) and Model 3 (HASBLAD score; *C* statistic, 0.843; 95% CI: 0.804-0.883) both performed well in the validation set, while the performance of RCRI (*C* statistic, 0.660; 95%CI: 0.613-0.708) was relatively poor (**Figure 6**). The performance of the nomogram and the HASBLAD score was significantly better than RCRI in the evaluation of discrimination (Delong test: $P < 0.05$). The difference between the nomogram and the HASBLAD score was not statistically significant, suggesting that the predictive performance of the models was comparable ($P > 0.05$).

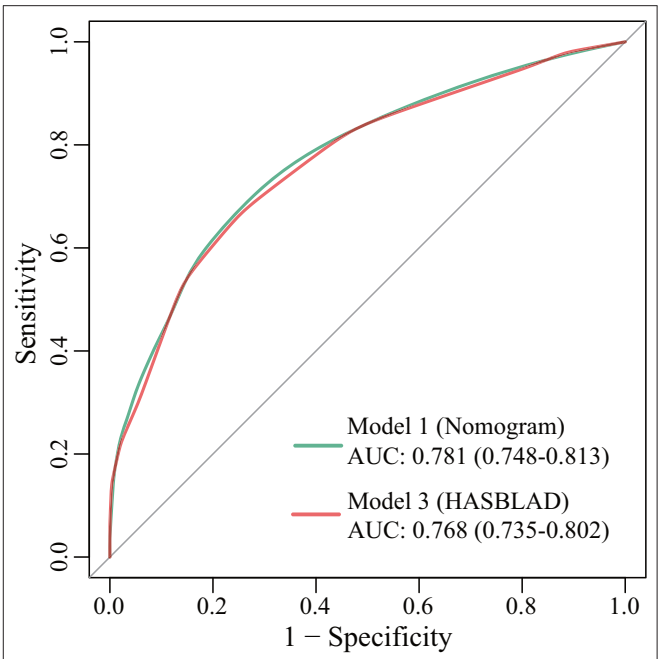

FIGURE 4 | ROC curves for Model 1, Model 3 in the training set. AUC, area under the curve; ROC, receiver operating characteristic.

The calibration curve of the nomogram and the HASBLAD score for the probability of MACE both demonstrated good agreement between prediction and observation in the validation set (**Figure 7**).

Risk Stratification of Patients in the Validation Set With HASBLAD Score

The incidence of perioperative MACEs was relatively low in our hospital (0.29% in the validation set), and the positive predictive value (PPV) was significantly higher than the observed incidence (**Supplementary Tables 3**-**5**). By calculating the prevalence of patients with different scores, we divided patients into low-risk (Points: < 4), moderate-risk (Points: 4-7), and high-risk (Points: ≥ 8) groups according to different ranges of HASBLAD score. The risk of MACEs in low-risk, moderate-risk, and high-risk groups were 0.12, 1.23, 14.61%, respectively. Details were showed in **Table 7**.

DISCUSSION

In recent years, China has witnessed the rapid development of medical technology and reform, with the aging population becoming increasingly prominent. The likelihood of having surgery was quadrupled in the elderly group incorporating cardiovascular diseases, HT, and DM (17). Our research was

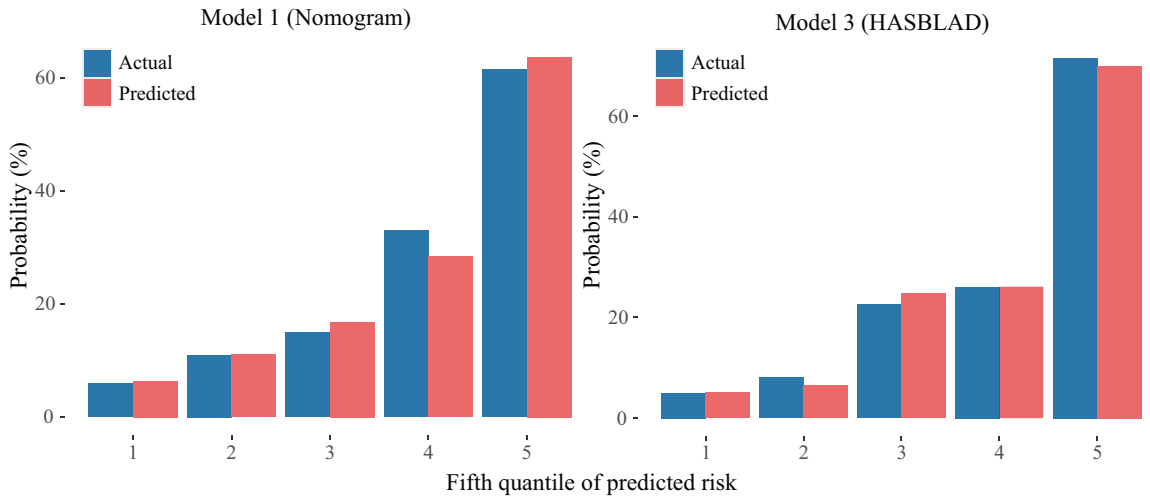

FIGURE 5 | Calibration curves of the Model 1 and the Model 3 in the derivation set. The left plot was the calibration curve of the Model 1 (Nomogram) in the derivation set. The right plot was the calibration curve of the Model 3 (HASBLAD) in the derivation set.

TABLE 6 | Baseline Characteristics of the validation set.

Variables	Event (n = 112)	Non-MACEs (n = 38,785)	*P*-value
Age (years)[a]	67.56 ± 14.89	49.59 ± 16.63	<0.001
>70	56 (50%)	4213 (10.9%)	<0.001
Sex (males)	49 (43.8%)	16265 (41.9%)	0.77
General anesthesia	74 (66.1%)	19269 (49.7%)	0.001
Cardiac disease	44 (39.3%)	1112 (2.9%)	<0.001
HT	67 (59.8%)	7965 (20.5%)	<0.001
DM	36 (32.1%)	4090 (10.5%)	<0.001
Leukocyte ($\times 10^9$ l^{-1})[b]	7.91 (5.92, 10.40)	6.73 (5.67, 8.11)	<0.001
HGB (g l^{-1})[b]	119 (102, 133)	138 (128, 152)	<0.001
PLT ($\times 10^9$ l^{-1})[b]	215 (167, 269)	240 (202, 279)	<0.001
ALT (U l^{-1})[b]	19 (11, 27)	20 (15, 26)	0.118
AST > 40 U l^{-1}	17 (15.2%)	1282 (3.3%)	<0.001
Fibrinogen (g l^{-1})[a]	3.79 ± 1.25	3.14 ± 0.72	<0.001

[a]*Mean (SD).* [b]*Median (IOR).*
HT, hypertension; DM, diabetes mellitus; HGB, hemoglobin; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

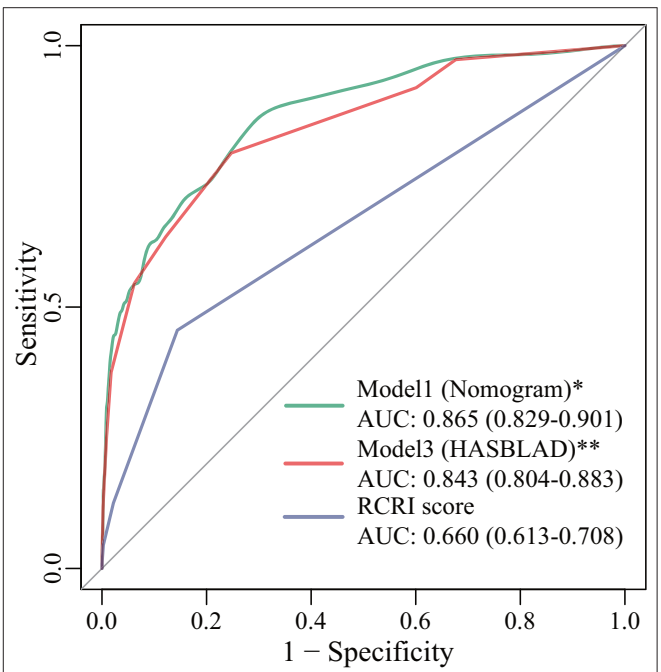

FIGURE 6 | ROC curves for Model 1, Model 3, and RCRI score in the validation set. *: $P < 0.001$ compared with RCRI score; **: $P < 0.001$ compared with RCRI score. AUC, area under the curve; RCRI, the revised cardiac risk index; ROC, receiver operating characteristic.

to target the patients who were likely to suffer perioperative MACEs in all surgical populations. So, the physicians could take measures to reduce perioperative risk promptly for patients in high-risk MACE grading. Risk stratification assists us to be well prepared to respond to emergencies and complications occurred in the perioperative period. On the other hand, timely warning and pre-operative risk information which are included in every pre-operative consultation, will improve the communication consequence between clinicians and patients. It is the main significance of this study. We verified the RCRI score in the validation set, and the result showed its discrimination efficiency was poor (AUC: 0.734; 95%CI: 0.698-0.771), indicating that the differentiation efficiency of the RCRI score may not be superior in Chinese population. Therefore, there is an urgent need for a perioperative cardiac risk model to adapt to the increasing number of patients requiring surgeries in China.

We developed and validated the simple risk assessment tool for the preoperative individualized prediction of MACEs in hospitalized patients who prepared to accept non-cardiac surgery. Our prediction models incorporated seven risk factors, including four clinical factors (general anesthesia, cardiac

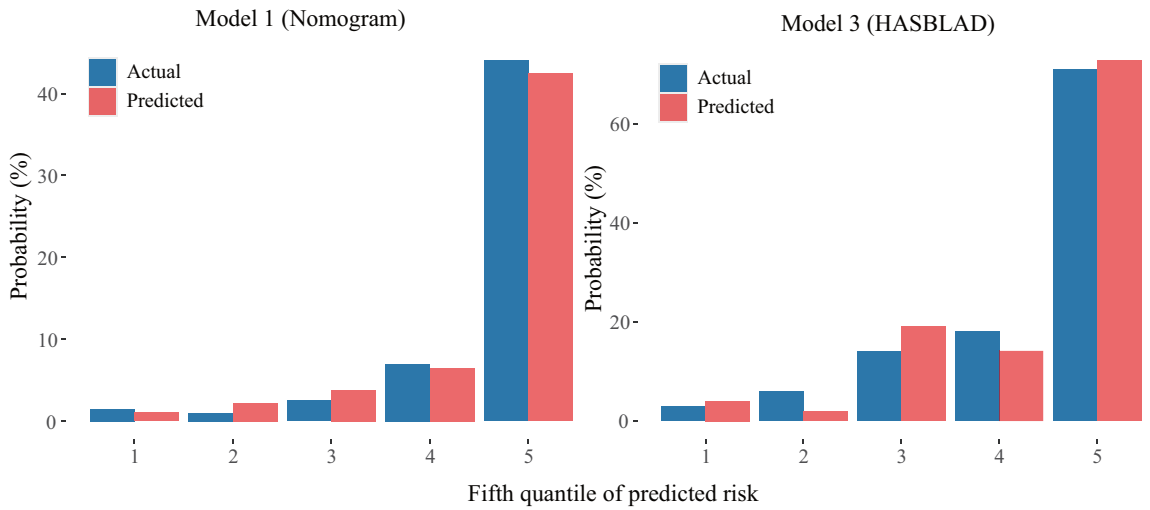

FIGURE 7 | Calibration curves of the Model 1 and the Model 3 in the validation set. The left plot was the calibration curve of the Model 1 (Nomogram) in the validation set. The right plot was the calibration curve of the Model 3 (HASBLAD) in the validation set.

diseases, DM, and HT), and three laboratory results (HGB, AST, and leukocyte). Current guidelines recommended the use of biomarkers in perioperative evaluation, including N-terminal pro-B type natriuretic peptide (NT-pro BNP), cardiac troponin, and high sensitivity cardiac troponin. However, bringing them into routine screening will cause a serious waste of medical resources. Our model included AST, leukocyte, and HGB which will be screened routinely before operation in China, to evaluate perioperative risk, making full use of medical resources. Many researches have suggested that lower HGB values were associated with myocardial injury or MACEs after non-cardiac surgery (18–20). This was mainly because anemia will damage the ability of the body to compensate for hemodynamic changes, thus organizations were more prone to an imbalance between oxygen supply and demand, leading to an increase in the possibility of type 2 MI (14). Leukocyte played a causal role in the mechanisms of plaque progression, destabilization, erosion or rupture, which will be engendered by acute perioperative stress in major non-cardiac surgery, leading to myocardial injury, MI and stroke (21). Our finding showed that leukocyte was associated with MACEs, improved risk prediction in coronary heart disease patients undergoing non-cardiac surgery, which was in line with previous long-term prospective clinical trials. Both neutrophil to lymphocyte ratio (22) and regulatory T cells (23) were proved to be of additional value for preoperative risk stratification. And the subpopulation of leukocyte could be used as inexpensive and broadly available tools for perioperative risk assessment. Liver was the most important metabolic and detoxification organ in the body. Because the vast majority of operation, included the intermediate-risk and high-risk of MACEs all need the spinal anesthesia or general anesthesia. Most anesthetics are transformed and degraded by the liver. It will decrease liver blood flow of a different degree.

TABLE 7 | Risk stratification using HASBLAD Score in validation set.

Points	Incidence of MACEs	Risk stratification
<4	0.12%	Low risk
4-7	1.23%	Moderate risk
≥8	14.61%	High risk

MACEs, major adverse cardiovascular events.

There are sizeable amounts of patients suffered with the clinical condition that asymptomatic hepatic impairment and the hepatitis virus replicates actively, due to high infection rate of Hepatitis B and Hepatitis C viruses in China. Evaluation of pre-operative hepatic function impairment is extremely important, as the extent of perioperative liver injury caused by ischaemia and reperfusion depends primarily on the duration of ischaemia (24) as well as on pre-existing liver diseases. Hepatic ischaemia and subsequent liver dysfunction during perioperative period is associated with a significant deterioration in prognosis (25). Because of the central role of the liver in the metabolic and immunological response to stress, if the physician neglected the impact of liver function on multiple system organs, the consequence will be disastrous. Pre-existing hepatic dysfunction poses a great risk even for non-hepatic surgery, as shown by the higher blood transfusion requirements, longer hospital stays, more complications and increased mortality rate (26).

Elevated AST levels usually indicated liver or myocardium injury. In this study, the result of multivariate regression analysis showed that AST was an independent risk factor for perioperative cardiac events. It meant that liver functional test, especially the indicator of AST had predictive value for perioperative cardiovascular events, which was demonstrated by our study, this is an indicator received less attention in previous studies. If

conditions permit, liver function test, especially AST and ALT will be recommended for the vast majority of patients, unless local anesthesia is required and the patient does not have any risk factors in the scoring model.

Both the HASBLAD score and the nomogram performed adequate discrimination in the training set (*C* statistic, 0.781 vs. 0.768) and the validation set (*C* statistic, 0.865 vs. 0.843), which were significantly better than RCRI (*C* statistic, 0.660, $P < 0.05$). More importantly, our clinical models were developed based on patients of Asian origin and the current medical technology in China.

To our knowledge, Takotsubo cardiomyopathy had received insufficient clinical attention and was rarely included in the category of MACEs during the perioperative period. However, according to our preliminary observations and clinical experience, Takotsubo cardiomyopathy also appreciably contributed to the perioperative cardiac events. The clinical manifestations of Takotsubo cardiomyopathy can present as transient regional systolic left ventricular dysfunction (27), decreased ejection fraction, hemodynamic changes, myocardial injury, HF, ventricular arrhythmias, systemic thromboembolism, and cardiogenic arrest (28). The exact pathophysiological mechanisms remained unclear, but many researchers have suggested that the surgery was an important trigger for Takotsubo cardiomyopathy (29). The broader scope of surgical trauma and longer operation time, the more apparent sympathetic activation that patients will encounter, and thereby the incidence of Takotsubo cardiomyopathy will be higher during the perioperative period (30). This cardiovascular complication has received less attention in previous studies, but its incidence was not rare, and the perniciousness could not be ignored in our investigation. Therefore, we included this disease as an outcome event in our study, making the evaluation of perioperative MACEs more comprehensive.

There were some limitations to this study as well. Firstly, it was performed at a single academic medical center and lack of external validation, which may cause deficiencies in representativeness and universality. Secondly, the relatively low incidence of complications might underestimate the actual incidence, especially affected by the lack of routine postoperative surveillance with troponin, NT-pro BNP, and electrocardiography. The biomarker of myocardial injury could assist the physician to recognize the myocardial infarction or HF early before the symptoms flare up. Due to the limitations of medical record-controlled studies, some indicators of great value in the prediction of perioperative cardiovascular events, such as metabolic equivalent, were not recorded routinely in the medical documentation. This reflects the current situation that our physician may have insufficient understanding of the importance of NT-pro BNP, troponin and metabolic equivalent. Considering that MACE has a negative impact on outcome in patients underwent non-cardiac surgery, the awareness of the risk of MACE needs to be strengthened in the management of postoperative patients in Chinese hospitals. Finally, the population number of the validation group was 112 in 2020 and 253 cases of patients from 2010 to 2019, respectively. The relatively fewer quantity of training set was due to the refinement of diagnostic criteria of MACE and standardization of the medical record system. In recent years, the increasing attention to the harmfulness of MACEs in perioperative periods for hospitalized patients also contributes to this phenomenon.

In conclusion, we developed a nomogram and a risk score (HASBLAD) with prediction performance better than RCRI, which could be useful tools at the bedside. The significance of cardiac troponin and NT-pro BNP in perioperative period should be further investigated. At the same time, the focus on Takotsubo cardiomyopathy and the other cardiac complications that caused morbidity and mortality in patients during the perioperative period was necessary and should be further elucidated in future studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki and with approval from the Ethics Committee of Peking University Third Hospital (No. M2018258). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LZu, WG, and WX put forward the research idea for article. MZ, JC, MX, YX, CW, and HC were responsible for the study implementation and data collection. LZe, YL, and ZS performed the data analysis. MZ and ZS were jointly wrote the article. YF, WX, and LZu critically revised the work. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.774191/full#supplementary-material

REFERENCES

1. Sezen Ö, Çevik B. Emergency surgery in geriatrics: a retrospective evaluation in a single center. *Ulus Travma Acil Cerrahi Derg.* (2020) 26:411-7. English. doi: 10.14744/tjtes.2020.90914
2. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol.* (2017) 2:181-7. doi: 10.1001/jamacardio.2016.4792
3. Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. (2012) 307:2295-304. doi: 10.1001/jama.2012.5502
4. Vlisides PE, Moore LE, Whalin MK, Robicsek SA, Gelb AW, Lele AV, et al. Perioperative care of patients at high risk for stroke during or after non-cardiac, non-neurological surgery: 2020 Guidelines from the Society for Neuroscience in Anesthesiology and Critical Care. *J Neurosurg Anesthesiol.* (2020) 32:210-26. doi: 10.1097/ANA.0000000000000686
5. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* (2014) 130:2215-45. doi: 10.1161/CIR.0000000000000105
6. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al. Canadian Cardiovascular Society Guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol.* (2017) 33:17-32. doi: 10.1016/j.cjca.2016.09.008
7. Kyo S, Imanaka K, Masuda M, Miyata T, Morita K, Morota T, et al. Japanese Circulation Society Joint Working Group. Guidelines for perioperative cardiovascular evaluation and management for noncardiac surgery (JCS 2014) - digest version. *Circ J.* (2017) 81:245-67. doi: 10.1253/circj.CJ-66-0135
8. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* (1999) 100:1043-9. doi: 10.1161/01.CIR.100.10.1043
9. Gupta PK, Gupta H, Sundaram A, Kaushik M, Fang X, Miller WJ, et al. Development and validation of a risk calculator for prediction of cardiac risk after surgery. *Circulation.* (2011) 124:381-7. doi: 10.1161/CIRCULATIONAHA.110.015701
10. VISION Pilot Study Investigators, Devereaux PJ, Bradley D, Chan MT, Walsh M, Villar JC, et al. An international prospective cohort study evaluating major vascular complications among patients undergoing noncardiac surgery: the VISION Pilot Study. *Open Med.* (2011) 5:e193-200
11. Regenbogen SE, Lancaster RT, Lipsitz SR, Greenberg CC, Hutter MM, Gawande AA. Does the Surgical Apgar Score measure intraoperative performance? *Ann Surg.* (2008) 248:320-8. doi: 10.1097/SLA.0b013e318181c6b1
12. Wang Y, Li H, Ye H, Xie G, Wu S, Song S, et al. On behalf the International Surgical Outcomes Study. (ISOS) group in China. Postoperative infectious complications in elderly patients after elective surgery in China: results of a 7-day cohort study from the International Surgical Outcomes Study. *Psychogeriatrics.* (2021) 21:158-65. doi: 10.1111/psyg.12648
13. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent reporting of a multivariable prediction model for individual prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med.* (2015) 162:W1-73. doi: 10.7326/M14-0698
14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction: fourth Universal Definition of Myocardial Infarction 2018. *Circulation.* (2018) 138:e618-51. doi: 10.1161/CIR.0000000000000617
15. Amin HZ, Amin LZ, Pradipta A. Takotsubo cardiomyopathy: a brief review. *J Med Life*. (2020) 13:3–7. doi: 10.25122/jml-2018-0067
16. Vach W. Calibration of clinical prediction rules does not just assess bias. *J Clin Epidemiol.* (2013) 66:1296-301. doi: 10.1016/j.jclinepi.2013.06.003
17. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med.* (2009) 360:491-9. doi: 10.1056/NEJMsa0810119
18. Suresh KV, Wang K, Sethi I, Zhang B, Margalit A, Puvanesarajah V, et al. Spine surgery and preoperative hemoglobin, hematocrit, and hemoglobin A1c: a systematic review. *Global Spine J.* (2021) 21:2192568220979821. doi: 10.1177/2192568220979821
19. Turan A, Cohen B, Rivas E, Liu L, Pu X, Maheshwari K, et al. Association between postoperative haemoglobin and myocardial injury after noncardiac surgery: a retrospective cohort analysis. *Br J Anaesth.* (2021) 126:94-101. doi: 10.1016/j.bja.2020.08.056
20. Dakour-Aridi H, Nejim B, Locham S, Alshwaily W, Malas MB. Anemia and postoperative outcomes after open and endovascular repair of intact abdominal aortic aneurysms. *J Vasc Surg.* (2019) 69:738-51.e2. doi: 10.1016/j.jvs.2018.05.233
21. Swirski FK, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. *Science.* (2013) 339:161-6. doi: 10.1126/science.1230719
22. Larmann J, Handke J, Scholz AS, Dehne S, Arens C, Gillmann HJ, et al. Preoperative neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are associated with major adverse cardiovascular and cerebrovascular events in coronary heart disease patients undergoing non-cardiac surgery. *BMC Cardiovasc Disord.* (2020) 20:230. doi: 10.1186/s12872-020-01500-6
23. Scholz AS, Handke J, Gillmann HJ, Zhang Q, Dehne S, Janssen H, et al. Frontline science: low regulatory T cells predict perioperative major adverse cardiovascular and cerebrovascular events after noncardiac surgery. *J Leukoc Biol.* (2020) 107:717-30. doi: 10.1002/JLB.5HI1018-392RR
24. Gujral JS, Bucci TJ, Farhood A, Jaeschke H. Mechanism of cell death during warm hepatic ischemia-reperfusion in rats: apoptosis or necrosis? *Hepatology.* (2001) 33:397-405. doi: 10.1053/jhep.2001.22002
25. Maynard ND, Bihari DJ, Dalton RN, Beale R, Smithies MN, Mason RC. Liver function and splanchnic ischemia in critically ill patients. *Chest.* (1997) 111:180-7. doi: 10.1378/chest.111.1.180
26. del Olmo JA, Flor-Lorente B, Flor-Civera B, Rodriguez F, Serra MA, Escudero A, et al. Risk factors for nonhepatic surgery in patients with cirrhosis. *World J Surg.* (2003) 27:647-52. doi: 10.1007/s00268-003-6794-1
27. Poole-Wilson PA, Langer GA. Effect of pH on ionic exchange and function in rat and rabbit myocardium. *Am J Physiol.* (1975) 229:570-81. doi: 10.1152/ajplegacy.1975.229.3.570
28. Medina de Chazal H, Del Buono MG, Keyser-Marcus L, Ma L, Moeller FG, Berrocal D, et al. Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review. *J Am Coll Cardiol.* (2018) 72:1955-71. doi: 10.1016/j.jacc.2018.07.072
29. Hessel EA, 2nd. Takotsubo cardiomyopathy and its relevance to anesthesiology: a narrative review. *Can J Anaesth.* (2016) 63:1059-74. doi: 10.1007/s12630-016-0680-4
30. Gibson LE, Klinker MR, Wood MJ. Variants of Takotsubo syndrome in the perioperative period: a review of potential mechanisms and anaesthetic implications. *Anaesth Crit Care Pain Med.* (2020) 39:647-54. doi: 10.1016/j.accpm.2020.01.010

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Knowledge of Symptoms of Acute Myocardial Infarction, Reaction to the Symptoms, and Ability to Perform Cardiopulmonary Resuscitation: Results From a Cross-sectional Survey in Four Regions in Germany

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Background: Ischemic heart disease affects 126 million individuals globally which illustrates the importance of finding ways to decrease mortality and morbidity in case of an acute myocardial infarction (AMI). Since knowledge of symptoms, correct reaction to symptoms, and ability to perform cardiopulmonary resuscitation (CPR) decreases the time from symptoms-onset to reperfusion, which leads to lower AMI mortality, we aimed to examine those factors and identify predicting variables in regions with low and high AMI mortality rates.

Methods: We conducted a cross-sectional online survey including 633 respondents from the general population in four federal states in Germany with low and high AMI mortality and morbidity rates. We used uni- and multivariable regressions to find health-related and sociodemographic factors associated with knowledge, reaction to symptoms, and skills in CPR.

Results: Out of 11 symptoms, the mean of correctly attributed AMI symptoms was 7.3 (standard deviation 1.96). About 93% of respondents chose to call an ambulance when witnessing an AMI. However, when confronted with the description of a real-life situation, only 35 and 65% of the participants would call an ambulance in case of abdominal and chest pain, respectively. The predicting variables for higher knowledge were being female, knowing someone with heart disease, and being an ex-smoker compared to people who never smoked. Higher knowledge was associated with adequate reaction in the description of a real-life situation and ability to perform CPR. Prevalence ratio for being able to perform CPR was lower in females, older participants, and participants with low educational level. About 38% of participants state to know how to perform CPR. Our results indicate rather no difference regarding knowledge, reaction to AMI symptoms, and ability to perform CPR among different regions in Germany.

Conclusions: Knowledge of symptoms and first responder reaction including skills in CPR is inadequate when confronted with the description of a real-life situation. Educational health campaigns should focus on conveying information close to real-life situations. Interventions for enhancing ability to perform CPR should be compulsory in regular intervals. Interestingly, we found no difference regarding the factors in regions with high and low AMI mortality rates in Germany.

Keywords: epidemiology, acute myocardial infarction, knowledge about symptoms, cardiopulmonary resuscitation, help-seeking behavior, first responder reaction, awareness

INTRODUCTION

Ischemic heart disease (IHD) affects around 126 million individuals globally (1,655 per 100,000), the global prevalence is rising, and it is the leading cause of death and disability worldwide, as well as in Germany (1, 2). One main manifestation of IHD is myocardial infarction (AMI). When witnessing an AMI, a swift and appropriate reaction is crucial to decrease the time to reperfusion and therefore improve prognosis (3–5). In Germany, mortality of AMI differs across federal states. The highest mortality rates are observed in Eastern and the lowest in Southern and Western Germany (6). These differences are partly, but not fully explained by differences in the prevalence of cardiovascular risk factors (7). It is hypothesized that differences could also be due to the number of people able to perform cardiopulmonary resuscitation (CPR), knowledge of AMI symptoms, and behavior during AMI (8). However, to date it is unknown whether these factors differ in regions with different mortality rates. Additionally, few studies have examined which health-related and sociodemographic factors are associated with knowledge, reaction to AMI symptoms, and ability to perform CPR.

Awareness of differences in knowledge and reaction to AMI symptoms, as well as ability to perform CPR in regions with different AMI mortality rates, could refine interventions to improve the response when witnessing an AMI (9). Additionally, knowledge of influencing factors of this response is essential. The aim of this study was to investigate associations of knowledge and reaction to AMI symptoms, and ability to perform CPR with health, health behavior, and sociodemographic factors taking into account regions with different AMI mortality rates in Germany.

MATERIALS AND METHODS

Study Population

In December 2020 we re-contacted 35,835 people from a former survey (9,319 in Saxony-Anhalt with one of the highest AMI mortality rate, 9,182 in Baden-Wuerttemberg, 7,104 in North-Rhine Westphalia, and 10,230 in Schleswig-Holstein, among the federal states with the lowest AMI mortality rates) (6). Of these 35,835 invited, 857 persons conducted the cross-sectional online survey (2.4%).

Abbreviations: IHD, ischemic heart disease; AMI, acute myocardial infarction; CPR, cardiopulmonary resuscitation; PR, prevalence ratio; CI, confidence interval.

Outcomes

For evaluating participant's knowledge of AMI symptoms, we included 11 symptoms of which 10 were symptoms of AMI and one was not, and asked the participants whether these symptoms were AMI symptoms. We chose "sudden visual disturbances" as trap question, as it is not usually a symptom of AMI. We calculated a knowledge score for each participant by adding up the participant's correct answers about AMI symptoms, resulting in a score with a theoretical range from 0 to 11. We did not calculate the score in case of missing values. Our used question format was chosen as it has been used regularly in current literature as well as in Germany (10, 11). The included set of symptoms are based on the ten most frequently asked symptoms and trap symptom in the current literature (11).

We evaluated the participant's reaction when witnessing a potential AMI by describing the following everyday scenario and giving different options to choose from:

> You are talking on the phone to a female person you are close with. She is 60 years old and had no severe diseases to date. She says that she
> 1) suddenly has chest pain or
> 2) has abdominal pressure since an hour, but it is getting worse now. She feels weak and wants to lie down and rest. You say goodbye and finish the conversation.

The symptoms (chest or abdominal pain) were randomly assigned to the participants. The following answer options were given:

a) Chest pain/abdominal pain is common. You let her rest and decide to ask her about her health the next time you talk to her.
b) Chest pain/abdominal pain could be related to the heart. Lying down relieves the strain on the heart. You decide to call her back in 2 h and ask about her well-being.
c) Chest pain/abdominal pain could be a sign of a severe disease. You call her back and convince her to call an ambulance.
d) Do not know.
e) Something else (with a free-text field for describing the reaction).

Additionally, the survey included two multiple-choice questions with free-text fields that asked participants what they would do if they saw someone lying on the floor in a department store and what they would do if they thought someone had an AMI. We analyzed these two questions descriptively and did not use them as outcomes in regression.

TABLE 1 | Sociodemographic characteristics and reaction to other people's symptoms of myocardial infarction ($n = 633$).

Gender	
Female, *n* (%)[a]	322 (50.9)
Age	
Age, mean (SD)	49.2 (15.3)
Below 30 years old, *n* (%)	85 (13.4)
30–39 years old, *n* (%)	110 (17.4)
40–49 years old, *n* (%)	102 (16.1)
50–59 years old, *n* (%)	153 (24.1)
60–69 years old, *n* (%)	124 (19.6)
70 years and older, *n* (%)	59 (9.3)
Education	
Master, diploma, doctorate (PhD), *n* (%)	213 (33.6)
Bachelor or equivalent, *n* (%)	139 (22.0)
Vocational training, *n* (%)	245 (38.7)
No degree/still in training or studying, *n* (%)	36 (5.7)
Federal state	
Baden-Wuerttemberg	152 (24.0)
North Rhine-Westphalia	150 (23.7)
Saxony-Anhalt	171 (27.0)
Schleswig-Holstein	160 (25.3)
Disease related factors and risk factors of myocardial infarction	
Disease related to heart, *n* (%)	66 (10.4)
Knowing person with heart disease, *n* (%)	359 (56.7)
High blood pressure (currently/in the past), *n* (%)	220 (34.8)
Current smoker, *n* (%)	99 (15.6)
Former smoker, *n* (%)	204 (32.2)
Never smoked, *n* (%)	330 (52.1)

[a] *One person was diverse. SD, standard deviation.*

For examining the ability to perform CPR we asked the participants whether they know how to perform CPR and gave the following answer options:

a) Yes, I can perform it myself or instruct someone else to perform it.
b) Yes, theoretically, but I do not dare to perform it in a real-life situation.
c) No, I have learned it, but do not remember well how to perform it.
d) No, I never learned or knew how to perform it.

We included the following variables as possible predictors for the above-described outcomes: (1) Gender (self-classified as male, female, diverse), (2) age in years, (3) educational level, (4) federal state, (5) having a heart disease, (6) knowing someone with a heart disease, (7) self-reported high blood pressure, and (8) smoking status. Additionally, we included the knowledge score as predictor for reaction to AMI symptoms and ability to perform CPR. We chose the variables based on thorough literature review (8, 11).

Statistical Analysis

Data of 633 participants were analyzed after excluding observations with missing values for any of the included variables. Since there was only one diverse person, we excluded this observation in all analyses that included gender as variable.

For analyzing the reaction to AMI symptoms, we dichotomized the answer options. We chose convincing the women to call an ambulance as appropriate and all other options as less appropriate. We conducted all analyses separately for the symptoms chest and abdominal pain.

For analyzing the ability to perform CPR, we also dichotomized the answer options. We chose the answer option to be able to perform CPR or instruct someone else to perform it as one category, since this answer option reflects if someone would perform or help to perform it in a real-life situation. The other answer options were included in another category.

For the knowledge score, we performed linear regressions. For the binary outcomes, we estimated Prevalence Ratios (PRs) using binomial distribution with log link function, since the outcomes were common (35.4–64.6% for the certain outcomes) (12).

We conducted uni- and multivariable regressions to identify factors possibly associated with the different outcomes. Since there was no evidence for serious multicollinearity, we included all variables in multivariable regression (variance inflation factor < 5 for all variables) (13–17). Since there is some evidence in previous studies that the effect for age could be non-linear, we tested non-linear associations between age and the outcomes using thin plate splines in generalized additive models. Since non-linear associations did not improve model fit (Akaike Information Criteria < 10 for linear vs. non-linear terms), we included age as linear term in all models (18). We used R-Studio V.3.4.4 and SAS V. 9.4 for the analyses (19, 20).

RESULTS

Females, males, and the four federal states were equally represented in the sample. One person was diverse. The mean age was 49 years. About 56% of the participants held a university degree (Bachelor or higher). About 10% of the participants reported to have a heart disease and more than half of the sample indicated to know a person with heart disease. About 35% of the participants stated to have hypertension (currently or in the past), which is about the percentage of people with hypertension in the general middle-aged German population (21). About half of the sample stated to be current or former smokers (**Table 1**).

Almost all participants correctly identified chest pain/pressure as being a symptom of AMI. The four least known symptoms were abdominal pain, nausea/vomiting, headache, and jaw/neck/back pain (**Figure 1**; **Supplementary Figure 1**). In North Rhine-Westphalia, 63% correctly identified abdominal pain as symptom, while only 44% in Baden-Wuerttemberg did so (**Supplementary Figure 1**). The mean number of correctly attributed symptoms was 7.3 out of 11 symptoms (standard deviation 1.96).

Asking the participants what they would do when witnessing a person lying on the floor in a department store, about 10% would call an ambulance. About 40% stated to check whether the person was breathing before deciding to call an ambulance. Another 40% stated to start CPR, if necessary. About 6% would

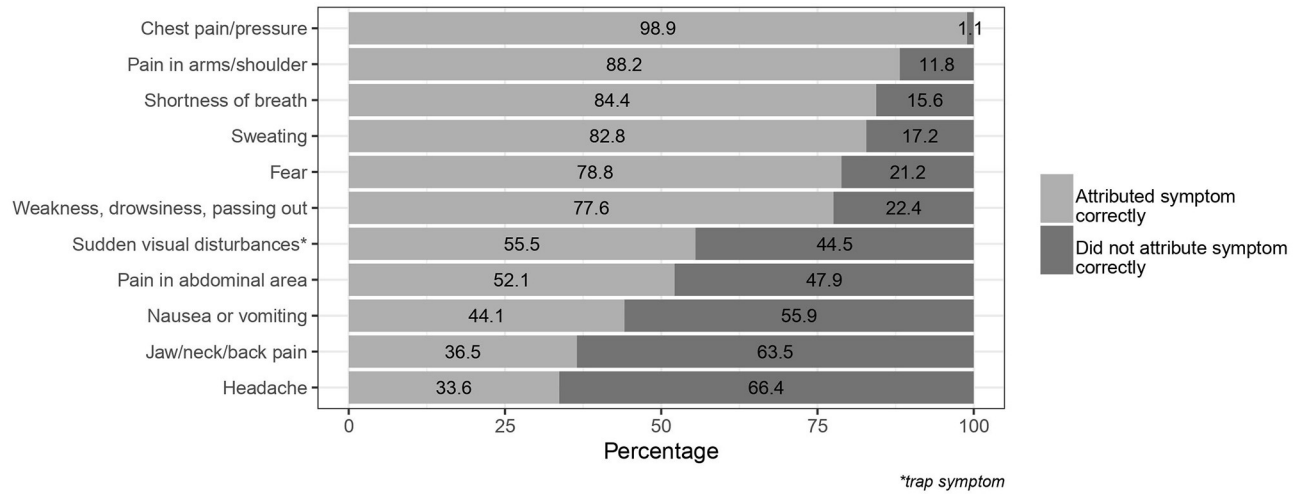

FIGURE 1 | Symptoms of myocardial infarction identified as correct/incorrect by the participants; *trap symptom.

ask somebody else for help, as they did not feel capable of gauging the situation correctly. Almost all participants stated to call an ambulance when they assume that someone has an AMI (**Supplementary Table 1**).

In the phone call scenario, 64% of the participants who received chest pain as symptom would convince the women to call an ambulance, while 35% of the participants who received abdominal pain would do so (**Figure 2**). This tendency was seen in all federal states. The proportion to convince the women to call an ambulance in both scenarios was highest in Saxony-Anhalt when compared to the other federal states (**Supplementary Figure 2**).

About 40% of the participants indicated that they could perform CPR themselves or instruct someone else to perform it. Around 30% indicated theoretically knowing how to perform it or have learned, but do not remember well how to perform it, respectively (**Figure 3**). The highest percentage regarding being able to perform CPR was in Schleswig-Holstein, while the highest percentage of theoretically knowing how to perform it was in Saxony-Anhalt (**Supplementary Figure 3**).

Examining the factors associated with knowledge of AMI symptoms, reaction to symptoms, and ability to perform resuscitation, we found that the mean knowledge score was higher in females when compared to males and lower in people aged 70 years or older when compared to the other age groups. The score was higher for people knowing someone with heart disease when compared to people not knowing someone with heart disease.

In the phone call scenario, the proportion of people choosing the adequate reaction in case of sudden chest pain was highest in the age groups 40–49 and 60–69 years when compared to the other age groups. The proportion was higher for people knowing someone with heart disease and in former smokers.

In case of abdominal pain, the proportion was highest in the age group 60–69 years and higher in people having heart disease.

Regarding the ability to perform CPR, more males than females reported to be able to perform it and the proportion decreased with increasing age. People with higher educational level reported more often to be able to perform CPR when compared to people with lower educational level. Higher proportion of former and current smokers reported to be able to perform CPR (**Table 2**).

Results of Regression Analyses

Estimates for the certain factors were comparable in uni- and multivariable regressions (**Table 3**; **Supplementary Table 2**).

For women, the knowledge score was 0.75 points higher than for men. Age, educational level, having heart disease, and hypertension were not associated with knowledge score. The knowledge score for participants knowing someone with heart disease was about half a point higher when compared to people not knowing anyone with heart disease. The knowledge score of former smokers was almost half a point higher when compared to people who never smoked. There was no consistent difference in the knowledge score among the federal states (**Table 3**). Regarding the symptom chest pain in the phone call scenario, estimates for all variables except knowledge score indicated no association (**Table 3**).

Regarding the symptom abdominal pain there was no association with gender, having heart disease, knowing someone with heart disease, hypertension, and smoking. PR for convincing the women to call an ambulance increased with older age. When compared to people with the highest educational level, PR for convincing the women to call an ambulance was higher in people still studying/having no degree, but CI included the null effect. PR for convincing the women to call an ambulance was lower in Baden-Wuerttemberg compared to Saxony-Anhalt, but again CI included the null effect. Higher knowledge score was associated with higher PR for convincing the women to call an ambulance (**Table 3**). Regarding the ability to perform CPR,

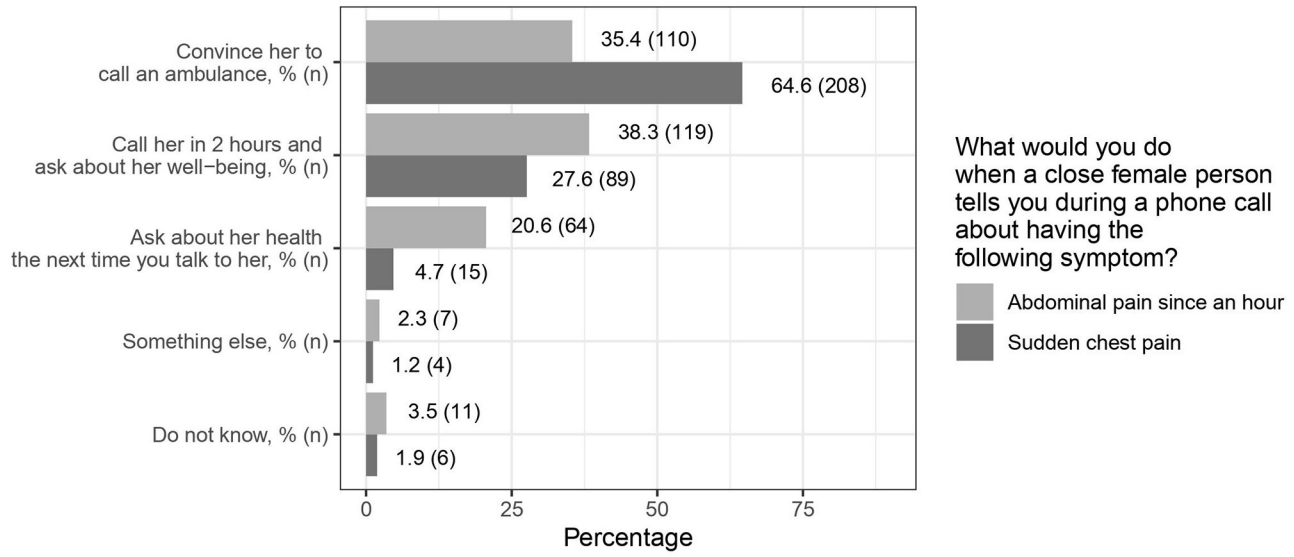

FIGURE 2 | Reaction to two symptoms of myocardial infarction.

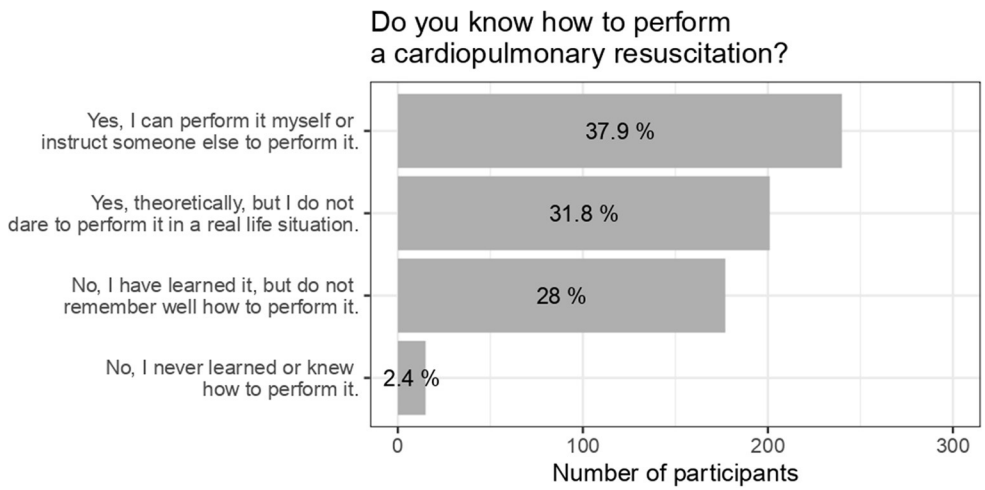

FIGURE 3 | Ability to perform a cardiopulmonary resuscitation.

there was no association with having and knowing someone with heart disease, and hypertension. Women were less likely to perform CPR compared to men. PR for the ability to perform CPR decreased with older age. PR of stating to be able to perform CPR was lower for people with vocational training and still studying/having no degree when compared to people with the highest educational level. When compared to people who never smoked, PR was higher in former and current smokers. However, CI included the null effect. Higher knowledge score was associated with higher PR to be able to perform CPR. There was no consistent difference among the federal states (**Table 3**).

DISCUSSION

In our study, we found that participants had a good understanding of how to react in case of an AMI since the vast majority would call an ambulance. In contrast, when confronted with the description of a phone call in which somebody displayed symptoms of an AMI, the proportion of participants who would convince the women to call an ambulance was considerably lower. Partly, this could be explained by the order of the questions, as the phone-call-scenario was the first question in the survey. Higher knowledge score was associated with higher PR of an adequate reaction in multiple regression. However, knowledge

TABLE 2 | Knowledge score, reaction to other people's symptoms of myocardial infarction, ability to perform CPR and their possible predictors.

	Knowledge score[b]	Would convince her to call ambulance in case of sudden chest pain ($n = 322$)[c]	Would convince her to call ambulance in case of abdominal pain ($n = 311$)[c]	Ability to perform CPR[d]
	Mean (SD)	% (*n*)	% (*n*)	% (*n*)
Female[a]	7.71 (1.84)	64 (103/161)	36 (58/161)	36.0 (116/322)
Male[a]	6.93 (2.00)	65.6 (105/160)	34.7 (52/150)	40.0 (124/310)
Below 30 years old	7.42 (1.87)	57.5 (23/40)	35.6 (16/45)	44.7 (38/85)
30–39 years old	7.29 (2.00)	56.6 (30/53)	26.3 (15/57)	43.6 (48/110)
40–49 years old	7.52 (2.08)	71.7 (38/53)	26.5 (13/49)	39.2 (40/102)
50–59 years old	7.37 (1.89)	64.6 (51/79)	37.8 (28/74)	37.9 (58/153)
60–69 years old	7.33 (1.93)	72.9 (51/70)	48.1 (26/54)	30.6 (38/124)
70 years and older	6.78 (2.03)	55.6 (15/27)	37.5 (12/32)	30.5 (18/59)
Master, diploma, doctorate (PhD)	7.38 (1.92)	63.2 (67/106)	30.8 (33/107)	39.4 (84/213)
Bachelor or equivalent	7.27 (1.95)	61.8 (42/68)	42.3 (30/71)	41.7 (58/139)
Vocational training	7.28 (2.00)	67.7 (88/130)	32.2 (37/115)	35.9 (88/245)
No degree/still in training or studying	7.47 (1.99)	61.1 (11/18)	55.6 (10/18)	27.8 (10/36)
Baden-Wuerttemberg	7.13 (2.08)	58.6 (41/70)	26.8 (22/82)	35.5 (54/152)
North Rhine-Westphalia	7.69 (1.84)	69.1 (56/81)	30.4 (21/69)	38.7 (58/150)
Saxony-Anhalt	7.27 (1.96)	70 (63/90)	46.9 (38/81)	36.3 (62/171)
Schleswig-Holstein	7.22 (1.92)	59.3 (48/81)	36.7 (29/79)	41.3 (66/160)
Heart disease	7.36 (1.97)	67.6 (23/34)	40.6 (13/32)	34.8 (23/66)
Having no heart disease	7.32 (1.87)	64.2 (185/288)	34.8 (97/279)	38.3 (217/567)
Knowing someone with heart disease	7.61 (1.86)	67 (118/176)	35 (64/183)	39.8 (143/359)
Not knowing anyone with heart disease	6.94 (2.02)	61.6 (90/146)	35.9 (46/128)	35.4 (97/274)
High blood pressure	7.24 (1.89)	66.1 (78/118)	37.3 (38/102)	32.3 (71/220)
No high blood pressure	7.37 (2.00)	63.7 (130/204)	34.4 (72/209)	40.9 (169/393)
Never smoked	7.22 (2.00)	62.1 (105/169)	33.5 (54/161)	35.2 (116/330)
Former smoker	7.59 (1.88)	69.3 (70/101)	35.9 (37/103)	39.7 (81/204)
Current smoker	7.12 (2.00)	63.5 (33/52)	40.4 (19/47)	43.4 (43/99)
Knowledge score	–	7.4 (1.8)	8.1 (1.8)	8.0 (1.8)

[a] *Because of only 1 observation, the category "diverse" was not included in the analysis, n = 632.*

[b] *Higher score indicating higher knowledge, possible range: 0–11, minimum in the sample: 2, maximum in the sample: 11.*

[c] *Refers to question: What would you do when a close female person tells you during a phone call about having abdominal pain since an hour/sudden chest pain? The symptom was randomly assigned to the participants.*

[d] *Refers to question: Do you know how to perform a cardiopulmonary resuscitation? The answer option: "Yes, I can perform it myself or instruct someone else to perform it" was considered "ability to perform resuscitation."*

CPR, cardiopulmonary resuscitation; SD, standard deviation.

might not translate directly into reacting appropriately when witnessing an AMI.

In our scenario, it is plausible that more participants chose to convince the women to call an ambulance when confronted with chest pain compared to abdominal pain since chest pain was more frequently recognized as AMI symptom than abdominal pain. This underlines the importance to educate about atypical symptoms of AMI. In fact, especially women present more often with only non-chest pain discomfort and the elderly experience more atypical symptoms (22–24).

Knowledge Score

Exploring the knowledge about symptoms of AMI, we found a mean knowledge score of 7.3/11. Hence, the mean proportion of symptoms that were correctly identified as belonging to AMI was 66.4%. This is considerably higher than in a previous study conducted in Germany in 2006 that found a proportion of 45.7% of symptoms to be correctly identified (10). The reason for the observed difference could be that selection bias in our sample might have influenced the results as well as the limitation to four regions of Germany, while the former study used a representative quota method across Germany. Possibly, in the time span from 2006 to 2020 the German population might have increased their knowledge due to efforts to better inform the public and educational campaigns as organized by the "Deutsche Herzstiftung e. V." (25).

Compared to the weighted mean of a sample of eight European countries, Russia, and Singapore, the proportion that we found in Germany is higher too (66.4 vs. 42.1%) (11).

When looking at the proportion of participants who identified a specific symptom correctly, the least well-known symptom

TABLE 3 | Multivariable regressions for knowledge and reaction to symptoms of myocardial infarction and possible predictors ($n = 632$[a]).

	Knowledge score, ß (95% CI)[b]	Would convince her to call ambulance in case of sudden chest pain ($n = 322$), PR (95% CI)[c]	Would convince her to call ambulance, in case of abdominal pain ($n = 311$), PR (95% CI)[c]	Ability to perform CPR, PR (95% CI)[d]
Male[a]		Reference		
Female[a]	0.75 (0.44, 1.06)	0.93 (0.78, 1.10)	1.00 (0.73, 1.36)	0.77 (0.63, 0.94)
Age (per 10 years)	−0.08 (−0.19, 0.03)	1.03 (0.97, 1.10)	1.11 (1.00, 1.24)	0.91 (0.85, 0.98)
Master, diploma, doctorate (PhD)		Reference		
Bachelor or equivalent	−0.11 (−0.52, 0.30)	0.93 (0.72, 1.19)	1.26 (0.85, 1.85)	1.01 (0.79, 1.29)
Vocational training	−0.23 (−0.59, 0.13)	1.08 (0.89, 1.32)	0.93 (0.64, 1.35)	0.91 (0.70, 1.15)
No degree/still in training or studying	−0.15 (−0.85, 0.56)	0.94 (0.63, 1.40)	1.72 (0.96, 3.06)	0.56 (0.34, 0.93)
Saxony-Anhalt		Reference		
Baden-Wuerttemberg	−0.11 (−0.53, 0.31)	0.89 (0.70, 1.15)	0.66 (0.43, 1.01)	0.93 (0.71, 1.23)
North Rhine-Westphalia	0.29 (−0.13, 0.72)	1.00 (0.80, 1.26)	0.72 (0.48, 1.09)	0.93 (0.71, 1.22)
Schleswig-Holstein	−0.12 (−0.54, 0.29)	0.87 (0.68, 1.13)	0.81 (0.56, 1.19)	1.09 (0.84, 1.41)
Having heart disease	0.18 (−0.33, 0.68)	0.96 (0.74, 1.24)	1.02 (0.67, 1.55)	1.03 (0.73, 1.46)
Knowing someone with heart disease	0.54 (0.24, 0.85)	1.02 (0.87, 1.21)	0.90 (0.67, 1.21)	1.08 (0.90, 1.31)
Having high blood pressure	0.03 (−0.31, 0.37)	1.05 (0.87, 1.26)	0.90 (0.65, 1.25)	0.86 (0.69, 1.08)
Never smoked		Reference		
Former smoker	0.48 (0.14, 0.82)	1.08 (0.91, 1.29)	0.91 (0.65, 1.29)	1.12 (0.90, 1.39)
Current smoker	0.10 (−0.34, 0.54)	1.01 (0.80, 1.28)	1.14 (0.75, 1.74)	1.20 (0.93, 1.54)
Knowledge score (1 unit increase)	–	1.06 (1.01, 1.11)	1.17 (1.07, 1.26)	1.19 (1.13, 1.26)

[a] *Because of only 1 observation, the category "diverse" was not included in the analysis, n = 632.*

[b] *Higher score indicating higher knowledge, possible range: 0-11, minimum: 2, maximum: 11.*

[c] *Refers to question: What would you do when a close female person tells you during a phone call about having abdominal pain since an hour/sudden chest pain?*

[d] *Refers to question: Do you know how to perform a cardiopulmonary resuscitation? The answer option: "Yes, I can perform it myself or instruct someone else to perform it" was considered "ability to perform resuscitation."*

PR, prevalence ratio; CI, confidence interval; CPR, cardiopulmonary resuscitation.

"headache" was still known by 33.8%, which is higher than in the previously mentioned studies (11, 24).

The before mentioned study from Germany observed a lower knowledge of abdominal pain (10). One possible explanation is that our observed higher knowledge of abdominal pain was influenced by our study set up, since half of the participants had already read about the woman on the phone with abdominal pain when we evaluated the knowledge of the AMI symptoms. Indeed, about 61% of the participants who were assigned to the scenario with abdominal pain identified it as symptom, while only 43% of the participants who were assigned to the scenario with chest pain did so.

The trap symptom "sudden visual disturbances" was falsely attributed to AMI by 44.5% of participants. This can be compared to the population in two studies from the United States (31.9%, 58%) and one from South Korea (33,8%), with a weighted mean proportion of 32.2% (11, 15, 17, 26). In a sample of AMI patients in Germany from 2016, the proportion of misattribution was only 19.2% (27). While this might suggest that AMI patients are better informed about this symptom, different forms of recruiting and the different areas in Germany might also influence the results. The false attribution of the symptom to AMI in our sample might point to a confusion about this symptom specifically or be influenced by the confounder that the participants were generally inclined to attribute the listed symptoms to AMI, a phenomenon that has been described by Greenlund et al. (28). However, this phenomenon could also be present in the other studies that were listed before.

Predictors of Knowledge of Symptoms of AMI

When analyzing predicting factors of knowledge of AMI symptoms, we found that factors that are in connection with a general interest in health are also predictors for a better knowledge of AMI symptoms:

(1) Being female was associated with higher knowledge similarly to the findings of previous studies (10, 14–16, 29).
(2) Higher knowledge in people who know someone with heart disease might be influenced by their increased interest and direct talks about the disease. This aligns with a study that found a better knowledge of at least one to four symptoms when relatives, acquaintances, or neighbors had a history of AMI (17).
(3) Being an ex-smoker in comparison to people who never smoked was positively associated with a higher knowledge scale. This might be a result of increased interest in healthy living. When comparing smokers to non-smokers we did not observe an effect.

While past literature observed an association for history of heart disease and a good knowledge of the symptoms, as well as for having coronary heart disease and a recommended heart attack knowledge, we did not observe an effect for having heart disease (15, 30). It is plausible that people with heart disease have a higher interest in AMI so it is not clear to us why this association could not be found in our survey. One possible reason could be that in light of the low response rate to our survey, the interest of the participants was generally higher than in the general population and therefore, the interest among participants with heart disease was similar to the interest of the other participants. However, since we could find an association for other factors related to interest, this might not be a sufficient explanation.

Similarly, we did not find an association between knowledge and hypertension which is a risk factor for AMI. This aligns with a previous study that did not find a significant association between hypertension and excellent knowledge (17).

While we found no association with age, previous studies found young or middle-aged adults to be most knowledgeable (14–17), except for one study that found people aged 14–35 years to be least knowledgeable which might be influenced by the inclusion of teenagers in the sample (10). Regarding the elderly in our study, the results might have been skewed by a selection bias since the observed participants were all mentally fit enough and resourceful enough to use the Internet in order to answer the online survey and additionally, there were only few people aged 70 or older in our sample.

We found that participants with the highest education had the highest knowledge score but the associations were very small including the null effect. Past literature observed a better knowledge of the AMI symptoms in adults with higher education (10, 14–17, 31).

We did not observe differences among the federal states. Our results indicate that differences among Federal States with high and low AMI mortality rates in Germany might not be explained by differences in knowledge of AMI symptoms.

Predictors of Reaction to Symptoms of AMI

When the participants were confronted with the symptom sudden chest pain in the phone call scenario, we observed an association with higher knowledge score and convincing the woman to call an ambulance. All other variables were not associated with the outcome.

When confronted with the symptom abdominal pain, older age and higher knowledge score were associated with convincing the woman to call an ambulance. Older people might be more aware that abdominal pain could be related to a severe disease than younger people and hence be more likely to convince the woman to call an ambulance. People in the federal states with low AMI mortality were less likely to convince the woman to call an ambulance when compared to people in Saxony-Anhalt, the state with the highest AMI mortality. Even though this result included the null effect, which might be partly due to small sample size, it is highly interesting, since it was hypothesized that people in federal states with a higher mortality of AMIs would rather not call an ambulance. This should be explored in further studies.

Since our chosen approach of analyzing the reaction to AMI symptoms by describing a real-life situation has, to our knowledge, not been conducted in the same way in previous literature, it needs more research to better understand the results and the associated factors for our observation.

Predictors of Ability to Perform CPR

Factors associated with performing CPR were a better knowledge of the symptoms, being male, and younger age. People having no degree/still in training or studying were less likely to perform CPR in comparison with people holding Master, diploma, or doctorate degree.

In Germany, training in CPR is mandatory when taking classes for a driving license and in most social and health-related professions. However, in contrast to many other countries, in Germany the population is not regularly trained in CPR (32). Trying to explain our predictors, it might be plausible that for younger people the time span since obtaining their driving license was smaller, so they were able to remember their training in CPR better and therefore showed an increased confidence.

Our results indicate that differences among federal states with high and low AMI mortality rates in Germany might not be explained by differences in the ability to perform CPR.

Limitations and Strength

One limitation of our study is the online assessment, which might exclude mainly the elderly, who are not familiar with the internet. Additionally, because of the low response rate and contacting only non-responders from a former survey, selection bias must be assumed. A strength of the study is that we assessed the knowledge and first responder reaction not only by testing the participants directly about their knowledge/preferred reaction without a practical context but also with real-life scenarios. The description of everyday scenarios could provide a higher external validity since it is closer to the actual experience of a bystander. Furthermore, this study is the first survey to assess knowledge,

reaction to AMI symptoms, and ability to perform CPR in German federal states with different AMI mortality rates.

CONCLUSIONS

This study indicates rather no differences regarding knowledge and reaction to AMI symptoms as well as ability to perform CPR among different regions with high and low AMI mortality rates when taking into account sociodemographic as well as health and health-related factors. Only few of the other examined factors showed an association with the outcomes. Further studies should explore which factors could influence knowledge, reaction to symptoms, and ability to perform CPR. This study highlights that less known AMI symptoms should be included in health campaigns. Educating the public about AMI symptoms and CPR may not be sufficient for enabling bystanders to gauge a real-life situation correctly and act accordingly. Educational health campaigns should focus on conveying the information in a format that is close to a real-life situation in order to have most impact (9). Interventions for enhancing ability to perform CPR should be compulsory in regular intervals.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Ethics Committee of the Medical Faculty of the Martin-Luther University Halle-Wittenberg.

AUTHOR CONTRIBUTIONS

RM and SH developed the general idea of the study and prepared the study protocol. SH, RM, and BB developed the questionnaire. BB drafted the initial manuscript. NK conducted the statistical analyses and contributed sections on methods and results. All authors contributed to the interpretation of the findings. All authors revised and commented on the manuscript and read and approved the final version.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SK, AlKatheeri R, et al. Global epidemiology of ischemic heart disease: results from the global burden of disease study. *Cureus.* (2020) 12:e9349–e9349. doi: 10.7759/cureus.9349
2. Robert Koch-Institut (Hrsg.). *Gesundheit in Deutschland. Gesundheitsberichterstattung des Bundes. Gemeinsam getragen von RKI und Destatis*. Robert Koch-Institut, Berlin (2015). Available online at: rki.de/DE/Content/Gesundheitsmonitoring/Gesundheitsberichterstattung/GBEDownloadsGiD/2015/02_gesundheit_in_deutschland.pdf?__blob$=$publicationFile (accessed April 19, 2021).
3. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction. *Circulation.* (2004) 109:1223–5. doi: 10.1161/01.CIR.0000121424.76486.20
4. Guerchicoff A, Brener SJ, Maehara A, Witzenbichler B, Fahy M, Xu K, et al. Impact of delay to reperfusion on reperfusion success, infarct size, and clinical outcomes in patients with ST-segment elevation myocardial infarction: the INFUSE-AMI trial (INFUSE-Anterior Myocardial Infarction). *JACC Cardiovasc Interv.* (2014) 7:733–40. doi: 10.1016/j.jcin.2014.01.166
5. Rollando D, Puggioni E, Robotti S, Lisi A de, Ferrari Bravo M, Vardanega A, et al. Symptom onset-to-balloon time and mortality in the first seven years after STEMI treated with primary percutaneous coronary intervention. *Heart.* (2012) 98:1738. doi: 10.1136/heartjnl-2012-302536
6. Deutsche Herzstiftung e. V. Deutscher Herzbericht: sektorenübergreifende Versorgungsanalyse zur Kardiologie, Herzchirurgie und Kinderherzmedizin in Deutschland. Frankfurt: Deutsche Herzstiftung 2019:28–9.
7. Stang A, Stang M. An inter-state comparison of cardiovascular risk factors in Germany: towards an explanation of high ischemic heart disease mortality in Saxony-Anhalt. *Dtsch Arztebl Int.* (2014) 111:530–6. doi: 10.3238/arztebl.2014.0530
8. Hirsch K, Bohley S, Mau W, Schmidt-Pokrzywniak A. The RHESA-CARE study: an extended baseline survey of the regional myocardial infarction registry of Saxony-Anhalt (RHESA) design and objectives. *BMC Cardiovasc Disord.* (2016) 16:159. doi: 10.1186/s12872-016-0336-x
9. Hoschar S, Albarqouni L, Ladwig K-H, A. systematic review of educational interventions aiming to reduce prehospital delay in patients with acute coronary syndrome. *Open Heart.* (2020) 7:e001175. doi: 10.1136/openhrt-2019-001175
10. Mata J, Frank R, Gigerenzer G. Symptom recognition of heart attack and stroke in nine European countries: a representative survey. *Health Expectations.* (2014) 17:376–87. doi: 10.1111/j.1369-7625.2011.00764.x
11. Birnbach B, Höpner J, Mikolajczyk R. Cardiac symptom attribution and knowledge of the symptoms of acute myocardial infarction: a systematic review. *BMC Cardiovasc Disord.* (2020) 20:445. doi: 10.1186/s12872-020-01714-8
12. Tamhane AR, Westfall AO, Burkholder GA, Cutter GR. Prevalence odds ratio versus prevalence ratio: choice comes with consequences. *Statist Med.* (2016) 35:5730–5. doi: 10.1002/sim.7059
13. Daoud JI. Multicollinearity and regression analysis. Bristol: IOP Publishing. p. 12009.
14. Fussman C, Rafferty AP, Reeves MJ, Zackery S, Lyon-Callo S, Anderson B. Racial disparities in knowledge of stroke and heart attack risk factors and warning signs among Michigan adults. *Ethn Dis.* (2009) 19:128–34.
15. Fang J, Gillespie C, Keenan NL, Greenlund KJ. Awareness of heart attack symptoms among US adults in 2007, and changes in awareness from 2001 to 2007. *Fut Cardiol.* (2011) 7:311–20. doi: 10.2217/fca.10.111
16. Quah JLJ, Yap S, Cheah SO, Ng YY, Goh ES, Doctor N, et al. Knowledge of signs and symptoms of heart attack and stroke among Singapore residents. *Biomed Res Int.* (2014) 2014:572425. doi: 10.1155/2014/572425
17. Kim H-S, Lee H, Kim K, Park H-K, Park K-S, Kang GW, et al. The General public's awareness of early symptoms of and emergency responses to acute

myocardial infarction and related factors in South Korea: a national public telephone survey. *J Epidemiol.* (2016) 26:233–41. doi: 10.2188/jea.JE20150074
18. Burnham KP, Anderson DR. *A Practical Information-Theoretic Approach. Model Selection and Multimodel Inference.* Springer, New York (2002). p. b97636.
19. SAS-Institute. Cary: SAS Institute (2017).
20. R Core Team. *R: A Language and Environment for Statistical Computing Foundation for Statistical Computing.* R Core Team (2013).
21. Diederichs C, Neuhauser H. Regional variations in hypertension prevalence and management in Germany: results from the German Health Interview and Examination Survey (DEGS1). *J Hypertension.* (2014) 32:1405–14. doi: 10.1097/HJH.0000000000000211
22. van Oosterhout RE, de Boer AR, Maas AH, Rutten FH, Bots ML, Peters SA. Sex differences in symptom presentation in acute coronary syndromes: a systematic review and meta-analysis. *J Am Heart Assoc.* (2020) 9:e014733. doi: 10.1161/JAHA.119.014733
23. Grosmaitre P, Le Vavasseur O, Yachouh E, Courtial Y, Jacob X, Meyran S, et al. Significance of atypical symptoms for the diagnosis and management of myocardial infarction in elderly patients admitted to emergency departments. *Arch Cardiovasc Dis.* (2013) 106:586–92. doi: 10.1016/j.acvd.2013.04.010
24. Gillis NK, Arslanian-Engoren C, Struble LM. Acute coronary syndromes in older adults: a review of literature. *J Emerg Nurs.* (2014) 40:270–5. doi: 10.1016/j.jen.2013.03.003
25. Gieelmann K. Herzwoche: Kompaktes Wissen zu Bluthochdruck, Cholesterin, Diabetes und Stress. *Dtsch Arztebl Int*. (2016) 113:A-1936.
26. Banharak S, Zahrli T, Matsuo H. Public knowledge about risk factors, symptoms, and first decision-making in response to symptoms of heart attack among lay people. *Pacific Rim Int J Nurs Res.* (2018) 22:18–29.
27. Albarqouni L, Smenes K, Meinertz T, Schunkert H, Fang X, Ronel J, et al. Patients' knowledge about symptoms and adequate behaviour during acute myocardial infarction and its impact on delay time: findings from the multicentre MEDEA Study. *Patient Educ Couns.* (2016) 99:1845–51. doi: 10.1016/j.pec.2016.06.007
28. Greenlund KJ, Neff LJ, Zheng Z-J, Keenan NL, Giles WH, Ayala CA, et al. Low public recognition of major stroke symptoms. *Am J Prev Med.* (2003) 25:315–9. doi: 10.1016/s0749-3797(03)00206-x
29. Dracup K, McKinley S, Doering LV, Riegel B, Meischke H, Moser DK, et al. Acute coronary syndrome: what do patients know? *Arch Intern Med.* (2008) 168:1049–54. doi: 10.1001/archinte.168.10.1049
30. Gill R, Chow C-M. Knowledge of heart disease and stroke among cardiology inpatients and outpatients in a Canadian inner-city urban hospital. *Can J Cardiol.* (2010) 26:537–40. doi: 10.1016/s0828-282x(10)70468-2
31. Memiş S, Evci ED, Ergin F, Beşer E. A population-based study on awareness of heart attack in Aydin city-Turkey. *Anadolu Kardiyol Derg.* (2009) 9:304–10.
32. Wissenberg M, Lippert FK, Folke F, Weeke P, Hansen CM, Christensen EF, et al. Association of national initiatives to improve cardiac arrest management with rates of bystander intervention and patient survival after out-of-hospital cardiac arrest. *JAMA.* (2013) 310:1377–84. doi: 10.1001/jama.2013.278483

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Trends in 10-Year Predicted Risk of Cardiovascular Disease Associated With Food Insecurity, 2007–2016

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Introduction: Consumption of a healthy diet improves cardiovascular (CV) risk factors and reduces the development of cardiovascular disease (CVD). Food insecure (FIS) adults often consume an unhealthy diet, which can promote obesity, type 2 diabetes mellitus (T2DM), hypertension (HTN), and hyperlipidemia (HLD). The Supplemental Nutrition Assistance Program (SNAP) is designed to combat food insecurity by increasing access to healthy foods. However, there is a paucity of data on the association of SNAP participation among FIS adults and these CVD risk factors.

Methods: The National Health and Nutrition Examination Survey (NHANES) is a publicly available, ongoing survey administered by the Centers for Disease Control and Prevention and the National Center for Health Statistics. We analyzed five survey cycles (2007–2016) of adult participants who responded to the CVD risk profile questionnaire data. We estimated the burden of select CVD risk factors among the FIS population and the association with participation in SNAP.

Results: Among 10,449 adult participants of the survey, 3,485 (33.3%) identified themselves as FIS. Food insecurity was more common among those who were younger, female, Hispanic, and Black. Among the FIS, SNAP recipients, when compared to non-SNAP recipients, had a lower prevalence of HLD (36.3 vs. 40.1% $p = 0.02$), whereas rates of T2DM, HTN, and obesity were similar. Over the 10-year survey period, FIS SNAP recipients demonstrated a reduction in the prevalence of HTN ($p < 0.001$) and HLD ($p < 0.001$) which was not evident among those not receiving SNAP. However, obesity decreased only among those not receiving SNAP. The prevalence of T2DM did not change over the study period in either group.

Conclusion: Over a 10-year period, FIS adults who received SNAP demonstrated a reduction in the prevalence of HTN and HLD, which was not seen among those not receiving SNAP. However, the prevalence of obesity and T2DM did not decline among SNAP recipients, suggesting that additional approaches are required to impact these important CVD risk factors.

Keywords: prevention, food insecuirty, nutrition, cardiovascular health, cardiovascular prevention

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INTRODUCTION

Cardiovascular disease (CVD) is a major global health challenge, and was responsible for 23% of total deaths in the United States (US) in 2017 (1). Consumption of a healthy and well-balanced diet is associated with better cardiovascular (CV) outcomes and has been demonstrated to improve CVD risk factors through decrease in body weight and various cardiometabolic pathways (2). Current guidelines emphasize a diet composed of fruits, vegetables, legumes, fish, nuts, whole grains, and fibers along with a reduction in sodium, processed meats, sugar-sweetened beverages (SSB), excess calories and refined foods (2, 3).

The US Department of Agriculture (USDA) defines food insecurity as economic and social conditions associated with limited and uncertain access to food (4). In 2018, 37.2 million Americans lived in food insecure (FIS) households (4). Inadequate financial resources, the high cost of food, and competing priorities often cause adults with food insecurity to consume an unhealthy and low quality diet (5–7). FIS adults often forgo purchasing specialized diets for medical conditions such as hypertension (HTN) or type 2 diabetes mellitus (T2DM) in favor of purchasing low-cost foods that are often energy dense but nutrient poor (8). As a result, food insecurity can lead to worsening of CVD risk factors including T2DM, HTN, hyperlipidemia (HLD), and obesity defined as BMI $\geq$ 30 kg/m^2 (9), thus contributing to poor CV health.

The Supplemental Nutrition Assistance Program (SNAP, formerly called Food Stamps Program) is the largest federal food assistance program available for low-income households, and is designed to directly combat food insecurity (10). SNAP eligibility is based on household income, specifically targeting low income Americans living under the poverty level (11). Access to SNAP can potentially address high rates of CVD risk factors in FIS adults by increasing access to healthy foods. While few studies have shown a link between CVD risk factors and food insecurity (12, 13), there is a paucity of data on the association of SNAP participation amongst FIS adults and CVD risk factors. Understanding this relationship is important to determine whether any future expansions, additions or modifications to the SNAP program are needed to better serve the FIS population in the United States (US). We designed this study to investigate the prevalence of CV risk factors among the FIS population, and analyze the association between participation in SNAP and the change in CVD risk factors over a 10-year study period.

MATERIALS AND METHODS

Data Source

The National Health and Nutrition Examination Survey (NHANES) is an ongoing cross-sectional survey administered by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS). It is designed to describe the health and nutritional status of the non-institutionalized population of the United States (14). The NHANES database is publicly available for researchers, and the data are released in 2-year cycles. All NHANES participants complete an English or Spanish language questionnaire during a home interview. Participants then undergo a standardized physical examination (including height, weight).

Food Security

The food security module within NHANES is a questionnaire developed by the USDA to measure adult food security over the 12 months preceding the survey. Adult food security is categorized by NHANES as: full food security, marginal food security, low food security, and very low food security. In this study, we considered adults in the full food security category to be food secure (FS) and those categorized as having marginal, low and very low food security to be FIS.

Study Population

We analyzed 10-year data from five survey cycles completed by adult participants $\geq$ 18 years of age, from months of January to December (2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2014–2016). A total of 10,449 adults who participated in the NHANES surveys from 2007 to 2016 were included in the full analytic sample. From this cohort, 6,964 adults were identified as FS (66.6%), and 3,485 adults were identified as FIS (33.3%). The FIS adult participants were further categorized into those receiving SNAP benefits (63.3%) and those not receiving SNAP benefits (36.6%).

The presence or absence of each CVD risk factor (T2DM, HTN, HLD, obesity) was determined based on the response to the survey question: "Have you ever been diagnosed by a physician with this risk factor?" Respondents who were classified as SNAP participants, had accepted SNAP benefits in the 12 months preceding the survey.

Statistical Analysis

All analyses were performed using SPSS, version 26 (IBM, Chicago). Stratified weighted data were utilized to obtain nationwide estimates. Continuous variables were reported as mean $\pm$ standard deviation and compared using the Student *t*-test, and the categorical variables were reported as proportions and compared using the Chi-square test. We used multiple logistic regression analysis to determine temporal trends with survey year as the independent variable and the CV risk factor of interest as the dependent variable. The yearly prevalence of various CV risk factors among the study cohorts was reported along with P-*trend.*

RESULTS

A total of 10,449 adults (mean age 53.16 $\pm$ 16.9, 41.6% females) who participated in the NHANES surveys from 2007 to 2016 were included in the full analytic sample. From this cohort, 6,964 adults were identified as FS (66.6%), and 3,485 adults were identified as FIS (33.3%). The prevalence of CVD risk factors in the total population, and according to food security status is shown in **Table 1**. CVD risk factors were highly prevalent among all participants. FIS adults were younger than those who were FS. The proportion of females (**Table 1**) and self-identified Blacks and

TABLE 1 | Baseline characteristics of the total adult participants of the survey, 2007–2016[a,b].

Population characteristics	Total patients *n* = 10, 449 (%)	FS, *n* = 6, 964 (%)	FIS, *n* = 3, 485 (%)	*P*-value
Age	53.16 ± 16.9	55.75 ± 16.8	48.0 ± 16.1	< 0.00
HTN	4581 (43.8)	3085 (44.3)	1496 (42.9)	0.183
HLD	4162 (39.8)	3048 (43.8)	1114 (31.9)	0
T2DM	1638 (15.7)	1060 (15.2)	578 (16.5)	0.071
Obesity[c]	4057 (38.8)	2549 (36.6)	1508 (43.3)	< 0.00
Female	4354 (41.6)	2776 (39.9)	1578 (45.3)	< 0.01
Race				
White	5192 (49.7)	3787 (54.3)	1405 (40.3)	< 0.00
Black	2213 (21.2)	1353 (19.4)	860 (24.7)	< 0.00
Hispanic/Mexican	2165 (20.7)	1206 (17.3)	959 (27.5)	< 0.00
Other	879 (8.4)	618 (8.9)	261 (7.4)	< 0.00

HTN, hypertension; HLD, hyperlipedemia; T2DM, type 2 diabetes mellitus; SNAP, Supplement Nutrition Assistance Program; FS, Food Secure; FIS, Food Insecure. All relationships are statistically significant for $p < 0.001$. Categorical variables are reported as proportions and compared using the Chi-square test. Continuous variables such as age is reported as mean ± standard deviation and compared using the Student t-test.

[a]Data from the National Health and Nutrition Examination Survey.

[b]Data were weighted to be nationally representative.

[c]Obesity defined as BMI (calculated as weight in kilograms divided by height in meters squared) ≥ 30 kg/m.

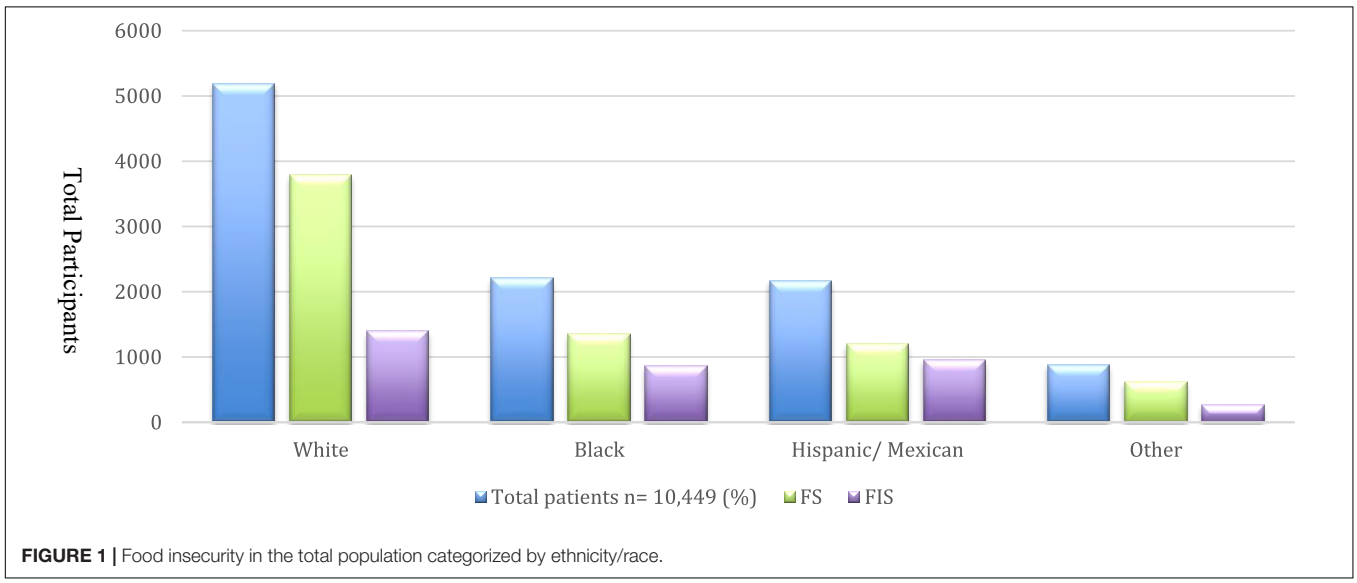

FIGURE 1 | Food insecurity in the total population categorized by ethnicity/race.

Hispanics was higher among FIS participants than FS participants of the survey (**Figure 1**). The prevalence of HLD and obesity were significantly higher among those with FIS, whereas rates of HTN and T2DM were similar in the two groups.

Characteristics of the FIS participants according to receipt of SNAP benefits are described in **Table 2**. Those receiving SNAP comprised 63.4% of the FIS population. SNAP participants were younger and more likely to be female and non-white. Among the FIS, higher proportion of self-identified whites (41.8%), participated in SNAP compared to self-identified Hispanics/Mexicans (23.2%) (**Figure 2**). As described in **Table 2**, FIS participants who received SNAP had a lower prevalence of HLD compared to those who did not receive SNAP (36.3 vs. 40.1%, $p = 0.02$). There was no significant difference in the prevalence of T2DM, HTN, or obesity between FIS participants receiving SNAP and FIS participants not receiving SNAP.

Among all NHANES participants, the prevalence of HTN and HLD decreased over the 10-year study period (**Table 3**). Rates of T2DM and obesity remained unchanged over the study period in the total population (**Table 3**). When analyzed according to food security status, similar trends were seen in both FS and FIS groups (**Table 4**). The prevalence of HTN and HLD showed statistically significant decrease over the study period in both FS and FIS groups (**Table 4**).

When FIS group was further analyzed according to participation in SNAP benefits, FIS SNAP participants demonstrated a significant reduction in the prevalence of HTN ($p < 0.001$) and HLD ($p < 0.001$) over the study period (**Table 5**). No significant change was noted in the prevalence

TABLE 2 | Baseline characteristics of the adult food insecure participants of the survey, 2007–2016[a–b].

Population characteristics	Total FIS participants, *n* = 3, 478 (%)	Receiving SNAP, *n* = 2205 (%)	Not receiving SNAP, *n* = 1273 (%)	*P*-value
Age	47.99 ± 16.1	46.55 ± 15.67	50.49 ± 16.5	< 0.00
HTN	1492 (42.9)	956 (43.3)	536 (42.1)	0.473
HLD	1311 (37.7)	800 (36.3)	511 (40.1)	0.024
T2DM	576 (16.6)	346 (15.7)	230 (18.0)	0.069
Obesity[c]	1503 (43.2)	970 (44)	533 (41.9)	0.224
Female	1574 (45.2)	1079 (48.9)	495 (38.9)	< 0.00
Race				
White	1402 (40.3)	921 (41.8)	481 (37.8)	< 0.00
Black	858 (24.7)	624 (28.3)	234 (18.4)	< 0.00
Hispanic/Mexican	957 (27.5)	511 (23.2)	446 (35.0)	< 0.00
Other	261 (7.5)	149 (6.7)	112 (8.8)	< 0.00

HTN, hypertension; HLD, hyperlipedemia; T2DM, type 2 diabetes mellitus; SNAP, Supplement Nutrition Assistance Program; FIS, Food Insecure. Continuous variables such as age is reported as mean ± standard deviation and compared using the Student t-test; categorical variables are reported as proportions and compared using the Chi-square test. All relationships are statistically significant for $p < 0.001$.

[a]Data from the National Health and Nutrition Examination Survey.

[b]Data were weighted to be nationally representative.

[c]Obesity defined as BMI (calculated as weight in kilograms divided by height in meters squared) ≥ 30 kg/m.

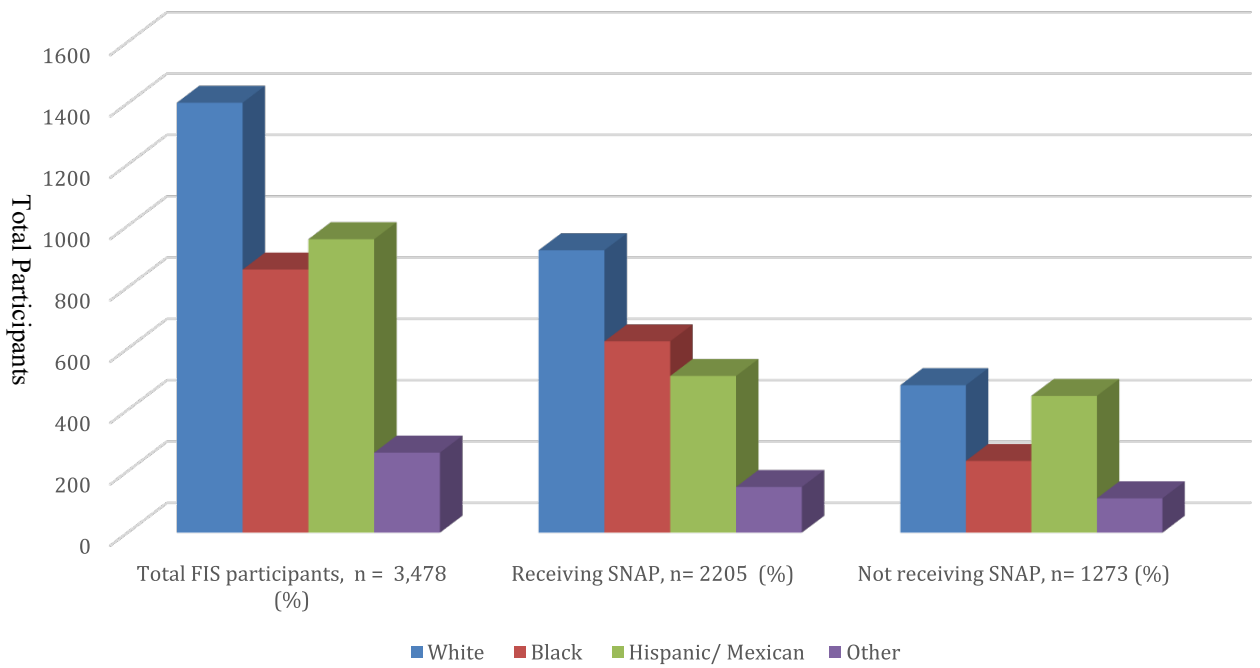

FIGURE 2 | SNAP participation in FIS population categorized by ethnicity/race.

of T2DM or obesity over 10 years (**Table 5**). Among the non-SNAP participants, HLD decreased significantly ($p = 0.007$) but HTN did not (**Table 5**). Remarkably, obesity rates decreased significantly only in the group not receiving SNAP (**Table 5**).

DISCUSSION

Our study provides important findings on the prevalence of CVD risk factors among FIS adults in the United States and the association with participation in SNAP.

The principal determinant of obesity and other cardiometabolic diseases is lifestyle, of which food habit is a main component (15). In our study, we found that the prevalence of obesity among FIS adults was higher compared to FS adults. Additionally, FIS SNAP participants did not show an improvement in the prevalence of obesity over 10 years. An interesting cross-sectional analysis by Myers et al. (16) from years 1999 to 2016 shows that prevalence of food insecurity has increased over the study period. Additionally, the study found that obese individuals had higher reports of food insecurity. Our study did not show

TABLE 3 | Trends of CVD risk factors of the total adult participants of the survey, 2007–2016[a–b].

	2007–2008 *n* = 1839 (%)	2009–2010 *n* = 1850 (%)	2011–2012 *n* = 2161 (%)	2013–2014 *n* = 2404 (%)	2015–2016 *n* = 2195 (%)	*p*-value
HTN	884 (48.1)	920 (49.7)	880 (40.7)	988 (41.4)	909 (41.4)	< 0.00
T2DM	309 (16.8)	316 (17.1)	316 (14.6)	332 (13.8)	365 (16.6)	0.173
HLD	909 (49.4)	890 (48.1)	821 (38)	904 (37.6)	838 (38.2)	< 0.00
Obesity[c]	718 (39)	786 (42.5)	764 (35.4)	896 (37.3)	893 (40.7)	0.649

HTN, hypertension; HLD, hyperlipedemia; T2DM, type 2 diabetes mellitus; BMI, Body Mass Index; CVD, cardiovascular disease. Multiple logistic regression analysis was used to determine temporal trends with survey year as the independent variable and the CVD risk factor of interest as the dependent variable. All relationships are statistically significant for $p < 0.001$.

[a]*Data from the National Health and Nutrition Examination Survey.*

[b]*Data were weighted to be nationally representative.*

[c]*Obesity defined as BMI (calculated as weight in kilograms divided by height in meters squared) ≥ 30 kg/m.*

TABLE 4 | Trends in CVD risk factors of adult food insecure participants of the survey, 2007–2016[a,b].

		2007–2008 *n* = 1418 (%)	2009–2010 *n* = 1320 (%)	2011–2012 *n* = 1392 (%)	2013–2014 *n* = 1572 (%)	2015–2016 *n* = 1262 (%)	*p*-value
HTN	FS	678, (47.8)	649 (49.2)	576 (41.4)	664 (42.2)	518 (41)	< 0.001
	FIS	206 (48.9)	271 (51.5)	304 (39.5)	324 (38.9)	391 (41.9)	< 0.001
T2DM	FS	233 (16.4)	221 (16.7)	194 (13.9)	222 (14.1)	190 (15.0)	0.07
	FIS	76 (18.0)	95 (17.9)	122 (15.9)	110 (13.2)	175 (18.7)	0.914
HLD	FS	701 (49.4)	630 (47.7)	559 (40.1)	646 (41.1)	512 (40.5)	< 0.00
	FIS	208 (49.4)	260 (49.0)	262 (34.0)	258 (31.0)	326 (34.9)	< 0.00
Obesity[c]	FS	527 (37.1)	530 (40.1)	443 (31.8)	557 (35.4)	492 (38.9)	0.708
	FIS	191 (45.4)	256 (48.3)	321 (41.7)	339 (40.7)	401 (42.9)	0.071

HTN, hypertension; HLD, hyperlipedemia; T2DM, type 2 diabetes mellitus; SNAP, Supplement Nutrition Assistance Program; FS, Food Secure; FIS, Food Insecure; CVD, cardiovascular disease. Multiple logistic regression analysis is used to determine temporal trends with survey year as the independent variable and the CV risk factor of interest as the dependent variable. All relationships are statistically significant for $p < 0.001$.

[a]*Data from the National Health and Nutrition Examination Survey.*

[b]*Data were weighted to be nationally representative.*

[c]*Obesity defined as BMI (calculated as weight in kilograms divided by height in meters squared) ≥ 30 kg/m.*

TABLE 5 | Trends in CVD risk factors of adult food insecure participants of the survey, categorized by SNAP participation, 2007–2016 [a–b].

	Column 1	2007-2008 *n* = 219 (%)	2009–2010 *n* = 296 (%)	2011–2012 *n* = 461 (%)	2013–2014 *n* = 558 (%)	2015–2016 *n* = 671 (%)	*p*-value
HTN	SNAP	113 (51.6)	157 (53.0)	187 (40.6)	218 (39.0)	281 (48.9)	< 0.00
	NO SNAP	93 (46)	114 (48.7)	113 (37.4)	106 (38.8)	110 (41.9)	0.087
T2DM	SNAP	34 (15.5)	56 (18.9)	73 (15.8)	75 (13.4)	108 (16.0)	0.476
	NO SNAP	42 (20.8)	39 (16.7)	47 (15.6)	35 (12.8)	67 (25.6)	0.354
HLD	SNAP	108 (49.3)	154 (52.0)	158 (34.3)	157 (28.1)	223 (33.2)	< 0.00
	NO SNAP	100 (49.5)	106 (45.3)	102 (33.8)	100 (36.6)	103 (39.3)	0.007
Obesity[c]	SNAP	97 (44.2)	143 (48.3)	190 (41.2)	230 (41.2)	310 (46.2)	0.99
	NO SNAP	94 (46.5)	113 (48.3)	126 (41.7)	109 (39.9)	91 (34.7)	0.001

HTN, hypertension; HLD, hyperlipedemia; T2DM, type 2 diabetes mellitus; SNAP, Supplement Nutrition Assistance Program; CVD, cardiovascular disease. Multiple logistic regression analysis is used to determine temporal trends with survey year as the independent variable and the CV risk factor of interest as the dependent variable. All relationships are statistically significant for $p < 0.001$.

[a]*Data from the National Health and Nutrition Examination Survey.*

[b]*Data were weighted to be nationally representative.*

[c]*Obesity defined as BMI (calculated as weight in kilograms divided by height in meters squared) ≥ 30 kg/m.*

statistically significant difference in prevalence of T2DM between FS and FIS groups. Similar prior studies (17, 18) however have shown association of food insecurity with poor glycemic and overall metabolic control in adults. Further studies are needed that examine association between food insecurity and CVD risk factors. Specific population subgroup analysis based on ethnicity, sex, and other social variables including economic, education level, geographic location, and marital status, can help identify factors which may reduce prevalence of both food insecurity and obesity in the long term.

Supplemental Nutrition Assistance Program is a federal program which offers financial assistance to eligible people, and is designed to strengthen food and nutritional security. Although previous reports (19) demonstrated that SNAP alleviates food insecurity and improves dietary quality, SNAP participants may in fact have lower quality diet than non-SNAP participants (20). While previous studies have shown that SNAP participation is

effective in increasing intake of caloric and nutritious foods, SNAP participants overall do not meet the key recommended nutrition guidelines in daily food habits (20). Greater emphasis is needed to improve the diet quality, and subsequently the CV health of SNAP participants. Further, health care providers should be trained to screen for food security and have knowledge on how to address this topic with their patients.

There was a significant downward trend in the prevalence of HTN and HLD among the FIS SNAP participants over 10 years. Unhealthy diet is one of the top contributors for worsening CVD and associated risk factors (21). SNAP improves access of nutritionally adequate foods, and therefore has the capacity to influence household wellbeing beyond just nutrition and hunger, by directly impacting health outcomes of participants (2, 10). Despite this favorable trend in HTN and HLD in our study, prior studies have shown disparities in the diet quality between SNAP participants and the high income population (22). United States fruit and vegetable consumption in the low-income population remains below recommended levels (23). SNAP-Ed program is a USDA program which promotes healthier eating choices with a limited budget through education and awareness (24). The education programs, national campaigns from groups like American Heart Association (AHA) (25), and increase in public awareness on nutrition have shown an improvement in diet components of SNAP participants, including increase in whole grain, fruits, vegetables and decrease in SSB consumption (26). SNAP benefits are critical for many FIS low income families. Along with improving public education on nutrition, urgent reform and policy changes at state and local level that promote and support a healthier diet are needed. Mozaffarian and colleagues (27) who studied a model evaluating one such possible policy disincentivizing unhealthy food purchases, and incentivizing healthy food purchases including fruits and vegetables, noted a significant decrease in CV deaths and substantial cost benefits. More public health research assisting SNAP and other similar federal programs improving dietary quality of the participants is needed.

Our study has several limitations. First, as with all observational studies, our study cannot prove direct causality. Second, our data also does not allow for long-term assessment in SNAP participation and cardiovascular outcomes. Food security, depending on the adequacy of food, can wax and wane. As such, an individual's level of food security, and therefore SNAP participation may change over time. The level of food security over time is not measured in our data, which focuses on the previous 12-months. Third, our analysis is based on the self-reported presence or absence of CVD risk factors, rather than actual measurement of these risk factors. Therefore, some misclassification is possible. Fourth, we were unable to exclude participants with established CVD, as the survey does not contain this information. Finally, NHANES only assesses responders' food insecurity over the last 12 months before survey participation, and thus we were not able to assess long-term food security levels amongst survey participants.

CONCLUSION

Ready access to guideline-recommended nutrient intake remains a challenge in the United States. Our study shows the favorable trends in the prevalence of HTN and HLD among FIS SNAP participants over a 10 year period. Our study also highlights the persistence of high levels of T2DM and obesity in the adult FIS population. These findings support the need for continuing efforts toward promoting a sustainable, healthy diet among the low-income population and the need to further reduce the health disparities caused by food insecurity.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: NHANES, https://www.cdc.gov/nchs/nhanes/index.htm.

AUTHOR CONTRIBUTIONS

PS designed and directed this study and wrote the manuscript. HC, JP, and WA provided conceptual and technical guidance. NS and JS provided guidance with statistical analysis for this study. RK, LM, and AS provided support with literature review and editing and background researching the topic of food insecurity. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Kochanek KD, Murphy SL, Xu J, Arias E. Deaths: final data for 2017. *Natl Vital Stat Rep.* (2019) 68:1–77.
2. Yu E, Malik VS, Hu FB. Cardiovascular disease prevention by diet modification: JACC Health Promotion Series. *J Am Coll Cardiol.* (2018) 72:914–26.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* (2019) 74:e177–232.
4. Coleman-Jensen A, Rabbitt MP, Gregory CA, Singh A. *Household Food Security in the United States in 2018*. Washington, DC: U.S. Department of Agriculture (2019).
5. Rose D, Oliveira V. Nutrient intakes of individuals from food-insufficient households in the United States. *Am J Public Health.* (1997) 87:1956–61. doi: 10.2105/ajph.87.12.1956
6. Mello JA, Gans KM, Risica PM, Kirtania U, Strolla LO, Fournier L. How is food insecurity associated with dietary behaviors? An analysis with low-income, ethnically diverse participants in a nutrition intervention study. *J Am Diet Assoc.* (2010) 110:1906–11. doi: 10.1016/j.jada.2010.09.011
7. Ford ES. Food security and cardiovascular disease risk among adults in the United States: findings from the National Health and Nutrition Examination

Survey, 2003-2008. *Prev Chronic Dis.* (2013) 10:E202. doi: 10.5888/pcd10.130244
8. Morales ME, Berkowitz SA. The relationship between food insecurity, dietary patterns, and obesity. *Curr Nutr Rep.* (2016) 5:54–60. doi: 10.1007/s13668-016-0153-y
9. Centers for Disease Control and Prevention [CDC]. *Defining Adult Overweight & Obesity*. Available online at: https://www.cdc.gov/obesity/adult/defining.html#:~{}:text=Adult%20Body%20Mass%20Index&text=If%20your%20BMI%20is%20less,falls%20within%20the%20obesity%20range (accessed June 7, 2021).
10. Ratcliffe C, McKernan SM, Zhang S. How much does the supplemental nutrition assistance program reduce food insecurity? *Am J Agric Econ.* (2011) 93:1082–98. doi: 10.1093/ajae/aar026
11. U.S. Department of Agriculture Food and Nutrition Service. *Supplement Nutrition Assistance Program (SNAP) Eligibility 2019*. (2019). Available online at: https://www.fns.usda.gov/snap/recipient/eligibility (accessed October 1, 2022).
12. Mendy VL, Vargas R, Cannon-Smith G, Payton M, Enkhmaa B, Zhang L. Food insecurity and cardiovascular disease risk factors among mississippi adults. *Int J Environ Res Public Health.* (2018) 15:2016. doi: 10.3390/ijerph15092016
13. Vercammen KA, Moran AJ, McClain AC, Thorndike AN, Fulay AP, Rimm EB. Food security and 10-Year cardiovascular disease risk among U.S. adults. *Am J Prev Med.* (2019) 56:689–97. doi: 10.1016/j.amepre.2018.11.016
14. Centers for Disease Control and Prevention [CDC]. *About the National Health and Nutrition Examination Survey*. (2017). Available online at: https://www.cdc.gov/nchs/nhanes/about_nhanes.htm (accessed October 1, 2022).
15. Sreenivasan J, Khan MS, Sharedalal P, Hooda U, Fudim M, Demmer RT, et al. Obesity and outcomes following cardiogenic shock requiring acute mechanical circulatory support. *Circ Heart Fail.* (2021) 14:e007937. doi: 10.1161/CIRCHEARTFAILURE.120.007937
16. Myers CA, Mire EF, Katzmarzyk PT. Trends in adiposity and food insecurity among US adults. *JAMA Netw Open.* (2020) 3:e2012767. doi: 10.1001/jamanetworkopen.2020.12767
17. Berkowitz SA, Baggett TP, Wexler DJ, Huskey KW, Wee CC. Food insecurity and metabolic control among U.S. adults with diabetes. *Diabetes Care.* (2013) 36:3093–9. doi: 10.2337/dc13-0570
18. Seligman HK, Bindman AB, Vittinghoff E, Kanaya AM, Kushel MB. Food insecurity is associated with diabetes mellitus: results from the National Health Examination and Nutrition Examination Survey (NHANES) 1999-2002. *J Gen Intern Med.* (2007) 22:1018–23. doi: 10.1007/s11606-007-0192-6
19. Executive Office of the President of the United States. *Long-Term Benefits of the Supplemental Nutrition Assistance Program*. Washington, DC: Executive Office of the President of the United States (2015).
20. Andreyeva T, Tripp AS, Schwartz MB. Dietary quality of americans by supplemental nutrition assistance program participation status: a systematic review. *Am J Prev Med.* (2015) 49:594–604. doi: 10.1016/j.amepre.2015.04.035
21. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* (2012) 380:2224–60. doi: 10.1016/S0140-6736(12)61766-8
22. Conrad Z, Rehm CD, Wilde P, Mozaffarian D. Cardiometabolic mortality by supplemental nutrition assistance program participation and eligibility in the United States. *Am J Public Health.* (2017) 107:466–74. doi: 10.2105/AJPH.2016.303608
23. Olsho LE, Klerman JA, Wilde PE, Bartlett S. Financial incentives increase fruit and vegetable intake among Supplemental Nutrition Assistance Program participants: a randomized controlled trial of the USDA Healthy Incentives Pilot. *Am J Clin Nutr.* (2016) 104:423–35. doi: 10.3945/ajcn.115.129320
24. Molitor F, Doerr C. SNAP-Ed policy, systems, and environmental interventions and caregivers' dietary behaviors. *J Nutr Educ Behav.* (2020) 52:1052–7. doi: 10.1016/j.jneb.2020.05.013
25. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* (2010) 121:586–613. doi: 10.1161/circulationaha.109.192703
26. Korczak R, Marquart L, Slavin JL, Ringling K, Chu Y, O'Shea M, et al. Thinking critically about whole-grain definitions: summary report of an interdisciplinary roundtable discussion at the 2015 Whole Grains Summit. *Am J Clin Nutr.* (2016) 104:1508–14. doi: 10.3945/ajcn.115.126672
27. Mozaffarian D, Liu J, Sy S, Huang Y, Rehm C, Lee Y, et al. Cost-effectiveness of financial incentives and disincentives for improving food purchases and health through the US Supplemental Nutrition Assistance Program (SNAP): a microsimulation study. *PLoS Med.* (2018) 15:e1002661. doi: 10.1371/journal.pmed.1002661

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Assessing Concurrent Adherence to Combined Essential Medication and Clinical Outcomes in Patients With Acute Coronary Syndrome. A Population-Based, Real-World Study Using Group-Based Trajectory Models

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Aim: Adherence to multiple medications recommended for secondary prevention of cardiovascular conditions represents a challenge. We aimed to identify patterns of concurrent adherence to combined therapy and assess their impact on clinical outcomes in a cohort of patients with acute coronary syndrome (ACS).

Methods: Population-based retrospective cohort of all patients discharged after hospitalization for ACS (2009–2011), prescribed ≥3 therapeutic groups within the first month. We assessed monthly concurrent adherence (≥24 days of medication out of 30) to ≥3 medications during the first year, and patterns were identified through group-based trajectory models. A composite clinical outcome during the second year was constructed. The association between adherence patterns and traditional refill adherence metrics [e.g., the proportion of days covered (PDC)], and outcomes were assessed through a multivariable Cox proportional hazards model.

Results: Among 15,797 patients discharged alive, 12,057 (76.32%) initiated treatment with ≥3 therapeutic groups after discharge. We identified seven adherence trajectories to ≥3 medications: Adherent (52.94% of patients); Early Gap (6.64%); Middle Gap (5.67%); Late Decline (10.93%); Occasional Users (5.45%); Early Decline (8.79%); Non-Adherent (9.58%). Compared to the Adherent group, patients belonging to Early Gap (HR:1.30, 95%CI 1.07;1.60), Late decline (hazards ratio (HR): 1.31, 95% CI 1.1; 1.56), and Non-Adherent trajectories (HR: 1.36, 95% CI 1.14; 1.63) had a greater risk of adverse clinical outcomes, which was also different to the risk ascertained through concurrent PDC < 80 (HR: 1.13, 95% CI 1.01; 1.27).

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Conclusion: Overall, seven adherence trajectories to ≥3 drugs were identified, with three distinct adherence patterns being at higher risk of adverse outcomes. The identification of patterns of concurrent adherence, a more comprehensive approach than traditional measurements, may be useful to target interventions to improve adherence to multiple medications.

Keywords: concurrent adherence, concomitant medications, acute coronary syndrome, group-based trajectory models, clinical outcomes, real-world data, population-based cohort

INTRODUCTION

Physicians treating patients with cardiovascular chronic conditions (such as hypertension or coronary artery disease) often prescribe multiple medications to treat a single disease, as recommended in clinical guidelines (1–5), but adherence to this more complex therapeutic regime is often inadequately captured by assessing adherence to an individual agent or drug class (6).

In the case of patients with acute coronary syndrome (ACS), international guidelines recommend the combined use of antiplatelets, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARB), and statins for the secondary prevention of this condition (3–5). Several studies have reported sub-optimal adherence to essential medications after an ACS (7–10). However, most of these studies have assessed drug classes individually. This might not reflect accurately the extent of adherence (or lack of it) to combined therapy as a whole, as regime complexity may decrease medication adherence (11–14). Therefore, it is plausible that real-world adherence to medication for any cardiovascular chronic condition requiring multiple concurrent drugs, such as ACS, is even lower than the already suboptimal figures analyzing individual drug classes (6). This may also have an impact on the accuracy of the estimates when assessing the relationship between adherence and clinical outcomes among these patients.

Furthermore, improving medication adherence is a challenge that requires methods that can reliably identify and predict when non-adherence could occur in order to customize interventions. To our knowledge, only two studies have concurrently assessed adherence to multiple therapies (statins, beta-blockers, and ACE/ARB) and tried to elucidate its relationship with clinical outcomes (all-cause mortality) (15, 16). The population groups of these studies were also conducted in patients with ACS and both used conventional measures of adherence. One study was set in the US and used the proportion of days covered (PDC) (15), while the other was a population-based, nationwide study set in Taiwan and used medication possession ratio (MPR) (16) to assess adherence.

However, grouping the patients based on a dichotomic measure may mask the changes in patients' refills, ignoring the dynamic phenomenon of adherence (17). The use of group-based trajectory models (GBTM) to measure adherence allows the identification of subgroups of patients with similar patterns of medication refill and shows the different trends in easily understandable graphics (18–21). Evidence shows that GBTM summarizes in a better way medication adherence than PDC and has better predictive accuracy on clinical outcomes (22, 23).

Therefore, adherence to therapy when a combination of medications is prescribed, as is the case of ACS, should be assessed by considering all drugs together and using approaches that allow the identification of differential patterns of medication refill. However, no studies have examined adherence trajectories to multiple concurrent medications when combined therapy is recommended or have assessed their relationship with clinical outcomes. Thus, the objective of our study was 2-fold: first, to identify adherence patterns to combined recommended medication using GBTM, and second, to examine the association between adherence trajectories and subsequent cardiovascular events and mortality, in a cohort of patients with ACS.

MATERIALS AND METHODS

Design

This study involved a population-based retrospective cohort of all patients discharged alive following an ACS from any Valencia Health System (VHS) hospital from January 2009 to December 2011. Patients were followed for 24 months from the date of hospital discharge (index date).

Setting

The study was conducted in the region of Valencia in Spain, and specifically in the population covered by the VHS, with an extensive network of hospitals, primary care centers, and other facilities managed by the regional government, which provides universal free healthcare services (except for drug copayment) to 97% of the regional population (∼5 million inhabitants, with 10% of the Spanish population).

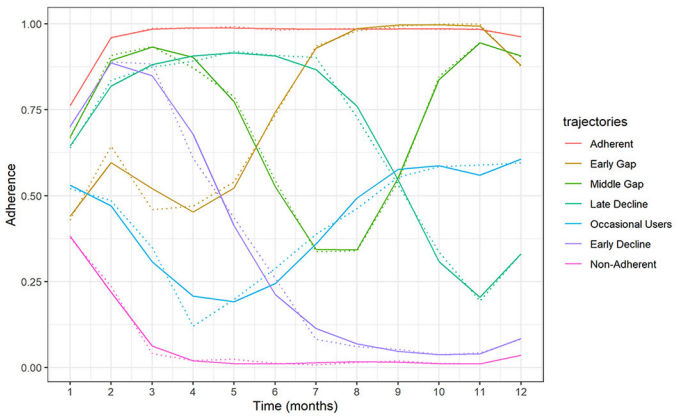
Population

We identified all patients aged 35 years and over who were discharged alive from VHS hospitals with the main diagnosis of ACS (ICD9-CM:410.xx—except 410.x2—and 411.xx) between January 2009 and December 2011, who had a prescription (filled or not) of three or more post-ACS prevention therapies (antiplatelet, beta-blockers, ACEI/ARB, and statins) within the first 30 days after discharge. Exclusion criteria were as follows: (1) deaths in the first year following hospital discharge (as this was the period to assess adherence); (2) people without pharmaceutical/health coverage by VHS; (3) non-residents, those who left the region, or who were discontinued from VHS coverage for other causes, due to limitations in follow-up.

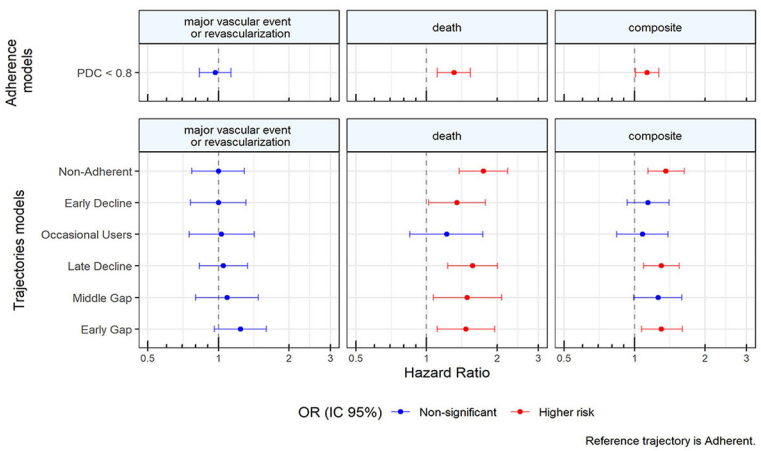
Assessing Concurrent Adherence to Combined Essential Medication and Clinical Outcomes in Acute Coronary Syndrome Patients. A Population-Based, Real-world Study using Group-based Trajectory Models

Among 15,797 ACS patients discharged alive, 12,057 (76.32%) initiated treatment with ≥3 therapeutic groups

For the first time, we assessed concurrent adherence to combined therapy (≥3 medications) through group-based trajectory models (GBTM) and their impact on clinical outcomes, using as an example a cohort of ACS patients.
We identified seven distinct adherence trajectories to related medications taken concomitantly.



Association with clinical outcomes



Compared to the adherent group, patients belonging to Early Gap (HR:1.30, 95%CI 1.07;1.60), Late decline (HR:1.31, 95%CI 1.10;1.56), and Non-Adherent trajectories (HR:1.36, 95%CI 1.14;1.63) had a greater risk of adverse clinical outcomes which also was different to the risk ascertained through concurrent PDC<80 (HR:1.13,95%CI 1.01;1.27).

Conclusion: The identification of patterns of concurrent adherence, a more comprehensive approach than traditional measurements, may be useful to target interventions to improve adherence in medical conditions in which multiple medications are recommended, as is the case of ACS.

Graphical Abstract | Our paper at a glance: assessing concurrent adherence to combined essential medication and clinical outcomes in acute coronary syndrome patients. A population-based, real-world study using group-based trajectory models.

Data Sources

Data were obtained from the VHS Integrated Database (VID), which combines data sources linking them at an individual level through a single anonymized patient identifier. The main source of data was the ambulatory Electronic Medical Record, which includes information on diagnoses, personal medical history, laboratory test results, lifestyle factors, as well as information on both physician prescriptions and dispensations from pharmacy claims. The information on hospitalizations was based on the Minimum Basic Dataset (MBDS) at hospital discharge, and the synopsis of clinical and administrative information on all hospital discharges, including diagnoses and procedures. The Population Information System provides information on the population covered by the VHS and registers certain demographic characteristics, including the geographical location of each person and the dates and causes of VHS discharge, including deaths. A detailed description of the sources of data can be found elsewhere (24). The Ethics Committee of the Public Health General Directorate of the Valencia Health Authority and the Center for Public Health Research approved the protocol and waived the need for obtaining informed consent. All data used was pseudoanonymized.

Clinical Outcome Measures

The three pre-specified clinical outcomes, measured within the second year of initial prescription of secondary prevention medications, were the first hospitalization for a major vascular event (acute myocardial infarction, unstable angina, stroke, or congestive heart failure) or coronary revascularization (identified by the following procedures: coronary bypass, stenting, or angioplasty); death by any cause (captured from the mortality registry); and a composite outcome of either a major vascular event, coronary revascularization or death. Only principal discharge diagnoses based on ICD9CM (**Supplementary Table S1**) were used to define endpoints. Out-of-hospital mortality was collected from the SIP system which, in turn, obtains the information from the mortality register. All outcomes were analyzed separately and only the first event was considered for analysis. Patients were followed from the start of the second year after the index event (day 366) until the end of that second year (day 730) or death, whichever came first.

Drug Exposure: Adherence to Post-ACS Prevention Therapies

Based on electronic prescription and dispensation information, we constructed for each drug class a day of supply for the 365 days after the index date which indicates whether the medication was available or not on each day. The days of supply were estimated using the dosing regimen specified in the prescription (one tablet every 8, 12, or 24 h) and the number of pills per package/prescribed. If a dispensing occurs before the previous dispensing should have run out, days' supply was accumulated up to a maximum excess of 90 days of medication.

We first calculated a monthly PDC for the first 12 months after discharge for each patient's therapeutic group and created a binary indicator for "adherent" in each month defined as PDC $\geq$0.8 (i.e., 24 out of 30 days covered by medication). In the case of dual antiplatelet therapy, which is not recommended for all patients and with recommendations to be prescribed only for short-term (3, 5), we used a less restrictive approach, which required having at least one antiplatelet agent available to be classified as adherent to that group. To measure adherence to multiple concurrent drugs, we aggregated the monthly indicators of adherence to each therapeutic group and calculated a new binary indicator, identifying patients who were adherent to 3 or more medications each month.

Group-based trajectory models were used to identify and characterize different patterns of adherence to medication over time. This method is an application of finite mixture modeling that through maximum likelihood, identifies clusters of individuals and classifies individuals with similar trends and evolution of longitudinal measures (25, 26). We estimated logistic group-based trajectory models with 2 to 8 groups using a binary indicator of monthly adherence to three or more medications for the first 12 months as the longitudinal response, to model the probability of being adherent. We used until five-order polynomial in each model to allow the most flexibility to the trajectories. Model selection was based on the following parameters: (1) Bayesian information criterion (BIC) where the largest value indicates the best-fitting model, STATA traj module implementation: BIC = log(L) -0.5 * log(n) p, where L = log-likelihood, n = sample size and p = number of parameters); (2) a minimum proportion of the study sample in a class group or trajectory of 5%; (3) average posterior probability >0.7 in each group (25, 26). Additionally, we calculated the annual PDC for the first 12 months after discharge and defined adherence as having 80% of days covered by medication dispensed with 3 or more medications.

Covariates

Covariates included relevant sociodemographic and clinical characteristics and measures of health service use at the time of discharge. We identified the following variables: main admission diagnosis (AMI, angina), age at hospital admission, gender, and copayment. Comorbidities included were the following: atrial fibrillation, congestive heart failure, chronic obstructive pulmonary disease (COPD), hyperlipidemia, hypertension, peripheral vascular disease, stroke, diabetes mellitus, dementia. Procedures at index hospitalization included the following: systemic or intracoronary thrombolysis, angiography, coronary artery bypass grafting (CABG), and percutaneous coronary intervention (PCI). Lifestyle included variables such as tobacco smoking and alcohol abuse. Additionally, we included the cardiovascular events that occurred during the year of adherence assessment for further adjustment. Health services use variables including outpatient visits, ED visits, and hospitalizations, as well as preventive medication use before the index date, and polypharmacy.

Statistical Analysis

First, patients were classified according to their adherence patterns within the first year after discharge using GBTM. Then, the characteristics of patients were described according to each adherence trajectory group

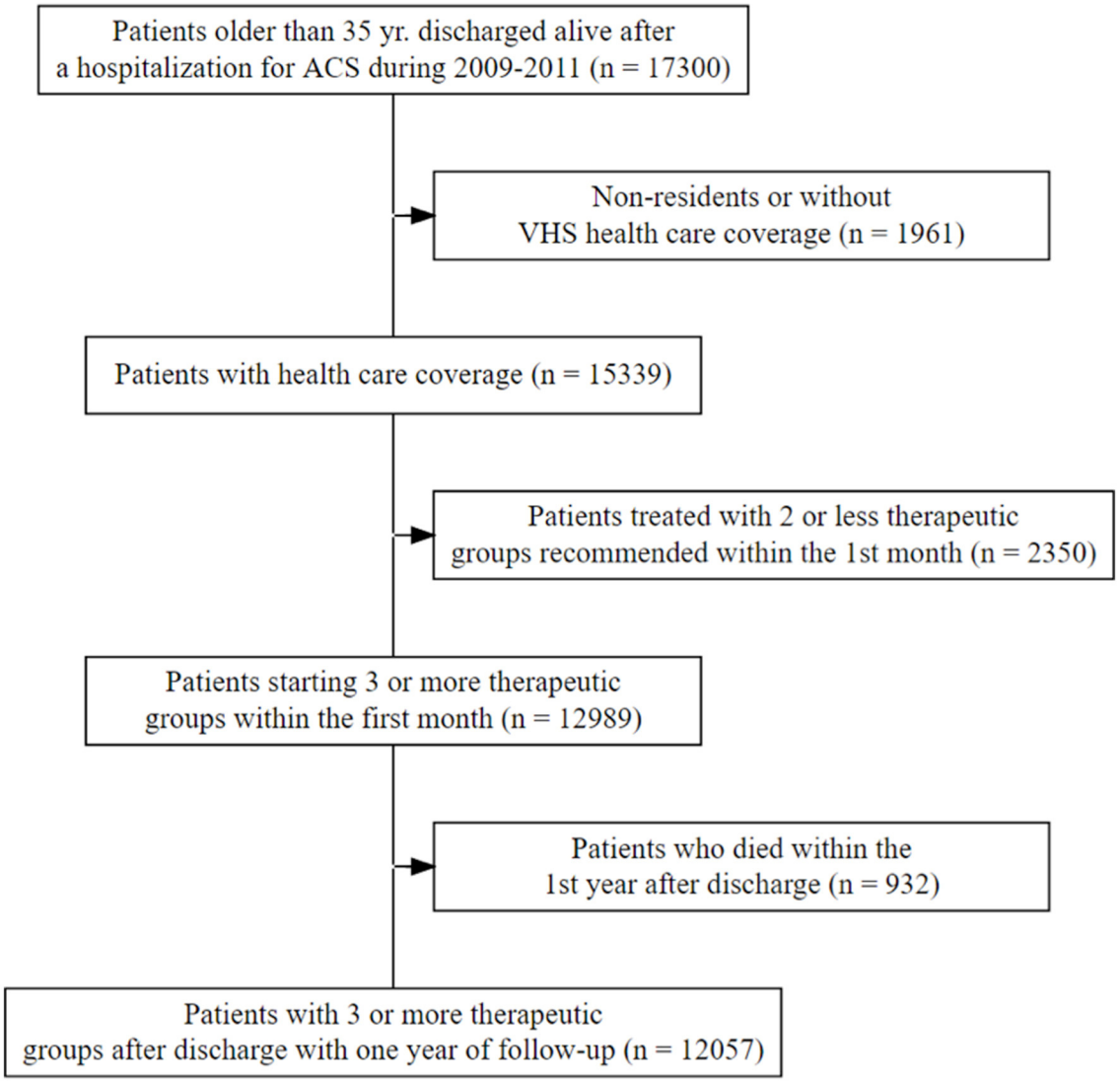


FIGURE 1 | Flowchart of the population.

identified. Categorical variables were expressed as numbers and percentages, and continuous variables as mean and *SD*.

Incidence rates (per 100 person-year) for the clinical outcomes occurred within 365 days after the first-year treatment were calculated. Kaplan-Meier curves were plotted for each outcome. Multivariable Cox proportional hazards models were used to assess the association between trajectories of adherence to three or more secondary prevention medications and post-cardiovascular event and death within the 12 months after the first-year treatment exposure. We estimated a model for cardiovascular events and mortality independently, and another combining both events, whichever came first for the composite outcome. The model included all patient characteristics. Hazard ratios (HR) with their respective 95% CI were estimated for the final models.

Additionally, we performed a secondary analysis, in order to assess the robustness of our results, using the conventional adherence measure (e.g., annual PDC).

All analyses were performed using Stata 14 (StataCorp LP, College Station, TX, USA) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) statistical software. The Traj module for Stata was used to run the GBTM (27).

RESULTS

General Characteristics

A total of 15,797 patients with ACS were discharged alive from 2009 to 2011. From these, 12,989 (82.2%) started treatment with ≥3 therapeutic groups during the first month after hospital discharge (**Figure 1**). Finally, a total of 12,057 (76.3%), who were prescribed at least 3 therapeutic groups during the adherence

TABLE 1 | Patient characteristics by adherence trajectory group.

Characteristics	Adherent	Early gap	Middle gap	Late decline	Occasional users	Early decline	Non-adherent	Total
N	6,383 (52.94%)	800 (6.64%)	684 (5.67%)	1,318 (10.93%)	657 (5.45%)	1,060 (8.79%)	1,155 (9.58%)	12,057 (100%)
Age (%)								
<45 years	3.95	3.38	3.95	5.16	5.02	9.34	5.45	4.72
45–64	35.47	36.62	40.94	40.44	43.99	40.66	37.84	37.55
65–79	44.37	42.88	41.08	37.56	35.46	31.60	35.06	40.84
80 and over	16.21	17.12	14.04	16.84	15.53	18.40	21.65	16.89
Female (%)	28.07	28.50	28.51	26.40	28.31	26.13	29.87	27.96
Copayment (%)	16.51	17.50	19.59	21.55	22.98	29.53	27.19	19.82
Main diagnosis at discharge (%)								
Acute Myocardial Infarction	80.54	71.50	77.05	75.64	73.36	77.08	70.39	77.54
Angina	19.46	28.50	22.95	24.36	26.64	22.92	29.61	22.46
Medication use before hospitalization (%)								
ACEI or ARB	53.64	59.50	53.51	50.38	50.84	41.60	46.84	51.80
Antiplatelet	33.98	49.38	40.06	39.53	41.55	30.75	38.44	36.51
Beta-blocker	23.58	36.00	23.25	28.60	31.05	19.81	23.55	25.01
Statin	43.16	53.75	47.51	46.97	46.88	35.09	40.78	43.79
Comorbidity (%)								
Hypertension	63.67	65.75	61.99	61.68	59.51	51.13	57.40	61.57
Diabetes	34.64	39.88	36.55	34.60	30.59	30.47	30.74	34.13
Lipid disorder	51.51	55.88	53.07	51.75	51.14	43.58	45.19	50.59
Congestive heart failure	6.74	11.62	7.60	7.66	11.42	8.40	10.39	7.96
Coronary heart disease	22.00	37.75	27.49	29.67	32.12	23.02	27.88	25.40
Arrhythmias	8.90	15.12	9.94	10.93	10.50	11.32	15.50	10.53
COPD	10.65	14.50	13.16	11.91	14.31	11.51	13.16	11.70
Chronic renal disease	4.07	6.50	4.53	5.39	6.09	5.38	7.97	5.00
Malignancy	8.15	8.62	6.87	6.37	8.52	5.38	7.10	7.59
Dementia	2.65	4.75	2.92	3.41	1.83	1.79	3.72	2.87
Stroke	10.97	13.00	14.33	13.81	10.05	9.53	13.51	11.67
Smoking	16.03	15.38	18.86	17.15	18.11	17.26	14.37	16.33
Alcohol	0.99	0.62	1.61	1.29	1.37	1.70	1.21	1.14
Health care utilization, mean (SD)								
No. ED visits	1.58 (1.35)	1.98 (1.89)	1.72 (1.40)	1.85 (1.71)	1.80 (1.65)	1.78 (1.61)	2.07 (2.22)	1.72 (1.58)
No. of Hospitalization visits	0.17 (0.55)	0.32 (0.74)	0.24 (0.69)	0.29 (0.75)	0.27 (0.69)	0.22 (0.67)	0.34 (0.87)	0.23 (0.66)
No. of outpatient physician visits	17.97 (16.90)	21.74 (21.55)	18.33 (17.69)	17.39 (16.72)	17.74 (18.80)	17.12 (19.85)	18.56 (20.44)	18.15 (18.03)
No. of prescription drugs	7.67 (5.37)	8.90 (5.72)	7.72 (5.61)	7.56 (5.52)	7.48 (5.67)	6.50 (5.79)	7.25 (5.85)	7.59 (5.55)
Procedure on index hospitalization (%)								
Angiography	49.60	44.12	49.42	45.68	47.64	46.04	46.93	48.12
Percutaneous coronary intervention	50.98	37.12	42.84	43.02	40.64	42.08	35.76	45.92
Coronary-artery bypass grafting	3.29	4.62	4.39	3.57	3.20	3.21	4.94	3.62
Systemic thrombolysis	10.03	6.50	8.92	7.21	8.83	9.15	6.67	8.96
Intracoronary thrombolysis	1.60	1.38	1.46	0.76	0.91	1.13	0.61	1.31
Length hospitalization, mean (SD)	8.82 (6.63)	9.15 (7.47)	8.92 (6.03)	8.59 (5.40)	8.32 (5.49)	8.87 (8.30)	9.88 (11.54)	8.90 (7.27)
Cardiovascular event during first year (%)	9.07	14.62	12.57	13.43	13.09	12.74	15.84	11.30
Conventional measures of adherence								
Annual PDC, mean (SD)	97.37 (3.54)	84.15 (7.77)	81.63 (9.58)	75.95 (11.85)	57.51 (14.75)	44.10 (15.00)	15.01 (14.38)	78.51 (28.08)
PDC >80 (%)	99.94	75.38	62.28	42.34	5.63	0.47	0.09	66.43

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; ED, emergency department; SD, standard deviation; PDC, Proportion of days covered.

follow-up (i.e., 1 year after discharge), were kept for analysis. Of those, 98% were prescribed antiplatelets (78.1% had dual therapy), 82.1% beta-blockers, 82.4% ACEI/ARB, and 93.9% statins. Overall, 77.5% of patients had an acute myocardial infarction (AMI) as the main diagnosis of admission, 28% were women, and the median age was 68 years old. The

average annual PDC for three or more medication therapies was 78.5 (*SD* 28.1; Median 92.1), and 66.4% of the cohort had a PDC ≥80% in the first year after hospital discharge (**Table 1**).

Adherence Trajectories

In the GBTM analysis, we identified seven adherence trajectories after applying the pre-specified criteria. Adherence trajectories over the first year after an ACS are presented in **Figure 2**. These trajectories can be categorized into the following: (1) Adherent (52.94% of cohort patients); (2) Early Gap (6.64%); (3) Middle Gap (5.67%); (4) Late decline (10.93%); (5) Occasional Users (5.45%); (6) Early Decline (8.79%); (7) Non-Adherent (9.58%).

Adherent patients were less likely to have a copayment, cardiovascular comorbidities as well as chronic renal disease, ED and hospitalization visits, and were also less likely to have cardiovascular events during the first year after discharge but were more likely to have AMI as the main diagnosis at discharge

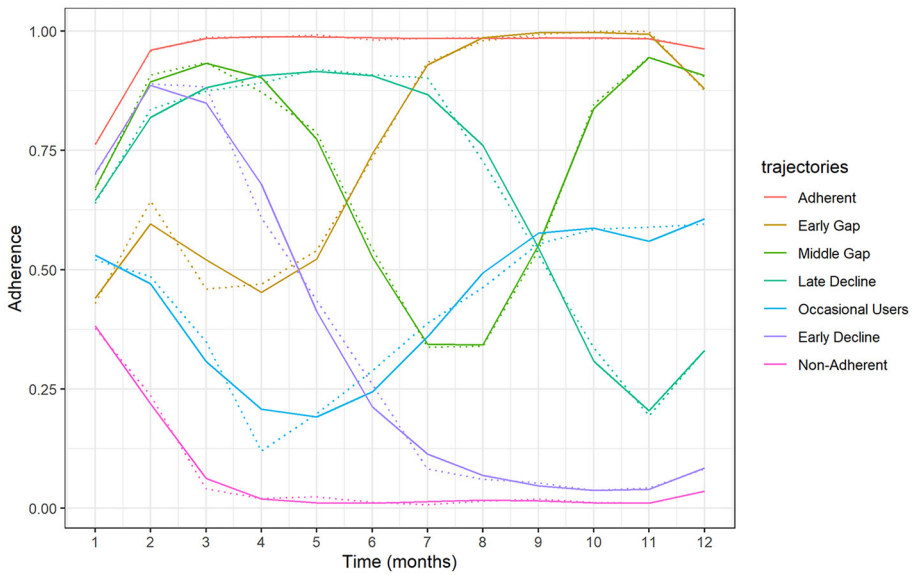


FIGURE 2 | Adherence trajectories identified over the first year after an ACS.

TABLE 2 | Incidence rates (per 100 person-year) for adverse clinical outcomes.

	Major vascular event or revascularization			Death			Composite		
	New cases	Person-years	Incidence rate (95%CI)	Deaths	Person-years	Incidence rate (95%CI)	New cases	Person-years	Incidence rate (95%CI)
Adherent	383	6081.4	6.30 (5.68–6.96)	249	6245.8	3.99 (3.51–4.51)	572	6081.4	9.41 (8.65–10.21)
Early Gap	71	735.8	9.65 (7.54–12.17)	62	765.8	8.10 (6.21–10.38)	117	735.8	15.90 (13.15–19.06)
Middle Gap	46	644.0	7.14 (5.23–9.53)	40	664.1	6.02 (4.30–8.20)	78	644.0	12.11 (9.57–15.12)
Late Decline	87	1231.8	7.06 (5.66–8.71)	89	1271.2	7.00 (5.62–8.62)	165	1231.8	13.40 (11.43–15.60)
Occasional Users	43	621.5	6.92 (5.01–9.32)	35	639.6	5.47 (3.81–7.61)	69	621.5	11.10 (8.64–14.05)
Early Decline	62	1000.9	6.19 (4.75–7.94)	64	1026.2	6.24 (4.80–7.96)	113	1000.9	11.29 (9.30–13.57)
Non-Adherent	72	1063.7	6.77 (5.30–8.52)	105	1094.1	9.60 (7.85–11.62)	162	1063.7	15.23 (12.97–17.76)
Full cohort	764	11379.1	6.71 (6.25–7.21)	644	11706.8	5.50 (5.08–5.94)	1276	11379.1	11.21 (10.61–11.85)

CI, confidence interval.

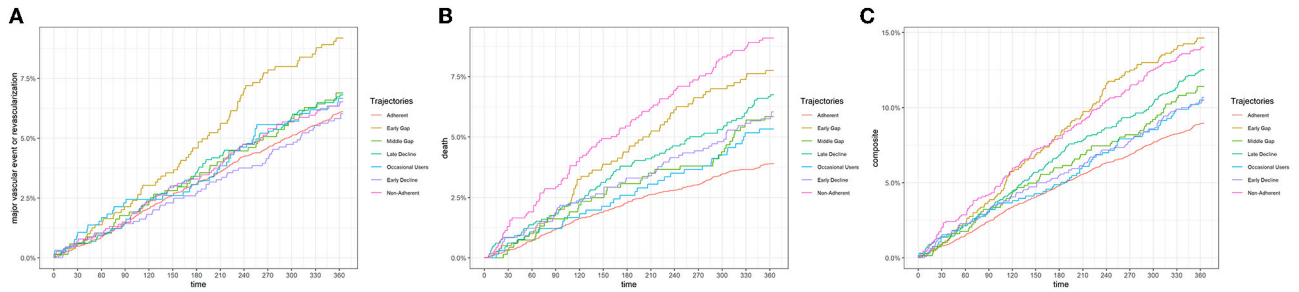


FIGURE 3 | (A) Unadjusted incidence rates of major cardiovascular events. **(B)** Unadjusted incidence rates of death. **(C)** Unadjusted incidence rates of the composite outcome.

and to have more revascularization procedures on the index hospitalization (**Table 1**).

Patients belonging to the early-gap group were less likely to be in the younger age category, and to report alcohol consumption, and showed higher use of medication before hospitalization, and were more likely to have most comorbidities studied (i.e., diabetes, lipid disorder, congestive heart failure, coronary heart disease, COPD, malignancy, and dementia).

The early decline group was more likely to have copayment and to be in the younger age category and showed lesser medication use before hospitalization in all therapeutic groups. It was also less likely to have comorbidities such as hypertension, diabetes, lipid disorder, chronic renal disease, malignancy dementia, and stroke.

Non-adherent patients were more likely to be aged 80 and over, to be female, and to have arrhythmias and chronic renal disease, they were also the second group most likely to have copayment (after the early-decline patients). Those belonging to this group also had more ED- and hospitalization visits, longer hospitalizations, and showed the highest percentage of cardiovascular events during the first-year post-discharge (**Table 1**).

Clinical Outcomes

Regarding the unadjusted incidence rates of CV events, death, and the composite outcome for each adherence trajectory (**Table 2**, **Figures 3A–C**), no major differences were observed. The Early Gap trajectory showed the highest incidence of major vascular events or revascularization [9.65 per 100 person-year (p-y), 95% CI: 7.54, 12.17]. Regarding death, the non-adherent and the early-gap trajectories showed the highest rates (9.6 deaths per 100 p-y; 95% CI: 7.85, 11.62, and 8.1 deaths per 100 p-y; 95% CI: 6.21, 10.38, respectively). The adherent pattern showed the lowest incidence in the composite outcome (9.41 events per 100 p-y; 95% CI: 8.65, 19.06).

Figure 4 shows the adjusted association between adherence trajectories and clinical outcomes (see also **Supplementary Table S2** for the full model). None of the trajectories was significantly associated with recurrence of major vascular events or revascularization in the adjusted analysis. Regarding mortality, compared to the adherent group, patients belonging to Middle-Gap (hazards ratio (HR): 1.5; 95% CI: 1.07, 2.09), Early-Gap (HR: 1.47; 95% CI: 1.11, 1.95), Late-decline (HR: 1.58; 95% CI: 1.24, 2.02), Early- Decline (HR: 1.35; 95% CI: 1.02, 1.79), and Non-Adherent (HR: 1.76; 95% CI: 1.38, 2.23) groups had a greater risk of mortality, being the non-adherent, the group with the highest likelihood of death. Similar associations were found for the composite outcome. Earl-Gap (HR: 1.3; 95% CI: 1.07, 1.6), Late-decline (HR: 1.31; 95% CI: 1.1, 1.56), and Non-Adherent patients (HR: 1.36; 95% CI: 1.14, 1.63) had a significantly greater risk of a major vascular event, revascularization or death as compared to Adherent patients.

When using dichotomized groups based on PDC, results were found to be robust, with the non-adherent patients being at higher risk of death or of presenting the composite outcome but showing no association with recurrent major vascular events (**Figure 4**, **Supplementary Table S3**). However, the risk found by using PDC < 80 was of lesser magnitude (HR: 1.31; 95% CI: 1.14, 1.54 for death and HR: 1.13; 95% CI: 1.01, 1.27 for the composite outcome) than those found in the poor adherence trajectories (Early Gap, Late Decline, and Non-Adherent; See **Figure 4**, **Supplementary Tables S2**, **S3**).

DISCUSSION

In the present study, we used group-based trajectory models to identify adherence patterns to three or more combined evidence-based medications in a concurrent manner in a population-based cohort of patients after hospitalization for acute coronary syndrome and evaluated which adherence patterns were associated with adverse clinical outcomes in the second year after discharge.

Although nowadays GBTM is not an uncommon tool to identify adherence patterns to medication over time using pharmacy claims databases (21–23, 28); to our knowledge, this is virtually the first time that adherence to multiple concurrent recommended medications is assessed through GBTM and compared to PDC estimates. GBTM accounts for the dynamic nature of adherence and allows the identification of differential behaviors in patients that otherwise would be classified simply

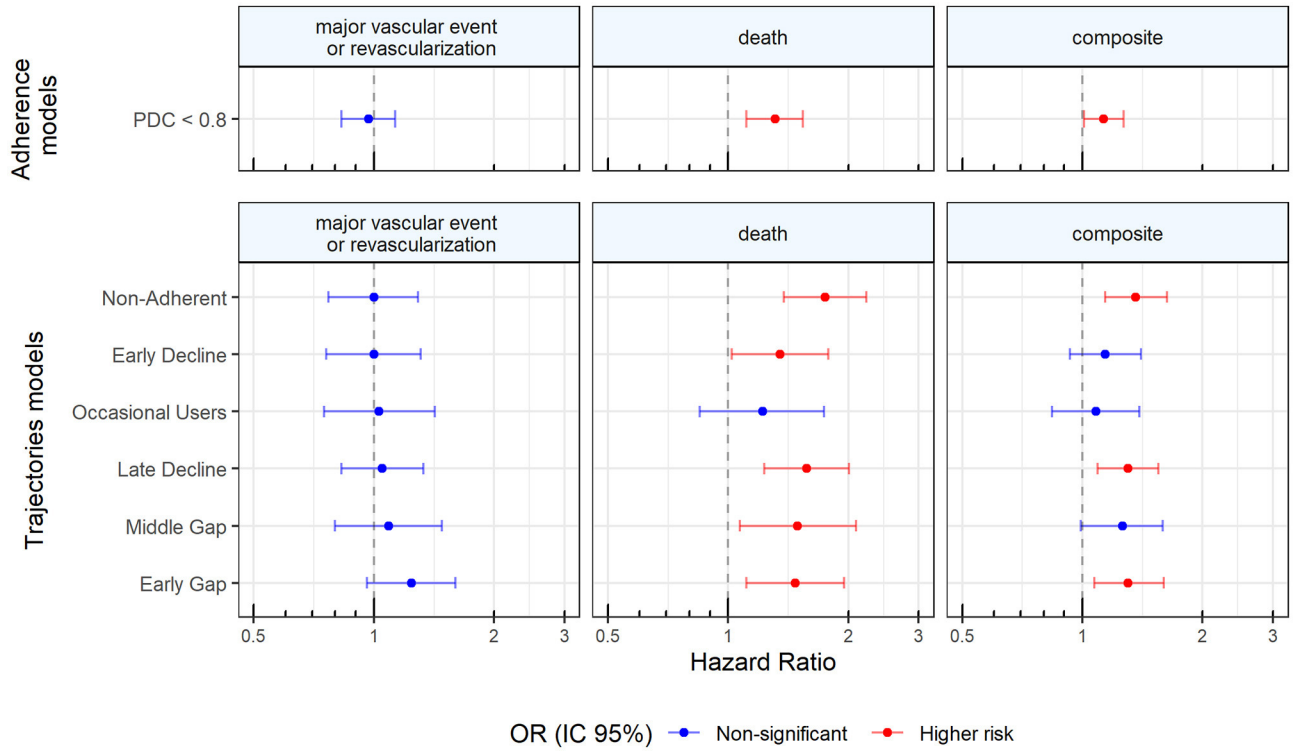


FIGURE 4 | Adjusted association between adherence trajectories and clinical outcomes.

as "non-adherent" (18–21). We identified seven adherence trajectories that best-summarized adherence patterns to three or more combined therapies for the secondary prevention of ACS. According to these trajectories, 47% of patients did not adhere to their treatment at some point in the first year post-ACS, but their patterns were very different, as were the baseline characteristics related to each pattern. *Non-adherence*, *Early gap*, and *Late Decline* trajectory groups were associated with a higher risk of the composite outcome of recurrent cardiovascular events, and all-cause death, compared to the adherent group. Furthermore, each of these patterns also showed differential risks (and of higher magnitude) when compared to PDC $<$ 80 (the classical measure for non-adherent patients).

In a previous study of our group assessing adherence trajectories to the same medication groups, but individually, some of the patterns identified were similarly found here, including *adherent*, *early gap*, and *occasional users* (29). However, others differ from those shown in the present study. It could be possible that when accounting for the adherence to several drugs altogether, new patterns arise, as this represents a more complex scenario.

Through the patterns identified, we found that medication adherence was suboptimal, with 53% of participants belonging to the "Adherent" trajectory (sustained and continuous adherence) to $\geq$3 secondary prevention drugs. In the aforementioned study (29), we found that around 66% (for antiplatelet, beta-blockers, and ACEI/ARB) and 75% (for statins) of patients after hospitalization for coronary heart disease, were adherent (29). Again, differences could be explained; first, by the added complexity that means adhering to at least three different medications combined as a treatment, and second, by the different timespan in which adherence was assessed. These two factors can translate into findings of reduced adherence. The former factor is very important, as assessing drugs prescribed in combination, separately, could lead to overestimation of adherence. The two studies assessing 3 medications altogether: ACEI/ARB, beta-blockers, and statins (although using the traditional PDC or MPR) (15, 16), found that 49% and 34% of patients, respectively, adhere to all three therapies (15, 16). However, those figures are not directly comparable to our findings, as it does not provide information on adherence behaviors over time. For example, static PDC measures would classify patients into groups of adherent and non-adherent without differentiating the dynamics of the various non-adherent trajectories shown in our results. These differential behaviors are associated with different baseline characteristics and also differential risks for clinical outcomes as seen in our study. Identifying these features is key for targeting interventions aiming to improve adherence. For example, a modifiable factor, such as having copayment was found to be related to non-adherent

trajectories. Other factors such as older age or female sex are indeed non-modifiable but can be considered when designing interventions.

We found that the adherence trajectories to ≥3 medications were associated with a higher risk of a composite outcome including major adverse cardiovascular events and death. We found an absence of a relationship between adherence trajectories and cardiovascular events alone, and such an absence of association was also observed in the analysis using PDC. These findings are likely to be due to the greater impact that adherence to preventive medication has in the acute phase post-ACS on the likelihood of a cardiovascular event. In fact, 11% of cohort patients experienced a cardiovascular event during the adherence assessment period and patients belonging to the Non-Adherent trajectory had the highest rate. On the other hand, our results show that increasing adherence to preventive therapies is associated with a significantly decreased risk of mortality in post-AMI patients similar to the previous study (10). It is important to note that outcomes were assessed during the second year after the index date, which is a common approach (15, 16). Therefore, we did not provide information regarding the impact of adherence to recommended therapies in the longer term, which should be further studied.

For the secondary prevention of acute coronary syndrome, clinical guidelines recommend all 4 therapies (antiplatelets, beta-blockers, ACE inhibitors/ARB, and statins) for long-term use for a major benefit. Hence, ideally, adherence to therapy when a combination of medications is prescribed should be assessed by considering all drugs together and using approaches that allow the identification of differential patterns of medication refill. This was the main focus of our study, and this principle could be applied to any other condition where combined therapy is recommended.

There were some limitations to this study. First, we used electronic prescription and dispensation information for measuring adherence that lacked information if dispensed medications were consumed by the patient. Second, we evaluated outcomes in the second year post-ACS and patients may have changed their adherence behavior to medication during this period. However, this is necessary to ensure the separation of our adherence and outcome measurement and to protect against bidirectional bias. Third, we only evaluated adherence for 12 months after hospitalization. Although non-adherence to secondary prevention post-ACS during the initial year of treatment is important, these medications are recommended for long-term use. Fourth, despite the availability of a wide range of potential confounders, unmeasured residual confounding by lack of adjustment for variables such as education or race and ethnicity cannot be ruled out.

CONCLUSION

In this population-based study, we identified seven trajectories of adherence to three or more combined essential medications after ACS. Non-adherence, Early gap, and Late Decline trajectory groups were associated with a higher risk of the composite outcome of recurrent cardiovascular events and all-cause death, compared to the adherent group. Identification of patient subgroups with suboptimal adherence patterns may be useful to target interventions to improve medication adherence and health outcomes of patients when a therapy composed of several concurrent medications is recommended.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because we have no permission to make generated datasets available. We have been granted access to data by the Valencia Health Department, so we could make the analysis for this study, but are not allowed to share it. Requests to access the datasets should be directed to Unit of Analysis of Health Information Systems, Valencia Health Department (Servicio de Análisis De Sistemas de Información Sanitaria, Consellería de Sanitat). www.san.gva.es.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Public Health General Directorate of the Valencia Health Authority and the Center for Public Health Research approved the protocol and waived the need for obtaining inform consent. All data used was pseudoanonymized. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

GS-G conceived the study. FS-S and DB-Q carried out the main statistical analyses. CR-B wrote the manuscript. IH prepared the database. CR-B and IH assisted with statistical analysis. CR-B, DB-Q, FS-S, IH, AG-S, SP, and GS-G participated in the study design and interpretation of data and contributed to the critical revision of the manuscript for important intellectual content. All authors agree to be accountable for all aspects of the work and have read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.863876/full#supplementary-material

REFERENCES

1. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International society of hypertension global hypertension practice guidelines. *Hypertension*. (2020) 75:1334–57. doi: 10.1161/HYPERTENSIONAHA.120.15026
2. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. (2013) 127:e362–425. doi: 10.1161/CIR.0b013e3182742c84
3. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. (2014) 130:e344–426. doi: 10.1161/CIR.0000000000000134
4. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. (2013) 34:2949–3003. doi: 10.1093/eurheartj/eht296
5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. (2016) 37:267–315. doi: 10.1093/eurheartj/ehv320
6. Choudhry NK, Shrank WH, Levin RL, Lee JL, Jan SA, Brookhart MA, et al. Measuring concurrent adherence to multiple related medications. *Am J Manag Care*. (2009) 15:457–64.
7. Sanfélix-Gimeno G, Peiró S, Ferreros I, Pérez-Vicente R, Librero J, Catalá-López F, et al. Adherence to evidence-based therapies after acute coronary syndrome: a retrospective population-based cohort study linking hospital, outpatient, and pharmacy health information systems in Valencia, Spain. *J Manag Care Pharm*. (2013) 19:247–57. doi: 10.18553/jmcp.2013.19.3.247
8. Mathews R, Wang TY, Honeycutt E, Henry TD, Zettler M, Chang M, et al. Persistence with secondary prevention medications after acute myocardial infarction: insights from the TRANSLATE-ACS study. *Am Heart J*. (2015) 170:62–9. doi: 10.1016/j.ahj.2015.03.019
9. Lauffenburger JC, Robinson JG, Oramasionwu C, Fang G. Racial/Ethnic and gender gaps in the use of and adherence to evidence-based preventive therapies among elderly Medicare Part D beneficiaries after acute myocardial infarction. *Circulation*. (2014) 129:754–63. doi: 10.1161/CIRCULATIONAHA.113.002658
10. Chen HY, Saczynski JS, Lapane KL, Kiefe CI, Goldberg RJ. Adherence to evidence-based secondary prevention pharmacotherapy in patients after an acute coronary syndrome: a systematic review. *Heart Lung*. (2015) 44:299–308. doi: 10.1016/j.hrtlng.2015.02.004
11. Choudhry NK, Fischer MA, Avorn J, Liberman JN, Schneeweiss S, Pakes J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Arch Intern Med*. (2011) 171:814–22. doi: 10.1001/archinternmed.2010.495
12. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. (2007) 120:713–9. doi: 10.1016/j.amjmed.2006.08.033
13. Castellano JM, Fuster V, Jennings C, Prescott E, Bueno H. Role of the polypill for secondary prevention in ischaemic heart disease. *Eur J Prev Cardiol*. (2017) 24:44–51. doi: 10.1177/2047487317707324
14. Wimmer BC, Cross AJ, Jokanovic N, Wiese MD, George J, Johnell K, et al. Clinical outcomes associated with medication regimen complexity in older people: a systematic review. *J Am Geriatr Soc*. (2017) 65:747–53. doi: 10.1111/jgs.14682
15. Korhonen MJ, Robinson JG, Annis IE, Hickson RP, Bell JS, Hartikainen J, et al. Adherence tradeoff to multiple preventive therapies and all-cause mortality after acute myocardial infarction. *J Am Coll Cardiol*. (2017) 70:1543–54. doi: 10.1016/j.jacc.2017.07.783
16. Chen CW, Lin YC, Shih CM, Chen WT, Lin FY, Bi WF, et al. Association of multiple preventive therapies postdischarge and long-term health outcomes after acute myocardial infarction. *J Chin Med Assoc*. (2021) 84:1084–91. doi: 10.1097/JCMA.0000000000000621
17. MacEwan JP, Forma FM, Shafrin J, Hatch A, Lakdawalla DN, Lindenmayer JP. Patterns of adherence to oral atypical antipsychotics among patients diagnosed with schizophrenia. *J Manag Care Spec Pharm*. (2016) 22:1349–61. doi: 10.18553/jmcp.2016.22.11.1349
18. Franklin JM, Gopalakrishnan C, Krumme AA, Singh K, Rogers JR, Kimura J, et al. The relative benefits of claims and electronic health record data for predicting medication adherence trajectory. *Am Heart J*. (2018) 197:153–62. doi: 10.1016/j.ahj.2017.09.019
19. Hargrove JL, Pate V, Casteel CH, Golightly YM, Loehr LR, Marshall SW, et al. Antihypertensive adherence trajectories among older adults in the first year after initiation of therapy. *Am J Hypertens*. (2017) 30:1015–23. doi: 10.1093/ajh/hpx086
20. Newman-Casey PA, Blachley T, Lee PP, Heisler M, Farris KB, Stein JD. Patterns of glaucoma medication adherence over four years of follow-up. *Ophthalmology*. (2015) 122:2010–21. doi: 10.1016/j.ophtha.2015.06.039
21. Franklin JM, Shrank WH, Pakes J, Sanfélix-Gimeno G, Matlin OS, Brennan TA, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Med Care*. (2013) 51:789–96. doi: 10.1097/MLR.0b013e3182984c1f
22. Lo-Ciganic WH, Donohue JM, Jones BL, Perera S, Thorpe JM, Thorpe CT, et al. Trajectories of diabetes medication adherence and hospitalization risk: a retrospective cohort study in a large state medicaid program. *J Gen Intern Med*. (2016) 31:1052–60. doi: 10.1007/s11606-016-3747-6
23. Franklin JM, Krumme AA, Tong AY, Shrank WH, Matlin OS, Brennan TA, et al. Association between trajectories of statin adherence and subsequent cardiovascular events. *Pharmacoepidemiol Drug Saf*. (2015) 24:1105–13. doi: 10.1002/pds.3787
24. García-Sempere A, Orrico-Sánchez A, Muñoz-Quiles C, Hurtado I, Peiró S, Sanfélix-Gimeno G, et al. Data resource profile: the valencia health system integrated database (VID). *Int J Epidemiol*. (2020) 49:740–1. doi: 10.1093/ije/dyz266
25. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. (2010) 6:109–38. doi: 10.1146/annurev.clinpsy.121208.131413
26. Nagin DS. Group-based trajectory modeling: an overview. *Ann Nutr Metab*. (2014) 65:205–10. doi: 10.1159/000360229
27. Jones BL, Nagin DS. A note on a stata plugin for estimating group-based trajectory models. *Sociol Methods Res*. (2013) 42:608–13. doi: 10.1177/0049124113503141
28. Dillon P, Stewart D, Smith SM, Gallagher P, Cousins G. Group-based trajectory models: assessing adherence to antihypertensive medication in older adults

in a community pharmacy setting. *Clin Pharmacol Ther*. (2018) 103:1052–60. doi: 10.1002/cpt.865

29. Librero J, Sanfélix-Gimeno G, Peiró S. Medication adherence patterns after hospitalization for coronary heart disease. a population-based study using electronic records and group-based trajectory models. *PLoS ONE*. (2016) 11:e0161381. doi: 10.1371/journal.pone.0161381

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Prognostic Value of Metabolic Syndrome in Patients With Non-ST Elevated Myocardial Infarction Undergoing Percutaneous Coronary Intervention

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Objective: We aim to investigate the prognostic effects of metabolic syndrome (MS) on patients with non-ST elevated myocardial infarction (NSTEMI) after percutaneous coronary intervention (PCI).

Methods: Patients with NSTEMI undergoing PCI were consecutively collected. According to the presence or absence of MS, they were divided into two groups and followed up for 1 year. The endpoint was major adverse cardiovascular events (MACE), including all-cause death, unstable angina hospitalization, heart failure (HF) hospitalization, non-fatal recurrent myocardial infarction (MI), and target lesion revascularization. Also, six subgroups were made according to gender, age, left ventricular ejection fraction (LVEF), Global Registry of Acute Coronary Events (GRACE) score, hypersensitive troponin (hsTNT), and several diseased vessels. Cox proportional hazard model was adopted to analyze the effect of MS on MACE in all the patients and different subgroups.

Results: A total of 1,295 patients were included in the current analysis and 660 (50.97%) of them had MS. About 88 patients were lost to follow-up, and the overall average follow-up was 315 days. MS was an independent risk factor for MACE (HR 1.714, CI 1.265–2.322, $p = 0.001$), all-cause death, heart failure (HF) hospitalization, and non-fatal recurrent MI. In the MS component, BMI $\geq$28 kg/m^2 was positively associated with MACE. Subgroup analysis indicated the prognostic value of MS was more striking for patients with the following: age of >60, LVEF of $\leq$40%, GRACE of >140, multivessel disease, or hsTNT of >0.1 ng/ml.

Conclusions: The MS was a robust adverse prognostic factor in patients diagnosed with NSTEMI, especially among those of older age and at higher ischemic risk. A BMI

of ≥28 kg/m^2 independently predicted the occurrence of MACE. Prognosis may be improved by controlling abdominal obesity.

Keywords: metabolic syndrome, non-ST elevated myocardial infarction, prognostic value, percutaneous coronary intervention, cohort study

INTRODUCTION

Metabolic syndrome (MS) is a disease state that involves multiple metabolic abnormalities and is closely related to cardiovascular disease (CVD), mainly including central obesity, hypertension, dyslipidemia, and diabetes or abnormal glucose tolerance. Furthermore, MS is associated with future incidence of diabetes and CVD and subsequent adverse cardiovascular events (1, 2). The increasing incidence of the syndrome worldwide, as well as the number of people with MS, will continue to rise, which has made it a serious public health problem.

As a serious cardiac emergency, patients with non-ST elevated myocardial infarction (NSTEMI) are likely to have more comorbidities and a worse prognosis than patients with ST-elevation myocardial infarction (STEMI) (3). Hospitalization rates for NSTEMI are increasing, and a transition from STEMI to NSTEMI in acute myocardial infarction (AMI) has been observed in China (4, 5). However, studies on the effects of MS on CVD were mostly focused on acute coronary syndrome (ACS) and acute STEMI and those results were controversial. Studies in non-ST elevation acute coronary syndrome (NSTEACS) or patients with NSTEMI are still scarce. Beyond that, controversy exists about whether there is a correlation between each component and prognosis, and which component is more important. As for patients with NSTEMI undergoing PCI, it is unclear whether the presence or absence of MS affects the occurrence of major adverse cardiovascular events in patients with different clinical and angiographic outcomes. Therefore, the current study aimed to evaluate the impact of MS and its components on cardiovascular outcomes in patients with NSTEMI undergoing PCI within 12 months after discharge. In addition, we further explored the prognostic value of MS in different subgroups of patients with NSTEMI.

METHODS

Study Design and Participants

From January 2018 to December 2019, consecutive patients with NSTEMI undergoing percutaneous coronary intervention (PCI) in Tianjin Chest Hospital were included. The inclusion criteria are as follows: (1) Age ≥18 years old; (2) In line with the diagnostic criteria of NSTEMI, cardiac troponin and/or CKMB above the 99th percentile of healthy individuals, and the following with at least one: (i) ST-segment depression or T wave inversion on ECG; (ii) Chest pain persists longer than 30 min; (3) Onset time <30 days; and (4) Patients undergoing coronary angiography and treated with PCI during the period of admission. The exclusion criteria are as follows: (1) Myocardial infarction (MI) patients if those ECG were persistent ST-segment elevation during diagnosis and treatment; (2) Chest pain caused by non-cardiac diseases, such as aortic dissection and pulmonary embolism, etc.; (3) Active bleeding, severe thrombocytopenia, severe liver or kidney diseases, malignant tumors, etc.; and (4) Lack of diagnostic data related to MS. After screening and meeting the above inclusion and exclusion criteria, 1,295 patients were eventually included. The study was performed by the Declaration of Helsinki and was approved by the Ethics Committee of Tianjin Chest Hospital (No. 2018KY-010-01). All included patients provided signed informed consent forms before study participation.

Definition of Metabolic Syndrome

The MS was defined according to a scientific statement (6) from the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI). Patients with 3 or more of the following risk factors were considered to have MS: (i) Central obesity: waist circumference (WC) of ≥102 cm in men and ≥88 cm in women. (ii) hypertriglyceridemia (triglycerides ≥1.7 mmol/L or on drug treatment for elevated triglycerides), (iii) low HDL-C (<1.03 mmol/L in men and <1.29 mmol/L in women or on drug treatment for reduced HDL-C), (iv) arterial hypertension [≥130 mmHg systolic blood pressure (SBP) or ≥85 mmHg diastolic blood pressure (DBP) or antihypertensive therapy], and hyperglycemia (fasting blood glucose ≥5.6 mmol/L or antidiabetic treatment). Since the patient's WC was not available, we used BMI as a surrogate parameter for WC, which had been adopted and verified in previous studies (7, 8). We utilized the BMI of ≥28 kg/m^2 as a diagnostic criterion of obesity proposed by the Working Group on Obesity of China (WGOC) (9).

Clinical and Biochemical Measurements

The basic data of gender, age, BMI, and previous medical history of all patients were recorded on admission, and the admission conditions of the patients were evaluated, including sitting blood pressure (measured by senior doctors on the non-dominant arm supported by the heart level), Killip class, and Global Registry of Acute Coronary Events (GRACE) score. The emergency laboratory indexes of admission, such as creatine kinase (CK), creatine kinase MB (CK-MB), hypersensitive troponin T (hsTnT), etc., were recorded. After fasting overnight for 12 h, fasting blood glucose (FBG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) total cholesterol were measured. GRACE was calculated for all patients on admission using eight variables, including age, systolic blood pressure, heart rate, serum creatinine, Killip class, cardiac arrest, elevated cardiac biomarkers (hsTnT), and ST deviation. The calculator used is available at (http://www.outcomes-umassmed.org/GRACE/). Ejection fraction (EF) was assessed

TABLE 1 | Baseline patient characteristics according to metabolic syndrome.

Variables	MS (-) (*n* = 635)	MS (+) (*n* = 660)	*P*
Age (years)	65 (57.72)	66 (57.73)	0.552
Female, gender *n* (%)	150 (23.6)	242 (36.7)	<0.001
BMI (%) <24 (kg/m^2), *n* (%)	401 (63.1)	241 (36.5)	<0.001
24–28 (kg/m^2), *n* (%)	165 (26.0)	185 (28.0)	
≥28 (kg/m^2), *n* (%)	69 (10.9)	234 (35.5)	
BMI (kg/m^2)	22.9 (21.5, 24.6)	27.2 (22.3, 29.0)	<0.001
Medical history			
Hypertension, *n* (%)	318 (50.1)	557 (84.4)	<0.001
Diabetes, *n* (%)	110 (17.3)	316 (47.9)	<0.001
Previous MI, *n* (%)	105 (16.5)	132 (20.0)	0.107
Previous stroke, *n* (%)	158 (24.9)	176 (26.7)	0.463
Previous PCI, *n* (%)	94 (14.8)	114 (17.3)	0.226
Previous CABG, *n* (%)	27 (4.3)	40 (6.1)	0.142
Family history of CVD, *n* (%)	62 (9.8)	72 (10.9)	0.499
Smoking, *n* (%)	384 (60.5)	430 (65.2)	0.081
Admission			
Systolic blood pressure (mmHg)	130 (120, 145)	135 (122, 150)	<0.001
Diastolic blood pressure (mmHg)	75 (69.84)	76 (70.85)	0.142
Killip class, *n* (%)			0.481
I	542 (85.4)	564 (85.5)	
II	79 (12.4)	73 (11.1)	
III	11 (1.7)	19 (2.9)	
IV	3 (0.5)	4 (0.6)	
Killip ≥II, *n* (%)	93 (14.6)	96 (14.5)	0.959
Laboratory			
LVEF≤40%, *n* (%)	84 (14.3)	85 (13.9)	0.825
LVEF (%)	55 (47, 59)	54 (45, 58)	0.008
Fasting plasma glucose (mmol/L)	5.21 (4.72, 5.95)	6.63 (5.64, 8.76)	<0.001
Triglyceride (mmol/L)	1.30 (1.04, 1.58)	1.96 (1.50, 2.52)	<0.001
Total cholesterol (mmol/L)	4.36 (3.73, 5.09)	4.50 (3.79, 5.14)	0.1
HDL-C (mmol/L)	1.09 (0.93, 1.30)	0.90 (0.78, 1.01)	<0.001
LDL-C (mmol/L)	2.93 (2.28, 3.55)	2.99 (2.37, 3.60)	0.275
hsCRP (mg/L)	4.71 (1.72, 16.36)	5.97 (2.65, 15.96)	0.002
NT-proBNP (pg/ml)	896.9 (380, 2287)	907 (349.6, 2961.75)	0.627
hsTnT (ng/mL)	0.57 (0.24, 1.24)	0.54 (0.24, 1.23)	0.741
CK (U/L)	222.5 (110, 519.5)	208.5 (103.5, 455)	0.299
CK-MB (U/L)	28 (17, 55)	26 (16, 47)	0.255
CAG and treatment			
Single-vessel disease, *n* (%)	147 (23.1)	131 (19.8)	0.148
Double-vessel disease, *n* (%)	161 (25.4)	162 (24.5)	0.737
Triple-vessel disease, *n* (%)	312 (49.1)	352 (53.3)	0.131
Left main, *n* (%)	94 (14.8)	95 (14.4)	0.835
Multi-vessel disease, *n* (%)	488 (76.9)	529 (80.2)	0.148
Grace Grade, *n* (%)			0.454
<109, *n* (%)	192 (30.2)	206 (31.2)	
109–140, *n* (%)	246 (38.7)	234 (35.5)	
>140, *n* (%)	197 (31.0)	220 (33.3)	
IABP, *n* (%)	19 (3.0)	29 (4.4)	0.182
Respirator, *n* (%)	72 (11.3)	81 (12.3)	0.603
Baseline medication			
DAPT, *n* (%)	625 (98.4)	649 (98.3)	0.896
Beta-blocker, *n* (%)	478 (75.3)	522 (79.1)	0.102
ACEI/ARB, *n* (%)	394 (62.0)	429 (65.0)	0.270
Statin, *n* (%)	612 (96.4)	638 (96.7)	0.777
Anticoagulants, *n* (%)	624 (98.3)	649 (98.3)	0.927

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CK, creatine kinase; CK-MB, creatine kinase MB; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; GRACE, Global Registry of Acute Coronary Events; HDL-C, high-density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; hsTnT, hypersensitive troponin T; IABP, intra-aortic balloon pump; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MS, metabolic syndrome; NT-proBNP, N-Terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention.

TABLE 2 | Comparison of clinical outcomes between two groups.

Variables	MS (-) (*n* = 635)	MS (+) (*n* = 660)	*P*
MACE	76 (12)	121 (18.3)	0.001
All-cause death	17 (2.7)	35 (5.3)	0.016
UA hospitalization	29 (4.6)	27 (4.1)	0.674
HF hospitalization	28 (4.4)	48 (7.3)	0.028
Non-fatal recurrent MI	5 (0.8)	21 (3.2)	0.002
TLR	1 (0.2)	4 (0.6)	0.193

HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; MS, metabolic syndrome; TLR, target lesion revascularization; UA, unstable angina.

by echocardiography in the first week after AMI according to the clinical standards and current echocardiography guidelines (10). Coronary angiography and PCI were performed by two cardiologists with qualifications for coronary artery diagnosis and treatment simultaneously according to the international standards and guidelines (11). Postoperative antiplatelet therapy with 100 mg/d of aspirin and 75 mg/d of clopidogrel, or 90 mg of ticagrelor twice per day is recommended for at least 1 year.

Study Endpoint and Follow-Up

All patients were followed up for 1 year after discharge, including outpatient visits, telephone interviews, and the recording of recurrent all-cause events by trained nurses or cardiologists, after the initial appointment.

The endpoint was MACE, including all-cause death, unstable angina (UA) hospitalization, heart failure (HF) hospitalization, non-fatal recurrent MI, and target lesion revascularization (TLR). TLR therapy was for either lesion with ischemia symptoms or

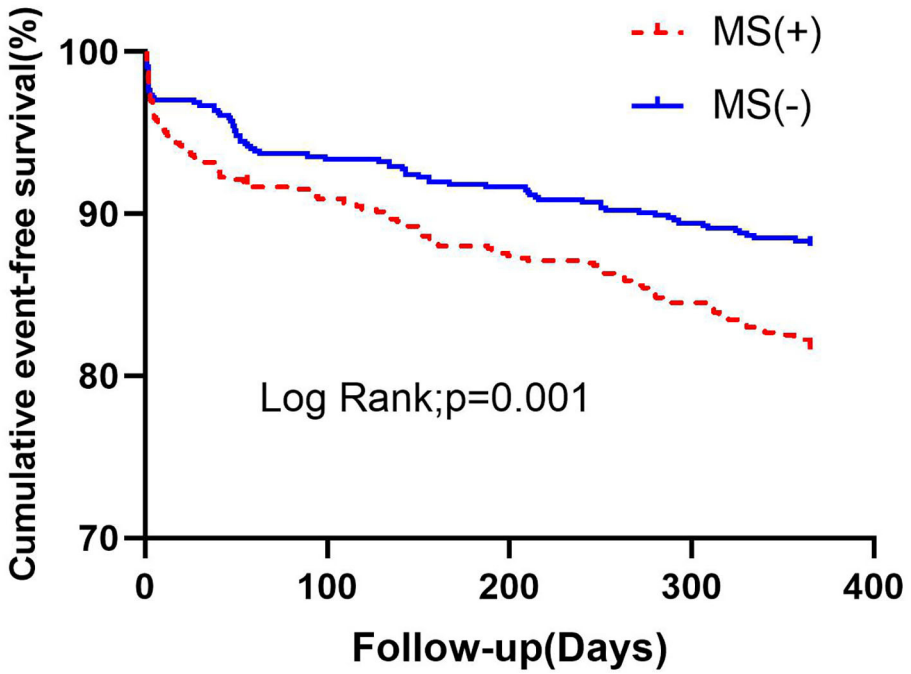

FIGURE 1 | Kaplan-Meier survival analysis of cumulative event-free survival curves within 1 year according to MS. MS, metabolic syndrome.

TABLE 3 | Multivariate COX regression analysis of each adverse event.

Variables	HR (95% CI)	*P*
MACE	1.714 (1.265–2.322)	0.001
All-cause death	2.184 (1.137–4.197)	0.019
UA hospitalization	0.890 (0.508–1.559)	0.683
HF hospitalization	1.662 (1.031–2.680)	0.037
Non-fatal recurrent MI	3.621 (1.324–9.904)	0.012
TLR	5.215 (0.545–49.861)	0.152

CI, confidence interval; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; MS, metabolic syndrome; NSTEMI, non-ST elevated myocardial infarction; UA, unstable angina; TLR, target lesion revascularization.

event-driven, including PCI and coronary artery bypass grafting (CABG). In the case of more than one clinical event in the same patient, only the first event was considered, and follow-up was discontinued. Patients lost to follow-up or those without MACE were treated as censored.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median with an interquartile range based on its distribution, and categorical variables were expressed as frequency and percentage. For comparison of continuous variables, the independent Student's *t*-test or Mann-Whitney *U*-test was used, and for comparison of categorical variables, the chi-square test or Fisher's exact tests was used, where appropriate. Event-free survival curves were analyzed by the Kaplan-Meier method, and a comparison between curves was carried out by the log-rank test. Multivariate Cox regression analysis was performed to evaluate the impact of MS and its five components on MACE in all enrolled patients with NSTEMI and various subgroups. The covariates included in the multivariable model were as follows: age, gender, history of smoking, family history of CVD, Killip ≥II, LVEF of ≤40%, multi-vessel disease, ACEI/ARB, and Beta-blocker. All statistical tests were 2-sided with $p < 0.05$ considered statistically significant. SPSS software (version 25.0, SPSS, Inc., Chicago, Illinois, USA) was used for statistical analysis. Subgroups were classified: 1,295 patients with NSTEMI by male vs. female; age of ≤60 vs. age of >60; LVEF of ≤40% vs. LVEF of >40%; low/medium (≤140) vs. high (>140) GRACE score; single-vessel disease (SVD) vs. multivessel disease (MVD); and hsTNT of ≤0.1 ng/ml vs. hsTNT of >0.1 ng/ml, respectively.

RESULTS

Clinical Characteristics

Among 1,295 patients with NSTEMI, there were 660 patients with MS (50.97%) and 635 patients without MS (49.03%). About 88 patients were lost to follow-up, and the overall average follow-up was 315 days. Women accounted for 36.7% in the MS group and 23.6% in the non-MS group, with statistical significance between the two groups. Compared with the non-MS group, the MS group had a higher body mass index (BMI), an average lower LVEF, and a higher hypersensitive C-reactive protein (hs-CRP) level. Among the components of MS, obesity, diabetes, and hypertension were more prevalent, HDL-C was lower, and TG and FBG were higher in patients with MS, as compared

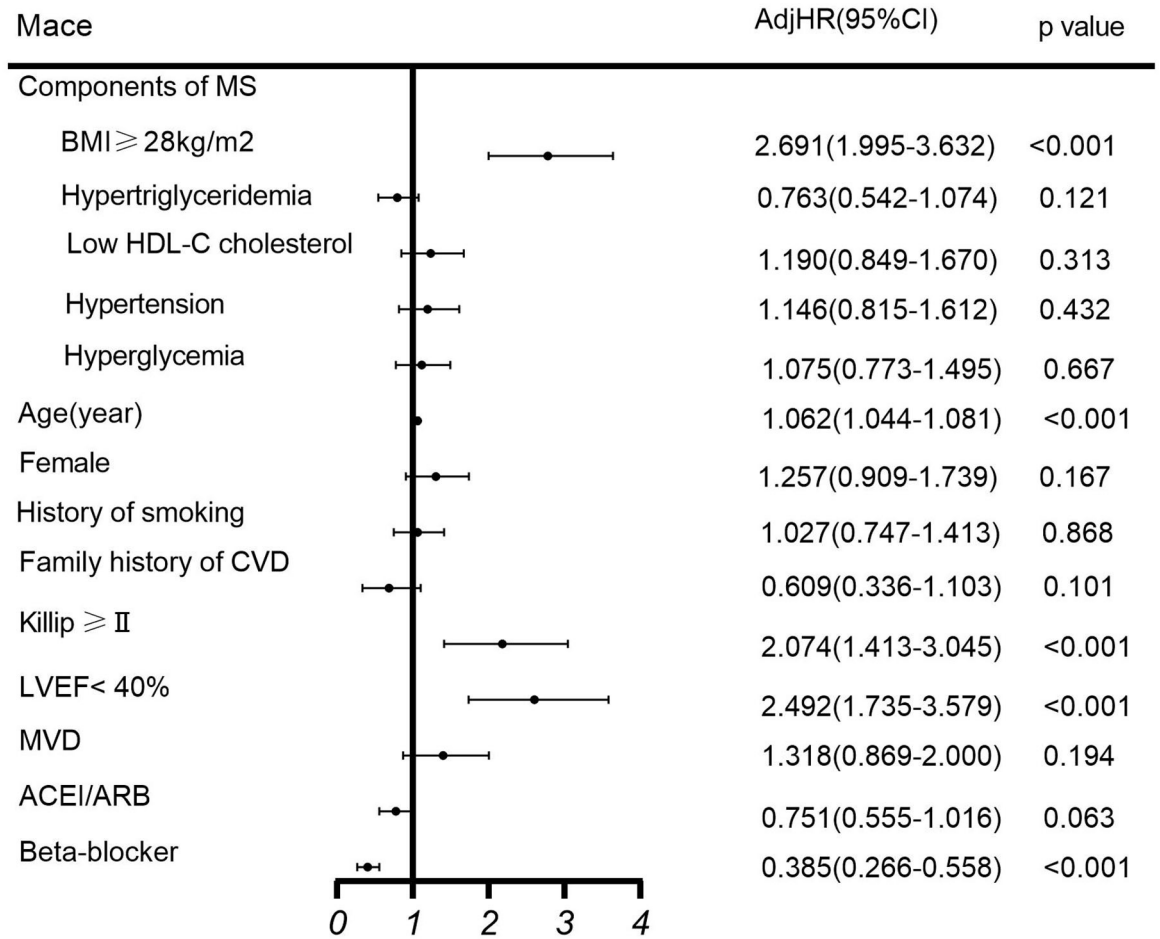

FIGURE 2 | Multivariate COX regression analysis of MACE. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MS, metabolic syndrome; MVD, multivessel disease.

to those without MS, as expected. There was no significant difference between the two groups in age, family history of CVD, history of smoking, previous PCI, previous CABG, and the use of medications. There was no difference in GRACE score between the two groups. No significant differences were observed between the groups concerning the proportion of SVD and MVD and the application of intra-aortic balloon pump or ventilator (**Table 1**).

Clinical Prognosis

Procedural success was achieved in all patients. Throughout the follow-up period, patients with MS had significantly higher rates of MACE than those without MS. Of the 1,295 people, 197 (15.2%) were involved in the MACE. There were 52 (4%) patients with all-cause death, 56 (4.3%) patients with UA hospitalization, 76 (5.9%) patients with HF hospitalization, 26 (2%) patients with non-fatal recurrent myocardial infarction (MI), and 5 (.4%) patients with TLR. During 1-year follow-up, it was found that there was a significant difference in MACE between the two groups (18.3 vs. 12%, $p = 0.001$), mainly due to the incidence of all-cause death, HF hospitalization, and non-fatal recurrent MI, which were significantly higher in the MS group than that of the non-MS group (5.3 vs. 2.7%, $p = 0.016$; 7.3 vs. 4.4%, $p = 0.028$; 3.2–0.8%, $p = 0.002$, **Table 2**). There was a significant difference in the Kaplan-Meier curve between the two groups ($p = 0.001$) (**Figure 1**).

Association MS and Its Components With MACE

The COX regression analysis showed that MS was an independent risk factor for MACE [HR 1.714, 95% confidence interval (CI) 1.265–2.322, $p = 0.001$], mainly due to the increased risk of all-cause death, HF hospitalization, and non-fatal recurrent MI (HR 2.184, 95% CI 1.137–4.197, $p = 0.019$; HR 1.662, 95% CI 1.031–2.680, $p = 0.037$; HR 3.621, 95% CI 1.324–9.904, $p = 0.012$) (**Table 3**).

Among the MS components, multivariate COX regression analysis showed that BMI of $\geq$28 mg/m^2 was

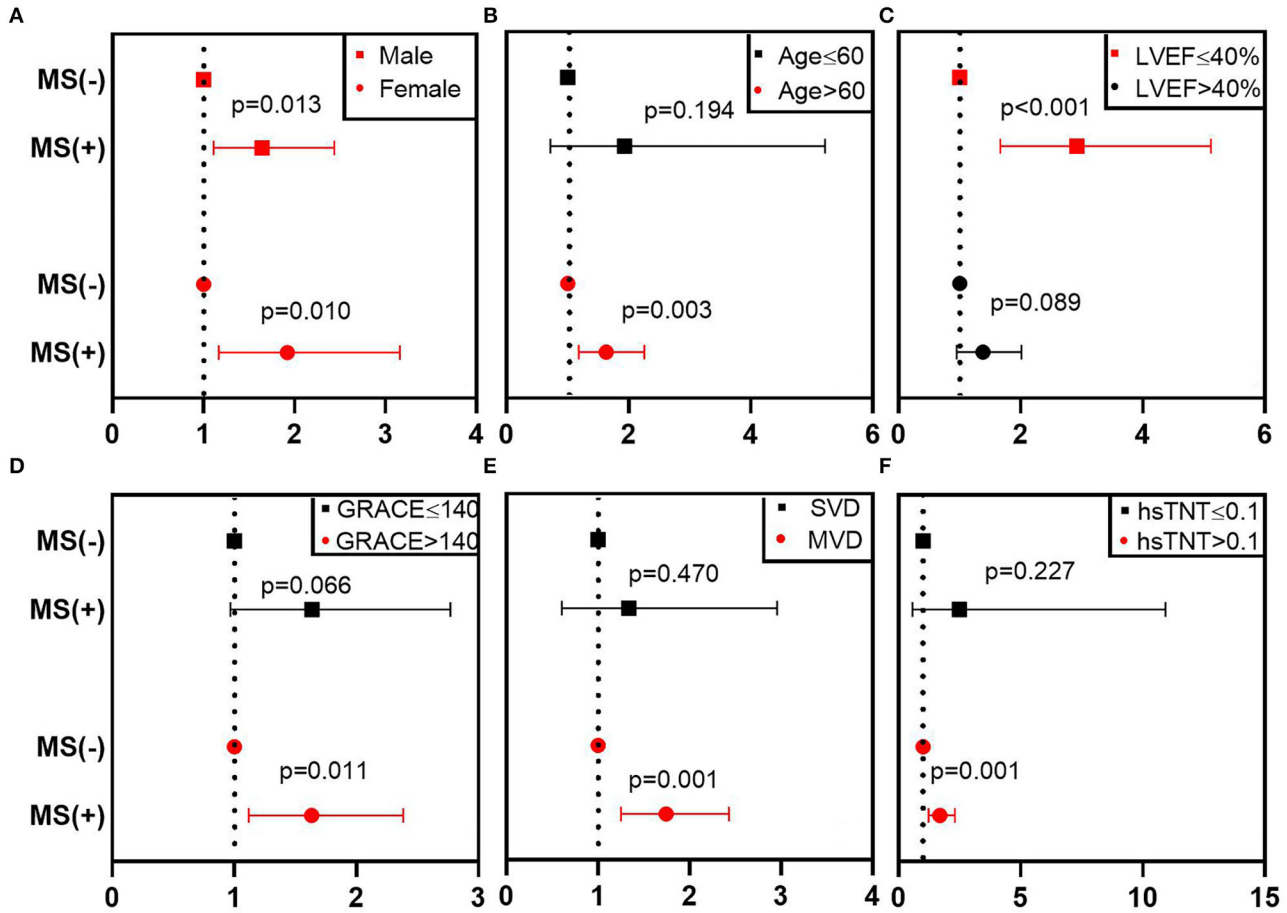

FIGURE 3 | Subgroup analysis of MS on MACE in different patients. This figure shows the adjusted HR (95% CI) of the subgroup analysis from the multivariable Cox model. **(A–F)** Represent the subgroups according to different gender, age, LVEF, GRACE, number of stenosis vessels, hsTNT. The red line denotes a statistically significant subgroup. CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; hsTnT, hypersensitive troponin T; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MS, metabolic syndrome; MVD, multivessel disease; SVD, single-vessel disease.

an independent risk factor for MACE (HR 2.691, 95% CI 1.995–3.632, $p < 0.001$) in patients with NSTEMI undergoing PCI, while other components of MS are not (**Figure 2**).

Association of MS With MACE in Subgroups

Furthermore, subgroup analysis of MS on MACE was performed using a Cox model. We found that MS was a robust factor across different genders, and the prognostic value was more evident for patients who have the following: age of >60 (HR 1.633, 95% CI 1.182–2.256, $p = 0.003$), LVEF of ≤40% (HR 2.922, 95% CI 1.668–5.119, $p < 0.001$), GRACE of >140 (HR1.633, 95% CI 1.118–2.385, $p = 0.011$), MVD (HR 1.744, 95% CI 1.251–2.432, $p = 0.001$), or hsTNT of >0.1 ng/ml (HR 1.689, 95% CI 1.237–2.307, $p = 0.001$) (**Figure 3**; **Table 4**).

DISCUSSION

To the best of our knowledge, this is the first report to show the prognostic impact of MS in patients with NSTEMI undergoing PCI. The main findings were: (1) The prevalence rate of MS in patients with NSTEMI was 50.97%. Compared with the non-MS group, the MS group had more females; (2) After a year of follow-up, MACE in the MS group was significantly higher than that in the non-MS group, and MS was an independent risk factor for MACE, mainly due to the increased risk of all-cause death, HF hospitalization, and non-fatal recurrent MI; (3) BMI of ≥28 kg/m^2 in the MS components independently predict the occurrence of MACE; and (4) Subgroup analysis suggested that MS was a robust factor across different genders. However, the prognostic value was more evident for patients with the following: older than 60 years; LVEF ≤40%, GRACE >140, and MVD or hsTNT >0.1 ng/ml.

It is not surprising to find that the prevalence of MS in patients with NSTEMI was higher than that from population-based surveys. A survey indicated that 33.9% (31% in males and 36.8% in females) had MS in mainland China in 2010 (12). In patients with established CVD, the prevalence of MS ranged from 29 to 66% in previous reports (13–17). A single-center, prospective, and observational study was conducted by Sinha et al. showed that patients with NSTEACS were more common than STEMI in MS group (18). Al-Rasadi et al. also found that MS was more likely associated with NSTEMI (16). The prevalence of MS as seen in our study was similar when compared with previous reports. In our study, there were more women in the MS group than in the non-MS group. This finding was consistent with previous research (19).

After 1 year follow-up, we found that MS was independently associated with MACE, and some previous studies had similar results (17, 20, 21). We found that this was due to the increased risk of all-cause death, HF hospitalization, and non-fatal recurrent MI, which has been similarly reported in previous studies (22–25).

In our study of MS components, obesity was the only independent risk factor for MACE, while other components including hyperglycemia were not. Patients with obesity are in a state of chronic inflammation and pre-thrombotic state, which plays an important role in the process of atherosclerosis and will lead to adverse cardiovascular events (26). It has been confirmed by previous research that abdominal obesity is independently associated with CVD (27, 28). Visceral fat was almost a good predictor of MS (29). It is now generally accepted that the increase in obesity is the most important in the five components of the MS, because it provides the core of the other four components (30). The obesity paradox (31) had not been observed in our study. Previous research has suggested that this obesity paradox may exist due to BMI being not a good indicator of obesity in general obesity because it does not distinguish between fat and lean mass, and may rely more on measurements of fat distribution than the amount of body fat (28). Incidence and outcomes of CVD vary by nations and country of origin (32). The prevalence of CVD is particularly high among South Asians [people originate from the Indian subcontinent (SA)], including SA immigrants living outside the Asian subcontinent, also known as the SA diaspora (33). SA had a larger percentage of body fat and larger visceral adipose tissue at a given BMI compared with other ethnic groups. Asians, including Chinese, have more visceral fat and less skeletal muscle mass than westerners (30). Therefore, the association between BMI and CVD risk may be underestimated in Asians (34). Therefore, the obesity paradox is not evident in the Chinese population. A similar study extends the observation made by Chen et al., which demonstrated (35) that obesity (BMI $\geq$28 kg/m^2) increased the risk of all-cause mortality in Chinese patients with CVD. Our study found that hyperglycemia in MS component was not an independent risk factor for MACE. This finding was in accordance with Grundy SM's conclusion that the independent contribution of hyperglycemic status to the risk of CVD is rather weak and mainly caused by excess visceral fat in patients with obesity (36). Xu et al. (37) dissociated and analyzed the contribution of diabetes to the incidence of post-stent MACE by excluding those studies with diabetes patients from the MS group, and concluded that there was no significant difference in the incidence of MACE in the MS group with or without diabetes patients, which is consistent with our findings. The discrepancies between existing studies and our study may be mainly due to the dissimilarities of patient populations. Patients should be classified as at high risk even if there are no obvious blood glucose abnormalities. Therefore, MS phenotypes are important in CV risk assessment and in educating patients and physicians about preventive measures.

We found that HDL-C was associated with a neutral risk of 1-year MACE in patients with NSTEMI, as confirmed by a previous study (38). This may be due to HDL function being impaired with CVD (39). Under certain conditions, HDL would lose its protective functions (antioxidant, anti-inflammation, anti-apoptotic, and ameliorate endothelial dysfunction) and gain dysfunction, which might contribute to the inflammatory process of CVD in patients with atherosclerosis. With respect to hypertriglyceridemia, a previous study also showed that hypertriglyceridemia did not have any association to high-risk all-cause mortality in men and for CVD mortality in women (40). Hypertriglyceridemia and mortality in older adults could be due to selective survival, since individuals with higher cardiovascular risk associated with elevated triglycerides could have died earlier, while more resilient adults reached older age (41). The neutral effect of hypertension on patients with NSTEMI undergoing PCI has been previously demonstrated. Cecchi et al. conducted a study (42) on the impact of hypertension on MI patients undergoing PCI, and came to the conclusion that hypertension was not associated with either in-hospital and long-term mortality in patients with NSTEMI, which was consistent with our results. The reason for the scarce impact of hypertension on NSTEMI outcome can be ascribed to our study population, which is only the patients undergoing PCI, playing a critical role

TABLE 4 | Multivariate COX regression analysis of each subgroup.

Variables		HR (95% CI)	*P*
Gender	Male	1.644 (1.110–2.437)	0.013
	Female	1.921 (1.168–3.157)	0.010
Age	≤60	1.931 (0.715–5.218)	0.194
	>60	1.633 (1.182–2.256)	0.003
LVEF	<40%	2.922 (1.668–5.119)	<0.001
	≥40%	1.384 (0.952–2.013)	0.089
GRACE	≤140	1.637 (0.968–2.770)	0.066
	>140	1.633 (1.118–2.385)	0.011
Number of stenosis vessels	SVD	1.339 (0.606–2.957)	0.470
	MVD	1.744 (1.251–2.432)	0.001
hsTNT	≤0.1	2.488 (0.567–10.925)	0.227
	>0.1	1.689 (1.237–2.307)	0.001

CI, confidence interval; GRACE, Global Registry of Acute Coronary Events; HR, hazard ratio; hsTnT, hypersensitive troponin T; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MS, metabolic syndrome; SVD, single-vessel disease; MVD, multivessel disease.

in restoring coronary artery perfusion, alleviating myocardial ischemia, and, ultimately, improving their long-term survival.

Although the subgroup analyses conducted in this study were exploratory, the results raised some important points, as limited data are available on the prognostic value of MS in different subgroups of patients with NSTEMI. Our study showed that MS was correlated with higher MACE, especially in older patients and those with LVEF of ≤40%, GRACE of >140, and MVD or hsTNT of >0.1 ng/ml. Previous studies have proven that age is a powerful predictor of adverse events after ACS (43). GRACE risk score is recommended by international guidelines to assess the risk of future ischemic events in patients with NSTEACS to facilitate evidence-based treatment in the future (44, 45). Kim et al. assumed that MVD involvement might negatively influence cardiovascular outcomes in patients with MS (46). Al Suwaidi et al. (47) found recurrent ischemia was more common in MS group, which leads to lower LVEF in patients with MS, and statistically significant difference in mortality compared with those without MS. All these conditions indicate myocardial ischemia. In practice, advanced vascular damage is often associated with the presence of MS in patients with CVD, and it is significantly associated with lipid-rich plaques in coronary arteries, which increases the risk of rupture and leads to poor outcomes (48, 49). In other words, we concluded that the impact of MS on prognosis value was evident when the amount of myocardial necrosis is greater and cardiac function is worse.

Azarfarin et al. (50) found that increased WC was associated with greater myocardial necrosis and worsening LVEF in patients with AMI. This suggested that obesity was associated with adverse cardiovascular outcomes, which also supported our finding.

LIMITATIONS

There are several limitations in the present study. First, abdominal obesity has a better predictive value for the risk of CVD than BMI. In this paper, BMI was used to replace abdominal circumference in the diagnosis of MS, which may have a certain impact on the results. Second, the patients were followed up for only 1 years, which may have some effect on the final clinical outcome analysis. Third, considering that the patients in our study were all from China, which might limit the generalization of the fingings to other races. Last, dynamic changes in MS status may confuse the association between MS individual components and MACE.

CONCLUSION

As far as we know, no previous studies have investigated the prognostic value of MS in patients with NSTEMI undergoing PCI. Our study demonstrated that MS had a negative impact on MACE in those patients. In MS component analysis, a BMI of ≥28 kg/m^2 independently increased the occurrence of MACE. Therefore, we suggest that patients with NSTEMI should be aware of the presence of MS, especially in older patients who have higher ischemic risk. Active prevention and treatment of MS may improve its clinical efficacy by controlling abdominal obesity.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study was approved by the Ethics Committee (No. 2018KY-010-01). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

L-HZ, YL, and JG: conceptualization and design. J-YX, J-XW, and X-WL: resources. L-HZ, YL, and ZC: formal analysis and data curation. L-HZ: writing—original draft preparation. JG: project administration and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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REFERENCES

1. Zhou J, Liu C, Zhou P, Li J, Chen R, Wang Y, et al. Prevalence and impact of metabolic syndrome in patients with multivessel coronary artery disease and acute coronary syndrome. *Nutr Metab Cardiovasc Dis.* (2021) 31:2693–9. doi: 10.1016/j.numecd.2021.05.029
2. Lee SH, Jeong MH, Kim JH, Kim MC, Sim DS, Hong YJ, et al. Influence of obesity and metabolic syndrome on clinical outcomes of ST-segment elevation myocardial infarction in men undergoing primary percutaneous coronary intervention. *J Cardiol.* (2018) 72:328–34. doi: 10.1016/j.jjcc.2018.03.010
3. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American college of cardiology/American heart association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes,

and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. (2016) 134:e123–55. doi: 10.1161/CIR.0000000000000404

4. Zhang Q, Zhao D, Xie W, Xie X, Guo M, Wang M, et al. Recent trends in hospitalization for acute myocardial infarction in beijing: increasing overall burden and a transition from ST-segment elevation to non-ST-segment elevation myocardial infarction in a population-based study. *Medicine*. (2016) 95:e2677. doi: 10.1097/MD.0000000000002677
5. Yong JW, Wang ZJ, Lin XZ, Gao F, Yang LX, Shi DM, et al. [Trends of in-hospital mortality and constituent ratio of patients with acute myocardial infarction]. *Zhonghua Xin Xue Guan Bing Za Zhi*. (2019) 47:209–14. doi: 10.3760/cma.j.issn.0253-3758.2019.03.006
6. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood institute scientific statement. *Circulation*. (2005) 112:2735–52. doi: 10.1161/CIRCULATIONAHA.105.169404
7. Samanta R, Narayan A, Kovoor P, Thiagalingam A. Influence of BMI on short and long-term outcomes in patients with STEMI and LV dysfunction. *Heart Lung Circ*. (2020) 29:361–7. doi: 10.1016/j.hlc.2019.01.017
8. Hanley AJ, Karter AJ, Williams K, Festa A, D'Agostino RB, Jr., et al. Prediction of type 2 diabetes mellitus with alternative definitions of the metabolic syndrome: the insulin resistance atherosclerosis study. *Circulation*. (2005) 112:3713–21. doi: 10.1161/CIRCULATIONAHA.105.559633
9. Zhou BF. Effect of body mass index on all-cause mortality and incidence of cardiovascular diseases–report for meta-analysis of prospective studies open optimal cut-off points of body mass index in Chinese adults. *Biomed Environ Sci*. (2002) 15:245–52.
10. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College Of Cardiology/American heart association task force on practice guidelines (ACC/AHA/ASE committee to update the 1997 guidelines for the clinical application of echocardiography). *Circulation*. (2003) 108:1146–62. doi: 10.1161/01.CIR.0000073597.57414.A9
11. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. (2019) 40:87–165. doi: 10.1093/eurheartj/ehy394
12. Lu J, Wang L, Li M, Xu Y, Jiang Y, Wang W, et al. Metabolic syndrome among adults in China: the 2010 China noncommunicable disease surveillance. *J Clin Endocrinol Metab*. (2017) 102:507–15. doi: 10.1210/jc.2016-2477
13. Deo SV, Sundaram V, Wilson B, Sahadevan J, Madan Mohan SK, Rubelowsky J, et al. Adverse events after coronary artery bypass grafting in patients with preoperative metabolic syndrome: a 10-year follow-up of the veterans affairs database. *J Thorac Cardiovasc Surg*. (2022). 163:2096–103 e3. doi: 10.1016/j.jtcvs.2020.08.018
14. Levantesi G, Macchia A, Marfisi R, Franzosi MG, Maggioni AP, Nicolosi GL, et al. Metabolic syndrome and risk of cardiovascular events after myocardial infarction. *J Am Coll Cardiol*. (2005) 46:277–83. doi: 10.1016/j.jacc.2005.03.062
15. Lekoubou A, Ovbiagele B, Markovic D, Sanossian N, Towfighi A. Age, sex, and race/ethnic temporal trends in metabolic syndrome prevalence among individuals with myocardial infarction or stroke in the United States. *J Neurol Sci*. (2017) 376:24–8. doi: 10.1016/j.jns.2017.01.073
16. Al-Rasadi K, Sulaiman K, Panduranga P, Al-Zakwani I. Prevalence, characteristics, and in-hospital outcomes of metabolic syndrome among acute coronary syndrome patients from Oman. *Angiology*. (2011) 62:381–9. doi: 10.1177/0003319710382419
17. Cavallari I, Cannon CP, Braunwald E, Goodrich EL, Im K, Lukas MA, et al. Metabolic syndrome and the risk of adverse cardiovascular events after an acute coronary syndrome. *Eur J Prev Cardiol*. (2018) 25:830–8. doi: 10.1177/2047487318763897
18. Sinha SK, Goel A, Madaan A, Thakur R, Krishna V, Singh K, et al. Prevalence of metabolic syndrome and its clinical and angiographic profile in patients with naive acute coronary syndrome in north indian population. *J Clin Med Res*. (2016) 8:667–73. doi: 10.14740/jocmr2655w
19. Ji MS, Jeong MH, Ahn YK, Kim SH, Kim YJ, Chae SC, et al. Comparison of resolute zotarolimus-eluting stents versus everolimus-eluting stents in patients with metabolic syndrome and acute myocardial infarction: propensity score-matched analysis. *Int J Cardiol*. (2015) 199:53–62. doi: 10.1016/j.ijcard.2015.07.010
20. Lovic MB, Djordjevic DB, Tasic IS, Nedeljkovic IP. Impact of metabolic syndrome on clinical severity and long-term prognosis in patients with myocardial infarction with ST-segment elevation. *Hellenic J Cardiol*. (2018) 59:226–31. doi: 10.1016/j.hjc.2018.02.002
21. Bin H, Yujie Z, Yuyang L, Dongmei S, Yingxin Z, Dean J, et al. Impact of metabolic syndrome on clinical outcomes after drug-eluting stent implantation in patients with coronary artery disease. *Angiology*. (2011) 62:440–6. doi: 10.1177/0003319711398473
22. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. (2010) 56:1113–32. doi: 10.1016/j.jacc.2010.05.034
23. Kul S, Uyarel H, Gul M, Kucukdagli OT, Bacaksiz A, Erdogan E, et al. Metabolic syndrome and long-term cardiovascular outcomes in NSTEMI with unstable angina. *Nutr Metab Cardiovasc Dis*. (2014) 24:176–82. doi: 10.1016/j.numecd.2013.07.003
24. Perrone-Filardi P, Paolillo S, Costanzo P, Savarese G, Trimarco B, Bonow RO. The role of metabolic syndrome in heart failure. *Eur Heart J*. (2015) 36:2630–4. doi: 10.1093/eurheartj/ehv350
25. Zeller M, Steg PG, Ravisy J, Laurent Y, Janin-Manificat L, L'Huillier I, et al. Prevalence and impact of metabolic syndrome on hospital outcomes in acute myocardial infarction. *Arch Intern Med*. (2005). 165:1192–8. doi: 10.1001/archinte.165.10.1192
26. Goyal SN, Bharti S, Krishnamurthy B, Agrawal Y, Ojha SK, Arya DS. Impact of metabolic syndrome on re-stenosis development: role of drug-eluting stents. *Diab Vasc Dis Res*. (2012) 9:177–88. doi: 10.1177/1479164111430336
27. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev*. (2007) 8:41–59. doi: 10.1111/j.1467-789X.2006.00248.x
28. Coutinho T, Goel K, Correa de Sa D, Kragelund C, Kanaya AM, Zeller M, et al. Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. *J Am Coll Cardiol*. (2011) 57:1877–86. doi: 10.1016/j.jacc.2010.11.058
29. Kishida K, Funahashi T, Matsuzawa Y, Shimomura I. Visceral adiposity as a target for the management of the metabolic syndrome. *Ann Med*. (2012) 44:233–41. doi: 10.3109/07853890.2011.564202
30. Guo SX, Zhang XH, Zhang JY, He J, Yan YZ, Ma JL, et al. Visceral adiposity and anthropometric indicators as screening tools of metabolic syndrome among low income rural adults in Xinjiang. *Sci Rep*. (2016) 6:36091. doi: 10.1038/srep36091
31. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet*. (2006) 368:666–78. doi: 10.1016/S0140-6736(06)69251-9
32. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med*. (2014) 371:818–27. doi: 10.1056/NEJMoa1311890
33. Rafnsson SB, Bhopal RS, Agyemang C, Fagot-Campagna A, Harding S, Hammar N, et al. Sizable variations in circulatory disease mortality by region and country of birth in six European countries. *Eur J Public Health*. (2013) 23:594–605. doi: 10.1093/eurpub/ckt023
34. Tillin T, Hughes AD, Whincup P, Mayet J, Sattar N, McKeigue PM, et al. Ethnicity and prediction of cardiovascular disease: performance of QRISK2 and framingham scores in a U.K. tri-ethnic prospective cohort study (SABRE–Southall And Brent REvisited). *Heart*. (2014) 100:60–7. doi: 10.1136/heartjnl-2013-304474
35. Chen Q, Zhang Y, Ding D, Li D, Xia M, Li X, et al. Metabolic syndrome and its individual components with mortality among patients with coronary heart disease. *Int J Cardiol*. (2016) 224:8–14. doi: 10.1016/j.ijcard.2016.08.324
36. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? *Am J Clin Nutr*. (2006) 83:1248–51. doi: 10.1093/ajcn/83.6.1248
37. Xu D, Guo Y, Wang H, Gu B, Liu G, Zhou C, et al. The angiographic and clinical outcomes after coronary stenting

in patients with metabolic syndrome. *Atherosclerosis.* (2012) 221:416–21. doi: 10.1016/j.atherosclerosis.2011.12.016
38. Gianfagna F, Veronesi G, Guasti L, Chambless LE, Brambilla P, Corrao G, et al. Do apolipoproteins improve coronary risk prediction in subjects with metabolic syndrome? Insights from the North Italian Brianza cohort study. *Atherosclerosis.* (2014) 236:175–81. doi: 10.1016/j.atherosclerosis.2014.06.029
39. Rosenson RS, Brewer HB, Jr., Ansell BJ, Barter P, Chapman MJ, et al. Dysfunctional HDL and atherosclerotic cardiovascular disease. *Nat Rev Cardiol.* (2016) 13:48–60. doi: 10.1038/nrcardio.2015.124
40. Sun DL, Wang JH, Jiang B, Li LS, Li LS, Wu L, et al. Metabolic syndrome vs. its components for prediction of cardiovascular mortality: a cohort study in Chinese elderly adults. *J Geriatr Cardiol.* (2012) 9:123–9. doi: 10.3724/SP.J.1263.2012.01172
41. Sergi G, Dianin M, Bertocco A, Zanforlini BM, Curreri C, Mazzochin M, et al. Gender differences in the impact of metabolic syndrome components on mortality in older people: a systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis.* (2020) 30:1452–64. doi: 10.1016/j.numecd.2020.04.034
42. Cecchi E, D'Alfonso MG, Chiostri M, Parigi E, Landi D, Valente S, et al. Impact of hypertension history on short and long-term prognosis in patients with acute myocardial infarction treated with percutaneous angioplasty: comparison between STEMI and NSTEMI. *High Blood Press Cardiovasc Prev.* (2014) 21:37–43. doi: 10.1007/s40292-013-0032-1
43. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American heart association council on clinical cardiology: in collaboration with the society of geriatric cardiology. *Circulation.* (2007) 115:2549–69. doi: 10.1161/CIRCULATIONAHA.107.182615
44. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *Circulation.* (2012) 126:875–910. doi: 10.1161/CIR.0b013e318256f1e0
45. Task Force on the management of STseamiotESoC, Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* (2012) 33:2569–619. doi: 10.1093/eurheartj/ehs215
46. Kim CS, Choi JS, Bae EH, Ma SK, Ahn YK, Jeong MH, et al. Association of metabolic syndrome and renal insufficiency with clinical outcome in acute myocardial infarction. *Metabolism.* (2013) 62:669–76. doi: 10.1016/j.metabol.2012.11.002
47. Al Suwaidi J, Zubaid M, El-Menyar AA, Singh R, Rashed W, Ridha M, et al. Prevalence of the metabolic syndrome in patients with acute coronary syndrome in six middle eastern countries. *J Clin Hypertens.* (2010) 12:890–9. doi: 10.1111/j.1751-7176.2010.00371.x
48. Marso SP, Mercado N, Maehara A, Weisz G, Mintz GS, McPherson J, et al. Plaque composition and clinical outcomes in acute coronary syndrome patients with metabolic syndrome or diabetes. *JACC Cardiovasc Imag.* (2012) 5:S42–52. doi: 10.1016/j.jcmg.2012.01.008
49. Arai K, Ishii H, Amano T, Uetani T, Nanki M, Marui N, et al. Volumetric analysis of coronary plaque characterization in patients with metabolic syndrome using 64-slice multi-detector computed tomography. *Circ J.* (2010) 74:2146–51. doi: 10.1253/circj.cj-10-0219
50. Azarfarin R, Samadikhah J, Shahvalizadeh R, Golzari SE. Evaluation of anthropometric indices of patients with left ventricle dysfunction fallowing first acute anterior myocardial infarction. *J Cardiovasc Thorac Res.* (2012). 4:11–5. doi: 10.5681/jcvtr.2012.003

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Effect of Maternal Antidepressant Use During the Pre-pregnancy/Early Pregnancy Period on Congenital Heart Disease: A Prospective Cohort Study in Central China

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Background: With the increase in maternal antidepressant prescribing before/during pregnancy, concerns about the safety of antidepressants have come into focus. The purpose of this study was to explore the association between maternal antidepressant use before pregnancy/in early pregnancy and the risk of congenital heart disease (CHD) in children, and to provide a scientific basis for clinical safety of antidepressant use.

Methods: The prospective cohort study ultimately included 34,104 singleton pregnancies. Modified Poisson regression model with robust error variances was used to evaluate RRs and 95% confidence intervals (CIs) for the risk of CHD in offspring exposed to maternal antidepressant in the 3 months before pregnancy and early pregnancy. In addition, sensitivity analysis was further performed to explore the robustness of the results.

Results: In this study, the maternal antidepressant exposure rate was 2.83% in the 3 months before pregnancy, 2.42% in early pregnancy, and the incidence of CHD was 8.973 per 1,000 live births. We found that maternal antidepressant use in the 3 months before pregnancy and early pregnancy were all associated with an increased risk of CHD, ∼2.54 times and 2.87 times, respectively, of non-use of antidepressants after adjusting for potential confounders. This association was also found in CHD specific phenotypic analysis. Of these, offspring whose mothers were exposed to antidepressants in the 3 months before pregnancy had the highest risk of transposition of the great arteries (aOR = 5.50, 95% CI: 1.91–15.88). The offspring of mothers exposed to antidepressants in early pregnancy had the highest risk of developing ventricular septal defect (aOR = 4.80, 95% CI: 2.50–9.24). Sensitivity analysis verified the stability of the results.

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Conclusions: Maternal antidepressant use in the 3 months before pregnancy and early pregnancy were all associated with an increased risk of CHD in their offspring. In order to reduce the risk of teratogenesis, we recommend that pregnant women prepare for pregnancy after their condition improves or receive the minimum effective dose of medication.

Keywords: antidepressant, pregnancy, offspring, congenital heart disease, risk factor

INTRODUCTION

Compared with men, women are more vulnerable to depression due to their differences in physiological anatomy, endocrine metabolism, social role and inner quality (1). This is especially true when a woman's pregnancy is accompanied by potential physical stress, putting her at an increased risk of depression. A recent meta-analysis reported that the prevalence of perinatal depression in China has shown a significant upward trend in recent 10 years, reaching 16.3% (95% CI: 14.7–18.2%), among which 19.7% (95%CI: 15.8–24.2%) was prenatal depression (2). As the number of pregnant women suffering from depression has increased significantly, so has the prescription of antidepressants. However, a new challenge arises: can antidepressants affect a developing fetus? Studies have reported the teratogenicity of antidepressants in early pregnancy, which have raised serious concerns about the safety of antidepressants used by mothers in early pregnancy, especially the risk of congenital heart defects in offspring (3, 4).

At present, congenital heart disease (CHD) is the most common birth defect in the world. It was reported that the prevalence of CHD was as high as 9.410 per 1,000 live births from 2010 to 2017, and is rising globally (5). The prevalence of CHD in China is 8.89 per 1,000 live births, close to the global incidence of CHD (6). In the long-term exploration of the pathogenesis and development of CHD, CHD is considered to be a lifelong disease (7), and children with CHD may be at high risk of long-term health risks such as brain damage, neurodevelopmental disorders, growth and development disorders or disability (8, 9). It is suggested that neonatal CHD seriously threatens the healthy development of mothers and infants, and is an important public health problem to be solved urgently in China. The etiological mechanism of CHD is complex. The current consensus is that CHD is the result of genetic and environmental factors as well as the interaction between the two, which may alter the structure of the heart by affecting the placenta (10). With the passionate study efforts of researchers, up to 400 genes associated with the pathogenesis of CHD have been found (11). However, the study reported that routine whole genome sequencing of a large number of CHD patients and their families can only provide a genetic explanation for 30% of CHD cases (12). In addition, considering that genetic factors are difficult to prevent and change, it is very important to find and identify environmental risk factors related to offspring CHD for the primary prevention of CHD.

Researchers have raised questions about the teratogenicity of antidepressant use during pregnancy after an epidemiological study conducted in 2005 found that paroxetine use during pregnancy increased the risk of heart malformations (13). Subsequent studies continue to explore the truth of this claim (14–16). A study has found that the use of fluoxetine in early pregnancy increases the risk of abnormal pulmonary venous reflux in offspring [OR = 2.56; 95% confidence interval (CI): 1.10–5.93] (17). A large meta-analysis of more than 6 million people found that sertraline use in early pregnancy significantly increased the risk of CHD in offspring (OR = 1.36, 95% CI: 1.06–1.74) (18). A recent meta-analysis also showed an odds ratio of 1.28 (95% CI: 1.17–1.41) between use of any antidepressant in the first trimester of pregnancy and congenital heart defects in the offspring (19). However, this association may be due to confusion about maternal characteristics, such as lifestyle, diet, personal history of illness, and exposure to other risk factors, resulting in inaccurate risk estimates.

Prohibition of antidepressants during pregnancy is of course an ideal state, but it may lead to the aggravation of depression related diseases and even suicidal tendencies (20). Therefore, it is particularly important to elucidate the relationship between antidepressant use and CHD risk in pregnant women. We believe that different races may have different results due to great differences in various aspects. Considering the impact of pharmacokinetics, there is no evidence of the association between maternal antidepressant use before pregnancy and the risk of CHD in offspring. Here, we constructed a prospective cohort study to evaluate the association between antidepressant use (in 3 months before pregnancy and in early pregnancy, respectively) and total CHD and its specific phenotype in offspring for the first time in China.

MATERIALS AND METHODS

Ethics Statement

This study is a prospective cohort study on maternal and child health in Hunan province based on Hunan Maternal and Child Health Hospital. This study was approved by the Ethics Committee of Xiangya School of Public Health, Central South University and registered in The Chinese Clinical Trial Registry (Registration number: ChiCTR1800016635). All subjects were informed of the study protocol in detail and provided written informed consent before entering the cohort, and the ethical principles of the Declaration of Helsinki of the World Medical Association were strictly followed in this study.

Study Population and Information Collection

The cohort was conducted in Hunan Maternal and Child Health Hospital from March 13, 2013 to December 31, 2019. Hunan Maternal and Child Health Hospital is a class A, grade III hospital with a long history, located in Hunan Province, central China. All subjects were enrolled in the cohort at the time of their first prenatal care. For study purposes, we excluded pregnant women using assisted reproductive technology, pregnant women with multiple pregnancies, and offspring diagnosed with chromosomal abnormalities or syndromic CHD. Finally, a total of 34,104 pregnant women were included in the analysis.

In this study, we designed a structured questionnaire, including the sociodemographic characteristics of the subjects, obstetric and reproductive history, lifestyle, other health-related factors and health information of their offspring. In order to ensure the accuracy of the collected research data, our investigators underwent strict unified training in accordance with the standard way before the field investigation, and then completed the questionnaire survey through face-to-face interview with our participants. The relevant health information of the offspring was completed by telephone follow-up 3 months after delivery and reconfirmed in the medical record system of the hospital.

Exposures

To assess exposure, information on the prescribing of antidepressants by mothers in the 3 months before pregnancy and early pregnancy was collected. The prescribing information was obtained from the pregnant women's prescriptions and secondary confirmations from the hospital's medical system. The information was collected by the investigator when conducting face-to-face interviews. First, the investigator asked the pregnant women whether they had received antidepressant drugs. If so, the pregnant women were required to provide a doctor's prescription or confirm by querying the hospital's electronic medical records system. If the medicine was not prescribed in this hospital, let pregnant women query the medical records by logging in to the hospital's app or Wechat applet. Women who used only prescribed 1 consistent antidepressant in the 3 months before pregnancy and early pregnancy were considered to be the exposure group. Antidepressant use was defined as at least one prescription for an oral antidepressant drug during the exposure period, which ranged from the 3 months before pregnancy to the beginning of pregnancy, or the day of pregnancy initiation up to the end of the first 3 months of gestation. This avoided the confusion of subsequent results caused by the simultaneous use of multiple antidepressants and the replacement of antidepressants.

Diagnosis of CHD

In this study, CHD was defined as malformation of heart cavities, heart valves, great arteries, veins, and septal defects (ICD10: Q20.0–Q28.0). Infants with CHD were diagnosed by neonatal echocardiography. Seven CHD phenotypes were evaluated, including atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular septal defect (AVSD), patent ductus arteriosus (PDA), Tetralogy of Fallot (TOF), pulmonary stenosis (PS), and transposition of the great arteries (TGA) (21). The ICD diagnostic codes corresponding to each CHD phenotype were shown in **Table 1**.

TABLE 1 | Prevalence of CHD in offspring.

Type of CHD	ICD-10 diagnosis codes	Number of cases	Prevalence (95% CI)
Total CHD	–	306	8.97‰ (7.97–9.97‰)
ASD	Q21.0	86	2.52‰ (1.99–3.05‰)
VSD	Q21.1	105	3.08‰ (2.49–3.67‰)
AVSD	Q21.2	6	0.18‰ (0.04–0.32‰)
PDA	Q25.0	50	1.47‰ (1.06–1.87‰)
TOF	Q21.3	24	0.70‰ (0.42–0.99‰)
PS	Q25.6	36	1.06‰ (0.71–1.40‰)
TGA	Q20.3	28	0.82‰ (0.52–1.13‰)

ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart disease; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TGA, transposition of the great arteries; TOF, tetralogy of fallot; VSD, ventricular septal defect.

Covariates

In this study, the information about covariates involved maternal sociodemographic characteristics, obstetric and reproductive history, lifestyle before and during pregnancy, and other health-related factors. Among them, sociodemographic characteristics include maternal age, education level, main residence, and nationality. The maternal age was divided into <35 years old and ≥ 35 years old (advanced maternal age). The education level was divided into four categories, including junior high and below, high school or technical secondary school, junior college and Bachelor degree or above. The main areas of residence were urban and rural areas. Ethnic groups were divided into Han and minorities (55 ethnic minorities except Han). Obstetric and reproductive history included consanguineous marriage (i.e., yes or no), family history of congenital malformation (i.e., yes or no), history of gestational diabetes mellitus (GDM) (i.e., yes or no) and history of gestational hypertension (GH) (i.e., yes or no). Lifestyle includes pre-pregnancy/early pregnancy smoking (i.e., yes or no) and pre-pregnancy/early pregnancy alcohol consumption (i.e., yes or no). Alcohol consumption was defined as consuming at least one standard alcoholic beverage during exposure, and smoking was defined as smoking at least one cigarette during exposure. Health related factors included maternal pre-pregnancy body mass index (BMI), folic acid use in 3 months before pregnancy or in early pregnancy (i.e., yes or no), house decoration in 3 months before pregnancy or in early pregnancy (i.e., yes or no), and exposure to radioactive substances at work in 3 months before pregnancy or in early

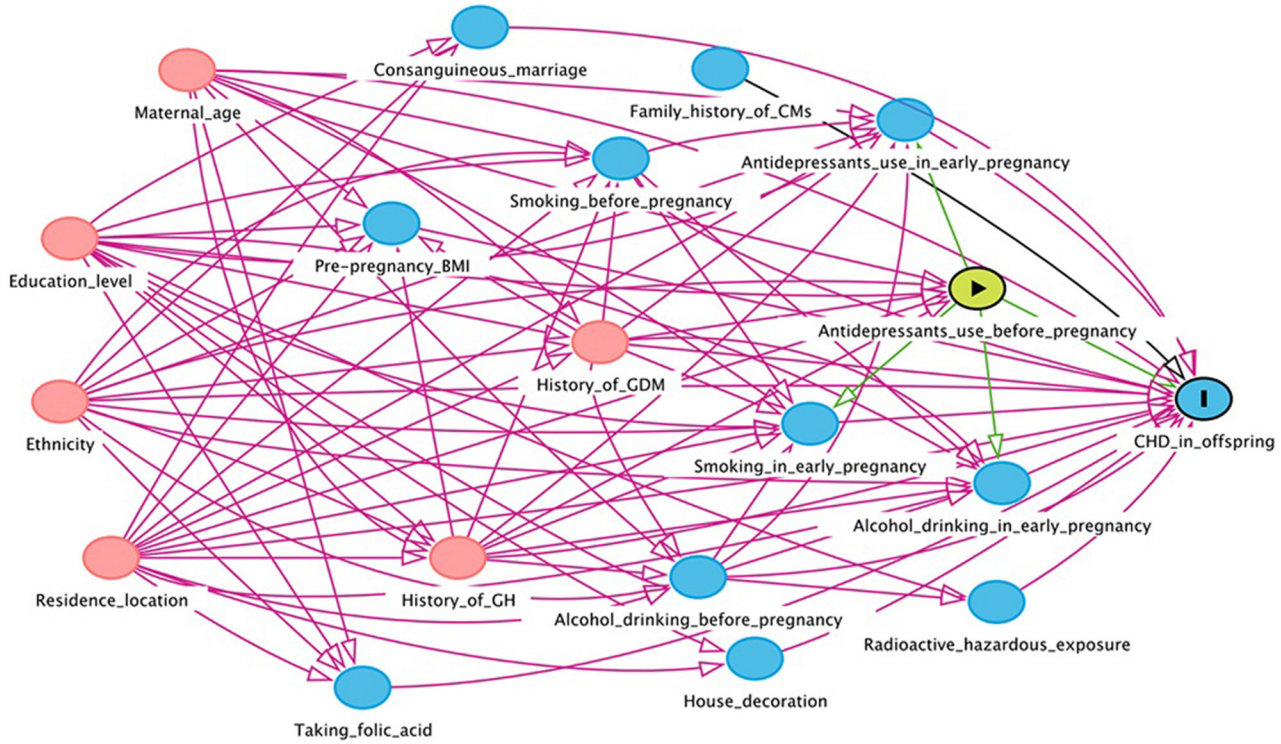

FIGURE 1 | Directed acyclic graph for the association between maternal antidepressant use in 3 months before pregnancy and risk of CHD in offspring. Red arrows indicate biasing paths, green arrows indicate causal paths. Minimal sufficient adjustment sets for estimating the effect of maternal antidepressant use in 3 months before pregnancy on offspring CHD: maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus and history of gestational hypertension. BMI, body mass index; CHD, congenital heart disease; CM, congenital malformation; GDM, gestational diabetes mellitus; GH, gestational hypertension.

pregnancy (i.e., yes or no). Pre-pregnancy BMI was divided into four categories according to the appropriate BMI for Asians recommended by the World Health Organization, including $<$ 18.5 kg/m^2 (underweight), 18.5–$<$23.0 kg/m^2 (normal weight), 23.0–$<$27.5 kg/m^2 (overweight) and $\geq$27.5 kg/m^2 (obesity).

Statistical Analysis

In this study, EpiData version 3.1 was used to input the collected maternal and infant health data. In order to ensure the preciseness of the data, the double entry mode was adopted. The Directed Acyclic Graph (DAG) was used to construct a causal network based on the offspring CHD theory to identify variables that might confound the association between maternal antidepressant use and offspring CHD risk (**Figures 1**, **2**). DAG was built through DAGitty online software (22).

We assessed sociodemographic distribution and maternal characteristics based on antidepressant use and CHD, respectively. Comparisons between categorical variables were tested using χ^2 tests and Fisher's exact probability. Poisson regression model is a common model for influencing factors of rare disease occurrence frequency, which is mainly used to analyze prospective data such as cohort follow-up. When poisson regression is applied to binomial data, the error of estimation relative risk is overestimated. Zou proposed to rectify this by using a robust error variance procedure known as sandwich estimation, that is, Modified Poisson regression model (23). In this study, Modified Poisson regression model with robust error variances was used to evaluate RRs and 95% confidence intervals (CIs) for the risk of CHD in offspring exposed to maternal antidepressant in the 3 months before pregnancy and early pregnancy. In addition to the risk of total CHD in offspring, we further analyzed the phenotypes of CHD (i.e., ASD, VSD, AVSD, PDA, TOF, PS and TGA). Since the number of AVSD, TOF and PS events in the exposed group was zero, they were not taken into account. Finally, we analyzed the association between maternal antidepressant use in the 3 months before pregnancy/early pregnancy and total CHD and its four phenotypes (i.e., ASD, VSD, PDA and TGA) in the offspring. Among them, the crude RRs and their corresponding 95% CI were obtained without any adjustment in Model 1; minimum sufficient adjustment set obtained in DAG analysis was adjusted in Model 2; smoking and alcohol drinking in the 3 months before pregnancy (or smoking and alcohol drinking in early pregnancy and antidepressants use before pregnancy) were further adjusted in Model 3 on the basis of adjusting the minimum sufficient adjustment set.

We further performed two sensitivity analyses to explore the robustness of the results. The association between maternal antidepressant use and offspring CHD was reanalyzed by excluding women whose offspring had any congenital malformations other than CHD or women whose offspring

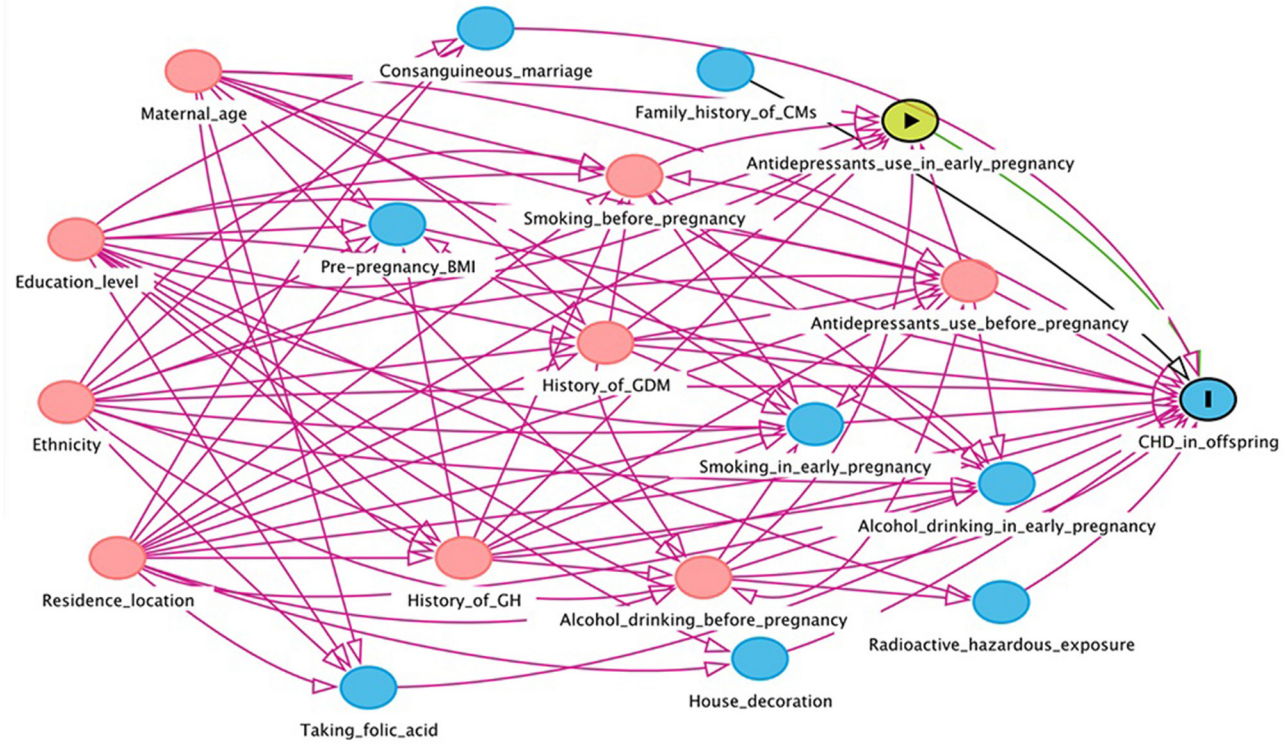

FIGURE 2 | Directed acyclic graph for the association between maternal antidepressant use in early pregnancy and risk of CHD in offspring. Red arrows indicate biasing paths, green arrows indicate causal paths. Minimal sufficient adjustment sets for estimating the effect of maternal antidepressant use in early pregnancy on offspring CHD: maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus, history of gestational hypertension, smoking before pregnancy, alcohol drinking before pregnancy and antidepressants use before pregnancy. BMI, body mass index; CHD, congenital heart disease; CM, congenital malformation; GDM, gestational diabetes mellitus; GH, gestational hypertension.

had more than one CHD phenotype. Two-sided $P < 0.05$ was considered statistically significant. All analyses were completed in SPSS 26.0 software, and forest map was completed by R 4.1.2 software.

RESULTS

Characteristics of the Study Objects

A total of 34,104 pregnant women were included in the final analysis of this study. Among them, we identified 964 (2.83%) mothers took antidepressant prescription in the 3 months before pregnancy and 824 (2.42%) mothers took antidepressant prescriptions in early pregnancy. After follow-up and secondary confirmation of medical records, 306 fetuses were diagnosed with non-syndromic CHD (the incidence of CHD was 8.973 per 1,000 live births), including 86 with ASD, 105 with VSD, 6 with AVSD, 50 with PDA, 24 with TOF, 36 with PS and 28 with TGA. It is worth noting that some cases have been diagnosed with multi-phenotypic CHD. Therefore, the sum of phenotypes was not equal to 306. The incidence of each type of CHD was shown in **Table 1**. The distribution of baseline characteristics according to the status of maternal antidepressant use in 3 months before pregnancy as well as in early pregnancy is summarized in **Table 2**.

Maternal Antidepressant Use in 3 Months Before Pregnancy and Risk of CHDs in Offspring

We constructed DAGs to identify potential causal frameworks and covariables for maternal antidepressant use in 3 months before pregnancy/antidepressant use in early pregnancy-CHDs associations. In the maternal antidepressant use in 3 months before pregnancy-CHDs associations, we considered 14 covariates and retained 6 based on our DAG (covariates selected by DAG are presented in the footnotes of **Figure 1**). In the maternal antidepressant use in early pregnancy-CHDs associations, we further considered the three covariates of alcohol drinking in early pregnancy, smoking in early pregnancy and maternal antidepressant use before pregnancy. In total, we considered 17 covariates and retained 9 based on our DAG (covariates selected by DAG are presented in the footnotes of **Figure 2**). We obtained a minimum sufficient adjustment set to estimate the effect of maternal antidepressant use in 3 months before pregnancy on offspring CHD including 6 covariates including maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus and history of gestational hypertension. In the minimum sufficient adjustment set to estimate the effect of maternal antidepressant use in

TABLE 2 | The distribution of baseline characteristics according to status of maternal antidepressant use before pregnancy or in early pregnancy.

Variables	Total, No. (%) (*N* = 34,104)	Antidepressants use before pregnancy		Antidepressants use in early pregnancy	
		No (*n* = 33,140)	Yes (*n* = 964)	No (*n* = 33,280)	Yes (*n* = 824)
Maternal age					
<35 years	26,445 (77.5)	25,715 (77.6)	730 (75.7)	25,810 (77.6)	635 (77.1)
≥35 years	7,659 (22.5)	7,425 (22.4)	234 (24.3)	7,470 (22.4)	189 (22.9)
Maternal education level					
Junior high and below	2,547 (7.5)	2,465 (7.4)	82 (8.5)	2,496 (7.5)	51 (6.2)
High school or technical secondary school	9,695 (28.4)	9,409 (28.4)	286 (29.7)	9,471 (28.5)	224 (27.2)
Junior college	15,594 (45.7)	15,151 (45.7)	443 (46.0)	15,218 (45.7)	376 (45.6)
Bachelor degree or above	6,268 (18.4)	6,115 (18.5)	153 (15.9)	6,095 (18.3)	173 (21.0)
Residence location					
Urban areas	21,074 (61.8)	20,460 (61.7)	614 (63.7)	20,552 (61.8)	522 (63.3)
Rural areas	13,030 (38.2)	12,680 (38.3)	350 (36.3)	12,728 (38.2)	302 (36.7)
Ethnicity					
Han	33,656 (98.7)	32,708 (98.7)	948 (98.3)	32,845 (98.7)	811 (98.4)
Minority	448 (1.3)	432 (1.3)	16 (1.7)	435 (1.3)	13 (1.6)
Pre-pregnancy BMI categories					
<18.5 kg/m^2	4,920 (14.4)	4,765 (14.4)	155 (16.1)	4,796 (14.4)	124 (15.0)
18.5–<23.0 kg/m^2	21,056 (61.7)	20,482 (61.8)	574 (59.5)	20,554 (61.8)	502 (60.9)
23.0–<27.5 kg/m^2	6,963 (20.4)	6,757 (20.4)	206 (21.4)	6,792 (20.4)	171 (20.8)
≥27.5 kg/m^2	1,165 (3.4)	1,136 (3.4)	29 (3.0)	1,138 (3.4)	27 (3.3)
Smoking before pregnancy					
No	33,762 (99.0)	32,818 (99.0)	944 (97.9)	32,942 (99.0)	820 (99.5)
Yes	342 (1.0)	322 (1.0)	20 (2.1)	338 (1.0)	4 (0.5)
Alcohol drinking before pregnancy					
No	33,524 (98.3)	32,586 (98.3)	938 (97.3)	32,710 (98.3)	814 (98.8)
Yes	580 (1.7)	554 (1.7)	26 (2.7)	570 (1.7)	10 (1.2)
Smoking in early pregnancy					
No	33,650 (98.7)	32,706 (98.7)	944 (97.9)	32,832 (98.7)	818 (99.3)
Yes	454 (1.3)	434 (1.3)	20 (2.1)	448 (1.3)	6 (0.7)
Alcohol drinking in early pregnancy					
No	33,606 (98.5)	32,666 (98.6)	940 (97.5)	32,794 (98.5)	812 (98.5)
Yes	498 (1.5)	474 (1.4)	24 (2.5)	486 (1.5)	12 (1.5)
Consanguineous marriage					
No	33,956 (99.6)	32,996 (99.6)	960 (99.6)	33,134 (99.6)	822 (99.8)
Yes	148 (0.4)	144 (0.4)	4 (0.4)	146 (0.4)	2 (0.2)
History of gestational diabetes					
No	31,280 (91.7)	30,398 (91.7)	882 (91.5)	30,504 (91.7)	776 (94.2)
Yes	2,824 (8.3)	2,742 (8.3)	82 (8.5)	2,776 (8.3)	48 (5.8)
History of gestational hypertension					
No	31,816 (93.3)	30,920 (93.3)	896 (92.9)	31,048 (93.3)	768 (93.2)
Yes	2,288 (6.7)	2,220 (6.7)	68 (7.1)	2,232 (6.7)	56 (6.8)
Family history of congenital malformations					
No	34,042 (99.8)	33,082 (99.8)	960 (99.6)	33,222 (99.8)	820 (99.5)
Yes	62 (0.2)	58 (0.2)	4 (0.4)	58 (0.2)	4 (0.5)
Taking folic acid in 3 months before pregnancy or in early pregnancy					
No	32,556 (95.5)	31,646 (95.5)	910 (94.4)	31,776 (95.5)	780 (94.7)
Yes	1,548 (4.5)	1,494 (4.5)	54 (5.6)	1,504 (4.5)	44 (5.3)

(Continued)

TABLE 2 | Continued

Variables	Total, No. (%) (*N* = 34,104)	Antidepressants use before pregnancy		Antidepressants use in early pregnancy	
		No (*n* = 33,140)	Yes (*n* = 964)	No (*n* = 33,280)	Yes (*n* = 824)
House decoration in 3 months before pregnancy or in early pregnancy					
No	32,510 (95.3)	31,584 (95.3)	926 (96.1)	31,722 (95.3)	788 (95.6)
Yes	1,594 (4.7)	1,556 (4.7)	38 (3.9)	1,558 (4.7)	36 (4.4)
Exposure to radioactive hazardous while at work in 3 months before pregnancy or in early pregnancy					
No	32,980 (96.7)	32,058 (96.7)	922 (95.6)	32,186 (96.7)	794 (96.4)
Yes	1,124 (3.3)	1,082 (3.3)	42 (4.4)	1,094 (3.3)	30 (3.6)

BMI, body mass index.

early pregnancy on offspring CHD, 3 covariables including smoking before pregnancy, alcohol drinking before pregnancy and antidepressants use before pregnancy were added on the basis of the 3 months before pregnancy.

In the overall population, mothers who used antidepressant in 3 months before pregnancy had an increased risk of CHD in their offspring compared with mothers without used antidepressant. The adjusted RR of total CHDs was 2.54 (95% CI, 1.64–3.93) for maternal antidepressant use in 3 months before pregnancy after adjusting for maternal age, ethnicity, residence location, education level, history of GDM, history of GH, smoking before pregnancy and alcohol drinking before pregnancy. To understand whether maternal antidepressant use before pregnancy has different effects on offspring CHD phenotypes, we further analyzed 4 different CHD phenotypes. Similarly, we found that maternal antidepressant use in 3 months before pregnancy was independently associated with ASD, PDA, and TGA in offspring in model 3, and the corresponding adjusted RR was 2.33 (95% CI, 1.01–5.38) for ASD, 2.99 (95% CI, 1.07–8.31) for PDA and 5.50 (95% CI, 1.91–15.88) for TGA respectively (**Figure 3**).

Maternal Antidepressant Use in Early Pregnancy and Risk of CHDs in Offspring

Then, we analyzed the association between maternal antidepressant use in early pregnancy and CHD risk in offspring (**Figure 4**). Encouragingly, we also found that maternal antidepressant use in early pregnancy significantly increased the risk of total CHDs in offspring. The adjusted RR of total CHDs was 2.87 (95% CI, 1.78–4.62) for maternal antidepressant use in early pregnancy after adjusting for maternal age, ethnicity, residence location, education level, history of GDM, history of GH, smoking before pregnancy, alcohol drinking before pregnancy, antidepressants use before pregnancy, smoking in early pregnancy and alcohol drinking in early pregnancy. In CHD phenotypic analysis, maternal antidepressant use in early pregnancy was only significantly associated with VSD in offspring in Model 3, and the corresponding adjusted RR was 4.80 (95% CI, 2.50–9.24). We speculated that it might be due to the small sample size.

Sensitivity Analysis

The reliability of the previous results was shown in the results of two sensitivity analyses that excluded women whose children had any congenital malformations other than CHD (**Figure 5**) or whose children had more than one CHD phenotype (**Figure 6**).

DISCUSSION

Previous studies have suggested that antidepressant use by pregnant women may increase the risk of CHD in their offspring. As most of the studies were analyzed the data from developed countries, our study is the first to explore this association using data from Hunan province in central China. This prospective cohort study was conducted from March 13, 2013 to December 31, 2019 at Hunan Maternal and Child Health Hospital. In our study, the incidence of CHD was 8.97 per 1,000 live births (306/34,104). We found that maternal antidepressant use in 3 months before pregnancy and early pregnancy were associated with a significant increase in CHD in offspring, with adjusted RRs of 2.54 (95% CI, 1.64–3.93) and 2.87 (95% CI, 1.78–4.62), respectively. In CHD-specific phenotypic analysis, maternal antidepressant use in the 3 months before pregnancy significantly increased the risk of ASD, PDA, and TGA in children, with having a highest estimated risk of 5.50 for TGA. However, maternal antidepressant use in early pregnancy increased the risk for VSD by ∼4.80 times that of the group not using antidepressant in early pregnancy. Sensitivity analysis verified the stability of the results. We believe that the difference between pre-pregnancy and early pregnancy phenotype results may be due to the fact that different phenotypes may have different etiologies and, conceivably, different risks for each phenotype. In addition, the number of cases for each CHD phenotype is very small and there may not be sufficient statistical detection capacity available.

In China, the prescription of antidepressants for pregnant women is conservative, and there are many pregnant women who take antidepressants before pregnancy and stop treatment after pregnancy. However, there were few studies on the adverse pregnancy outcomes of pre-pregnancy antidepressant use in children. This study was the first to provide strong evidence that maternal antidepressant use in the 3 months before pregnancy increased the risk of CHD in children. Therefore, we call for

Type of CHD	No (n= 33140)	Yes (n= 964)	Model 1	Model 2	Model 3
Total CHD	284	22	2.66 (1.73–4.12)	2.70 (1.75–4.16)	2.54 (1.64–3.93)
ASD	80	6	2.58 (1.13–5.91)	2.60 (1.14–5.97)	2.33 (1.01–5.38)
VSD	103	2	0.67 (0.17–2.71)	0.68 (0.17–2.76)	0.64 (0.16–2.58)
PDA	46	4	2.99 (1.08–8.30)	3.00 (1.08–8.34)	2.99 (1.07–8.31)
TGA	24	4	5.73 (1.99–16.51)	5.49 (1.90–15.84)	5.50 (1.91–15.88)

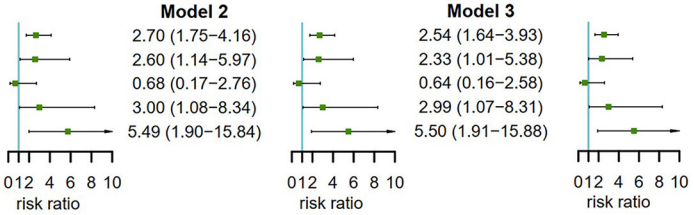

FIGURE 3 | Maternal antidepressant use in 3 months before pregnancy and risk of CHD and its phenotypes in offspring. Model 1 was a crude model without any variable adjusted. Model 2 adjusted for maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus and history of gestational hypertension. Model 3 adjusted for maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus, history of gestational hypertension, smoking before pregnancy and alcohol drinking before pregnancy. CHD, congenital heart disease.

Type of CHD	No (n= 33280)	Yes (n= 824)	Model 1	Model 2	Model 3
Total CHD	288	18	2.52 (1.57–4.06)	2.81 (1.74–4.52)	2.87 (1.78–4.62)
ASD	84	2	0.96 (0.24–3.91)	1.09 (0.27–4.45)	1.10 (0.27–4.47)
VSD	95	10	4.25 (2.22–8.16)	4.75 (2.47–9.13)	4.80 (2.50–9.24)
PDA	48	2	1.68 (0.41–6.92)	1.47 (0.36–6.05)	1.52 (0.37–6.29)
TGA	26	2	3.11 (0.74–13.09)	2.85 (0.67–12.05)	2.79 (0.66–11.83)

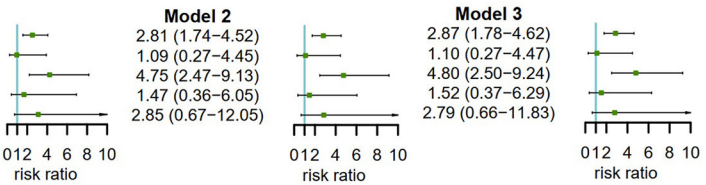

FIGURE 4 | Maternal antidepressant use in early pregnancy and risk of CHD and its phenotypes in offspring. Model 1 was a crude model without any variable adjusted. Model 2 adjusted for maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus, history of gestational hypertension, smoking before pregnancy, alcohol drinking before pregnancy and antidepressants use before pregnancy. Model 3 adjusted for maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus, history of gestational hypertension, smoking before pregnancy, alcohol drinking before pregnancy, antidepressants use before pregnancy, smoking in early pregnancy and alcohol drinking in early pregnancy. CHD, congenital heart disease.

A Antidepressants use before pregnancy

Type of CHD	No (n= 31988)	Yes (n= 923)	Model 1	Model 2	Model 3
Total CHD	284	22	2.69 (1.74–4.14)	2.71 (1.75–4.18)	2.58 (1.67–3.99)
ASD	80	6	2.60 (1.13–5.96)	2.61 (1.14–5.98)	2.36 (1.02–5.44)
VSD	103	2	0.67 (0.17–2.73)	0.68 (0.17–2.76)	0.64 (0.16–2.60)
PDA	46	4	3.01 (1.09–8.37)	3.03 (1.09–8.42)	3.01 (1.08–8.38)
TGA	24	4	5.78 (2.00–16.65)	5.55 (1.93–16.03)	5.56 (1.93–16.05)

B Antidepressants use in early pregnancy

Type of CHD	No (n= 32127)	Yes (n= 784)	Model 1	Model 2	Model 3
Total CHD	288	18	2.56 (1.59–4.12)	2.85 (1.77–4.59)	2.93 (1.82–4.72)
ASD	84	2	0.98 (0.24–3.97)	1.11 (0.27–4.53)	1.12 (0.28–4.57)
VSD	95	10	4.31 (2.25–8.28)	4.86 (2.52–9.34)	4.94 (2.57–9.52)
PDA	48	2	1.71 (0.42–7.03)	1.50 (0.36–6.20)	1.57 (0.38–6.47)
TGA	26	2	3.15 (0.75–13.28)	2.89 (0.68–12.21)	2.84 (0.67–12.01)

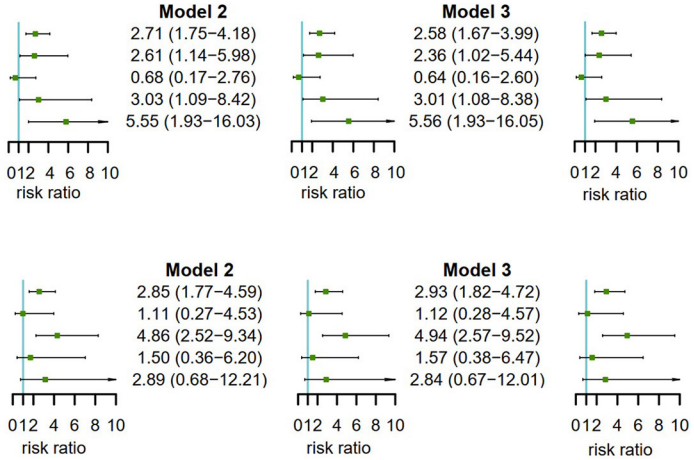

FIGURE 5 | The risks of CHD in offspring of pregnant women exposured to antidepressant in 3 months before pregnancy and in early pregnancy after excluding pregnant women whose children had non-cardiac defects. Model 1 was a crude model without any variable adjusted. Model 2 adjusted for maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus and history of gestational hypertension. Model 3 adjusted for maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus, history of gestational hypertension, smoking before pregnancy and alcohol drinking before pregnancy. CHD, congenital heart disease. **(A)** Antidepressants use before pregnancy. **(B)** Antidepressants use in early pregnancy.

attention to avoid the risk factors related to the adverse pregnancy outcomes of the offspring as much as possible during the preparation of pregnancy, and try to choose pregnancy when the mother's personal disease improves, which is also one of the best choices for healthy birth and healthy education.

A recent meta-analysis based on 20 studies from 14 countries was consistent with our study, finding that mothers who used any antidepressant in early pregnancy were 1.2 to 1.4 times more likely to have a child with a congenital heart defect than those who did not (19). This meta-analysis limited the

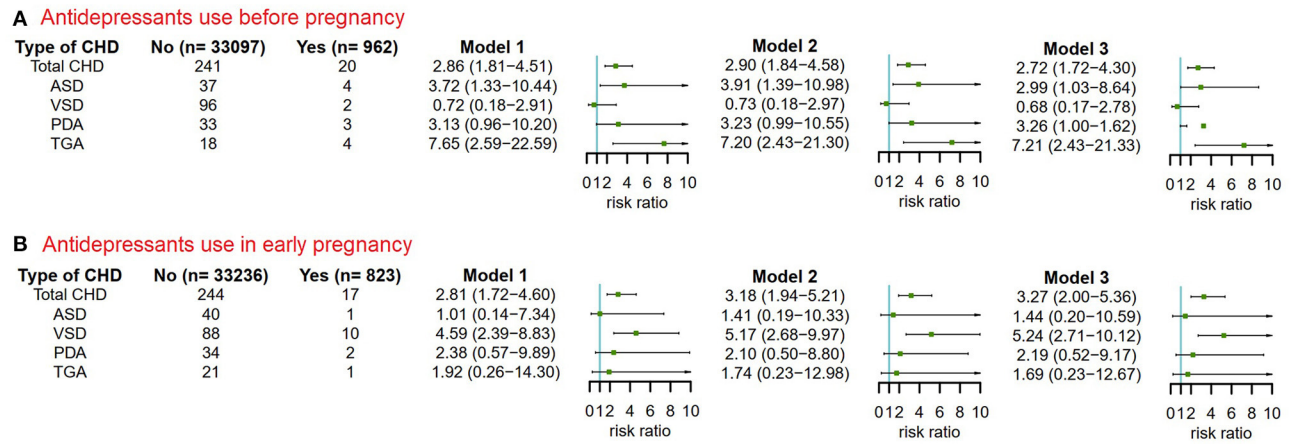

FIGURE 6 | The risks of CHD in offspring of pregnant women exposured to antidepressant in 3 months before pregnancy and in early pregnancy after excluding pregnant women whose children were diagnosed with more than one CHD phenotypes. Model 1 was a crude model without any variable adjusted. Model 2 adjusted for maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus, history of gestational hypertension, smoking before pregnancy, alcohol drinking before pregnancy and antidepressants use before pregnancy. Model 3 adjusted for maternal age, ethnicity, residence location, education level, history of gestational diabetes mellitus, history of gestational hypertension, smoking before pregnancy, alcohol drinking before pregnancy, antidepressants use before pregnancy, smoking in early pregnancy and alcohol drinking in early pregnancy. CHD, congenital heart disease. **(A)** Antidepressants use before pregnancy. **(B)** Antidepressants use in early pregnancy.

high quality of all studies through strict inclusion criteria, and the results had low heterogeneity. In addition, the largest current meta-analysis from Shen et al., involving more than 6 million pregnant women, found an increased risk of atrial and/or ventricular septal defects in infants using sertraline (18), which is similar to our analysis of CHD specific phenotypes. In addition, a study from the Danish Registry reported an increased risk of severe heart malformations from early pregnancy exposure to venlafaxine, but the absolute risk was low (24). One point of concern is that the risk may differ for each class of antidepressant, so more research is needed to explore the differences.

There were still some studies that put forward the opposite view. Kayla et al. found some association between maternal antidepressant use and CHD, but this association weakened after partially accounting for underlying conditions (17). In a cohort study of over 60,000 pregnant women, Krista et al. found that the association between antidepressants in early pregnancy and cardiac malformations decreased as the level of confounder adjustment increased, suggesting that antidepressant use in early pregnancy did not significantly increase the risk of cardiac malformations. However, antidepressant exposure rates in this cohort (6.80%) were much higher than in our study (2.42%) (25). Few Asian countries have studied this association, and a retrospective cohort study in Japan found no increased risk of total congenital malformations in children whose mothers used antidepressants of any type in early pregnancy (aOR = 0.86; 95% CI: 0.52–1.42). In addition, there was no increased risk of organ-specific abnormalities in the analysis by antidepressant type. However, total antidepressant use in the study was only 0.7% (392/53,638) (26). This may be related to the background that the teratogenic potential of drugs became widely recognized after the harmful effects of thalidomide occurred in Japan in the 1960s (27).

This study identified a significant association between maternal antidepressant use and increased CHD risk in children. However, the potential biological mechanisms involved in the association between maternal antidepressant use and offspring CHD remain to be elucidated. In recent years, ion channels as target receptors for antidepressant drugs have attracted much attention. One potential mechanism is the delayed-rectifier potassium current (I_K), which is a common teratogenic mechanism. I_K includes I_{Kr}, which activates quickly, and I_{Ks}, which activates slowly (28). The K_r (KCNH2 gene) and K_s ion channel (KCNQ1 + KCNE1 gene) are highly expressed in human embryos and adult hearts (29). Genetic mutations in the human subunits that form the K_r and K_s channels prolong cardiac action potentials (AP), leading to a prolonged QT interval, known as long QT syndrome (30, 31). Recent epidemiological studies have reported an association between antidepressants with a risk of long QT syndrome and cardiac defects. The use of antidepressants cimipramil (32) and clomiphene (33) has been identified to double the risk of ventricular-septal defects. In animal experiments, it has also been found that several drugs that block the K_r channel can lead to malformations (including heart defects) and embryo death (29).

Currently, there is an alternative view on the biological mechanism between antidepressants with selective serotonin reuptake inhibitors (SSRIs) and CHD. Serotonin (5-HT) is a neurotransmitter that plays an important role in embryonic development as a signaling molecule (34). It is also reported that 5-HT may be involved in cardiac development, such as progenitor cell formation and outflow tract lengthening (35–37). SSRIs can cross the placental barrier and block 5-HT reuptake,

which provides biological justification for their teratogenic effect on heart development (38). However, there is a trend of diversification of drugs on the market, with each drug exhibiting its own unique receptor binding profile (39). Therefore, there may be different complex mechanisms that need to be explored by a large number of animal experiments, cell experiments and epidemiological studies.

LIMITATION

In this study, exposure information was collected prospectively to control for recall bias as much as possible. In addition, many confounding factors, including women's lifestyle and obstetric history, were adjusted. However, there were still several limitations in this study. The data collected in this study came from only one hospital, which inevitably resulted in the deviation of admission rate. The number of cases in this study for some CHD phenotypes was very small and may not have obtained sufficient statistical detection capabilities. However, considering that CHD is a rare disease with a low incidence, and the incidence of its subtypes is even lower, it is difficult to avoid a small number of cases in the cohort study of influencing factors of CHD. We will continue to collect samples to expand the number of cases. In addition, we analyzed the relationship between exposure and CHD by Modified Poisson regression, which can provide more stable estimates. In this study, we did not focus on the dose of medication to determine the effect of persistent or intermittent medication patterns on CHD. We only paid attention to frequency, which is the limitation of this study. Different antidepressants may have different teratogenic effects, and this study also failed to record the types of drugs prescribed. However, the number of women using antidepressants during pregnancy in this study was relatively small, and we may not be able to ensure a sufficient sample size to conduct a more detailed analysis in subgroups. Despite the abundance of information available to adjust for confounders, there is always the possibility of residual confounders in observational studies. Therefore, sensitivity analysis was used to minimize this possibility. The fetuses of the mothers included in this study were all live births, so it was inevitable that the parents may terminate pregnancy when they find that there may be adverse pregnancy outcomes, so some cases or events would be missed.

CONCLUSION

In conclusion, it is of concern that antidepressant use in the 3 months before pregnancy and in the early pregnancy may significantly increase the risk of CHD in children. According to the results of our study, we suggest that women should avoid taking some teratogenic drugs as much as possible during pregnancy preparation, and try to prepare for pregnancy after their condition is stable, which is beneficial to women's mental state and children's development. In addition, when prescribing drugs for pregnant women with depression, it is important to consider the balance between the benefits and risks of antidepressant use, and it is recommended to avoid prescribing drugs that may have teratogenic effects in clinical practice. Finally, more studies are needed to further elucidate the association between pre-pregnancy/early pregnancy antidepressant use and CHD in children, given the differences in antidepressant classes and CHD phenotypes. It is more critical to study the biological mechanism of antidepressants that may lead to CHD and determine the teratogenic pathway in order to avoid the clinical use of teratogenic drugs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Xiangya School of Public Health, Central South University, and registered in the Chinese Clinical Trial Registry (Registration Number: ChiCTR1800016635). Prior written informed consent was obtained from all study participants additionally. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MS conceptualized the study and drafted the initial manuscript. MS, SZ, and LC analyzed and explained the data. JD, SZ, JL, YLi, LC, YLiu, JW, XS, and JS have collected the data. TW, PH, and JQ conceptualized and designed the study and critically reviewed and revised the manuscript. All authors contributed to the article and approved the final version of the manuscript.

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REFERENCES

1. Faravelli C, Alessandra Scarpato M, Castellini G, Lo Sauro C. Gender differences in depression and anxiety: the role of age. *Psychiatry Res.* (2013) 210:1301–3. doi: 10.1016/j.psychres.2013.09.027
2. Nisar A, Yin J, Waqas A, Bai X, Wang D, Rahman A, et al. Prevalence of perinatal depression and its determinants in Mainland China: a systematic review and meta-analysis. *J Affect Disord.* (2020) 277:1022–37. doi: 10.1016/j.jad.2020.07.046
3. Louik C, Kerr S, Mitchell AA. First-trimester exposure to bupropion and risk of cardiac malformations. *Pharmacoepidemiol Drug Saf.* (2014) 23:1066–75. doi: 10.1002/pds.3661
4. Shealy KM. Are antidepressants safe in the first trimester of pregnancy? *JAAPA*. (2015) 28:16–7. doi: 10.1097/01.JAA.0000460911.55472.76
5. Liu Y, Chen S, Zuhlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. *Int J Epidemiol.* (2019) 48:455–63. doi: 10.1093/ije/dyz009
6. Zhao QM, Liu F, Wu L, Ma XJ, Niu C, Huang GY. Prevalence of congenital heart disease at live birth in China. *J Pediatr.* (2019) 204:53–8. doi: 10.1016/j.jpeds.2018.08.040
7. Marelli A, Miller SP, Marino BS, Jefferson AL, Newburger JW. Brain in congenital heart disease across the lifespan: the cumulative burden of injury. *Circulation.* (2016) 133:1951–62. doi: 10.1161/CIRCULATIONAHA.115.019881
8. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation.* (2012) 126:1143–72. doi: 10.1161/CIR.0b013e318265ee8a
9. Leonetti C, Back SA, Gallo V, Ishibashi N. Cortical dysmaturation in congenital heart disease. *Trends Neurosci.* (2019) 42:192–204. doi: 10.1016/j.tins.2018.12.003
10. Courtney JA, Cnota JF, Jones HN. The role of abnormal placentation in congenital heart disease; cause, correlate, or consequence? *Front Physiol.* (2018) 9:1045. doi: 10.3389/fphys.2018.01045
11. Williams K, Carson J, Lo C. Genetics of congenital heart disease. *Biomolecules.* (2019) 9:879. doi: 10.3390/biom9120879
12. Szot JO, Cuny H, Blue GM, Humphreys DT, Ip E, Harrison K, et al. A screening approach to identify clinically actionable variants causing congenital heart disease in exome data. *Circ Genom Precis Med.* (2018) 11:e001978. doi: 10.1161/CIRCGEN.117.001978
13. Williams M, Wooltorton E. Paroxetine (Paxil) and congenital malformations. *CMAJ.* (2005) 173:1320–1. doi: 10.1503/cmaj.051421
14. Cole JA, Ephross SA, Cosmatos IS, Walker AM. Paroxetine in the first trimester and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf.* (2007) 16:1075–85. doi: 10.1002/pds.1463
15. Bakker MK, Kerstjens-Frederikse WS, Buys CH, de Walle HE and de Jong-van den Berg LT. First-trimester use of paroxetine and congenital heart defects: a population-based case-control study. *Birth Defects Res A Clin Mol Teratol.* (2010) 88:94–100. doi: 10.1002/bdra.20641
16. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA, National Birth Defects Prevention. Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. *BMJ.* (2015) 351:h3190. doi: 10.1136/bmj.h3190
17. Anderson KN, Lind JN, Simeone RM, Bobo WV, Mitchell AA, Riehle-Colarusso T, et al. Maternal use of specific antidepressant medications during early pregnancy and the risk of selected birth defects. *JAMA Psychiatry.* (2020) 77:1246–55. doi: 10.1001/jamapsychiatry.2020.2453
18. Shen ZQ, Gao SY, Li SX, Zhang TN, Liu CX, Lv HC, et al. Sertraline use in the first trimester and risk of congenital anomalies: a systemic review and meta-analysis of cohort studies. *Br J Clin Pharmacol.* (2017) 83:909–22. doi: 10.1111/bcp.13161
19. De Vries. A systematic review and meta-analysis considering the risk for congenital heart defects of antidepressant classes and individual antidepressants. *Drug Saf.* (2021) 44:291–312. doi: 10.1007/s40264-020-01027-x
20. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA.* (2006) 295:499–507. doi: 10.1001/jama.295.5.499
21. Wang T, Li Q, Chen L, Ni B, Sheng X, Huang P, et al. Effect of maternal alcohol consumption during the pre-pregnancy/early-pregnancy period on congenital heart disease: a prospective cohort study in Central China. *Prev Med.* (2022) 155:106963. doi: 10.1016/j.ypmed.2022.106963
22. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. *Epidemiology.* (2011) 22:745. doi: 10.1097/EDE.0b013e318225c2be
23. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* (2004) 159:702–6. doi: 10.1093/aje/kwh090
24. Kolding L, Ehrenstein V, Pedersen L, Sandager P, Petersen OB, Uldbjerg N, et al. Antidepressant use in pregnancy and severe cardiac malformations: Danish register-based study. *BJOG.* (2021) 128:1949–57. doi: 10.1111/1471-0528.16772
25. Huybrechts KF, Palmsten K, Avorn J, Cohen LS, Holmes LB, Franklin JM, et al. Antidepressant use in pregnancy and the risk of cardiac defects. *N Engl J Med.* (2014) 370:2397–407. doi: 10.1056/NEJMoa1312828
26. Yamamoto-Sasaki M, Yoshida S, Takeuchi M, Tanaka-Mizuno S, Kawakami K. Association between antidepressant use during pregnancy and congenital anomalies in children: a retrospective cohort study based on Japanese claims data. *Congenit Anom (Kyoto).* (2020) 60:180–8. doi: 10.1111/cga.12386
27. Takagi K, Onda M, Iwaki A, Nishikawa N, Arakawa Y. Survey on the attitudes of pregnant and lactating women about the use of drugs. *Yakugaku Zasshi.* (2010) 130:1381–5. doi: 10.1248/yakushi.130.1381
28. Abbott GW, Xu X, Roepke TK. Impact of ancillary subunits on ventricular repolarization. *J Electrocardiol.* (2007) 40:S42–46. doi: 10.1016/j.jelectrocard.2007.05.021
29. Danielsson C, Brask J, Skold AC, Genead R, Andersson A, Andersson U, et al. Exploration of human, rat, and rabbit embryonic cardiomyocytes suggests K-channel block as a common teratogenic mechanism. *Cardiovasc Res.* (2013) 97:23–32. doi: 10.1093/cvr/cvs296
30. Turker I, Ai T, Itoh H, Horie M. Drug-induced fatal arrhythmias: acquired long QT and Brugada syndromes. *Pharmacol Ther.* (2017) 176:48–59. doi: 10.1016/j.pharmthera.2017.05.001
31. Shah SR, Park K, Alweis R. Long QT syndrome: a comprehensive review of the literature and current evidence. *Curr Probl Cardiol.* (2019) 44:92–106. doi: 10.1016/j.cpcardiol.2018.04.002
32. Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ.* (2009) 339:b3569. doi: 10.1136/bmj.b3569
33. Kallen B, Otterblad Olausson P. Antidepressant drugs during pregnancy and infant congenital heart defect. *Reprod Toxicol.* (2006) 21:221–2. doi: 10.1016/j.reprotox.2005.11.006
34. Buznikov GA, Lambert HW, Lauder JM. Serotonin and serotonin-like substances as regulators of early embryogenesis and morphogenesis. *Cell Tissue Res.* (2001) 305:177–86. doi: 10.1007/s004410100408
35. Choi DS, Ward SJ, Messaddeq N, Launay JM, Maroteaux L. 5-HT2B receptor-mediated serotonin morphogenetic functions in mouse cranial neural crest and myocardiac cells. *Development.* (1997) 124:1745–55. doi: 10.1242/dev.124.9.1745
36. Mjaatvedt CH, Nakaoka T, Moreno-Rodriguez R, Norris RA, Kern MJ, Eisenberg CA, et al. The outflow tract of the heart is recruited from a novel heart-forming field. *Dev Biol.* (2001) 238:97–109. doi: 10.1006/dbio.2001.0409
37. Abu-Issa R, Kirby ML. Heart field: from mesoderm to heart tube. *Annu Rev Cell Dev Biol.* (2007) 23:45–68. doi: 10.1146/annurev.cellbio.23.090506.123331
38. Sadler TW. Selective serotonin reuptake inhibitors (SSRIs) and heart defects: potential mechanisms for the observed associations. *Reprod Toxicol.* (2011) 32:484–9. doi: 10.1016/j.reprotox.2011.09.004
39. Sanchez C, Hyttel J. Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor

binding. *Cell Mol Neurobiol.* (1999) 19:467–89. doi: 10.1023/A:1006986824213

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Assessment of Human Factors After Advanced Life Support Courses Comparing Simulated Team and Real Team Assessment: A Randomized Controlled Cohort Trial

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Aim: Human factors are essential for high-quality resuscitation team collaboration and are, therefore, taught in international advanced life support courses, but their assessment differs widely. In Europe, the summative life support course assessment tests mainly adhere to guidelines but few human factors. This randomized controlled simulation trial investigated instructors' and course participants' perceptions of human factors assessment after two different summative assessments.

Methods: All 5th/6th-year medical students who attended 19 advanced life support courses according to the 2015 European Resuscitation Council guidelines during one study year were invited to participate. Each course was randomized to either: (1) Simulated team assessment (one instructor simulates a team, and the assessed person leads this "team" through a cardiac-arrest scenario test); (2) Real team assessment (4 students form a team, one of them is assessed as the team leader; team members are not assessed and act only on team leader's commands). After the summative assessments, instructors, and students rated the tests' ability to assess human factors using a visual analog scale (VAS, 0 = no agreement, 10 = total agreement).

Results: A total of 227 students participated in the 1-day Immediate Life Support courses, 196 students in the 2-day Advanced Life Support courses, additionally 54 instructors were included. Instructors judged all human factors significantly better in real team assessments; students rated leadership and situational awareness comparable between both assessments. Assessment pass rates were comparable between groups.

Conclusion: Summative assessment in real teams was perceived significantly better to assess human factors. These results might influence current summative assessment practices in advanced life support courses.

Keywords: education, CPR, life support, European Resuscitation Council (ERC), human factors

INTRODUCTION

The incidence of cardiac arrests ranges between one and five cardiac arrests per 1,000 hospital admissions (1), and 67–170 per 1,000,000 citizens (2). Cardiopulmonary resuscitation (CPR) is a key skill that all health care professionals should master in order to improve patient outcomes after cardiac arrests. Especially faster and more efficient in-hospital cardiopulmonary resuscitation and early defibrillation can improve patient outcomes significantly (1–3).

All health care professionals should be proficient in basic life support measures (4, 5) and should be regularly trained in small groups with a maximum instructor to participant ratio of 1:6 (6). Health care professionals who regularly treat cardiac arrests need to participate in Advanced Life Support (ALS) courses to improve their patients' outcomes (7, 8). Those health care professionals who are infrequently involved in cardiac arrest management should at least participate in Immediate Life Support (ILS) courses (4, 9).

During a cardiac arrest, physicians usually assume the role of the team leader and need to be proficient in guiding an interdisciplinary resuscitation team through the management of a cardiac arrest. The 2015 and 2021 Guidelines of the European Resuscitation Council (ERC) emphasize that team membership and leadership training are essential (5, 9–11).

Prerequisites for proper team performance were identified earlier, and include: team leadership, task management, teamwork, situational awareness, decision-making, adaptability, event and mission analysis, and communication (12, 13). ERC ALS courses include training of technical skills, adherence to current resuscitation guidelines, and training of human factors focusing on team membership and leadership, task management, communication, and situational awareness (14).

Different approaches to assessing human factors in different fields were described (e.g., the ANTS framework, the Oxford NOTECHS, the Mayo High performance teamwork scale, the adapted LOSA checklist from aviation, the Queen's Simulation Assessment Tool, etc.) (12, 15–18). The paradigm shift to also include human factor training in cardiopulmonary resuscitation courses took place over the last years, however, the practical end-of-course summative assessment has remained largely unchanged and tests predominantly the participants' ability to adhere to current resuscitation guidelines. Currently, the ERC uses simulated team assessments of one candidate during the summative practical end-of-course assessment. One instructor simulates a team, the assessed person leads this "team" through a cardiac arrest scenario test. Other organizations like the American Heart Association use real team assessments, where a group of participants forms a team. One of them is then assessed as the team leader; the team members are usually not assessed and act only on the commands of the team leader. There is currently no evidence available as to what extent different assessment methods can test human factors.

Therefore, the aim of this study was to investigate which variant of these two different summative end-of-course assessment methods is perceived as being superior in their ability to assess human factors, as judged by instructors and students. This is an evaluation of the opinions of course participants and instructors, the null hypothesis was that there is no difference between leadership skills comparing both assessment methods. The results of this study might influence the development of a different assessment approach in such cardiopulmonary resuscitation courses.

MATERIALS AND METHODS

Participants and Ethics

After reviewing the protocol, the Cantonal Ethics Committee of Bern, Switzerland (Req-2017-00579, 07.08.2017) judged the study as non-human research according to the Swiss Human Research Act. After registration at clinicaltrials.gov (NCT 03381443), this randomized controlled simulation trial was performed at the University of Bern, Switzerland between December 2017 and March 2019.

All 5th-year medical students in the study year 2017/2018 took the mandatory 8-h ILS course; all 6th-year medical students the 16-h ALS course. These courses followed the 2015 ERC course structure and students earned an internationally valid certification (9). All course instructors were ERC certified ILS/ALS instructors. With written informed consent from all participants and instructors, all assessments were video recorded. Course participants participated only once, whereas most instructors participated more than once.

Procedures

The advanced life support courses ended with a mandatory summative assessment that used four different, validated ERC cardiac arrest scenario tests (19). All courses were randomized to one of two different assessment methods:

1. Simulated team assessment: One instructor mimes a whole team, and the assessed course participant acts as team leader, leading this "team" through a cardiac arrest scenario test. This is the current standard ERC ILS/ALS course assessment.
2. Real team assessment: Four course participants are together in the assessment room and form a team. However, only the predefined team leader is assessed, all other team members act as resuscitation team, but they are not allowed to help the team leader with medical decisions and act only on commands of the assessed team leader. This corresponds to the American Heart Association Advanced Cardiac Life Support course assessment.

Randomization

All participants were scheduled for their respective courses by the University of Bern, the study team had no influence on which participant attended which course. Due to the study design, each course was randomized, not the individual

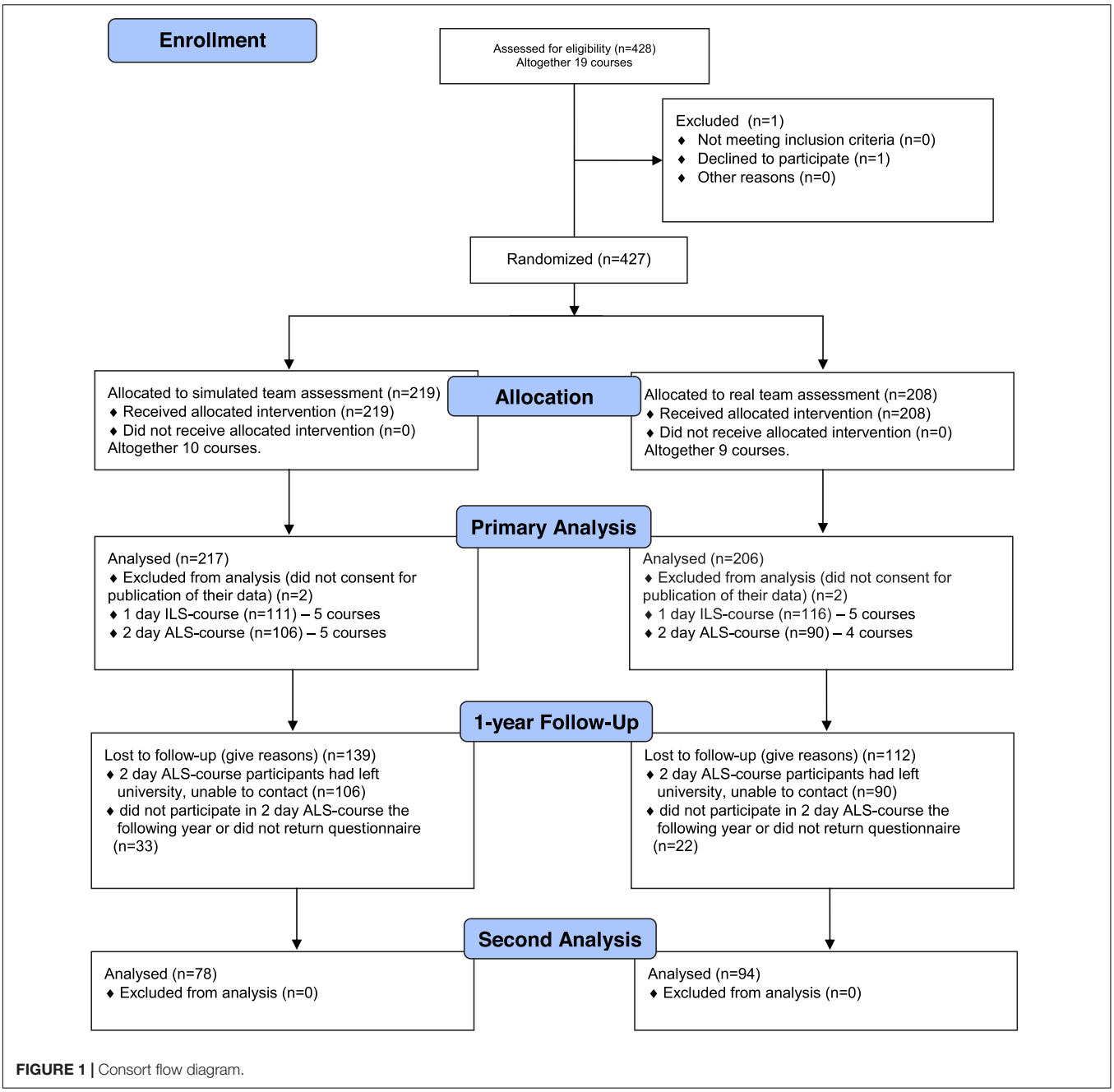

FIGURE 1 | Consort flow diagram.

participant. Randomization was performed using the online software "Research Randomizer[1]."

Data Analysis

Participants provided general characteristics including age, gender, primary language, experience as an instructor or real-life CPR experience, number of courses taught, and registration as Bern First Responder.

After the assessment, all course participants answered a questionnaire on their opinion to what extent the assessment was able to assess human factors such as team leadership, team membership, communication skills, team management skills, and situational awareness. They rated their self-assessed level of competence as a team member and team leader and judged their need for further training as a team member or team leader. In addition, they were asked to judge the assessment's ability to test medical resuscitation knowledge and technical CPR-skills. All measurements used a visual analog scale (VAS) ranging from 0 to 10, where 0 meant no agreement and 10 meant total agreement. Participation in the study was voluntary and had no effect on the medical students' grading at the university (20). All participating ILS/ALS instructors were also asked to fill out the

[1]https://www.randomizer.org

same questionnaire, once after each assessment day, not after each individual assessment. The primary outcome parameter is the difference in team leadership assessment in participants' and instructors' opinions.

After 1 year, participants of the former ILS-course were asked to fill out a follow-up questionnaire before they took their 6th-year ALS-course. Participants of the original ALS-course could not take part in the follow-up, because they had already graduated from university and were not accessible to the study team.

For pass or fail ratings of the assessments, the official ERC course-grading scheme on the official ERC ALS scenario test assessment forms was used. Participants are judged for each parameter on a scale from 1 to 4 (1 = outstanding, 2 = adequate, 3 = marginal, 4 = insufficient).

Statistics

No formal sample size calculation was performed as we did not find any literature to base such a calculation on. All students of the entire study year taking these advanced life support courses were included.

Statistical analysis was performed using the software STATA version 16.0 (StataCorp LT, TX, United States). Descriptive statistics analyzed participants' characteristics by using either a *t*-test or Chi-square test as applicable. Questionnaire results were non-parametric and therefore Mann–Whitney-*U* test was used to evaluate them. Assessment sub-items were evaluated using Chi-square tests. Data are presented as value (percentage) or mean ± SD (95% CI)—we opted to visualize our data with mean ± SD to allow for better comparability as the data was not that skewed compared to the median (interquartile range). We considered a two-sided p-value < 0.05 as statistically significant.

RESULTS

A total of 427 medical students participated in the study (in 19 courses), and one declined participation. **Figure 1** shows the Consort Flow Diagram. Four students had to be excluded from the analysis because they withdrew their consent to publication after participating in the advanced life support course and assessment. In the 1-day ILS-course, 111 students were randomized to the simulated team assessment, and 116 to the real team assessment (5 courses each). In the 2-day ALS-course, 106 students to the simulated team assessment (5 courses), and 90 to the real team assessment (4 courses). The 1-year follow-up reached 172 students, 78 from the simulated team assessment and 94 from the real team assessment.

A total of 54 instructors participated in the study; they were aged 39 ± 8 years; 17 (31%) were women; the primary language reported was: 51 German (94%), 2 French (4%), and 1 (2%) other; mean experience as the instructor was 4 ± 4 years; courses taught before participating in the study: 3 ± 2; 17 (31%) were registered Bern First Responders. Most instructors participated more than once.

Participating instructors judged the real team assessment overall significantly better than the simulated team assessment ($p = 0.029$, **Table 1**). All human factors were judged significantly better in the real team assessment ($p < 0.01$ to 0.024), and so was the ability to test CPR skills ($p < 0.01$). In contrast, knowledge could be tested equally well with both assessment methods ($p = 0.842$, **Table 1**).

TABLE 1 | Usefulness of the assessment method to assess human factors as perceived by the instructor.

Characteristic/Assessment	Simulated team	Real team	*P-value*[a]
	(*n* = 49)	(*n* = 40)	
Team leader	5.6 ± 2.4	7.2 ± 2.5	<0.01
	(5.0–6.3)	(6.5–8.0)	
Team member	1.9 ± 2.2	3.6 ± 2.9	<0.01
	(1.3–2.6)	(2.7–4.5)	
Communication	3.9 ± 2.7	6.1 ± 3.0	<0.01
	(3.1–4.7)	(5.2–7.1)	
Team management	3.7 ± 3.0	6.7 ± 2.5	<0.01
	(2.8–4.6)	(5.9–7.5)	
CPR skills	3.4 ± 3.2	5.9 ± 3.2	<0.01
	(2.5–4.3)	(4.9–6.9)	
Knowledge	7.2 ± 1.8	7.1 ± 2.2	0.842
	(6.7–7.7)	(6.4–7.8)	
Situational awareness	6.1 ± 2.4	7.1 ± 2.2	0.024
	(5.4–6.8)	(6.4–7.8)	
Assessment overall	5.7 ± 1.9	6.5 ± 2.7	0.029
	(5.2–6.3)	(5.6–7.3)	

Data are mean ± SD (95% CI).Values: VAS, Visual Analog Scale (0–10).
[a]Mann–Whitney-U test. Altogether 54 instructors participated in the study, some instructors participated more than once. This table shows the answers from each instructor after 1 day of assessments, not after each individual assessment.

Table 2 shows details of the participating students' characteristics. Of note, even though courses were randomized, we found in the 2-day ALS course cohort in the real team assessment group significantly more women (67% vs. 38% in the simulated team assessment group, $p < 0.01$). Also regardless of randomization, more registered Bern First Responders were found in the 2-day ALS course assessed with the simulated team assessment method (15% vs. 2% for team assessment, $p < 0.01$).

After 1 year, in the ILS cohort, 22 students reported having resuscitated a patient in real life after passing the last year's ILS-course (15 in the simulated team assessment group, 7 in the real team assessment group). Additional 11 students were recruited as Bern First Responders (4 in the simulated team assessment group and 7 in the real team assessment group).

Details of the students' subjective ratings of their assessments are displayed in **Table 3**. Self-assessed competence as a team member was judged significantly better for the real team assessment (ILS-course $p = 0.032$; ALS-course $p < 0.01$). Real team assessment was judged consistently significantly better in the ability to assess team membership, communication skills, team management skills, and CPR skills (all $p < 0.01$). Situational awareness was judged only in the ILS-course cohort in favor of real team assessments ($p = 0.023$, **Table 3**).

In the 1-year follow-up, both the self-assessed competence as a team member and team leader

TABLE 2 | Course participants' characteristics.

Characteristic	1-day ILS-course			2-day ALS-course		
Assessment	**Simulated team** ***n* = 111**	**Real team** ***n* = 116**	***P-value***	**Simulated team** ***n* = 106**	**Real team** ***n* = 90**	***P-value***
Age, years	24.5 ± 1.7 (24.2–24.9)	24.6 ± 2.7 (24.1–25.1)	0.833[a]	26.0 ± 1.8 (25.7–26.4)	25.6 ± 1.9 (25.2–26.0)	0.111[a]
Female	72 (65)	69 (59)	0.403[b]	40 (38)	60 (67)	< 0.01[b]
Primary language						
- German	97 (87)	96 (83)	0.342[b]	91 (86)	85 (95)	0.112[b]
- French	9 (8)	9 (8)		6 (6)	3 (3)	
- Other	5 (5)	11 (9)		9 (8)	2 (2)	
Real life CPR experience	5 (5)	6 (5)	0.803[b]	31 (29)	23 (26)	0.564[b]
Bern First Responder	16 (14)	22 (19)	0.359[b]	16 (15)	2 (2)	< 0.01[b]

[a]t-test, [b]Chi-square test. ILS, Immediate Life Support; ALS, Advanced Life Support; CPR, cardiopulmonary resuscitation. A First Responder is a trained layperson or healthcare professional who is dispatched via an app to a medical emergency in addition to an ambulance. Data are value (percentage) or mean ± SD (95% CI).

TABLE 3 | Course participants self-evaluation and usefulness of the assessment method to assess human factors as perceived by the course participants.

Characteristic	1-day ILS-course			2-day ALS-course		
Assessment	**Simulated team** ***n* = 111**	**Real team** ***n* = 116**	***P-value*[a]**	**Simulated team** ***n* = 106**	**Real team** ***n* = 90**	***P-value*[a]**
Competent as team member	7.1 ± 1.6 (6.8–7.4)	7.6 ± 1.2 (7.4–7.9)	0.032	7.2 ± 1.7 (6.9–7.6)	7.8 ± 1.5 (7.5–8.1)	<0.01
Further training as team member needed	6.4 ± 2.3 (6.0–6.8)	5.8 ± 2.9 (5.3–6.4)	0.189	6.8 ± 2.6 (6.3–7.3)	5.5 ± 3.1 (4.9–6.2)	<0.01
Competent as team leader	5.8 ± 1.8 (5.4–6.1)	6.0 ± 1.8 (5.7–6.3)	0.422	5.7 ± 2.2 (5.3–6.1)	6.0 ± 1.9 (5.6–6.4)	0.286
Further training as team leader needed	8.4 ± 1.6 (8.1–8.7)	8.2 ± 1.8 (7.9–8.5)	0.791	8.7 ± 1.5 (8.4–8.9)	8.1 ± 2.0 (7.7–8.5)	0.064
Team leader	8.1 ± 1.8 (7.7–8.4)	8.5 ± 1.2 (8.3–8.7)	0.327	7.5 ± 2.3 (7.1–8.0)	8.0 ± 2.0 (7.6–8.4)	0.145
Team member	4.2 ± 3.4 (3.5–4.8)	6.0 ± 2.9 (5.5–6.6)	<0.01	4.0 ± 3.3 (3.4–4.6)	5.3 ± 3.3 (4.6–6.0)	<0.01
Communication	6.7 ± 2.3 (6.3–7.1)	7.6 ± 1.8 (7.3–8.0)	<0.01	5.9 ± 3.0 (5.3–6.5)	7.4 ± 2.5 (6.9–7.9)	<0.01
Team management	6.4 ± 2.6 (5.9–6.9)	8.1 ± 1.6 (7.8–8.4)	<0.01	5.7 ± 3.1 (5.1–6.3)	7.7 ± 2.3 (7.2–8.2)	<0.01
CPR skills	5.9 ± 3.3 (5.3–6.6)	7.8 ± 2.0 (7.5–8.2)	<0.01	5.8 ± 3.4 (5.1–6.5)	7.1 ± 2.6 (6.6–7.7)	<0.01
Knowledge	7.0 ± 2.0 (6.6–7.3)	7.1 ± 1.9 (6.8–7.5)	0.734	7.8 ± 1.5 (7.6–8.1)	7.6 ± 1.9 (7.2–8.0)	0.585
Situational awareness	7.8 ± 1.6 (7.5–8.1)	8.2 ± 1.6 (7.9–8.5)	0.023	8.0 ± 1.9 (7.7–8.4)	8.0 ± 2.2 (7.6–8.5)	0.673
Assessment overall	7.9 ± 1.8 (7.6–8.3)	8.2 ± 1.4 (8.0–8.5)	0.515	7.5 ± 2.3 (7.0–7.9)	7.5 ± 2.1 (7.0–7.9)	0.756

Data are mean ± SD (95% CI). ILS, Immediate Life Support; ALS, Advanced Life Support; VAS, Visual Analog Scale (0–10); CPR, cardiopulmonary resuscitation.
[a]Mann–Whitney-U test.

were comparable (p = 0.194 and 0.372). The team member and team leader competences dropped for both assessment methods (all $p < 0.01$). All students agreed at the time of the follow-up that further training is necessary for team members and leaders (all $p > 0.05$).

Table 4 shows the detailed results of the assessments. ILS course participants had a first attempt cardiac-arrest simulation-test passing rate of 80–84%; whereas ALS course participants in 92-95%. The detailed results are comparable between both course types and assessments, but some items scored differently (**Table 4**).

DISCUSSION

Instructors of advanced life support courses judge the real team assessment overall significantly better and rate its ability to test all human factors and CPR-skills better compared to the simulated team assessment. Participating students agree that team membership and management, communication, and CPR skills were better assessed by

TABLE 4 | Objective results from the official European Resuscitation Council cardiac arrest scenario teaching forms as judged by the instructors.

Characteristic	1-day ILS course			2-day ALS course		
Assessment	**Simulated team** ***n*** **= 111**	**Real team** ***n*** **= 116**	***P-value***[a]	**Simulated Team** ***n*** **= 106**	**Real team** ***n*** **= 90**	***P-value***[a]
Overall Result						
First attempt successful	93 (84)	93 (80)	0.480	101 (95)	83 (92)	0.373
Detailed Results						
ABCDE*	17/49/18/4 (19/56/20/5)	17/54/39/1 (15/49/35/1)	0.065	57/34/12/1 (55/33/11/1)	51/28/7/0 (59/33/8/0)	0.673
Oxygen and vascular access*	28/45/16/2 (31/49/18/2)	29/76/2/0 (27/71/2/0)	< 0.01	58/43/4/0 (55/41/4/0)	55/31/3/0 (62/35/3/0)	0.652
Recognizes condition*	28/36/14/11 (31/41/16/12)	14/52/16/13 (15/54/17/14)	0.053	69/27/8/1 (65/26/8/1)	58/20/6/0 (69/24/7/0)	0.811
Gives medication*	18/31/10/21 (22/39/13/26)	20/27/8/33 (23/31/9/37)	0.408	60/27/13/1 (59/27/13/1)	62/15/6/2 (73/18/7/2)	0.169
Further medication*	7/18/4/35 (11/28/6/55)	8/23/8/33 (11/32/11/46)	0.659	33/34/15/5 (38/39/17/6)	29/21/12/4 (44/32/18/6)	0.823
Other treatment*	2/15/2/38 (4/26/4/66)	7/12/9/39 (10/18/14/58)	0.078	28/24/18/5 (37/32/24/7)	31/20/11/7 (45/29/16/10)	0.514
Recognizes arrest*	65/33/8/3 (60/30/7/3)	61/48/6/1 (53/41/5/1)	0.264	76/25/4/0 (72/24/4/0)	67/17/6/0 (74/19/7/0)	0.511
Call for help*	44/29/10/20 (43/28/10/19)	38/48/8/8 (37/47/8/8)	0.015	30/38/16/4 (34/43/18/5)	43/25/6/0 (58/34/8/0)	< 0.01
CPR 2 min*	67/37/4/1 (61/34/4/1)	61/48/3/0 (54/43/3/0)	0.422	74/26/3/1 (71/25/3/1)	68/16/3/0 (78/18/4/0)	0.544
Airway*	57/47/3/0 (53/44/3/0)	45/62/2/1 (41/56/2/1)	0.201	65/30/2/1 (66/31/2/1)	69/16/2/1 (79/18/2/1)	0.278
Monitoring*	62/38/3/2 (59/36/3/2)	54/49/0/1 (52/47/0/1)	0.153	66/26/3/0 (70/27/3/0)	61/21/3/0 (72/25/3/0)	0.917
Epinephrine*	61/34/6/5 (57/32/6/5)	47/44/12/10 (41/39/11/9)	0.088	75/18/7/2 (73/18/7/2)	62/19/4/1 (73/20/6/1)	0.787
Reversible causes*	37/35/16/10 (38/36/16/10)	8/42/24/14 (9/48/27/16)	< 0.01	55/35/7/2 (56/35/7/2)	46/23/11/2 (56/28/14/2)	0.458
Recognizes rhythm change*	68/31/5/3 (63/29/5/3)	75/36/3/1 (65/31/3/1)	0.587	85/16/3/1 (81/15/3/1)	66/18/2/1 (76/21/2/1)	0.794
Defibrillation*	67/31/6/4 (62/29/5/4)	73/41/1/0 (63/36/1/0)	0.029	85/16/3/1 (81/15/3/1)	68/15/3/2 (77/17/4/2)	0.858
CPR 2 min*	68/35/2/0 (65/33/2/0)	70/41/2/1 (61/36/2/1)	0.769	79/22/2/0 (77/21/2/0)	68/15/1/1 (80/18/1/1)	0.621
Recognizes rhythm change*	64/30/3/3 (64/30/3/3)	61/41/1/2 (58/39/1/2)	0.414	83/16/2/1 (81/16/2/1)	59/17/1/1 (76/22/1/1)	0.743
Further Epinephrine*	40/31/6/15 (43/34/7/16)	26/37/10/9 (32/45/12/11)	0.142	34/26/23/3 (40/30/27/3)	34/22/8/7 (48/31/11/10)	0.050
Minimizes interruptions*	61/32/3/1 (63/33/3/1)	58/38/5/2 (56/37/5/2)	0.742	68/32/1/1 (67/31/1/1)	63/14/4/1 (77/17/5/1)	0.074
Defibrillation*	57/28/9/5 (58/28/9/5)	42/44/9/4 (42/45/9/4)	0.115	78/16/8/3 (74/15/8/3)	61/14/3/2 (76/18/4/2)	0.722

(Continued)

TABLE 4 | (Continued)

Characteristic	1-day ILS course			2-day ALS course		
Assessment	**Simulated team** ***n*** **= 111**	**Real team** ***n*** **= 116**	***P-value***[a]	**Simulated Team** ***n*** **= 106**	**Real team** ***n*** **= 90**	***P-value***[a]
Detailed Results						
CPR 2 min*	65/29/2/1	53/37/6/0	0.159	74/23/3/0	61/16/1/1	0.557
	(67/30/2/1)	(55/39/6/0)		(74/23/3/0)	(77/21/1/1)	
Recognizes rhythm change*	58/30/1/2	48/45/5/0	0.039	76/24/2/0	65/18/1/1	0.679
	(64/33/1/2)	(49/46/5/0)		(75/23/2/0)	(77/21/1/1)	
Signs of life*	51/32/4/2	44/46/3/2	0.395	70/26/6/0	66/18/1/1	0.186
	(57/36/5/2)	(46/49/3/2)		(69/25/6/0)	(77/21/1/1)	
Post resuscitation care*	31/36/11/1	14/39/11/1	0.156	46/36/4/1	39/22/4/1	0.779
	(39/46/14/1)	(22/60/17/1)		(53/41/5/1)	(59/33/6/2)	

*Data are value (percentage). ILS, Immediate Life Support; ALS, Advanced Life Support; CPR, cardiopulmonary resuscitation. Scale: 1 = outstanding, 2 = adequate, 3 = marginal, 4 = insufficient. ABCDE, Airway, Breathing, Circulation, Disability, Exposure/Environment. *Missing values, [a]Chi-square test.*

the real team assessment. However, students rated the assessments as comparable in the following categories: the assessment in general, team leadership, and knowledge. Situational awareness was only rated better in the 1-day ILS course, whereas judged as comparable in the 2-day ALS course.

Our course participants self-assessed their competence as team members higher than as team leaders, regardless of the assessment method used. They also agreed that further training as a team leader is more important than team membership training. These findings are consistent with findings from other researchers (21, 22).

The importance of training human factors in cardiopulmonary resuscitation courses is well established (23–25). Resuscitation teams who applied human factors efficiently also performed better in technical resuscitation skills (26). If a team leader performs hands-on procedures, the whole team is less effective (27). Prior participation in an advanced life support course improved the team leader's ability to stay hands off (27). Nowadays, all courses include team leadership training, even though there is very little evidence that such specific leadership training during those courses leads to improved patient outcome (10). However, training in resuscitation skills, in general, was able to improve patient outcome (7).

It was unclear if current end-of-course summative assessments can test these human factor competences adequately. Therefore, the current study asked participants and instructors to judge subjectively two different assessment methods, the simulated team assessment, and the real team assessment. Participants found that both assessments are equally effective to test their team leadership skills. However, the included instructors who have experience with multiple course participants have a different opinions. The instructors clearly judge the real team assessment as superior in its ability to test team leadership skills. Training leadership skills prior to being involved in a real cardiac arrest is important (28, 29). Unfortunately, our data shows only the opinions of course participants and instructors. Further research is necessary to objectively assess the competences for such team leadership factors, and if one assessment approach is suitable to assess these competences in different advanced life support formats (e.g., for neonatal, pediatric, or adult resuscitation).

Participants of a qualitative analysis of human factors identified teamwork issues as most challenging during pediatric cardiac arrests (21). Our participants rated team membership competences consistently lower than team leadership competences. The real team assessment was judged to be better suitable to test team membership compared to the simulated team assessment. The lower scores for team membership compared to the other aspects of this study introduces the question if there is a need to adjust the current assessment method to allow better assessment of team membership competences. Regardless of the assessment method used, team members are not allowed to act as "real team members" during an assessment, they only act on team leaders' commands. Assessment of team member competences is therefore not possible. In contrast, during cardiopulmonary resuscitation courses, team membership skills are trained, and course participants are encouraged to act as they would in real life and support their team leader with all their knowledge and skills.

Communication during a cardiac arrest needs to be clear, concise, brief, empathetic, and trigger a feedback loop. It needs to be targeted directly at a person and closing the loop is advisable (30, 31). ERC cardiopulmonary resuscitation courses emphasize proper communication and specifically focus on hindering factors for speaking up, which is key for success in cardiac arrest situations (29, 30). Research showed that simple and short ongoing educational interventions on leadership principles can improve team leadership and communication competences significantly (24, 32, 33). Our results show that such communication competences can be better assessed with the real team assessment compared to the simulated team assessment.

Shared situational awareness enables better teamwork (30). Both assessment methods were rated comparably by our ALS course participants. However, ILS course participants and instructors think situational awareness can be better assessed by real team assessments. The inconsistency in these findings

suggests that situational awareness might depend more on the assessment setting itself, than on the assessment method.

Interestingly, over the 1 year between the initial study and the follow-up, 11 medical students (participants of the 1-day ILS course) were successfully recruited as Bern First Responders, some of them during the ILS courses (34) (A First Responder is a trained layperson or healthcare professional who is dispatched *via* an app to a medical emergency in addition to an ambulance). This should be considered a positive outcome given that health care professionals might get easily overwhelmed with the additional burden of being a First Responder (35).

This study has several limitations. It was a single-center study focusing on medical students as course participants in official European Resuscitation Council advanced life support courses. The University of Bern offers a large medical program with more than 340 medical students per study year. The medical students were randomly assigned by the University to their courses. There is a slight chance that medical students assessed together also worked together during course work or clinically as a team of students prior to their participation in the respective courses, therefore, we cannot exclude an effect of this on leadership and teamwork. Groups for the real team assessment were chosen randomly, and care was taken that students who had trained together during the course were not assessed together. Although there have been many study participants in this study, there are two cohorts of participants which limits the generalizability of the data, half of the study participants participated in a 1-day ILS course, and half in a 2-day ALS course. Randomization was performed for the whole course due to practical reasons and not for the individual course participant.

On the other hand, this study has several strengths as it was planned and executed as a large randomized controlled trial and each participant was only included once. Both the instructors' and the participants' perspectives are included.

In conclusion, instructors of advanced life support courses rated a summative course assessment in real teams significantly better regarding the ability to test team leadership, team membership, communication, team management, and situational awareness compared to simulated team assessments, which is the current European Resuscitation Council's standard end-of-course assessment. Course participants rated team leadership and partly situational awareness as comparable between both assessment methods. These results might influence current summative assessment practices in advanced life support courses.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author with a dedicated research question and local ethics committee approval.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Cantonal Ethics Committee of Bern, Switzerland. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SN had the idea of the study, performed data acquisition, data evaluation, first manuscript, and approved final manuscript. SH and LT contributed to data evaluation, significant contribution to manuscript, and approved final manuscript. CS and AH contributed to data acquisition, significant contribution to manuscript, and approved final manuscript. RG performed data acquisition, data evaluation, significant contribution to manuscript, and approved final manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Sandroni C, Nolan J, Cavallaro F, Antonelli M. In-hospital cardiac arrest: incidence, prognosis and possible measures to improve survival. *Intensive Care Med.* (2007) 33:237–45. doi: 10.1007/s00134-006-0326-z
2. Grasner JT, Herlitz J, Tjelmeland IBM, Wnent J, Masterson S, Lilja G, et al. European resuscitation council guidelines 2021: epidemiology

of cardiac arrest in Europe. *Resuscitation.* (2021) 161:61–79. doi: 10.1016/j.resuscitation.2021.02.007
3. Perkins GD, Graesner JT, Semeraro F, Olasveengen T, Soar J, Lott C, et al. European resuscitation council guidelines 2021: executive summary. *Resuscitation.* (2021) 161:1–60. doi: 10.1016/j.resuscitation.2021.02.003
4. Smith GB, Welch J, DeVita MA, Hillman KM, Jones D. Education for cardiac arrest–treatment or prevention? *Resuscitation.* (2015) 92:59–62. doi: 10.1016/j.resuscitation.2015.04.018
5. Greif R, Lockey A, Breckwoldt J, Carmona F, Conaghan P, Kuzovlev A, et al. European resuscitation council guidelines 2021: education for resuscitation. *Resuscitation.* (2021) 161:388–407. doi: 10.1016/j.resuscitation.2021.02.016
6. Nabecker S, Huwendiek S, Theiler L, Huber M, Petrowski K, Greif R, et al. The effective group size for teaching cardiopulmonary resuscitation skills - A randomized controlled simulation trial. *Resuscitation.* (2021) 165:77–82.
7. Lockey A, Lin Y, Cheng A. Impact of adult advanced cardiac life support course participation on patient outcomes-A systematic review and meta-analysis. *Resuscitation.* (2018) 129:48–54. doi: 10.1016/j.resuscitation.2018.05.034
8. Greif R, Bhanji F, Bigham BL, Bray J, Breckwoldt J, Cheng A, et al. Education, implementation, and teams: 2020 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Resuscitation.* (2020) 156:A188–239. doi: 10.1016/j.resuscitation.2020.09.014
9. Greif R, Lockey AS, Conaghan P, Lippert A, De Vries W, Monsieurs KG, et al. European resuscitation council guidelines for resuscitation 2015: section 10. Education and implementation of resuscitation. *Resuscitation.* (2015) 95:288–301. doi: 10.1016/j.resuscitation.2015.07.032
10. Kuzovlev A, Monsieurs KG, Gilfoyle E, Finn J, Greif R, Education Implementation and Teams Task Force of the International Liaison Committee on Resuscitation. The effect of team and leadership training of advanced life support providers on patient outcomes: a systematic review. *Resuscitation.* (2021) 160:126–39. doi: 10.1016/j.resuscitation.2021.01.020
11. Wyckoff MH, Singletary EM, Soar J, Olasveengen TM, Greif R, Liley HG, et al. 2021 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: summary From the Basic Life Support; Advanced Life Support; Neonatal Life Support; Education, Implementation, and Teams; First Aid Task Forces; and the COVID-19 Working Group. *Resuscitation.* (2021) 69:229–311. doi: 10.1016/j.resuscitation.2021.10.040
12. Fletcher G, Flin R, McGeorge P, Glavin R, Maran N, Patey R. Anaesthetists' non-technical skills (ANTS): evaluation of a behavioural marker system. *Br J Anaesth.* (2003) 90:580–8. doi: 10.1093/bja/aeg112
13. Gerstle CR. Parallels in safety between aviation and healthcare. *J Pediatr Surg.* (2018) 53:875–8. doi: 10.1016/j.jpedsurg.2018.02.002
14. Cooper S, Cant R, Porter J, Sellick K, Somers G, Kinsman L, et al. Rating medical emergency teamwork performance: development of the team emergency assessment measure (TEAM). *Resuscitation.* (2010) 81:446–52. doi: 10.1016/j.resuscitation.2009.11.027
15. Mishra A, Catchpole K, McCulloch P. The Oxford NOTECHS System: reliability and validity of a tool for measuring teamwork behaviour in the operating theatre. *Qual Saf Health Care.* (2009) 18:104–8. doi: 10.1136/qshc.2007.024760
16. Malec JF, Torsher LC, Dunn WF, Wiegmann DA, Arnold JJ, Brown DA, et al. The mayo high performance teamwork scale: reliability and validity for evaluating key crew resource management skills. *Simul Healthc.* (2007) 2:4–10. doi: 10.1097/SIH.0b013e3180315539
17. Moorthy K, Munz Y, Adams S, Pandey V, Darzi A. A human factors analysis of technical and team skills among surgical trainees during procedural simulations in a simulated operating theatre. *Ann Surg.* (2005) 242:631–9. doi: 10.1097/01.sla.0000186298.79308.a8
18. Dagnone JD, Hall AK, Sebok-Syer S, Klinger D, Woolfrey K, Davison C, et al. Competency-based simulation assessment of resuscitation skills in emergency medicine postgraduate trainees - a Canadian multi-centred study. *Can Med Educ J.* (2016) 7:e57–67.
19. Ringsted C, Lippert F, Hesselfeldt R, Rasmussen MB, Mogensen SS, Frost T, et al. Assessment of Advanced Life Support competence when combining different test methods–reliability and validity. *Resuscitation.* (2007) 75:153–60. doi: 10.1016/j.resuscitation.2007.03.003
20. Boileau E, Patenaude J, St-Onge C. Twelve tips to avoid ethical pitfalls when recruiting students as subjects in medical education research. *Med Teach.* (2018) 40:20–5. doi: 10.1080/0142159X.2017.1357805
21. Walsh O, Lydon S, O'Connor P. A mixed methods evaluation of paediatric trainee preparedness to manage cardiopulmonary arrests. *Eur J Pediatr.* (2017) 176:1653–62. doi: 10.1007/s00431-017-3017-6
22. Manser T. Teamwork and patient safety in dynamic domains of healthcare: a review of the literature. *Acta Anaesthesiol Scand.* (2009) 53:143–51. doi: 10.1111/j.1399-6576.2008.01717.x
23. Norris EM, Lockey AS. Human factors in resuscitation teaching. *Resuscitation.* (2012) 83:423–7. doi: 10.1016/j.resuscitation.2011.11.001
24. Hunziker S, Johansson AC, Tschan F, Semmer NK, Rock L, Howell MD, et al. Teamwork and leadership in cardiopulmonary resuscitation. *J Am Coll Cardiol.* (2011) 57:2381–8. doi: 10.1016/j.jacc.2011.03.017
25. Fernandez Castelao E, Boos M, Ringer C, Eich C, Russo SG. Effect of CRM team leader training on team performance and leadership behavior in simulated cardiac arrest scenarios: a prospective, randomized, controlled study. *BMC Med Educ.* (2015) 15:116. doi: 10.1186/s12909-015-0389-z
26. Peltonen V, Peltonen LM, Salantera S, Hoppu S, Elomaa J, Pappila T, et al. An observational study of technical and non-technical skills in advanced life support in the clinical setting. *Resuscitation.* (2020) 153:162–8. doi: 10.1016/j.resuscitation.2020.06.010
27. Cooper S, Wakelam A. Leadership of resuscitation teams: "Lighthouse Leadership'. *Resuscitation.* (1999) 42:27–45. doi: 10.1016/s0300-9572(99)00080-5
28. Cant RP, Porter JE, Cooper SJ, Roberts K, Wilson I, Gartside C. Improving the non-technical skills of hospital medical emergency teams: the team emergency assessment measure (TEAM). *Emerg Med Australas.* (2016) 28:641–6. doi: 10.1111/1742-6723.12643
29. Andersen PO, Jensen MK, Lippert A, Østergaard D. Identifying non-technical skills and barriers for improvement of teamwork in cardiac arrest teams. *Resuscitation.* (2010) 81:695–702. doi: 10.1016/j.resuscitation.2010.01.024
30. Jones CPL, Fawker-Corbett J, Groom P, Morton B, Lister C, Mercer SJ. Human factors in preventing complications in anaesthesia: a systematic review. *Anaesthesia.* (2018) 73:12–24. doi: 10.1111/anae.14136
31. Ulmer FF, Lutz AM, Muller F, Riva T, Bütikofer L, Greif R. Communication patterns during routine patient care in a pediatric intensive care unit: the behavioral impact of in situ simulation. *J Patient Saf.* (2021) 18:e573–9. doi: 10.1097/PTS.0000000000000872
32. Lee SH, Khanuja HS, Blanding RJ, Sedgwick J, Pressimone K, Ficke JR, et al. Sustaining teamwork behaviors through reinforcement of TeamSTEPPS principles. *J Patient Saf.* (2017) 17:e582–6. doi: 10.1097/PTS.0000000000000414
33. Hunziker S, Buhlmann C, Tschan F, Balestra G, Legeret C, Schumacher C, et al. Brief leadership instructions improve cardiopulmonary resuscitation in a high-fidelity simulation: a randomized controlled trial. *Crit Care Med.* (2010) 38:1086–91. doi: 10.1097/CCM.0b013e3181cf7383
34. Marx D, Greif R, Egloff M, Balmer Y, Nabecker S. Recruiting medical students for a first responder project in the social age: direct contact still outperforms social media. *Emerg Med Int.* (2020) 2020:9438560. doi: 10.1155/2020/9438560
35. Nabecker S, Theodorou M, Huwendiek S, Kasper N, Greif R. Out-of-hospital cardiac arrest: comparing organised groups to individual first responders: a qualitative focus group study. *Eur J Anaesthesiol.* (2021) 38:1096–104. doi: 10.1097/EJA.0000000000001335

Conflict of Interest: SN was a European Resuscitation Council—Instructor Educator Support Science and Education Committee (SEC-IES) member, and the current education representative of the young ERC group of the European Resuscitation Council. SN was also a Canadian Anesthesiologists' Society (CAS) CEPD (Continuing Education and Professional Development) Committee member. RG was the European Resuscitation Council's Board Director of Guidelines and ILCOR and Chair of the ILCOR Task Force on Education, Implementation, and Team. SN, CS, AH, and RG were currently Life Support instructors with the European Resuscitation Council.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Acute effects of singing on cardiovascular biomarkers

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Background: Singing is a physical activity involving components of the vagal nerves manifested as changes in cardiac autonomic regulation.

Aims: The aim of this pilot study is to investigate the acute effects of singing on biomarkers of cardiovascular health.

Methods: Adult subjects were recruited from cardiology clinics to participate in a single 90-min study visit. Vascular function was measured at the fingertips with peripheral arterial tonometry (PAT) before and after singing to a 14-min video led by a voice expert. Heart rate variability (HRV) was measured with a chest strap sensor at baseline, during, and after singing. PAT measurements were expressed as reactive hyperemia index (RHI) and Framingham reactive hyperemia index (fRHI). Measures of HRV included root mean square of successive RR interval differences (RMSSD) and standard deviation of NN (or RR) intervals (SDNN).

Results: Sixty subjects completed the study (68% female, mean age 61 ±13 years, mean BMI 32 ± 8). There was a significant increase in fRHI (1.88 ± 0.14 to 2.10 ± 0.14, $p = 0.02$) after singing with no significant change in the RHI (1.99 ± 0.10 to 2.12 ± 0.09, $p = 0.22$). There was a reduction in HRV during singing (compared to baseline) (RMSSD: 42.0 ± 5 to 32.6 ± 4, $p = 0.004$ and SDNN: 54 ± 4 to 33.5 ± 3, $p = 0.009$). HRV measures trended back toward baseline after singing.

Conclusions: A short duration of singing improved vascular function acutely. Improvements were more substantial in subjects with abnormal baseline endothelial function. HRV patterns were similar to that of light-intensity exercise. Future studies should confirm favorable vascular adaptation to more sustained singing interventions.

Clinical trial registration: ClinicalTrials.gov, identifer: NCT03805529.

KEYWORDS

singing, vascular function, endothelial function, heart rate variability (HRV), cardiac rehabilitation

Introduction

Cardiovascular disease (CVD) is the leading cause of death in most developed countries (in men and women), claiming more lives each year than cancer and chronic respiratory disease combined (1). Lifetime risk of CVD approaches 50% for persons age 30 years without known CVD (2). As of 2014, the prevalence of CVD in the US was 36.6%. By 2035, 45.1% of the US population is projected to have some form of CVD (3). Many patients diagnosed with CVD are eligible for participation in cardiac rehabilitation (CR) programs, which include comprehensive, long-term services involving medical evaluation, supervised exercise, cardiac risk factor modification, education, and counseling. Proven benefits include improvement in exercise capacity, risk factors, medication adherence, control of cardiac symptoms, reduction in recurrent myocardial infarction, improved survival after percutaneous coronary intervention and coronary artery bypass surgery, and improved quality of life (4–8). The safety and efficacy of cardiac rehabilitation have been demonstrated in all patients (9). Despite the benefits and safety, CR utilization rates are low. Reasons for non-participation include other comorbidities (arthritis, chronic obstructive pulmonary disease, diabetes with neuropathy) or disability, polypharmacy, frailty, deconditioning, and other challenges that make participation (or the perception of participation) difficult (10–12).

Alternative or adjunctive forms of rehabilitation to reduce CVD burden and improve health should be considered. Singing is a physical activity that involves many components of the vagal nerves (i.e., the pulmonary efferent fibers and afferent fibers of the recurrent laryngeal nerve) manifested as changes in cardiac autonomic regulation (13, 14). It requires both passive and active breathing, muscle coordination and various breathing techniques, with almost no reliance on mobility or skeletal muscle strength. Limited studies have shown potential for singing interventions in patients with chronic obstructive pulmonary disease—primarily by improved lung function (15, 16). Singing also holds promise for improving gait, vocal function and depression in neurological disorders, such as Parkinson's disease (17, 18). Another study examined the impact of singing in cancer patients and caregivers of cancer patients and found preliminary evidence that singing improves mood state and modulates components of the immune system—even after a single choir rehearsal session (19). However, patients with established CVD have not been studied in this context despite promising findings in other chronic disease populations. Because the cardiovascular and respiratory systems are intimately related and work together to deliver oxygen to all cells in the body, singing would be anticipated to have favorable effects on markers of cardiovascular health, and this is what we aim to investigate in this pilot study.

Two excellent biomarkers of cardiovascular health include non-invasive measures of vascular function, such as fingertip peripheral arterial tonometry (PAT), and heart rate variability (HRV). PAT measurements have significant predictive value for future cardiovascular events (20), and microvascular function can be improved by interventions known to reduce cardiovascular risk (21–23). HRV is the variability between R-R intervals in successive heartbeats and is the result of a complex interaction between respiratory activity and autonomic cardiovascular control between the two branches of the autonomic nervous system (sympathetic and parasympathetic) (24). Measurements of HRV have been found to be powerful predictors of cardiac morbidity and mortality (25, 26).

The aim of this pilot study is to investigate the acute effects of singing on biomarkers of cardiovascular health. Our hypothesis is that cardiac patients will have favorable improvements in vascular endothelial function and heart rate variability, after a single session of singing.

Methods

Subject recruitment

All subject-related study activities were performed at the Medical College of Wisconsin campus with IRB approval. Adult patients visiting our cardiology clinics were informed of the study and given an informational flyer by their clinic provider. If the patient contacted the study team, a brief overview of the study was provided over the phone and initial eligibility was determined in the form of a short screening questionnaire, which included inclusion and exclusion criteria. Subjects were $\geq$18 years of age and willing and able to sign informed consent. Exclusion criteria included: permanent pacemaker or implantable cardioverter defibrillator (ICD), history of atrial fibrillation, Parkinson's disease or tremor, amputated upper extremity, presence of upper-arm fistula, fingernail onychomycosis, pregnancy, current tobacco use, current illicit drug use, current excessive alcohol intake (defined as more than 14 drinks/week for women, more than 28 drinks/week for men) unstable coronary heart disease (active symptoms of chest discomfort), supplemental oxygen use, and non-English speaking. If the subject satisfied the above screening criteria, a copy of the IRB consent form was mailed to them, and a single 90-min visit was scheduled during clinic operating hours. Subjects were advised to remain fasting for a minimum of 3 h prior to the study visit.

General study design

At the study visit, written informed consent was obtained. Subjects were asked to complete a questionnaire including

the following information: age, gender, race/ethnicity, history of tobacco use, alcohol use, frequency and intensity of exercise and any physical limitations, past medical and surgical history including hypertension, coronary artery disease (as evidenced by coronary angiography, history of myocardial infarction, percutaneous coronary intervention, or coronary bypass surgery), diabetes mellitus, heart failure, chronic lung disease, high cholesterol, chronic kidney disease, thyroid disease, peripheral arterial disease, and stroke. Current medications were documented. Baseline vital signs (heart rate, blood pressure, pulse oximetry), weight and height were obtained prior to the music intervention.

Singing protocol

In a seated position in a private exam room, subjects watched and sang along to a 14-min coaching video created by a music professor, which included vocal warm-up exercises followed by the Star-Spangled Banner, repeated at various tempos and pitches. During this video, the professor played the piano and coached the subject through the warm-up and singing. Lyrics were displayed along the bottom of the video.

Peripheral vascular function assessment using digital peripheral arterial tonometry

Vascular endothelial function was measured by digital pulse arterial tonometry (Endo-PAT 2000, Itamar Medical, Israel). Endothelium-mediated changes in vascular tone after occlusion of the brachial artery are reflecting a downstream hyperemic response, which is a measure for arterial endothelial function (27). Measurements were performed prior to and 1 min following the 14-min singing protocol, according to the manufacturer's instructions (28). Briefly, the subjects were in a supine position for at least 20 min, in a quiet, temperature-controlled room (70–75°F) with a non-condensing humidity. Subjects were asked to remain still and silent during the measurement period with disposable, pneumatic probes on both index fingers. Each recording consisted of 5 min of baseline measurement, 5 min of occlusion measurement, and 5 min post-occlusion measurement (hyperemic period). Occlusion of the brachial artery was performed on the non-dominant upper arm and verified by the absence of a PAT signal from the occluded arm. The occlusion pressure was at least 60 mm Hg above the systolic blood pressure (maximum 200 mm Hg).

PAT measurements were expressed as reactive hyperemia index (RHI) and Framingham reactive hyperemia index (fRHI) (29). The RHI is the PAT signal at the 90–150 s post-deflation interval (30). A normal RHI was defined as >1.67; abnormal RHI was ≤1.67 (31, 32). To provide a better double-sided distribution closer to normal distribution, the log transformation of RHI was calculated (LnRHI). Normal LnRHI was defined as >0.51, abnormal LnRHI was ≤0.51. The fRHI is derived from the PAT signal at the 90- to 120-s post-deflation interval and is inversely related to cardiometabolic risk factors (29). The fRHI interval exhibited the strongest correlation to cardiovascular risk in the Framingham Third Generation Cohort participants using a multivariate risk model (29). Because preceding PAT measurements can affect subsequent measurements, a minimum period of 20 min was required between the pre- and post-singing measurements.

Heart rate variability assessment

To measure heart rate variability, an appropriately sized and Bluetooth-compatible heart rate sensor strap (Polar, Kempele, Finland) was applied to the subject's bare chest. One-minute-long heart rate and HRV recordings were taken before, during (about 10 min into singing the 14-min video) and (1 min) after completion of singing. The data was transmitted to an iPad using the Elite HRV (Asheville, NC) application and recorded on a study data sheet by research personnel. HRV was reported as the standard deviation of R-R (or NN) intervals (SDNN) and the root mean square of the successive differences (RMSSD), based on beat-to-beat differences in R-R intervals.

Additional measurements

Perceived exertion with singing was reported by study subjects using the Borg Rating of Perceived Exertion (RPE) scale (33). Subjects were education about the scale prior to the singing intervention. The numerical scale ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion". The Borg RPE is a well-validated, qualitative scale that is routinely used during cardiac treadmill testing to measure physical activity intensity level and is easy for patients to understand (34). The Borg RPE is the preferred method to assess intensity among those individuals who take medications that affect heart rate or pulse due to the scale's ability to capture exertion from central cardiovascular, respiratory, and nervous system functions (35). At the end of the singing intervention, subjects were asked to rate their perceived exertion level using the Borg RPE.

In addition, following the singing intervention, subjects were asked: On a scale of 1–10, how much did you enjoy singing today (where 1 is "not at all" and 10 is "very much enjoyed")? Two study staff agreed on a subjective rating of each subject's singing effort using a numerical scale of 1–5, with 1 indicating "very little effort" and 5 as "maximal effort" (see Supplementary Table 1 for more details). The study subjects were blinded to the effort rating.

TABLE 1 Baseline characteristics of participants ($n = 60$).

Age (range)	61 ± 13 (24–90)
Women (%)	41 (68)
Race	
% White	46 (77)
% Black	13 (22)
% Asian	1 (2)
BMI (kg/m^2)	32 ± 8
Prior tobacco use	18 (30)
Known coronary artery disease	26 (43)
History of congestive heart failure	10 (17)
Hypertension	36 (60)
Diabetes mellitus	14 (25)
Current statin use	33 (55)
Prior stroke/TIA	6 (10)
Chronic respiratory disease	17 (28)
Chronic physical or orthopedic limitations	26 (43)
ASCVD risk factors	
≤2 Risk factors	21 (35)
Known ASCVD or >2 risk factors	39 (65)
Baseline RHI	
Normal > 1.67	34 (57)
Abnormal ≤ 1.67	26 (43)

Age and BMI shown in mean years ± standard deviation (range). Other values shown as n (%).
RHI, reactive hyperemia index.

Statistical analysis

RHI by digital pulse arterial tonometry was the primary outcome of interest. For a 0.05 range in the RHI with 0.1 standard deviation, the effect size is 0.5. Our a priori power calculation determined that we would need 42 subjects to detect an effect size of 0.5 at $\alpha = 0.05$ significance level with 90% power. Generalized linear regression models were constructed to determine the effect of covariates (age, gender, history of CAD, prior tobacco use, history of heart failure, hypertension, statin medication use, diabetes, and beta blocker or calcium channel blocker use) on baseline RHI, fRHI, LnRHI, RMSSD, and SDNN.

Paired *t*-tests and repeated measures of variance were used to compare serial measures of vascular function and heart rate variability, respectively. Regression models were also performed to compare pre- and post-outcome measures, while adjusting for baseline values, to determine significant (covariate) predictors of change. In a separate analysis, models were adjusted for baseline RHI as a categorical variable (abnormal RHI ≤ 1.67 or normal RHI > 1.67). Linear mixed models were adjusted for repeated measures. Chi-square and Wilcoxon rank-sum tests were used to compare BORG RPE, self-reported enjoyment, and observed effort on improvement (yes or no) in vascular function and HRV outcome measures. *P*-values < 0.05 were considered significant.

Results

A total of 379 patients were informed of the study by their cardiologist. Of these, 63 patients had ≥1 exclusion criterion; 119 were not interested in participating (and were not approached by the study team). Of 215 interested in hearing more about the study, the most common reasons for non-participation were inability of study team to get in contact with the patient, travel distance to the hospital, and change of mind after hearing more about the study protocol. Subject characteristics are displayed in Table 1. Sixty subjects were enrolled (mean age 61 ± 13 years, 68% women). Hypertension was the most prevalent cardiovascular disease (CVD) risk factor, found in 60% of subjects, and 55% of subjects were currently on a statin medication. Forty-three percent of subjects had established coronary artery disease (as evidenced by obstructive disease on coronary angiography, history of myocardial infarction, percutaneous coronary intervention, or coronary bypass surgery). Eight subjects did not have one or both measures of RHI secondary to a weak or noisy PAT signal. Two subjects did not have usable HRV data secondary to technical difficulties with equipment.

Fifty-seven percent of subjects had abnormal baseline endothelial function (defined as an RHI ≤ 1.67). Statin use was associated with lower baseline RHI ($\beta = -0.40 \pm 0.2$, $p = 0.041$). Statin use and diabetes were associated with lower baseline fRHI ($\beta = -0.62 \pm 0.3$, $p = 0.015$ and -0.63 ± 0.3, $p = 0.006$, respectively). Results are displayed in Table 2. Although there was a trend toward improvement in the RHI after singing, this was not statistically significant (1.99 ± 0.10 to 2.12 ± 0.09, $p = 0.17$, Figure 1A). There was a significant increase in the fRHI after singing (1.88 ± 0.14 to 2.10 ± 0.14, $p = 0.023$, Figure 1B). Subjects with abnormal baseline endothelial function demonstrated significant improvement in the RHI after singing (1.40 ± 0.05 to 1.80 ± 0.13, $p = 0.01$, Figure 2B) compared to subjects with normal baseline RHI (2.32 ± 0.12 to 2.30 ± 0.11, $p = 0.82$, Figure 2A), with a similar result in the fRHI. Similarly, subjects at higher ASCVD risk, defined as established ASCVD or >2 risk factors, demonstrated a significant improvement in fRHI (1.82 ± 0.14 to 2.08 ± 0.13, $p = 0.015$) compared to subjects at lower ASCVD risk (2.35 ± 0.73 to 2.28 ± 0.70, $p = 0.78$). When stratified by gender, women (68% of cohort) had a statistically significant improvement in fRHI (1.80 ± 0.9 to 2.12 ± 0.9, $p = 0.007$) with singing when compared to males (2.04 ± 1.3 to 2.07 ± 1.2, $p = 0.83$). However, after adjustment for baseline fRHI, gender was no longer significant. The presence of abnormal RHI ≤ 1.67 at baseline consistently predicted improvement with singing after adjustment for pre-specified covariates (age, gender, history of

TABLE 2 Results ($n = 60$).

	Baseline	Singing	Post-singing
Vascular function			
RHI	1.99 ± 0.10	-	2.12 ± 0.09
fRHI	1.88 ± 0.14	-	*2.10 ± 0.14
LnRHI	0.63 ± 0.05	-	0.70 ± 0.04
HRV			
RMSSD	42.0 ± 4.9	*32.6 ± 4.0	40.4 ± 4.9
SDNN	54.0 ± 4.8	*33.5 ± 2.8	*42.9 ± 4.0
Average HR (bpm)	68.9 ± 1.8	70.3 ± 1.9	*66.8 ± 1.8
Blood pressure (mmHg)			
MAP	91 ± 1.3	*96 ± 2.2	*93 ± 1.3
SBP	128 ± 1.9	*136 ± 2.0	*131 ± 2.1
DBP	73 ± 1.3	*78 ± 1.5	74 ± 1.3
Oxygen saturation (%)	96.3 ± 0.27	*97.5 ± 0.22	96.0 ± 0.77
Enjoyment level	-	-	7.4 (1–10)
Observed effort	-	-	3.7 (1–5)
BORG RPE score	-	-	8.9 (6–14)

*$p < 0.05$ when compared to baseline.
Values represent means ± standard error or (range).
RHI, reactive hyperemia index; fRHI, Framingham reactive hyperemia index; LnRHI, log-transformed reactive hyperemia index; HRV, heart rate variability; RMSSD, root mean square of the successive differences; SDNN, standard deviation of R-R (or NN) intervals; HR, heart rate; MAP, mean arterial blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPE, rating of perceived exertion.

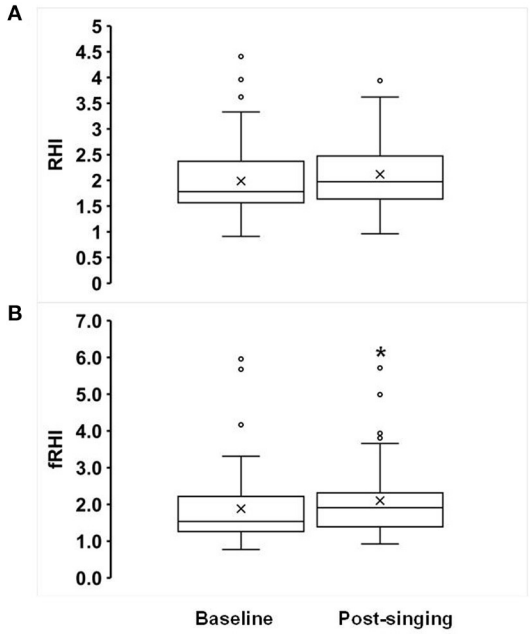

FIGURE 1
Effects of singing on Reactive Hyperemia Index (RHI, **A**) and Framingham RHI (fRHI, **B**). Box plots showing the following values: the mean (x), median, upper quartile (Q3), lower quartile (Q1), minimum and maximum whiskers as well as outliers. *$p < 0.05$.

CAD, hypertension, diabetes, history of heart failure, statin use; $\beta = 0.38 \pm 0.18$ to 0.43 ± 0.18, $p < 0.05$).

There was a significant decrease in both time-domain measures of HRV during singing: RMSSD decreased from 42 ± 4.9 ms to 33 ± 4.0 ms ($p = 0.004$, Figure 3A), and SDNN decreased from 54 ± 4.8 ms to 34 ± 2.8 ms ($p < 0.001$, Figure 3B). In addition, there was a reduction in SDNN post-singing (43 ± 4.0) compared to baseline ($p = 0.014$, Figure 3B). The mean heart rate (averaged over a 1-min recording) decreased pre- to post-singing (69 ± 2 to 67 ± 2 beats per min, $p = 0.008$, Supplementary Figure 1). The mean heart rate during singing (70 ± 2 bpm) was not different from baseline ($p = 0.16$). The oxygen saturation, as measured by pulse oximetry, increased while singing compared to baseline (97.5 ± 0.2% from 96.3 ± 0.3%, $p < 0.0001$). Mean arterial blood pressure (MAP, mm Hg) increased during (95.8 ± 2.2) and post-singing (93.3 ± 1.3) when compared to baseline [(91.5 ± 1.3), all $p \leq 0.02$].

Regression analyses were performed with HRV as the dependent variable and level of enjoyment (scale 1–10) as the independent variable. There were low-moderate, but statistically significant, positive correlations between both RMSSD and SDNN and enjoyment level during and after the singing intervention (Figure 4). There was no correlation between achieved BORG RPE score, level of enjoyment, or observed singing effort with the reactive hyperemic response (data not shown). In regression models (data not shown), none of the covariates (age, gender, history of CAD, hypertension, statin medication use, diabetes, and beta blocker use) were predictors of change in HRV or vascular function (RHI, LnRHI, fRHI), when adjusted for baseline values.

Discussion

To our knowledge, this is the first study to demonstrate acute improvement in peripheral endothelial function after a single, short period of singing. Subjects with abnormal baseline endothelial function and/or at highest ASCVD risk demonstrated the most significant improvement in endothelial function with singing when compared to subjects with normal baseline endothelial function and low ASCVD risk. As such, singing as a non-pharmacologic therapeutic may be most beneficial to patients with established atherosclerotic vascular disease.

A small number of prior studies have examined the impact of *listening* to music on markers of vascular health. Ripley et al. (36) randomized 70 subjects undergoing cardiac catherization for suspected coronary artery disease to music listening (slow, relaxing contemporary music) or no music. Vascular endothelial function, as measured by PAT, was performed before and after

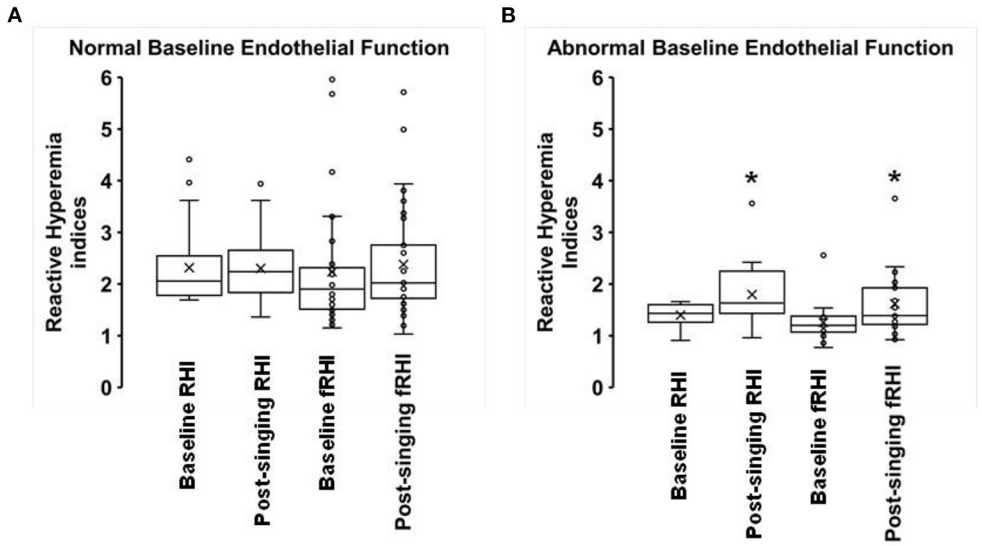

FIGURE 2
Baseline endothelial function and reactive hyperemia response **(A)** normal baseline, **(B)** $n = 34$; abnormal baseline, $n = 26$. Box plots showing the following values: the mean (x), median, upper quartile (Q3), lower quartile (Q1), minimum and maximum whiskers as well as outliers. *$p < 0.05$.

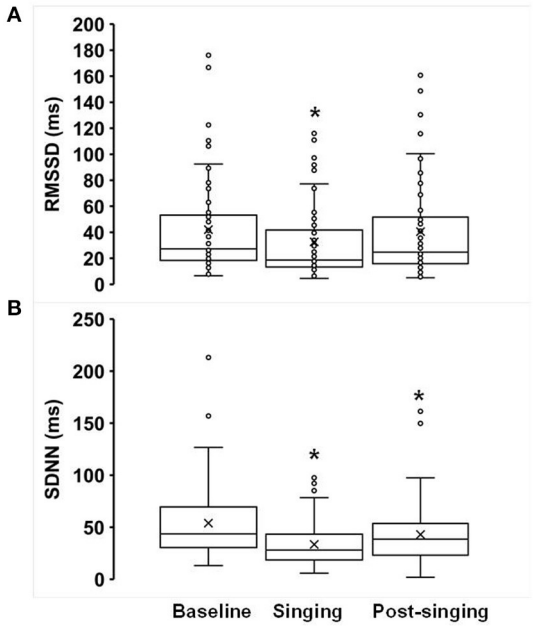

FIGURE 3
Effects of singing on heart rate variability **(A)** RMSSD and **(B)** SDNN. Box plots showing the following values: the mean (x), median, upper quartile (Q3), lower quartile (Q1), minimum and maximum whiskers as well as outliers. *$p < 0.05$.

catheterization. Listening to music did not elicit a vasodilator response, lower blood pressure, or heart rate, and did not relieve anxiety or stress. Patient musical preferences were not considered, and effects of moderate sedation and/or physical discomfort, may have contributed to the null findings. In a separate study, 9 of 10 volunteers experienced increased brachial artery flow-mediated dilation (FMD) (2.7% absolute increase; $p < 0.001$) after listening to 30 min of joyful music (self-selected by the subject). The mean FMD after listening to joyful music was significantly larger than the FMD response to anxiety-provoking music (0.6% absolute decrease; $p = 0.005$). However, this was a very small study consisting of young, healthy volunteers (37). Our study is larger with older subjects, many with established cardiovascular disease, and examines the impact of active singing rather than passive listening, on vascular health. In our study, active singing did not significantly improve endothelial function in healthy subjects with normal baseline endothelial function. These data suggest that subjects with healthier endothelium at baseline may need a larger stimulus to affect change or cannot augment their vascular endothelial function further. Vascular function remains an important biomarker to include in future studies since a meta-analysis concluded an 8–13% lower risk of cardiovascular events per 1%-point increase in brachial artery FMD (38).

Our study included 68% women. When stratified by gender, women had a statistically significant improvement in the fRHI ($n = 41$) compared to men ($n = 19$). Women had a lower mean baseline fRHI (1.80 ± 0.9 vs. 2.04 ± 1.3 for men, $p =$ NS), and the gender difference was no longer significant after adjustment for baseline fRHI. Our pilot study showed significantly more interest in (singing) participation by women. This is noteworthy since gender disparities in cardiac rehabilitation referral and adherence favor men even though women completing cardiac rehabilitation may experience greater reductions in mortality

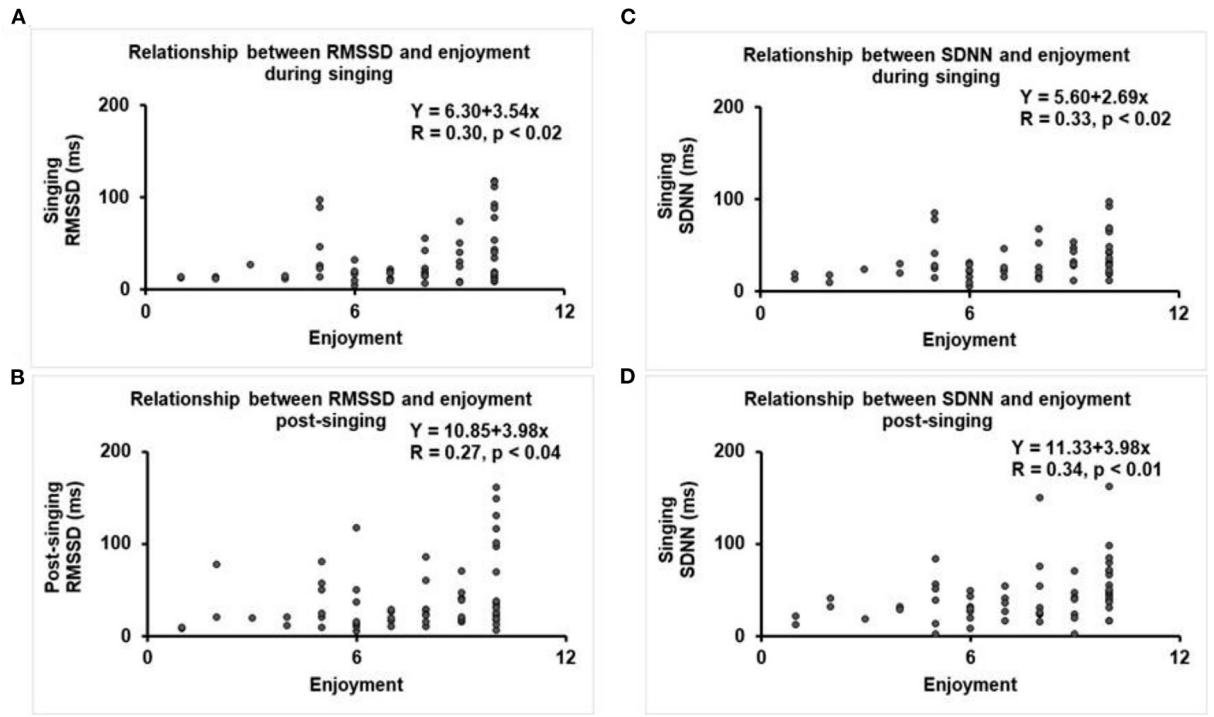

FIGURE 4
Regression plots between HRV and level of enjoyment (scale 1–10). **(A)** RMSSD during singing, **(B)** SDNN during singing, **(C)** RMSSD after singing, and **(D)** SDNN after singing.

(39, 40). Singing could serve as a more appealing therapy incorporated into traditional cardiac rehabilitation for older women (41). Moreover, whether singing as a component of cardiac rehabilitation could reduce barriers to referral and adherence to cardiac rehabilitation participation in women would be important to study in future trials.

Another means by which music may benefit the cardiovascular systems is by way of cardiac autonomic regulation. HRV reflects an interplay between the sympathetic and parasympathetic branches of the autonomic nervous system. Overall, systematic reviews demonstrate a positive impact of music listening on HRV, suggesting enhanced parasympathetic activity (42, 43). Far fewer studies have examined singing as a musical intervention. Singing and instrument playing, which are more active interventions, probably have different effects on cardiovascular physiology, as supported by the present study.

We examined measures of HRV prior to, during and after singing. The pattern of HRV changes observed were similar to those seen with exercise activity whereby exercise elicits a reduction in HRV when expressed in the time domain (SDNN and RMSSD), followed by a recovery toward baseline HRV post-exercise. The reduction in HRV during exercise is thought to be primarily mediated by reduced cardiac parasympathetic neural activity (cPNA), i.e., "parasympathetic withdrawal". The relative autonomic balance shifts from predominantly "parasympathetic control" at rest and with low exercise intensities to mainly "sympathetic control" at higher intensities. Loading of cardiopulmonary baroreceptors (due to increase in venous return from muscle pump action), muscle mechanoreceptors and systemic sympatho-adrenal activation are thought to also have roles in HRV changes associated with exercise (44). However, the physical act of singing has little to no reliance on any skeletal muscle activity. With singing, pulmonary receptors, lung mechanical effects and the adrenal response may be the drivers of "parasympathetic withdrawal". For example, respiratory sinus arrhythmia (RSA) occurs when a person's heart rate relates to their breathing cycle. Typically, the heart rate increases with inspiration and decreases during expiration (increasing overall HRV). Prior studies have shown that efficiency of pulmonary gas exchange is improved by RSA. Evidence is accumulating of a possible dissociation between RSA and vagal control of the heart rate, suggesting differential controls between respiratory modulation of cardiac vagal outflow and cardiac vagal tone (45). Evaluating the adrenal response to singing, perhaps with salivary cortisol levels, may help to elucidate contributions to "parasympathetic withdrawal" related to adrenal activation (or deactivation), and this should

be considered in future studies. Additionally, examining HRV in both the time and frequency domains can provide additional insight to the relative contributions of both the sympathetic and parasympathetic nervous systems.

We did see a modest, positive correlation between self-reported level of enjoyment with the singing intervention and HRV response. While this doesn't capture the subjects' musical preferences, it may serve as a rough surrogate for individual emotional valence (pleasure or displeasure). A narrative review of more than 1,300 subjects with 29 independent studies showed that the majority of studies did not consider music selection (43). Published studies to-date suffer from poor control of individual music preferences. Individual responses to music can be influenced by personal preferences, familiarity with music, environment, prior music experience, and other health factors (42). Furthermore, the construct of singing is complex. Singing happens in social contexts which complicates an objective assessment of the effects of singing itself. Other factors, including vocal contagion, social cohesion, alterations in breathing, other physiological changes, and song structure further add to this complexity (14, 46).

The limitations of this pilot study include the non-randomized, unblinded trial design, lack of a control arm, lack of consideration to personal music preferences with the intervention, and HRV measurements at only 1-min increments in the time domain. Some studies recommend HRV recordings longer than 2 min for improved accuracy (47). The recommended 3-h fast may be insufficient to exclude post-prandial vascular function measurements. Fortunately, almost all the study subjects had an overnight fast (at least 8 h) since the study visit was scheduled in advance and performed in the morning. Offsetting these weaknesses are strengths of this study including the active singing (rather than passive listening) music intervention, the high percentage of women enrolled, and a study population with known cardiovascular disease or risk factors.

Conclusions

A short duration of singing improves peripheral vascular function acutely in older adults, particularly those with established ASCVD or at high ASCVD risk. The HRV, blood pressure, and oxygen saturation responses to acute singing mirror the effects of light-intensity exercise. While the acute vascular response to a single bout of singing may be predictive of the vascular adaptation to longer and more sustained singing interventions, this remains to be confirmed in large, randomized trials. The promising effects of music interventions on cardiovascular physiology, coupled with the low cost and safety, warrant further exploration in subjects with cardiovascular disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Medical College of Wisconsin. The patients/participants provided their written informed consent to participate in this study. Written informed consent was not obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

JK and LT conceptualized the study design, obtained pilot funding, and executed the study. TR created the music video used for the singing intervention and was also involved in the study's conception. AV, MF, and EO performed data analyses and constructed graphs, plots, tables, and under the supervision of JK. JK and KS wrote the manuscript. MW provided vascular expertise and contributed to major manuscript revisions. All authors have reviewed and read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.869104/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Heart rate patterns before, during, and after singing **(A)** minimum heart rate, **(B)** average heart rate, **(C)** maximum heart rate. Box plots showing the following values: the mean (x), median, upper quartile (Q3), lower quartile (Q1), minimum and maximum whiskers as well as outliers. $*p < 0.05$.

SUPPLEMENTARY TABLE 1
Observed singing effort rating.

References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation.* (2018) 137:e67–e492. doi: 10.1161/CIR.0000000000000573

2. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 125 million people. *Lancet.* (2014) 383:1899–911. doi: 10.1016/S0140-6736(14)60685-1

3. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation.* (2011) 123:933–44. doi: 10.1161/CIR.0b013e31820a55f5

4. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. *N Engl J Med.* (2001) 345:892–902. doi: 10.1056/NEJMra001529

5. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 Accf/aha guideline for coronary artery bypass graft surgery: executive summary: a report of the american college of cardiology foundation/American Heart Association task force on practice guidelines. *Circulation.* (2011) 124:2610–42. doi: 10.1161/CIR.0b013e31823b5fee

6. Kwan G, Balady GJ. Cardiac rehabilitation 2012: advancing the field through emerging science. *Circulation.* (2012) 125:e369–73. doi: 10.1161/CIRCULATIONAHA.112.093310

7. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 Accf/Aha/Scai guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines and the society for cardiovascular angiography and interventions. *Circulation.* (2011) 124:e574–651. doi: 10.1161/CIR.0b013e31823a5596

8. Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. Aha/Accf secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation.* (2011) 124:2458–73. doi: 10.1161/CIR.0b013e318235eb4d

9. Pasquali SK, Alexander KP, Peterson ED. Cardiac rehabilitation in the elderly. *Am Heart J.* (2001) 142:748–55. doi: 10.1067/mhj.2001.119134

10. Farley RL, Wade TD, Birchmore L. Factors influencing attendance at cardiac rehabilitation among coronary heart disease patients. *Eur J Cardiovasc Nurs.* (2003) 2:205–12. doi: 10.1016/S1474-5151(03)00060-4

11. Schopfer DW, Priano S, Allsup K, Helfrich CD, Ho PM, Rumsfeld JS, et al. Factors associated with utilization of cardiac rehabilitation among patients with ischemic heart disease in the veterans health administration: a qualitative study. *J Cardiopulm Rehabil Prev.* (2016) 36:167–73. doi: 10.1097/HCR.0000000000000166

12. Williamson TM, Rouleau CR, Aggarwal SG, Arena R, Campbell TS. Bridging the intention-behavior gap for cardiac rehabilitation participation: the role of perceived barriers(). *Disabil Rehabil.* (2018) 42:1–8. doi: 10.1080/09638288.2018.1524519

13. Davidson JW, McNamara B, Rosenwax L, Lange A, Jenkins S, Lewin G. Evaluating the potential of group singing to enhance the well-being of older people. *Australas J Ageing.* (2014) 33:99–104. doi: 10.1111/j.1741-6612.2012.00645.x

14. Vickhoff B, Malmgren H, Astrom R, Nyberg G, Ekstrom SR, Engwall M, et al. Music structure determines heart rate variability of singers. *Front Psychol.* (2013) 4:334. doi: 10.3389/fpsyg.2013.00334

15. Ang K, Maddocks M, Xu H, Higginson IJ. The effectiveness of singing or playing a wind instrument in improving respiratory function in patients with long-term neurological conditions: a systematic review. *J Music Ther.* (2017) 54:108–31. doi: 10.1093/jmt/thx001

16. Morrison I, Clift S. A UK feasibility study on the value of singing for people with Chronic Obstructive Pulmonary Disease (COPD) September 2011 to June 2012: Ian Morrison. *Eur. J. Public Health* (2013) 23. doi: 10.1093/eurpub/ckt123.059

17. Han EY, Yun JY, Chong HJ, Choi KG. Individual therapeutic singing program for vocal quality and depression in Parkinson's disease. *J Mov Disord.* (2018) 11:121–8. doi: 10.14802/jmd.17078

18. Harrison EC, McNeely ME, Earhart GM. The feasibility of singing to improve gait in Parkinson disease. *Gait Posture.* (2017) 53:224–9. doi: 10.1016/j.gaitpost.2017.02.008

19. Fancourt D, Williamon A, Carvalho LA, Steptoe A, Dow R, Lewis I. Singing modulates mood, stress, cortisol, cytokine and neuropeptide activity in cancer patients and carers. *Ecancermedicalscience.* (2016) 10:631. doi: 10.3332/ecancer.2016.631

20. Matsuzawa Y, Kwon TG, Lennon RJ, Lerman LO, Lerman A. Prognostic value of flow-mediated vasodilation in brachial artery and fingertip artery for cardiovascular events: a systematic review and meta-analysis. *J Am Heart Assoc.* (2015) 4:e002270. doi: 10.1161/JAHA.115.002270

21. Goshima Y, Okada Y, Torimoto K, Fujino Y, Tanaka Y. Changes in endothelial function during educational hospitalization and the contributor to improvement of endothelial function in type 2 diabetes mellitus. *Sci Rep.* (2020) 10:1–9. doi: 10.1038/s41598-020-72341-8

22. Beaudry RI, Liang Y, Boyton ST, Tucker WJ, Brothers RM, Daniel KM, et al. Meta-analysis of exercise training on vascular endothelial function in cancer survivors. *Integr Cancer Ther.* (2018) 17:192–9. doi: 10.1177/1534735418756193

23. Bigornia SJ, Farb MG, Tiwari S, Karki S, Hamburg NM, Vita JA, et al. Insulin status and vascular responses to weight loss in obesity. *J Am Coll Cardiol.* (2013) 62:2297–305. doi: 10.1016/j.jacc.2013.07.078

24. Reyes del Paso GA, Langewitz W, Mulder LJ, van Roon A, Duschek S. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies. *Psychophysiology.* (2013) 50:477–87. doi: 10.1111/psyp.12027

25. Tsuji H, Venditti FJ, Jr., Manders ES, Evans JC, Larson MG, Feldman CL, et al. Reduced heart rate variability and mortality risk in an elderly cohort. *Framing Heart Study Circ.* (1994) 90:878–83. doi: 10.1161/01.CIR.90.2.878

26. Vaishnav S, Stevenson R, Marchant B, Lagi K, Ranjadayalan K, Timmis AD. Relation between heart rate variability early after acute myocardial infarction and long-term mortality. *Am J Cardiol.* (1994) 73:653–7. doi: 10.1016/0002-9149(94)90928-8

27. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J.* (2003) 146:168–74. doi: 10.1016/S0002-8703(03)00094-2

28. Moerland M, Kales AJ, Schrier L, van Dongen MG, Bradnock D, Burggraaf J. Evaluation of the endopat as a tool to assess endothelial function. *Int J Vasc Med.* (2012) 2012:904141. doi: 10.1155/2012/904141

29. Hamburg NM, Keyes MJ, Larson MG, Vasan RS, Schnabel R, Pryde MM, et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in the Framingham Heart Study. *Circulation.* (2008) 117:2467–74. doi: 10.1161/CIRCULATIONAHA.107.748574

30. Bruyndonckx L, Radtke T, Eser P, Vrints CJ, Ramet J, Wilhelm M, et al. Methodological considerations and practical recommendations for the application of peripheral arterial tonometry in children and adolescents. *Int J Cardiol.* (2013) 168:3183–90. doi: 10.1016/j.ijcard.2013.07.236

31. Tajima E, Sakuma M, Tokoi S, Matsumoto H, Saito F, Watanabe R, et al. The comparison of endothelial function between conduit artery and microvasculature in patients with coronary artery disease. *Cardiol J.* (2020) 27:38–46. doi: 10.5603/CJ.a2018.0077

32. Igari K, Kudo T, Toyofuku T, Inoue Y. The relationship between endothelial dysfunction and endothelial cell markers in peripheral arterial disease. *PLoS ONE.* (2016) 11:e0166840. doi: 10.1371/journal.pone.0166840

33. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc.* (1982) 14:377–81. doi: 10.1249/00005768-198205000-00012

34. Coquart JB, Garcin M, Parfitt G, Tourny-Chollet C, Eston RG. Prediction of maximal or peak oxygen uptake from ratings of perceived exertion. *Sports Med.* (2014) 44:563–78. doi: 10.1007/s40279-013-0139-5

35. Dawes HN, Barker KL, Cockburn J, Roach N, Scott O, Wade D. Borg's rating of perceived exertion scales: do the verbal anchors mean the same for different clinical groups? *Arch Phys Med Rehabil.* (2005) 86:912–6. doi: 10.1016/j.apmr.2004.10.043

36. Ripley L, Christopoulos G, Michael TT, Alomar M, Rangan BV, Roesle M, et al. Randomized controlled trial on the impact of music therapy during cardiac catheterization on reactive hyperemia index and patient satisfaction: the functional change in endothelium after cardiac catheterization, with and without music therapy (feat) study. *J Invasive Cardiol.* (2014) 26:437–42.

37. Miller M, Mangano CC, Beach V, Kop WJ, Vogel RA. Divergent effects of joyful and anxiety-provoking music on endothelial vasoreactivity. *Psychosom Med.* (2010) 72:354–6. doi: 10.1097/PSY.0b013e3181da7968

38. Thijssen DHJ, Bruno RM, van Mil A, Holder SM, Faita F, Greyling A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur Heart J.* (2019) 40:2534–47. doi: 10.1093/eurheartj/ehz350

39. Colbert JD, Martin BJ, Haykowsky MJ, Hauer TL, Austford LD, Arena RA, et al. Cardiac rehabilitation referral, attendance and mortality in women. *Eur J Prev Cardiol.* (2015) 22:979–86. doi: 10.1177/2047487314545279

40. Colella TJ, Gravely S, Marzolini S, Grace SL, Francis JA, Oh P, et al. Sex bias in referral of women to outpatient cardiac rehabilitation? A meta-analysis. *Eur J Prev Cardiol.* (2015) 22:423–41. doi: 10.1177/2047487314520783

41. Yoo BW, Wenger NK. Gender disparities in cardiac rehabilitation among older women: key opportunities to improve care. *Clin Geriatr Med.* (2019) 35:587–94. doi: 10.1016/j.cger.2019.07.012

42. Kulinski J, Ofori EK, Visotcky A, Smith A, Sparapani R, Fleg JL. Effects of music on the cardiovascular system. *Trends Cardiovasc Med.* (2021) S1050-1738(21)00070-0. doi: 10.1016/j.tcm.2021.06.004

43. Mojtabavi H, Saghazadeh A, Valenti VE, Rezaei N. Can music influence cardiac autonomic system? A systematic review and narrative synthesis to evaluate its impact on heart rate variability complement. *Ther Clin Pract.* (2020) 39:101162. doi: 10.1016/j.ctcp.2020.101162

44. Michael S, Graham KS, Davis GMO. Cardiac autonomic responses during exercise and post-exercise recovery using heart rate variability and systolic time intervals-a review. *Front Physiol.* (2017) 8:301. doi: 10.3389/fphys.2017.00301

45. Yasuma F, Hayano J. Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm? *Chest.* (2004) 125:683–90. doi: 10.1378/chest.125.2.683

46. Bernardi NF, Snow S, Peretz I, Orozco Perez HD, Sabet-Kassouf N, Lehmann A. Cardiorespiratory optimization during improvised singing and toning. *Sci Rep.* (2017) 7:8113. doi: 10.1038/s41598-017-07171-2

47. Wu L, Shi P, Yu H, Liu Y. An optimization study of the ultra-short period for hrv analysis at rest and post-exercise. *J Electrocardiol.* (2020) 63:57–63. doi: 10.3389/fcvm.2022.864173

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Reproductive lifespan in association with risk of hypertension among Chinese postmenopausal women: Results from a large representative nationwide population

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Background: The association between reproductive lifespan and risk of hypertension among postmenopausal women is unclear.

Methods: A total of 94,141 postmenopausal women with a mean age of 64.8 years from the China Hypertension Survey were enrolled at baseline from 2012 to 2015. A standardized questionnaire was used to collect relevant information by well-trained interviewers. Blood pressure and physical examination of the participants were performed by trained medical staff. Logistic regression was used to estimate the odds ratios for hypertension by years of reproductive lifespan.

Results: The average years of reproductive lifespan in Chinese women was 34.0 years. Women who were longer in reproductive lifespan were more likely to have older age at recruitment, higher body mass index, larger waist circumference, lower mean systolic blood pressure, and higher mean diastolic blood pressure ($p < 0.05$). After adjustments, odds ratios (95% confidence interval) for hypertension were 1.035 (0.988–1.085), 1.007 (0.966–1.048), 1.000 (reference), 0.932 (0.899–0.967), and 0.953 (0.909–0.997) for those with reproductive lifespan at $\leq$ 28, 29–31, 32–34 (reference), 35–37, and $\geq$ 38 years, respectively, with a significantly inverse association was seen in those with reproductive lifespan at 35–37 and $\geq$ 38 years. The overall risk of hypertension declined with the increase in reproductive lifespan, and the risk of hypertension was reduced by 1.1% for every 1-year increase in

the reproductive lifespan (odds ratio, 0.989; 95% confidence interval, 0985–0.994) per year. The negative association between reproductive lifespan and hypertension was evident among age at recruitment groups, body mass index categories, and education levels, with the strongest association among women aged ≥ 70 years. Positive associations between reproductive lifespan and risk of hypertension were evident among women aged < 60 years, and this association was stronger among current alcohol drinkers.

Conclusion: Based on the large nationally representative sample, Chinese postmenopausal women with a shorter reproductive lifespan have a higher risk of hypertension.

KEYWORDS

CHS, Chinese Hypertension Survey, postmenopausal women, reproductive lifespan, hypertension, risk, blood pressure

Introduction

Hypertension is one of the most important and preventable risk factors for cardiovascular diseases, which has been recognized as a public health challenge worldwide (1–3). It is estimated that approximately 1.56 billion adults worldwide will be diagnosed with hypertension by 2025 (4). In China, the prevalence of hypertension is increasing from 13.6% in 1991 to 23.2% in 2012 (5, 6). Data from the China National Hypertension Survey Epidemiology Follow-up Study show a strong, linear, and significant association between SBP and DBP and risk for cardiovascular disease (CVD), coronary heart disease (CHD), and stroke, independent of other risk factors (7). Previous studies suggested that premenopausal women typically have lower blood pressure (BP) than men. However, the prevalence of hypertension is higher in postmenopausal women than that in men (8). Therefore, it is important to identify potential risk factors for the prevention of hypertension, particularly among postmenopausal women.

The age of menarche and menopause as the two endpoints of reproductive lifespan may have an implication for trajectory of hypertension later in life. However, the available evidence has remained unclear whether reproductive lifespan is an important risk factor for hypertension due to limited studies. Earlier studies showed inconsistent results on the effect of timing of menarche (9–12) and menopause (13–15) on hypertension risk with very few studies conducted overall. If such a link exists, then the duration of the reproductive lifespan from menarche to menopause might serve as an improved marker of hypertension risk in women. Given that hypertension is an important risk factor for CVD, clarifying the association between reproductive lifespan and the risk of hypertension in postmenopausal women could help identify subgroups of women at risk for hypertension and confirm those who should be targeted for early intervention, which is critical for preventing hypertension.

There is nothing of nationally representative large-sample studies to explore the relationship between reproductive lifespan and hypertension in Chinese women. The present study aimed to investigate the associations between reproductive lifespan and the risk of hypertension among postmenopausal women participating in the Chinese Hypertension Survey (CHS), a large, nationally representative sample study conducted in China.

Abbreviations: BP, blood pressure; CHS, Chinese Hypertension Survey; CVD, Cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; SD, standard deviation; OR, odds ratio; CI, confidence interval; MHT, menopause hormone therapy.

Materials and methods

Study design and participants

All participants in this study were derived from the CHS, a nationally representative sample survey of the Chinese general population aged ≥ 15 years from all 31 provinces in the mainland conducted from October 2012 to December 2015. More details on CHS can be found in the previous publication (16). A stratified multistage random sampling method was used in the CHS. The first stage of sampling was to select four cities in urban areas and four counties in rural areas by using the probability proportional to size method within each province. Then, a simple random sampling method was used to select two districts or two townships in each city or county, and three communities or villages in each district or township. At the final stage of sampling, a certain number of participants from 14 sex/age groups (men and women aged 15–24, 25–34, 35–44, 45–54, 55–64, 65–74, and ≥ 75 years) were selected from communities using lists compiled by the local government registries of households.

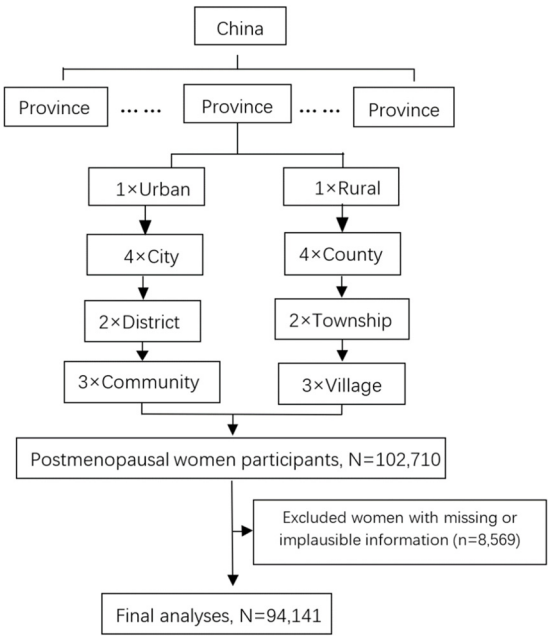

FIGURE 1
Chart of the subject inclusion and exclusion. PPS, probability proportional to size; SRS, simple random sampling.

A total of 487,353 participants from 262 urban resident cities and rural counties were enrolled, of which 253,531 (52.02%) were women. Of the total sample of 102,710 postmenopausal women, 94,141 participants were included in the analysis after exclusions of 8,569 women with missing or implausible information (**Figure 1**).

Prior to recruitment, written informed consent was obtained from each participant. This study was approved by the Ethics Committee of Fuwai Hospital (Beijing, China).

Measurement and data collection

Blood pressure on the right upper arm was measured three times by trained medical staff after the subjects rested for at least 5 min, with an interval of at least 30 s between each measurement with an observer present, using an OMRON HBP-1300 Professional Portable Blood Pressure Monitor (OMRON, Kyoto, Japan). The average of the three measurements was used for the analysis.

All subjects were interviewed by well-trained interviewers using standardized questionnaires developed by Fuwai Hospital, which covered social-demographic characteristics, lifestyle factors, disease history, and reproductive factors. The physical examinations were conducted by trained physicians and nurses. Height was measured without shoes using a standard right-angle device (accurate to 0.1 cm). Waist circumference was measured using a fixed measuring tape and at the midpoint of the line between the crest of the ilium and the inferior margin of the 12th rib with participants wearing thin clothing (to the nearest 0.1 cm). Body weight without wearing heavy clothing was measured using an OMRON body fat and weight measurement device (V-body HBF-371, OMRON, Japan). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Definitions

The reproductive lifespan was defined as the interval between age at menarche and menopause. At baseline, each female subject was asked her age at the time of her first period, which was recorded as age at menarche. The menopausal status was defined as menstruation stopped for at least 12 months and no history of hysterectomy or oophorectomy, or current pregnancy or lactation, and the age at which menopause occurred was recorded at baseline. According to the Chinese guidelines for hypertension management, hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg, and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg, and/or use of antihypertensive medication within 2 weeks.

Educational levels were divided into three groups: elementary or below, junior high school, and high school or above. Criteria for overweight and obesity were considered as BMI ranging from 24.0 to 27.9 kg/m^2 and BMI $\geq$ 28.0 kg/m^2, respectively. Current smoking was defined as someone who has smoked at least 20 packets of cigarettes in their lifetime and still smokes. Current alcohol drinking was defined as consuming alcoholic beverages at least once per week in the past month. A family history of hypertension refers to one in which parents, siblings, or children have hypertension.

Statistical analysis

Baseline characteristics of participants were presented as mean and standard deviation (SD) for normally distributed data or as a proportion for categorical data. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed by one-way analysis of variance (ANOVA). Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for hypertension associated with reproductive lifespan (classified as $\leq$ 28, 29–31, 32–34, 35–37, and $\geq$ 38 years) with 32–34 years as the reference group. This study further investigated these associations by making additional adjustments for age at recruitment (continuous), ethnicity (Han or other ethnicities), region (urban or rural), education level (elementary or below, junior high school, high school or above), BMI (continuous), waist circumference (continuous), current smoking (yes or no), current alcohol drinking (yes or no), previously pregnant (yes or no), contraceptive use (yes or no), breastfeeding experience

TABLE 1 Characteristics of study participants by reproductive lifespan.

Characteristics	Reproductive lifespan (year)						
	≤28	29–31	32–34	35–37	≥38	*N* (Mean = 34.0)	*P*-value
Number (%)	11,567 (12.3)	17,418 (18.5)	27,639 (29.3)	25,446 (27.0)	12,071 (12.8)	94,141 (100.0)	0.624
Age at recruitment, mean (SD)	64.5 (10.9)	64.4 (10.6)	64.7 (10.5)	64.8 (10.0)	65.4 (9.3)	64.8 (10.3)	0.037
Han ethnicity, *n* (%)	9,802 (84.7)	15,042 (86.3)	24,178 (87.5)	22,547 (88.6)	10,590 (87.7)	82,159 (87.3)	0.624
Urban resident, *n* (%)	4,454 (38.5)	7,336 (42.1)	12,939 (46.8)	13,158 (51.7)	6,495 (53.8)	44,382 (47.1)	0.505
Education level, *n* (%)							
Elementary or below	5,543 (47.9)	7,464 (42.8)	11,261 (40.7)	9,255 (36.4)	4,074 (33.7)	37,596 (39.9)	0.873
Junior high school	5,405 (46.7)	8,806 (50.5)	13,992 (50.6)	13,261 (52.1)	6,324 (52.4)	47,788 (50.8)	0.624
High school or above	619 (5.3)	1,148 (6.6)	2,386 (8.6)	2,390 (9.4)	1,673 (13.8)	8,756 (9.3)	0.188
Body measurements and lifestyle							
Body mass index (kg/m^2), mean (SD)	24.0 (3.8)	24.2 (3.8)	24.3 (3.8)	24.5 (3.8)	24.8 (3.8)	24.4 (3.8)	0.000
Waist circumference (cm), mean (SD)	82.2 (10.4)	82.8 (10.5)	83.2 (10.4)	83.6 (10.2)	84.1 (10.2)	83.2 (10.3)	0.000
Current alcohol drinking, *n* (%)	823 (7.1)	1,066 (6.1)	1,544 (5.6)	1,299 (5.1)	678 (5.6)	5,410 (5.7)	0.873
Current smoking, *n* (%)	385 (3.3)	622 (3.6)	822 (3.0)	734 (2.9)	349 (2.9)	2,912 (3.1)	0.873
Reproductive characteristics							
Ever pregnant, *n* (%)	11,339 (96.7)	17,114 (96.4)	27,143 (97.0)	24,942 (97.1)	11,831 (97.1)	92,369 (96.9)	0.624
Ever use of contraceptives, *n* (%)	547 (4.7)	901 (5.2)	1,418 (5.1)	1,323 (5.2)	756 (6.3)	4,945 (5.2)	0.624
Breastfeeding experience, *n* (%)	11,037 (95.4)	16,511 (94.8)	26,438 (95.6)	24,283 (95.4)	11,544 (95.6)	89,813 (95.4)	0.624
Age at menarche, mean (SD)	17.1 (2.3)	16.6 (2.02)	15.9 (1.7)	14.8 (1.6)	14.3 (1.7)	15.7 (2.1)	0.000
Age at menopause, mean (SD)	42.7 (2.8)	46.8 (2.1)	49.0 (1.7)	50.7 (1.6)	53.9 (2.4)	48.9 (3.7)	0.000
Blood pressure							
Hypertension, *n* (%)	5,822 (50.3)	8,735 (50.1)	13,953 (50.5)	12,591 (49.5)	6,211 (51.4)	47,312 (50.2)	0.624
SBP (mmHg), mean (SD)	137.7 (22.2)	137.5 (22.2)	137.4 (21.8)	136.3 (20.9)	136.8 (20.3)	137.1 (21.5)	0.037
DBP (mmHg), mean (SD)	75.8 (11.3)	76.2 (11.3)	76.8 (11.0)	77.1 (10.8)	77.5 (10.8)	76.7 (11.0)	0.000
Family history of hypertension, *n* (%)	3,272 (28.3)	5,190 (29.8)	8,230 (29.8)	7,740 (30.4)	3,860 (32.0)	28,292 (30.1)	0.624
Other diseases							
Stroke, *n* (%)	255 (2.2)	372 (2.1)	594 (2.1)	545 (2.1)	281 (2.3)	2,047 (2.2)	0.624
Myocardial infarction, *n* (%)	55 (0.5)	103 (0.6)	151 (0.6)	143 (0.6)	60 (0.5)	512 (0.5)	0.624

Percentages were calculated based on women with complete information for that specific variable; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

(continuous), stroke (yes or no), myocardial infarction (yes or no), and family history of hypertension (yes or no). We also examined the risk of hypertension in subgroups of women previously defined by age at recruitment, education level, and BMI. The threshold of statistical significance was set as $p < 0.05$. We used R 3.6.2 software to conduct our analyses.

Results

The characteristics of the study participants are listed in Table 1. The mean (SD) age of study participants at recruitment was 64.8 (10.3) years, and the mean age at menarche, age at menopause, and reproductive lifespan were 15.7 (2.1), 48.9 (3.7), and 34.0 (3.3) years, respectively. The mean (SD) BMI, SBP, and DBP were 24.4 (3.8) kg/m^2, 137.1 (21.5) mmHg, and 76.7 (11.0) mmHg, respectively. The proportions of women with reproductive lifespan at ≤ 28, 29–31, 32–34, 35–37, and ≥ 38 years were 12.3, 18.5, 29.3, 27.0, and 12.8%, respectively. A minority of women had an education level at high school or above (9.3%) and were current smokers (3.1%), current alcohol drinkers (5.7%), ever pregnant (3.1%), and users of contraceptives (5.2%). Women who were longer in reproductive lifespan were more likely to have older age at recruitment, higher BMI, larger waist circumference, and lower mean SBP and higher mean DBP ($p < 0.05$). Most women had been pregnant (96.9%) and had breastfed (95.4%).

Figure 2 shows the adjusted ORs for hypertension by reproductive lifespan (≤28, 29–31, 32–34, 35–37, and ≥ 38 years). After adjustment for age at recruitment, ethnicity, region, education level, BMI, waist circumference, current smoking, current alcohol drinking, family history of hypertension, stroke, myocardial infarction, and reproductive factors, the ORs (95%CIs) were 1.035 (0.988–1.085), 1.007

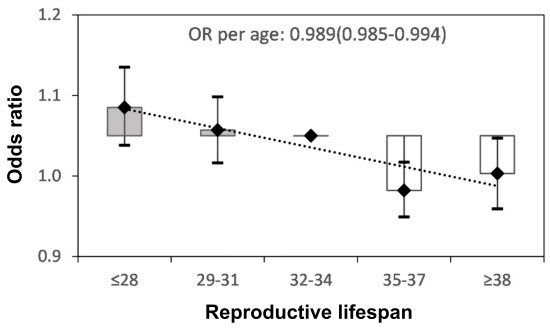

FIGURE 2
Adjusted odds ratio (OR) and 95% confidence interval (CI) for hypertension by the years of reproductive lifespan. Adjusted for age at recruitment, body mass index, waist circumference, region, ethnicity, education level, smoking, alcohol drinking, family history of hypertension, stroke, myocardial infarction, pregnant, contraceptive use status, and breastfeeding experience.

(0.966–1.048), 1.000 (reference), 0.932 (0.899–0.967) and 0.953 (0.909–0.997) for those with reproductive lifespan at ≤ 28, 29–31, 32–34 (reference), 35–37, and ≥ 38 years, respectively. The significantly inverse association was seen in those with reproductive lifespan at 35–37 and ≥ 38 years. The overall risk of hypertension declined with the increase of reproductive lifespan. After adjustments, ORs (95%CI) of hypertension in subgroups of women defined by age at recruitment, BMI, and education level are shown in **Table 2**. Subgroup analyses were also performed based on age at recruitment, region, education level, smoking status, alcohol consumption status, BMI, menopausal status, use of contraceptives, and family history of hypertension (**Figure 3**). Reproductive lifespan was inversely associated with hypertension, with an adjusted OR of 0.989 (95%CI: 0985–0.994) per year. The risk of hypertension was reduced by 1.1% for every 1-year increase in reproductive lifespan. Negative associations between reproductive lifespan and risk of hypertension were evident among urban and rural women; women aged ≥ 70 and 60–70 years; women with BMI < 24kgm^2; women with education level in junior high school and elementary or below groups; no current alcohol drinker, no current smoker, ever use of contraceptives, and no family history of hypertension. This association was strongest in women aged ≥ 70. Positive associations between reproductive lifespan and risk of hypertension were evident among women aged < 60 years and strongest among current alcohol drinkers.

Discussion

Based on a nationally representative sample, we found that women with a reproductive lifespan of 35–37 and ≥ 38 years had decreased risk of hypertension. The longer the reproductive lifespan, the lower the risk of hypertension. The risk of hypertension was reduced by 1.1% for every 1-year increase in the reproductive lifespan. This association also appeared to be similar among subgroups. To our knowledge, this was the first comprehensive study to investigate the associations between reproductive lifespan and risk of hypertension in Chinese postmenopausal women. It is helpful to identify markers that are critical for preventing hypertension in women.

The interval between menarche and menopause defines a woman's natural reproductive span. However, previous studies indicated both contradictory results about the effect of age at menarche and age at menopause on hypertension risk, and rare studies examined both factors during the reproductive lifespan. We found only one study conducted by Feng et al. that simultaneously examined the effects of age at menarche, reproductive lifespan, and menopause on the metabolic risk factors for cardiovascular diseases. The study found that every year's increase in reproductive lifespan was associated with only a marginal increase in SBP and DBP and did not reach statistical significance (9). However, this study only selected a certain southern city in China as the population source, which cannot well represent the whole population of China. In addition, the study adjusted for only a small number of confounding factors, perhaps leading to a statistical bias.

Although several studies have explored the association between the risk of hypertension and age at menarche in women in China, these studies were limited to one province/city/area, included a smaller number of participants, and the conclusions of those studies were inconsistent (11, 17, 18). Therefore, using data from a representative sample of 234,867 Chinese women, our findings confirmed the association between age at menarche and the risk of hypertension, and showed that each 1-year delay in menarche was associated with a 6.2% increase in the prevalence of hypertension. The relationships between age at menarche and hypertension were also inconsistent in other countries. The result from 12,336 participants in the Korean National Health and Nutrition Examination Survey manifested no significant association between age at menarche and hypertension (19). However, a Brazilian study of 33,715 participants found that age at menarche was inversely associated with increased blood pressure (10).

There was limited and contradictory literature on the effect of age at menopause on the risk of hypertension among postmenopausal women. One study among middle-aged and older Chinese women showed that for each 1-year delay in menopause, the prevalence of hypertension decreased by 2% (20). Another study from China reported that the association between post-menopause and blood pressure disappeared after adjusting for BMI (9).

The mechanisms by which age at menarche or menopause is associated with hypertension are complex and are yet to

TABLE 2 Association between reproductive lifespan and risk of hypertension.

Subgroups	Reproductive lifespan (year)						
	≤28	29–31	32–34	35–37	≥38	*N*	*P*-value
By age at recruitment							
< 60	0.955 (0.877–1.040)	0.992 (0.923–1.067)	Reference	0.985 (0.924–1.050)	1.058 (0.973–1.150)	1.022 (1.015–1.030)	<0.05
60–70	1.053 (0.973–1.140)	1.036 (0.967–1.110)	Reference	0.954 (0.897–1.016)	1.061 (0.984–1.154)	0.990 (0.983–0.997)	<0.05
≥ 70	1.055 (0.972–1.145)	0.971 (0.903–1.043)	Reference	0.856 (0.803–0.913)	0.732 (0.675–0.794)	0.973 (0.966–0.980)	<0.05
By body mass index (BMI), kg/m^2							
<24	1.047 (0.982–1.117)	0.999 (0.944–1.058)	Reference	0.918 (0.871–0.968)	0.885 (0.827–0.948)	0.985 (0.979–0.991)	0.106
24–28	1.043 (0.962–1.130)	1.014 (0.946–1.087)	Reference	0.943 (0.887–1.002)	1.031 (0.957–1.111)	0.994 (0.987–1.002)	0.098
≥28	0.956 (0.843–1.085)	1.007 (0.905–1.121)	Reference	0.939 (0.856–1.030)	0.952 (0.851–1.065)	0.995 (0.984–1.006)	<0.05
By education level							
Elementary or below	1.009 (0.943–1.081)	1.013 (0.952–1.078)	Reference	0.937 (0.884–0.994)	0.905 (0.839–0.977)	0.989 (0.983–0.996)	0.206
Junior high school	1.052 (0.983–1.126)	0.977 (0.923–1.035)	Reference	0.913 (0.867–0.960)	0.928 (0.871–0.989)	0.986 (0.980–0.992)	<0.05
High school or above	1.006 (0.822–1.229)	1.138 (0.971–1.335)	Reference	1.028 (0.910–1.162)	1.200 (1.104–1.380)	1.005 (0.989–1.021)	<0.05

ORs were estimated using a logistic regression model and adjusted for age at recruitment, body mass index, waist circumference, region, ethnicity, education level, smoking, alcohol drinking, family history of hypertension, stroke, myocardial infarction, pregnant, contraceptive use status, and breastfeeding experience. Women with reproductive lifespan of 32–34 were used as the reference category.

be fully elucidated. The reproductive years can be regarded as the simplest measurement of cumulative exposure to sex hormones. A systematic review on the association between reproductive lifespan characteristics and risk of Type 2 diabetes and hypertension suggests a protective effect for a longer reproductive lifespan, while estrogen exposure may have an independent effect. In addition, various genes that regulate the renin-angiotensin system and adrenergic system, estradiol, testosterone, estrogen/androgen ratio, and environmental factors such as age, BMI, insulin, oxidative stress, and cholesterol affect the risk of hypertension among postmenopausal women (21). In particular, the decrease of estrogen level reduces the vascular relaxation effect of estrogen and improves the vasoconstriction effect of endothelin (22), leading to an increased risk of hypertension during the menopausal transition (23). Therefore, future longitudinal studies are needed to examine the relationship between reproductive markers and the risk of hypertension as well as the risk attributable to the administration of exogenous hormones, such as contraceptives and menopause hormone therapy (MHT).

Interestingly, we also found that the reproductive lifespan at 35–37 years was most associated with hypertension compared to > 38 years. In addition, when stratified by the age of recruitment, compared with 60–70 years and ≥ 70 years, positive associations between reproductive lifespan and risk of hypertension were evident among women aged < 60 years. Age is an important risk factor due to reproductive stages being part of the aging process. Considering both the timing of menarche and menopause during the reproductive lifespan, the study found that the effect of menopausal status disappeared after adjusting for age implying that much of the hypertension risk in menopausal transition was possibly related to biological aging (14). This explains the rational behavior of the phenomenon to some extent. In our study, to assess the effects of the reproductive lifespan on hypertension independent of the normal aging process, we removed the effect of age at recruitment before the analyses. This may result in underestimated effect sizes. Even in this case, we still get a significant effect that reflects a possible real association between reproductive lifespan and hypertension. We also discovered that the positive association between reproductive lifespan and hypertension was stronger among current alcohol drinkers in subgroup analyses. The alcohol-hypertension relationship has been well documented (24, 25). The study found that chronic exposure to alcohol alters the production of this same set of hormones (i.e., estrogen and testosterone), and hence, alcohol's effects on the cardiovascular system could involve an indirect mechanism in which alcohol alters hormone levels and, in turn, the hormones affect the BP (26).

Limitations and strengths

The important strength of our study is to explore the relationship between reproductive lifespan and hypertension in Chinese women for the first time in a nationally representative sample. In addition, standardized approaches and stringent quality control measures were also taken to ensure data quality and reliability. We adjusted for potential risk factors for hypertension and performed a detailed subgroup analysis to improve the reliability of the findings. Several limitations need to be considered. First, our participants were Chinese women,

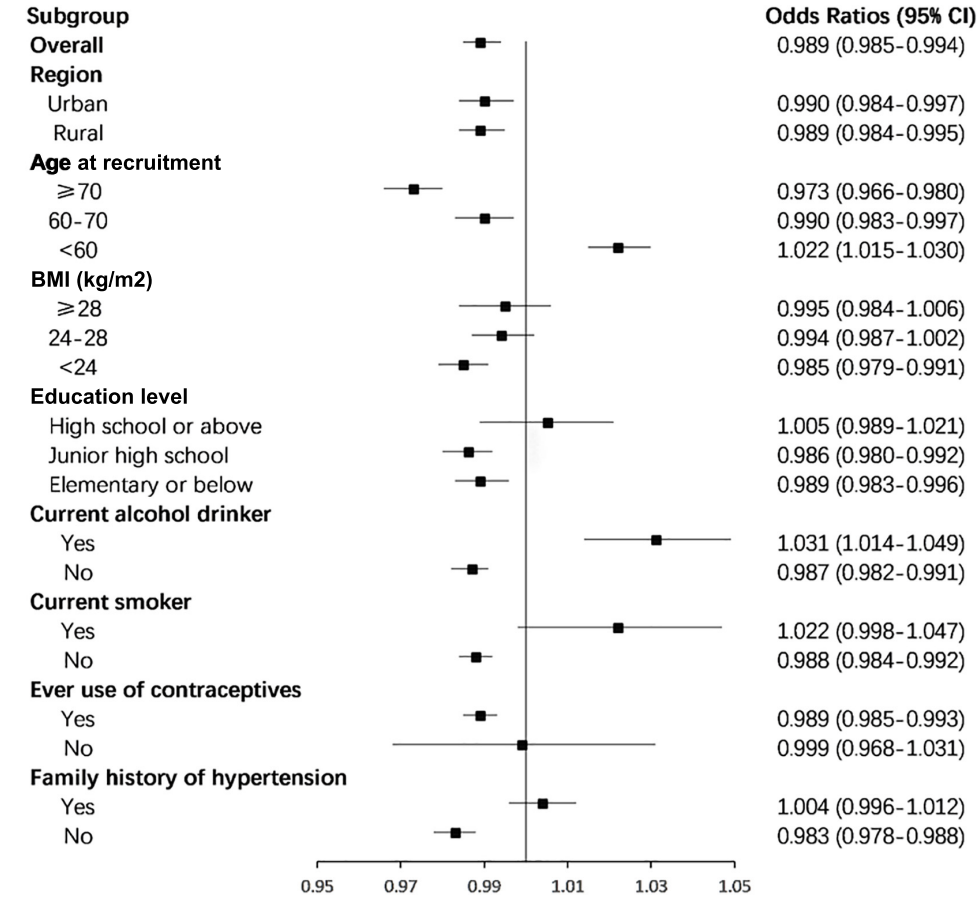

FIGURE 3
Subgroup analyses of the associations between total reproductive years and risk of hypertension according to possible influencing factors. Analyses were adjusted for age at recruitment, body mass index, waist circumference, region, ethnicity, education level, smoking, alcohol drinking, family history of hypertension, stroke, myocardial infarction, pregnant, contraceptive use status, and breastfeeding experience.

which minimized the confounding effects of ethnic background but might minish the generalization of our findings to other ethnic groups. Second, the reproductive lifespan was calculated based on age at menarche and menopause, which were self-reported and not based on medical documentation, raising the possibility of misclassification due to recall bias. However, previous studies have reported that the recall of age at menarche (27, 28) and menopause is relatively accurate (29, 30). Lastly, although we have fully adjusted for potential confounders, the possibility of residual confounding from other known or unknown risk factors cannot be completely ruled out. Finally, the cross-sectional design could not prove a causal relationship.

Conclusion

Based on a representatively national sample of 94,141 Chinese postmenopausal women, we found that the longer the reproductive lifespan, the lower the risk of hypertension. The risk of hypertension is reduced by 1.1% for every 1-year increase in reproductive lifespan.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital (Beijing, China). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for

the publication of any potentially identifiable images or data included in this article.

Author contributions

ZH: conceptualization and writing – original draft preparation. LC: methodology, formal analysis, and software. XW: investigation and writing – original draft preparation partly. ZC, LZ, and CZ: data curation, formal analysis, and software; HZ, XC, YT, JC, YH, RG, YT, and LS: investigation. ZW: conceptualization, funding acquisition, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.898608/full#supplementary-material

References

1. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet.* (2008) 371:1513–8. doi: 10.1016/S0140-6736(08)60655-8

2. Hussen FM, Adem HA, Roba HS, Mengistie B, Assefa N. Self-care practice and associated factors among hypertensive patients in public health facilities in Harar Town, Eastern Ethiopia: a cross-sectional study. *SAGE Open Med.* (2020) 8:2050312120974145. doi: 10.1177/2050312120974145

3. Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, Biryukov S, Brauer M, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the global burden of disease study 2013. *Lancet.* (2015) 386:2287–323.

4. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet.* (2005) 365:217–23.doi: 10.1016/S0140-6736(05)17741-1

5. National Blood Pressure Sampling Survey Collaboration Group. Prevalence, awareness, treatment and control of hypertension in china: results of the 1991 sample survey. *J Hyperten.* (1995) S1:16–20.

6. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, et al. Status of Hypertension in China: results from the China hypertension survey, 2012–2015. *Circulation.* (2018) 137:2344–56.

7. Gu D, Kelly TN, Wu X, Chen J, Duan X, Huang JF, et al. Blood pressure and risk of cardiovascular disease in Chinese men and women. *Am J Hypertens.* (2008) 21:265–72.

8. Lima R, Wofford M, Reckelhoff JF. Hypertension in postmenopausal women. *Curr Hypertens Rep.* (2012) 14:254–60. doi: 10.1007/s11906-012-0260-0

9. Feng Y, Hong X, Wilker E, Li Z, Zhang W, Jin D, et al. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. *Atherosclerosis.* (2008) 196:590–7. doi: 10.1016/j.atherosclerosis.2007.06.016

10. Werneck AO, Oyeyemi AL, Cyrino ES, Ronque ERV, Szwarcwald CL, Coelho ESMJ, et al. Association between age at menarche and blood pressure in adulthood:

is obesity an important mediator? *Hypertens Res.* (2018) 41:856–64. doi: 10.1038/s41440-018-0079-4

11. Zhang L, Li Y, Zhou W, Wang C, Dong X, Mao Z, et al. Mediation effect of BMI on the relationship between age at menarche and hypertension: the Henan rural cohort study. *J Hum Hypertens.* (2020) 34:448–56. doi: 10.1038/s41371-019-0247-2

12. Bubach S, De Mola CL, Hardy R, Dreyfus J, Santos AC, Horta BL. Early menarche and blood pressure in adulthood: systematic review and meta-analysis. *J Public Health.* (2018) 40:476–84. doi: 10.1093/pubmed/fdx118

13. de Kat AC, Dam V, Onland-Moret NC, Eijkemans MJ, Broekmans FJ, van der Schouw YT. Erratum to: unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. *BMC Med.* (2017) 15:74. doi: 10.1186/s12916-017-0841-5

14. Casiglia E, d'Este D, Ginocchio G, Colangeli G, Onesto C, Tramontin P. Lack of influence of menopause on blood pressure and cardiovascular risk profile: a 16-year longitudinal study concerning a cohort of 568 women. *J Hypertens.* (1996) 14:729–36. doi: 10.1097/00004872-199606000-00008

15. Dreyfus J, Jacobs DR Jr., Mueller N, Schreiner PJ, Moran A, Carnethon MR, et al. Age at menarche and cardiometabolic risk in adulthood: the coronary artery risk development in young adults study. *J Pediatr.* (2015) 167:344–52.e1. doi: 10.1016/j.jpeds.2015.04.032

16. Wang Z, Zhang L, Chen Z, Wang X, Shao L, Guo M, et al. Survey on prevalence of hypertension in China: background, aim, method and design. *Int J Cardiol.* (2014) 174:721–3.

17. Shen L, Wang L, Hu Y, Liu T, Guo J, Shen Y, et al. Associations of the ages at menarche and menopause with blood pressure and hypertension among middle-aged and older Chinese women: a cross-sectional analysis of the baseline data of the China Health and Retirement Longitudinal Study. *Hypertens Res.* (2019) 42:730–8. doi: 10.1038/s41440-019-0235-5

18. Liu G, Yang Y, Huang W, Zhang N, Zhang F, Li G, et al. Association of age at menarche with obesity and hypertension among southwestern Chinese women: a new finding. *Menopause.* (2018) 25:546–53. doi: 10.1097/GME.0000000000001027

19. Won JC, Hong JW, Noh JH, Kim DJ. Association between age at menarche and risk factors for cardiovascular diseases in Korean women: the 2010 to 2013 Korea national health and nutrition examination survey. *Medicine.* (2016) 95:e3580. doi: 10.1097/MD.0000000000003580

20. Song L, Shen L, Li H, Liu B, Zheng X, Zhang L, et al. Age at natural menopause and hypertension among middle-aged and older Chinese women. *J Hypertens.* (2018) 36:594–600. doi: 10.1097/HJH.0000000000001585

21. Coylewright M, Reckelhoff JF, Ouyang P. Menopause and hypertension: an age-old debate. *Hypertension.* (2008) 51:952–9. doi: 10.1161/HYPERTENSIONAHA.107.105742

22. Reckelhoff JF, Fortepiani LA. Novel mechanisms responsible for postmenopausal hypertension. *Hypertension.* (2004) 43:918–23. doi: 10.1161/01.HYP.0000124670.03674.15

23. Maas AH, Franke HR. Women's health in menopause with a focus on hypertension. *Neth Heart J.* (2009) 17:68–72. doi: 10.1007/BF03086220

24. Liu F, Liu Y, Sun X, Yin Z, Li H, Deng K, et al. Race- and sex-specific association between alcohol consumption and hypertension in 22 cohort studies: a systematic review and meta-analysis. *Nutr Metab Cardiovasc Dis.* (2020) 30:1249–59. doi: 10.1016/j.numecd.2020.03.018

25. Roerecke M, Tobe SW, Kaczorowski J, Bacon SL, Vafaei A, Hasan OSM, et al. Sex-specific associations between alcohol consumption and incidence of hypertension: a systematic review and meta-analysis of cohort studies. *J Am Heart Assoc.* (2018) 7:e008202. doi: 10.1161/JAHA.117.008202

26. Briasoulis A, Agarwal V, Messerli FH. Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. *J Clin Hypertens.* (2012) 14:792–8. doi: 10.1111/jch.12008

27. Must A, Phillips S, Naumova E, Blum M, Harris S, Dawson-Hughes B, et al. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol.* (2002) 155:672–9. doi: 10.1093/aje/155.7.672

28. Casey V, Dwyer J, Coleman K, Krall E, Gardner J, Valadian I. Accuracy of recall by middle-aged participants in a longitudinal study of their body size and indices of maturation earlier in life. *Ann Hum Biol.* (1991) 18:155–66. doi: 10.1080/03014469100001492

29. Colditz GA, Stampfer MJ, Willett WC, Stason WB, Rosner B, Hennekens CH, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am J Epidemiol.* (1987) 126:319–25. doi: 10.1093/aje/126.2.319

30. Den Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. *Maturitas.* (1997) 27:117–23. doi: 10.1016/s0378-5122(97)01122-5

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A nomogram predicting 30-day mortality in patients undergoing percutaneous coronary intervention

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Background and aims: Early detection of mortality after percutaneous coronary intervention (PCI) is crucial, whereas most risk prediction models are based on outdated cohorts before the year 2000. This study aimed to establish a nomogram predicting 30-day mortality after PCI.

Materials and methods: In total, 10,444 patients undergoing PCI in National Center for Cardiovascular Diseases in China were enrolled to establish a nomogram to predict 30-day mortality after PCI. The nomogram was generated by incorporating parameters selected by logistic regression with the stepwise backward method.

Results: Five features were selected to build the nomogram, including age, male sex, cardiac dysfunction, STEMI, and TIMI 0–2 after PCI. The performance of the nomogram was evaluated, and the area under the curves (AUC) was 0.881 (95% CI: 0.8–0.961). Our nomogram exhibited better performance than a previous risk model (AUC = 0.7, 95% CI: 0.586–0.813) established by Brener et al. The survival curve successfully stratified the patients above and below the median score of 4.

Conclusion: A novel nomogram for predicting 30-day mortality was established in unselected patients undergoing PCI, which may help risk stratification in clinical practice.

KEYWORDS

nomogram, risk prediction, percutaneous coronary intervention, 30-day mortality, model establishment

Introduction

Annually, percutaneous coronary intervention (PCI) has been widely used in millions of patients with ischemic heart diseases to save lives and improve the quality of life around the world (1), and the number of patients undergoing PCI is still increasing. However, mortality still exists after PCI, especially in high-risk patients (2). Therefore, it is valuable to develop a risk-prediction model which can help doctors identify patients who are at high-risk and select suitable treatment strategies.

Approximately two-thirds of death after PCI occurs within 30 days after the procedure (3). Therefore, evaluating 30-day mortality after PCI may help identify events related to PCI (4–6). In previous studies, several prediction models have been established to predict the mortality of patients undergoing PCI. However, most of them are based on outdated cohorts in the 1990s (5, 7, 8). In the past two decades, with the progression in intervention strategy, stent technology, and pharmacological therapy, the outcomes of patients undergoing PCI have improved considerably. Therefore, an updated risk prediction model is also needed. Recently, Brener et al. established a novel risk score predicting 30-day mortality after PCI (called Brener's score hereafter) (9). Brener's score was derived from 21 randomized PCI trials and showed a good concordance index value of 0.848 for predicting 30-day mortality after PCI. The Brener's score filled the blank of the risk score predicting 30-day mortality after PCI in the last 15 years. However, Brener's score lacks data on cardiac function and renal function, which were closely related to mortality after PCI.

Nomogram is a medical tool calculating the risk of a particular clinical outcome for each individual in a graphic manner. It has been applied in risk prediction for cancer, stroke, and surgery (10–12). However, there is no nomogram for predicting the risk of 30-day mortality after PCI. Therefore, this study aimed to establish a novel nomogram for predicting 30-day mortality from a large-scale PCI cohort.

Materials and methods

Study population

Our original cohort included 10,724 consecutive patients undergoing PCI at the National Center for Cardiovascular Diseases in China (Fuwai Hospital, Beijing, China) between January 2013 and December 2013. The clinical data were collected prospectively. Patients with age <18 and without left ventricular ejection fraction (LVEF) data were excluded. Finally, we enrolled 10,444 patients. All patients had written informed consent. The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the hospital.

Endpoint and definitions

The primary endpoint was all-cause mortality within 30 days after PCI. Left ventricular function was evaluated by echocardiography before the PCI procedure. Types of stents were recorded in the PCI procedure. Cardiac dysfunction was defined as LVEF <50% (13), and renal insufficiency was defined as the estimated Glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (14). Patients were followed up at a regular interval.

TABLE 1 Baseline characteristics.

	Alive ($n = 10419$)	Death ($n = 25$)	*P*-value
Age	58.3 (10.3)	69.5 (10.9)	<0.001
Men	8044 (77.2)	9 (36.0)	<0.001
Cardiac dysfunction	693 (6.7)	8 (32.0)	<0.001
Renal insufficiency	284 (2.7)	3 (12.0)	0.026
Diabetes mellitus	3165 (30.4)	4 (16.0)	0.179
Smoking	5950 (57.1)	8 (32.0)	0.02
Hypertension	6701 (64.3)	16 (64.0)	1
Hyperlipidemia	7033 (67.5)	13 (52.0)	0.15
Prior PCI	2568 (24.6)	7 (28.0)	0.876
Prior CABG	1110 (10.7)	5 (20.0)	0.235
Prior Cerebrovascular disease	428 (4.1)	1 (4.0)	1
Prior MI	3765 (36.1)	17 (68.0)	0.002
ACS	6498 (62.4)	17 (68.0)	0.708
Unstable angina	4496 (43.2)	2 (8.0)	0.001
NSTEMI	469 (4.5)	2 (8.0)	0.719
STEMI	1533 (14.7)	13 (52.0)	<0.001
Stable coronary artery disease	3921 (37.6)	8 (32.0)	0.708
Left main artery disease	650 (6.2)	3 (12.0)	0.438
LM-LAD	7546 (72.4)	16 (64.0)	0.473
Multivessel disease	7840 (75.2)	20 (80.0)	0.75
TIMI flow 0–1 before PCI	2240 (21.5)	10 (40.0)	0.045
TIMI flow 0–2 after PCI	366 (3.5)	6 (24.0)	<0.001
First-generation DES	995 (9.5)	2 (8.0)	2
Second-generation DES	8945 (85.9)	17 (68.0)	0.023
Lesion length	29.0 (19.3)	31.6 (16.9)	0.497

Variables are shown as mean (standard deviation, SD) or n (%). CABG, coronary artery bypass grafting; ACS, acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LM-LAD, left main coronary artery disease and left anterior descending artery disease; DES, drug-eluting stent; TIMI, thrombolysis in myocardial infarction. Cardiac dysfunction was defined as LVEF <50%. Renal insufficiency was defined as estimated Glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2.

Abbreviations: PCI, percutaneous coronary intervention; DES, drug-eluting stents; LAD, left anterior descending coronary artery; LM, left main coronary artery; TIMI, Thrombolysis in Myocardial Infarction; STEMI, ST-segment elevation myocardial infarction.

TABLE 2 Logistic regression model for 30-day mortality.

	Univariable		Multivariable		
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	Coefficient
Age	1.12 (1.08–1.18)	<0.001	1.1 (1.05–1.15)	<0.001	0.0924
Men	0.17 (0.07–0.38)	<0.001	0.22 (0.09–0.52)	0.001	−1.5214
BMI	0.97 (0.85–1.09)	0.58			
Diabetes mellitus	0.44 (0.15–1.27)	0.13			
Hypertension	0.99 (0.44–2.23)	0.97			
Hyperlipidemia	0.52 (0.24–1.14)	0.1			
Prior PCI	1.19 (0.5–2.85)	0.7			
Prior CABG	2.1 (0.79–5.6)	0.14			
Prior Cerebrovascular disease	0.97 (0.13–7.21)	0.98			
Prior MI	3.76 (1.62–8.71)	<0.001			
STEMI	6.28 (2.86–13.79)	<0.001	5.72 (2.44–13.38)	<0.001	1.7431
NSTEMI	1.84 (0.43–7.85)	0.41			
ACS	1.28 (0.55–2.97)	0.56			
Smoking	0.35 (0.15–0.82)	0.02			
LM-LAD	0.68 (0.3–1.53)	0.35			
Multivessel disease	1.32 (0.49–3.51)	0.58			
TIMI flow 0–1 before PCI	2.43 (1.09–5.43)	0.03			
TIMI flow 0–2 after PCI	8.67 (3.44–21.85)	<0.001	8.45 (3.22–22.17)	<0.001	2.1344
First-generation DES	0.82 (0.19–3.5)	0.79			
Second-generation DES	0.35 (0.15–0.81)	0.01			
Renal insufficiency	4.87 (1.45–16.35)	0.01			
Lesion Length	1.01 (0.99–1.02)	0.49			
Cardiac dysfunction	6.6 (2.84–15.36)	<0.001	3.02 (1.2–7.62)	0.019	1.1066

Variables are shown as mean (standard deviation, SD) or n (%). PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACS, acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; LM-LAD, left main artery disease and left anterior descending artery disease; DES, drug-eluting stent; TIMI, thrombolysis in myocardial infarction. Cardiac dysfunction was defined as LVEF <50%. Renal insufficiency was defined as estimated Glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2.

Statistical analysis

Continuous variables were compared by the Student's *t*-test, and categorical variables were compared by the chi-square test. Variables in Brener's model and traditional risk factors were candidates for univariable logistic analysis. Variables with a p-value < 0.1 in the univariable logistic analysis were selected for subsequent stepwise backward multivariable logistic analysis, and variables with a p-value < 0.05 were retained in the multivariable logistic regression. Then, the nomogram was established based on the results of the multivariable analysis, and the coefficient of each variable was converted into a 0–100-point scale. The area under the curves (AUC) was internally validated by bootstrapping with 1,000 resamples. Calibration plots were generated to evaluate the consistency between nomogram-predicting probability and actual probability. Also, the calibration plots were generated through bootstrapping with 1,000-fold resamples. The AUC was calculated to evaluate the performance of the predictive model. The AUC values between 0.7 and 0.8 are considered moderate, and the AUC values higher than 0.8 are considered good. The survival probability was observed by the Kaplan–Meier analysis. The p-value < 0.05 was considered to be statistically significant. The data were analyzed with SPSS version 24.0 (Chicago, IL, United States) and R statistical software version 4.0.3[1].

Results

Baseline characteristics

The baseline characteristics of the patients are shown in Table 1. Among 10,444 patients in our study, the patients who died were significantly older than the living patients and were more likely to be women and smokers ($p < 0.001$). Patients with renal insufficiency, cardiac dysfunction, STEMI, prior MI, TIMI flow 0–1 before PCI, TIMI flow 0–2 after PCI, unstable

1 https://www.r-project.org/

10.3389/fcvm.2022.897020

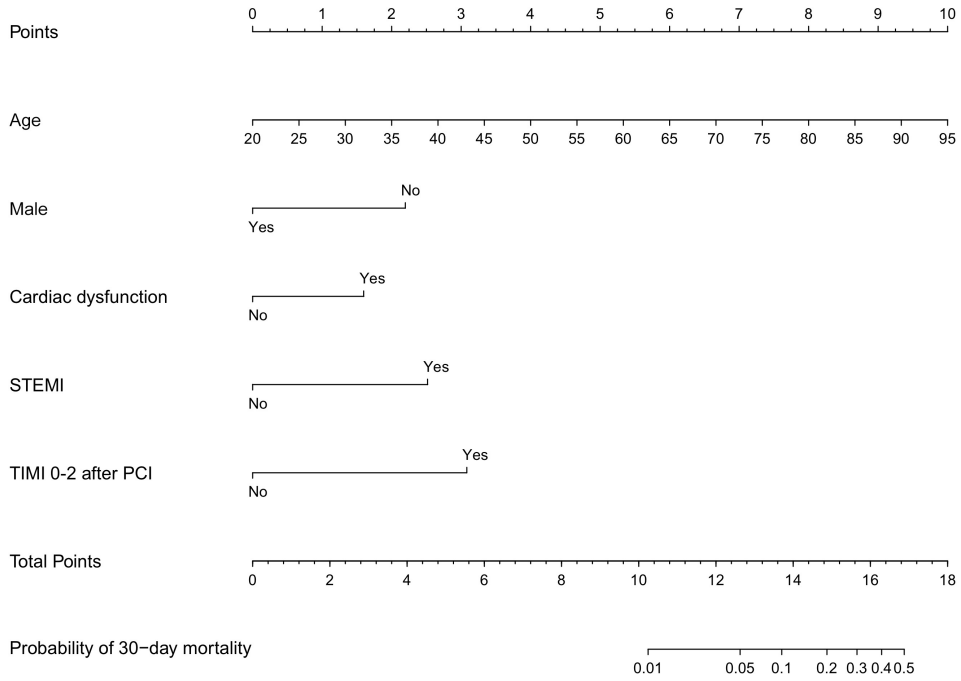

FIGURE 1
Nomogram scores of 30-day mortality. Nomogram for predicting the probability of 30-day mortality after PCI. Points were assigned for age, male sex, cardiac dysfunction, STEMI, and TIMI 0–2 after PCI by drawing a line upward from the corresponding values to the "points line". The "total points" are calculated as the sum of the individual score of each of the five variables included in the nomogram. STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention. Cardiac dysfunction was defined as LVEF <50%.

TABLE 3 Risk-prediction nomogram.

Age (years)	Score	Sex	Score
20	0	Male	0
25	1	Female	2
30	1	**Cardiac dysfunction**	**Score**
35	2	No	0
40	3	Yes	2
45	3	**STEMI**	**Score**
50	4	No	0
55	5	Yes	3
60	5	**TIMI 0–2 after PCI**	**Score**
65	6	No	0
70	7	Yes	3
75	7		
80	8		
85	9		
90	9		
95	10		

STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention. Cardiac dysfunction was defined as LVEF <50%.

angina, and second-generation DES implantation had a higher probability of death (all $p < 0.05$). Other characteristics had no significant difference.

Predictors of 30-day mortality after percutaneous coronary intervention

The results of the univariable logistic analysis are shown in Table 2. Variables with a p-value < 0.1 in the univariable logistic regression analysis, including age, male sex, prior MI, STEMI, smoking, TIMI flow 0–1 before PCI, TIMI flow 0–2 after PCI, second generation drug-eluting stent (DES), renal insufficiency, and cardiac dysfunction were selected for subsequent stepwise backward multivariable logistic analysis; variables with $p < 0.05$ were retained in the multivariable logistic regression (Table 2). Therefore, age, male sex, STEMI, TIMI flow 0–2 after PCI, and cardiac dysfunction were selected to formulate a nomogram (Figure 1 and Table 3). The average AUC generated by bootstrap resampling was 0.884. There was a good agreement between the predicted and the observed 30-day mortality risk (Figures 2, 3). The Hosmer–Lemeshow test also demonstrated that the model was a good fit ($X^2 = 10.605$, $p = 0.225$). The distribution of the risk scores of the population were shown in Figure 4.

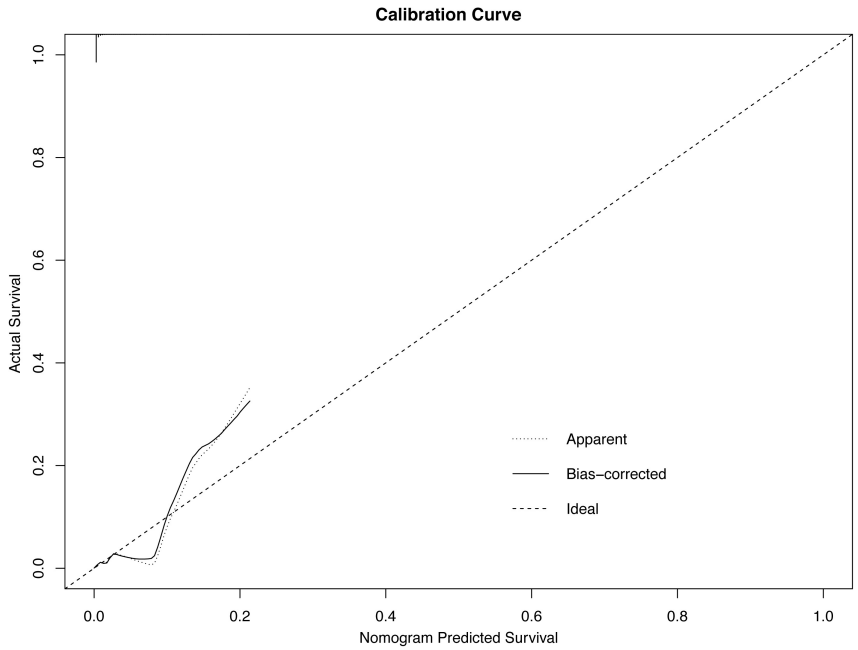

FIGURE 2
Calibration plots of the nomogram.

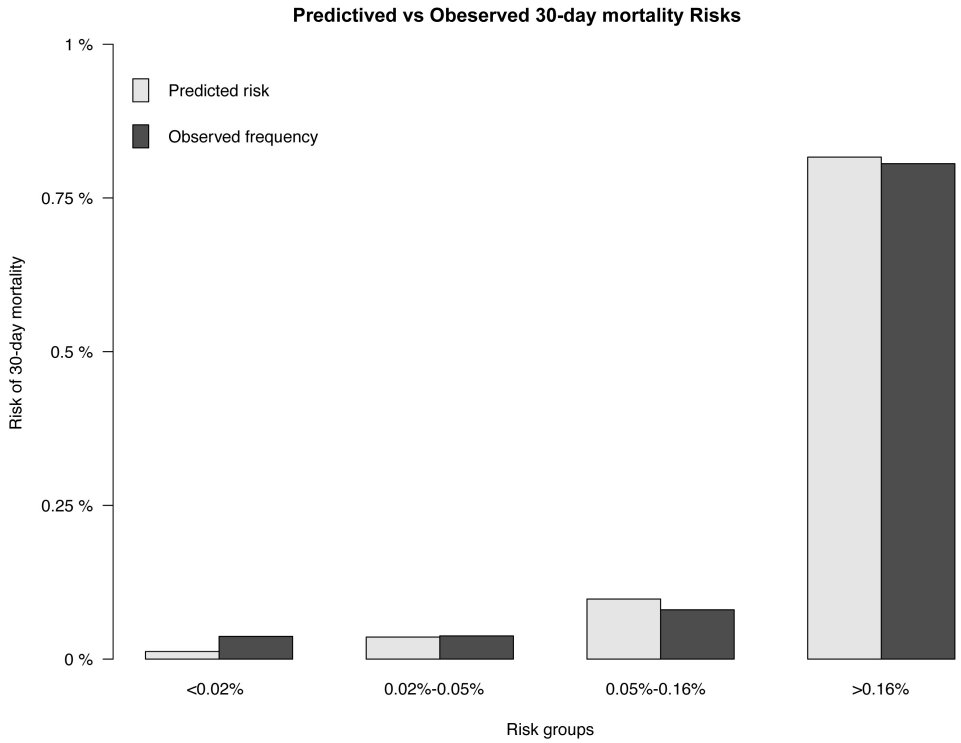

FIGURE 3
Predicted and observed 30-day mortality risk. The predicted (gray) and observed (black) risk of 30-day mortality for patients following PCI.

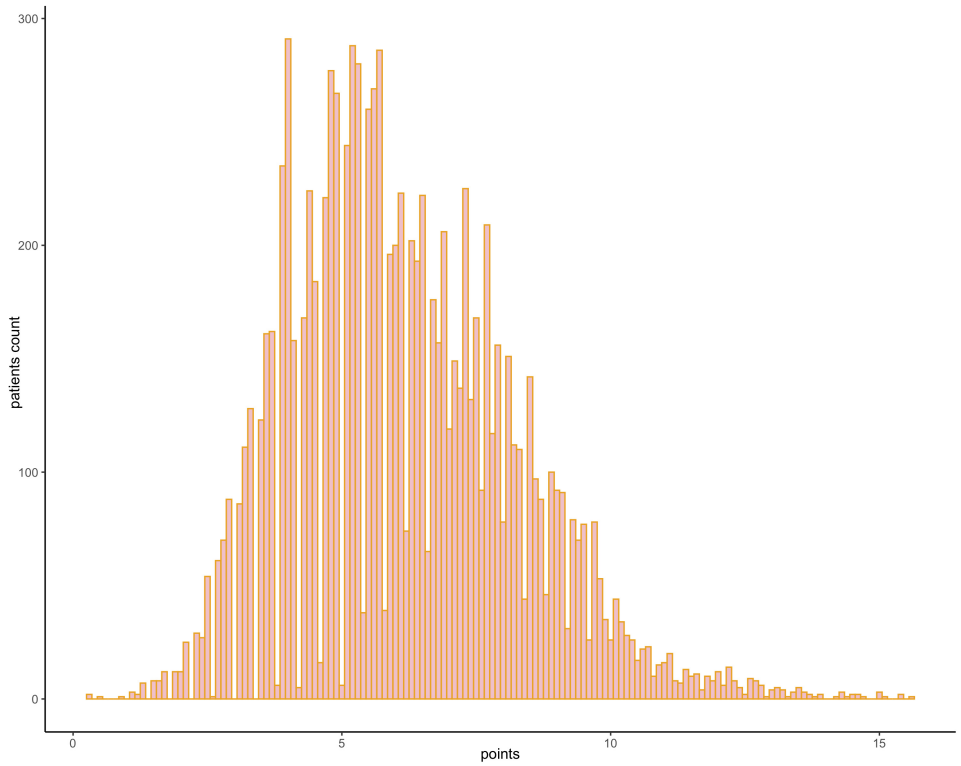

FIGURE 4
Frequency distribution bar graph of the cohort. The distribution of the risk scores of the population.

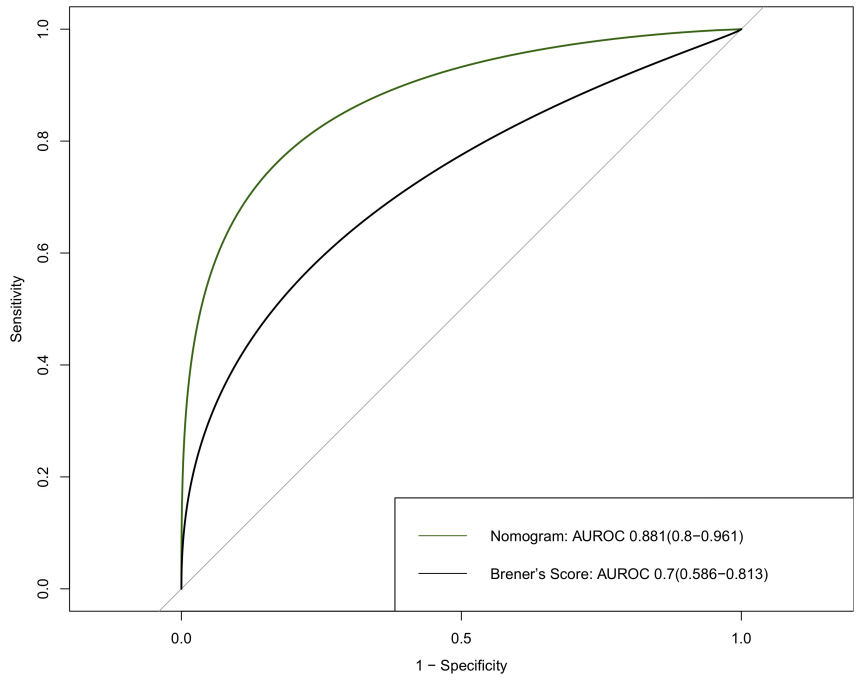

FIGURE 5
Discrimination of the 30-day mortality of derivation cohort. ROC curves of the nomogram and Brener's risk model predicting 30-day mortality with corresponding AUC values. ROC, receiver operating characteristic; AUC, area under curve.

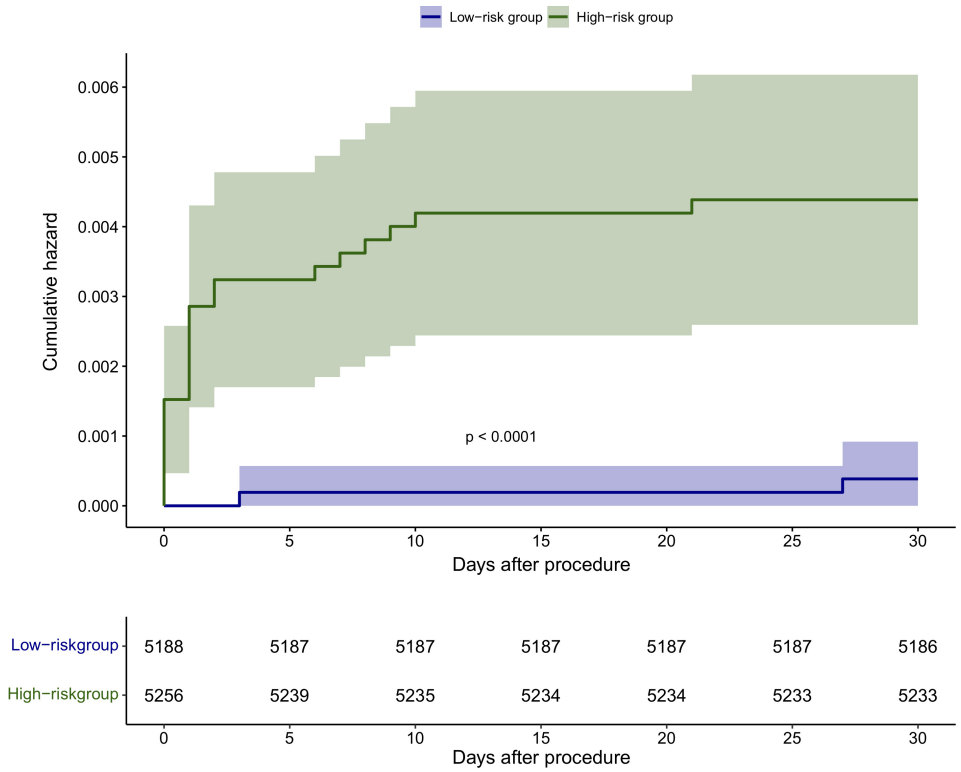

FIGURE 6
Kaplan–Meier analysis of the 30-day mortality based on the median score <4 and ≥4 in the cohort.

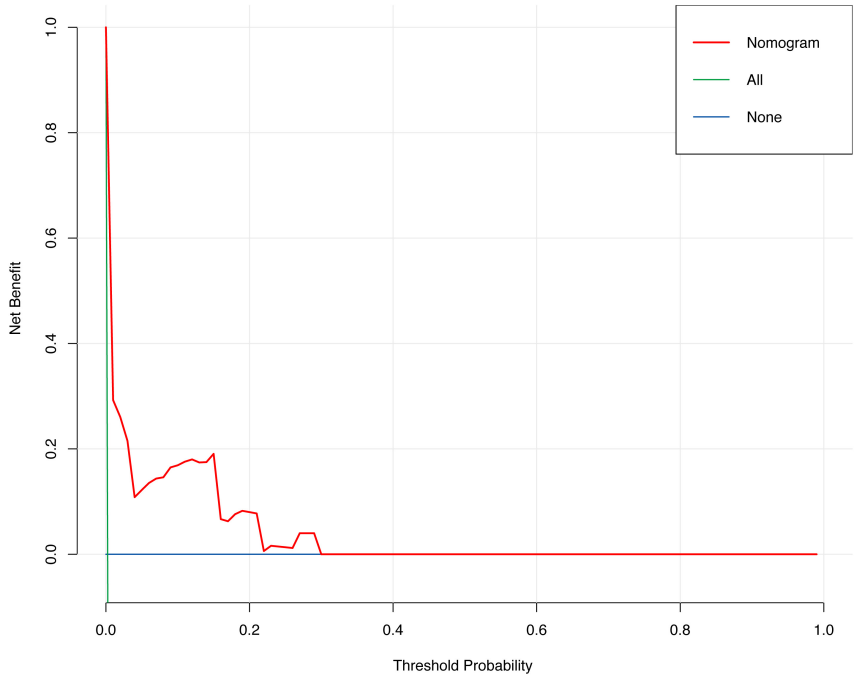

FIGURE 7
Decision carve analysis of the nomogram predicting 30-day mortality after PCI.

The nomogram had a good performance in predicting 30-day mortality after PCI, with an AUC of 0.881 (95% CI: 0.8–0.961), and the nomogram showed a better predictive performance than Brener's model with an AUC of 0.7 (95% CI: 0.586–0.813) (**Figure 5**).

The discrimination of the nomogram was also assessed by Kaplan–Meier analysis (**Figure 6**). The patients were stratified by the median of the risk score (score = 4) of our cohort. A total of 5,188 (49.67%) patients were stratified into the low-risk group and 5,256 (50.33%) patients were stratified into the high-risk group. The cumulative probability of the occurrence of 30-day mortality was significantly higher in patients with scores higher than 4 ($p < 0.0001$). The decision curve analysis (DCA) demonstrated that the nomogram predicting 30-day mortality confers a net benefit over the "full treatment" and "no treatment" strategies in our cohort (**Figure 7**).

Discussion

In the present study, we established a nomogram for predicting 30-day mortality after PCI in a large-scale, real-world PCI cohort. The nomogram shows excellent discrimination and calibration, which may help clinicians in risk prediction.

To our knowledge, this study firstly used a nomogram to predict the 30-day mortality of patients undergoing PCI. Nomogram is a graphic and easy-to-use calculation instrument which could make an individualized prediction of 30-day mortality after PCI. This nomogram incorporates clinical variables and angiographic variables: age, sex, cardiac dysfunction, STEMI, and TIMI flow after PCI. Previous scoring systems rarely incorporated angiographic variables (6, 15, 16).

In Brener's risk model, cardiac function and renal function were not included due to the lack of data (9). However, in previous studies, cardiac function and renal insufficiency are independent risk factors of 30-day mortality after PCI (3, 17–19), and both are included in several risk scores, such as the CADILLAC score (17), the New York State Risk Score (20), and Mayo Clinic Risk Score (5). To improve the predictive value of the risk score, left ventricular ejection fraction and renal function are added to our analysis. Finally, cardiac dysfunction was selected to incorporate the nomogram. Compared to Brener's score, this nomogram exhibited an enhanced 30-day mortality predictive value in Asian patients (0.7 vs. 0.881). Among the total patients undergoing PCI with a score of <4, 0.03% died within 30 days; while for those with scores of ≥4, 0.36% died within 30 days after PCI. The results showed that the risk of mortality increased as the sum of scores increased.

Previous studies established several risk models for predicting 30-day mortality after PCI, including the New York State risk score (20), the British Columbia PCI risk score (6), the ALPHA score (21), and the Mayo Clinic risk score (5); all of these scores focused on the European or American population. Our study is the first risk model aimed to predict the 30-day mortality of Asian patients undergoing PCI.

In conclusion, we established a graphic nomogram to predict 30-day mortality in patients who underwent PCI based on a large-scale real-world cohort study, and our nomogram exhibited better performance than Brener's score. This nomogram would be a good tool to help doctors identify patients with high risk and make better clinical decisions.

Data availability statement

The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

This study was reviewed and approved by the Institutional Review Board of the Fuwai Hospital, Beijing, China. Written informed consent was obtained from all participants for their participation in this study.

Author contributions

JS, YL, and WW participated in the research design. JS, YL, JC, JY, JW, and JG performed the data analysis and interpretation. JS and YL drafted the manuscript. Y-DT edited the manuscript and supervised the studies. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics—2018 update: a report from the American heart association. *Circulation.* (2018) 137:558. doi: 10.1161/CIR.0000000000000558

2. Castro-Dominguez YS, Wang Y, Minges KE, McNamara RL, Spertus JA, Dehmer GJ, et al. Predicting in-hospital mortality in patients undergoing percutaneous coronary intervention. *J Am Coll Cardiol.* (2021) 78:216–29. doi: 10.1016/j.jacc.2021.04.067

3. Serruys PW, Morice M-C, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med.* (2009) 360:961–72. doi: 10.1056/NEJMoa0804626

4. Holmes DR, Berger PB, Garratt KN, Mathew V, Bell MR, Barsness GW, et al. Application of the New York State PTCA mortality model in patients undergoing stent implantation. *Circulation.* (2000) 102:517–22.

5. Singh M, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside estimation of risk from percutaneous coronary intervention: the new mayo clinic risk scores. *Mayo Clinic Proc.* (2007) 82:701–8. doi: 10.4065/82.6.701

6. Hamburger JN, Walsh SJ, Khurana R, Ding L, Gao M, Humphries KH, et al. Percutaneous coronary intervention and 30-day mortality: the British Columbia PCI risk score. *Cathet Cardiovasc Intervent.* (2009) 74:377–85. doi: 10.1002/ccd.22151

7. Wu C, Hannan EL, Walford G, Ambrose JA, Holmes DR, King SB, et al. A risk score to predict in-hospital mortality for percutaneous coronary interventions. *J Am Coll Cardiol.* (2006) 47:654–60. doi: 10.1016/j.jacc.2005.09.071

8. Moscucci M, Kline-Rogers E, Share D, O'Donnell M, Maxwell-Eward A, Meengs WL, et al. Simple bedside additive tool for prediction of in-hospital mortality after percutaneous coronary interventions. *Circulation.* (2001) 104:263–8.

9. Brener SJ, Leon MB, Serruys PW, Smits PC, von Birgelen C, Mehran R, et al. Derivation and external validation of a novel risk score for prediction of 30-day mortality after percutaneous coronary intervention. *EuroIntervention.* (2019) 15:e551–7. doi: 10.4244/EIJ-D-19-00262

10. Cappellari M, Turcato G, Forlivesi S, Zivelonghi C, Bovi P, Bonetti B, et al. STARTING-SICH nomogram to predict symptomatic intracerebral hemorrhage after intravenous thrombolysis for stroke. *Stroke.* (2018) 49:397–404. doi: 10.1161/STROKEAHA.117.018427

11. Jehi L, Yardi R, Chagin K, Tassi L, Russo GL, Worrell G, et al. Development and validation of nomograms to provide individualised predictions of seizure outcomes after epilepsy surgery: a retrospective analysis. *Lancet Neurol.* (2015) 14:283–90. doi: 10.1016/S1474-4422(14)70325-4

12. Kim Y, Margonis GA, Prescott JD, Tran TB, Postlewait LM, Maithel SK, et al. Nomograms to predict recurrence-free and overall survival after curative resection of adrenocortical carcinoma. *JAMA Surg.* (2016) 151:365–73. doi: 10.1001/jamasurg.2015.4516

13. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, et al. Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet.* (2012) 379:815–22. doi: 10.1016/S0140-6736(12)60033-6

14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging.* (2015) 16:233–71. doi: 10.1093/ehjci/jev014

15. Klein LW, Block P, Brindis RG, McKay CR, McCallister BD, Wolk M, et al. Percutaneous coronary interventions in octogenarians in the American college of cardiology–national cardiovascular data registry. *J Am Coll Cardiol.* (2002) 40:394–402. doi: 10.1016/S0735-1097(02)01992-7

16. Brennan JM, Curtis JP, Dai D, Fitzgerald S, Khandelwal AK, Spertus JA, et al. Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention. *JACC.* (2013) 6:790–9. doi: 10.1016/j.jcin.2013.03.020

17. Halkin A, Singh M, Nikolsky E, Grines CL, Tcheng JE, Garcia E, et al. Prediction of mortality after primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol.* (2005) 45:1397–405. doi: 10.1016/j.jacc.2005.01.041

18. Rab T, Wilson H. Public reporting of mortality after PCI in cardiac arrest and cardiogenic shock. *JACC.* (2016) 9:496–8. doi: 10.1016/j.jcin.2015.12.006

19. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diab Endocrinol.* (2015) 3:514–25. doi: 10.1016/S2213-8587(15)00040-6

20. Hannan EL, Farrell LS, Walford G, Jacobs AK, Berger PB, Holmes DR, et al. The New York State risk score for predicting in-hospital/30-day mortality following percutaneous coronary intervention. *JACC.* (2013) 6:614–22. doi: 10.1016/j.jcin.2013.02.015

21. Hizoh I, Gulyas Z, Domokos D, Banhegyi G, Majoros Z, Major L, et al. A novel risk model including vascular access site for predicting 30-day mortality after primary PCI: the ALPHA score. *Cardiovasc Revasculariz Med.* (2017) 18:33–9. doi: 10.1016/j.carrev.2016.10.002

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ORIGINAL RESEARCH
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Age at Menarche and Menopause, Reproductive Lifespan, and Risk of Cardiovascular Events Among Chinese Postmenopausal Women: Results From a Large National Representative Cohort Study

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Background: At present, the association between age at menarche and menopause, reproductive lifespan, and cardiovascular disease (CVD) risk among Chinese postmenopausal women is not clear, and some related researches are contradictory.

Methods: A total of 6,198 Chinese postmenopausal women with a mean age of 63.6 years were enrolled at baseline in 2012–2015 and followed up for 5 years. A standardized questionnaire was used to collect relevant information by well-trained interviewers. Physical examination of the participants was performed by trained medical staff. CVD events were observed during follow-up. Cox proportional hazards models were used to estimate hazard ratios between reproductive characteristics and CVD events.

Results: Age at menarche was positively associated with CVD events (HR, 1.106; 95%CI, 1.047–1.167). There was a negative association between age at menopause and CVD risk in postmenopausal women with comorbidity (HR, 0.952; 95%CI, 0.909–0.996). Reproductive lifespan was negatively associated with CVD events (HR, 0.938; 95%CI, 0.880–0.999). The CVD risk increased by 10.6% for every 1-year increase in age at menarche. The CVD risk reduced by 6.2% for every 1-year increase in age at menopause in women with comorbidity. The CVD risk reduced by 3.8% for every 1-year increase in reproductive lifespan.

Conclusions: Based on the large prospective study with a nationally representative sample, Chinese postmenopausal women with late age at menarche and shorter reproductive lifespan have higher risk of CVD events.

Keywords: age at menarche, age at menopause, reproductive lifespan, cardiovascular events, postmenopausal women

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INTRODUCTION

Cardiovascular disease (CVD) is the dominant cause of death throughout the world (1), accounting for 32% of the total deaths (2). In China, CVD is the leading cause of death and disability (1), accounting for approximately 45% of all deaths (3). Meanwhile, CVD as the principle cause of death in women is still under-recognized and undertreated (4). Therefore, comprehensive recognition of CVD risk factors and timely implementation of appropriate interventions for women is of tremendous public health importance.

Menarche is a marker of puberty and the onset of ovarian and other endocrine functions relating to reproduction (5). The results of previous studies on the relationship between age at menarche, menopause, reproductive lifespan, and the risk of CVD are inconsistent (6–11). For example, a systematic review revealed that three out of four studies show a generally linear association between a decrease in age at menarche with an increase in CVD risk (11). However, the UK Million Women Study manifested a significant U-shaped relationship between age at menarche and coronary heart disease (CHD) risk (6). Data from Asian populations were also contradictory and inconclusive (11).

Age at onset of menopause may be a marker for not only reproductive aging but also for general health and somatic aging (12). Adverse changes in CVD risk factors occur around the menopausal transition (13–15). A meta-analysis including 50,000 Western women showed a negative linear association between age at menopause and CVD (16). A follow-up study found a non-significant increased risk of death caused by CHD and stroke among women with earlier natural menopause (12). This discrepancy may be due in part to a variety of confounding variables including genetic background, race, study design, or environmental factors amongst different populations.

The interval between menarche and menopause defines a woman's natural reproductive span. Due to exposure to different hormonal levels, early or late onset of these events may be associated with increased risk of many chronic health problems. However, the association between duration of reproductive lifespan and CVD risk has not been investigated thoroughly. A shorter duration of reproductive life span was associated with a higher Framingham Risk Score. However, this study was limited by its cross-sectional design to investigate a long-term CVD event risk (17). Results from the Australian Longitudinal Study of Women's Health showed that an increase in reproductive lifespan per year was associated with a 7% reduction in stroke risk, but this association disappeared when only the duration of endogenous estrogen exposure was considered (18). Further, the association was either null or mixed (19, 20). These findings suggest that the association between reproductive lifespan and CVD is not completely clear and requires further investigation.

Most previous studies addressing this objective are conducted in Western populations. Asian women, including Chinese women, have different menstrual and reproductive patterns as well as different lifestyle factors compared with women living in Western countries. At present, there is a lack of clear and comprehensive researches on the relationship between age at menarche, menopause, reproductive lifespan, and CVD risk in Chinese women. Based on a national representative cohort study, we investigate the associations between age at menarche and menopause, reproductive lifespan, and the CVD risk and examine the relationship in subgroups amongst Chinese postmenopausal women.

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; BMI, body mass index; SD, standard deviation; HRs, hazard ratios; CIs, confidence intervals; CKB: Chinese Kadoori Biobank.

MATERIALS AND METHODS

Study Design and Participants

The Study on Prevalence and Key Technologies of Important Cardiovascular Diseases in China conducted from October 2012 to December 2015 was a large-scale representative CVD cross-sectional survey in China. A stratified multistage random sampling method was used to select about 500,000 nationally representative subjects aged $\geq$15 years from 262 districts and counties in 31 provinces of mainland China to investigate demographic characteristics, lifestyle risk factors, pharmacological treatment, female reproductive related characteristics and so on. In addition, the second sampling was carried out on the project. The selected districts/counties were divided into eastern, central and western region, and then stratified by urban and rural areas, 16 cities and 17 counties were selected by simple random sampling method. Random sampling was carried out in the above 33 districts/counties by stages. In the last stage, only respondents aged 35 and above were randomly selected from eligible regions to obtain blood samples for investigation of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels. Finally, those 30,036 individuals who completed the baseline survey were followed up in 2018–2019. 5,361 people lost to follow-up within the 5 years and the overall rate of follow-up was 82.15%. A total of 6,198 postmenopausal women were included in the final analysis after exclusions of 916 people with history of CVD, 11,106 male participants, 5,379 non-menopausal women and 1,076 postmenopausal women with incomplete information or errors (**Figure 1**).

The written informed consent was obtained from each participant. The Ethics Committee of Fuwai Hospital (Beijing, China) approved this study.

Baseline Measurement and Data Collection

A standardized questionnaire was used to collect information on demographic characteristics, lifestyle risk factors, medical history, and characteristics related to female reproduction by well-trained interviewers in 2012–2015. Height and weight were measured using a standardized cartesian and an OMRON body fat and weight meter (V-body HBF-371, Omron, Japan) with participants wearing thin clothing and no shoes. Blood

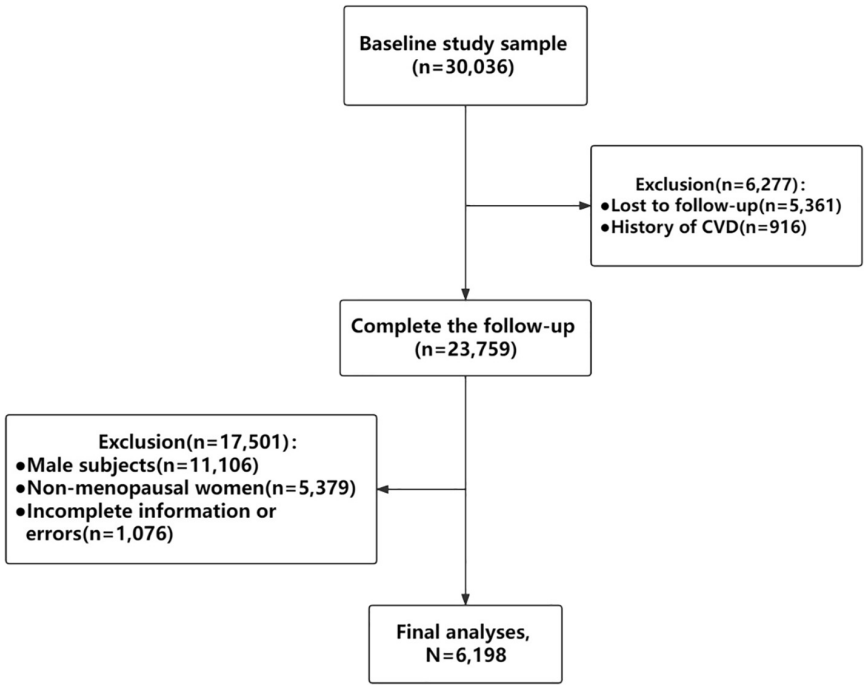

FIGURE 1 | Flowchart of inclusion and exclusion of study participants. CVD, cardiovascular disease.

pressure of the participant was measured using an Omron HBP-1300 professional portable sphygmomanometer (Omron, Kyoto, Japan) on the right arm in the sitting position after resting for at least 5 min. Laboratory examinations were performed on venous blood samples collected after at least 8 h of fasting at night. FPG, TC, TG, LDL-C, and HDL-C levels were measured by a central core laboratory (Beijing Adicon Clinical Labora-tories, Inc., Beijing, China).

Follow-Up and Outcome Measures

During 2018–2019, we tracked CVD events via interviewing participants or their proxies in-person or via telephone or mail questionnaires, and further examined medical records for reconfirmation. Participants' CVD events were initially recorded by local investigators, and then hospital records were reviewed by the central adjudication committee of Fuwai Hospital (Beijing, China) to determine the final diagnosis. CVD events were defined as CHD, stroke, chronic heart failure, and death due to CVD. The criteria for stroke included non-fatal and fatal stroke (subarachnoid hemorrhage, ischemic stroke, intracerebral hemorrhage, and unspecified stroke). CHD was defined as non-fatal (including myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention) and fatal CHD (such as fatal myocardial infarction and other coronary deaths).

Variable Definition

At baseline, each participant was asked her age at the time of her first period, which was recorded as age at menarche. Menopausal status was defined based on the World Health Organization's definition of menopause as the absence of menstruation for $\geq$12 months, and the age at which menopause occurred was recorded at baseline. The reproductive lifespan was defined as the interval between age at menarche and menopause.

Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m^2). Criteria for overweight and obese were defined as BMI between 24.0 and 27.9 kg/m^2 and BMI $\geq$ 28.0 kg/m^2, respectively (21). Alcohol drinking was defined as consuming an alcoholic beverage at least once per week in the past month. Smoking was defined as people who have smoked at least 20 packets of cigarettes in their lifetime and were still smoking (22). Diabetes was defined as fasting blood glucose $\geq$7 mmol/dL or was diagnosed with diabetes by a doctor or was prescribed hypoglycemic drugs within 2 weeks (23). According to the Guidelines for Dyslipidemia in China, TG $\geq$ 2.26mmol/L or TC $\geq$ 6.22mmol/L or HDL-C $<$ 1.04 mmol/L or LDL-C $\geq$ 4.14 mmol/L or prior lipid-lowering medication or prior diagnosis of dyslipidemia (24). Have pharmacological treatment is defined as taking any one of anti-hypertensive, hypoglycemic, or anti-hyperlipidemia drugs. Comorbidity refers to any combination of two or more of three diseases: diabetes, hypertension and hypercholesterolemia following previous study (25). Parity was defined as the number of live babies a woman gives birth to, whether or not the baby dies after delivery (26).

Statistical Analysis

Baseline characteristics of participants were presented as mean and standard deviation (SD) for normally distributed data or as a proportion for categorical data. The *t*-test, χ^2 test, and

variance analysis were used to compare variables between the different groups. Logistic linear regression model was used to explore the trend of variables. Multivariable Cox proportional hazard model was used to estimate Hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD events associated with age at menarche (classified as ≤13, 14, 15, 16, and ≥17 years) with 15 years as the reference group, age at menopause (classified as ≤44, 45–46, 47–48, 49–50, and ≥51 years) with 47–48 years as the reference group, and reproductive lifespan (classified as ≤28, 29–31, 32–34, 35–37, and ≥38 years) with 32–34 years as the reference group.

This study further investigated the associations by additionally adjusting for age at recruitment (continuous), BMI (continuous), waist circumference (continuous), ethnicity (Han or other ethnicities), region (urban or rural), marital status (unmarried/widowed, married/cohabiting), education level (elementary or below, junior high school, high school or above), alcohol drinking (yes or no), smoking (yes or no),

TABLE 1 | Characteristics of study participants by age at menarche.

	Age at menarche							
Characteristics	**≤13**	**14**	**15**	**16**	**≥17**	**All**	P_{value}	P_{trend}
Number (%)	754 (12.2)	860 (13.9)	1, 086 (17.5)	1, 108 (17.9)	2, 390 (38.6)	6, 198 (100)		
Age at recruitment								
Age, mean (SD)	62.0 (10.3)	62.3 (10.2)	63.9 (10.1)	63.2 (10.1)	64.7 (9.4)	63.6 (9.9)	< 0.001	< 0.001
<60, *n* (%)	358 (47.5)	398 (46.3)	407 (37.5)	443 (40.0)	744 (31.1)	2, 350 (38.0)	< 0.001	< 0.001
60–70, *n* (%)	206 (27.3)	232 (27.0)	338 (31.1)	370 (33.4)	942 (39.4)	2, 088 (33.7)		< 0.001
≥70, *n* (%)	190 (25.2)	230 (26.7)	341 (31.4)	295 (26.6)	704 (29.5)	1, 760 (28.4)		0.064
Baseline characteristics								
Urban resident, *n* (%)	449 (59.6)	397 (46.2)	462 (42.5)	512 (46.2)	911 (38.1)	2, 731 (44.1)	< 0.001	< 0.001
Han ethnicity, *n* (%)	684 (90.7)	738 (85.8)	927 (85.4)	961 (86.7)	2, 194 (91.8)	5, 504 (88.8)	< 0.001	0.001
Unmarried or widowed, n (%)	125 (16.6)	161 (18.7)	219 (20.2)	220 (20.0)	526 (22.1)	1, 251 (20.2)	0.016	
BMI								
BMI (kg/m^2), mean (SD)	25.2 (3.6)	24.8 (3.6)	25.0 (3.8)	24.8 (3.7)	24.6 (3.6)	24.8 (3.7)	< 0.001	< 0.001
<24 kg/m^2, *n* (%)	302 (40.1)	394 (45.8)	461 (42.5)	476 (43.0)	1, 080 (45.2)	2, 713 (43.8)	0.044	0.080
24–28 kg/m^2, *n* (%)	295 (39.1)	309 (35.9)	404 (37.2)	438 (39.5)	911 (38.1)	2, 357 (38.0)		0.680
≥28 kg/m^2, *n* (%)	157 (20.8)	157 (18.3)	221 (20.3)	194 (17.5)	399 (16.7)	1, 128 (18.2)		0.006
Waist circumference (cm), mean (SD)	84.5 (10.1)	83.9 (10.0)	84.1 (10.7)	84.2 (10.2)	83.5 (10.5)	83.9 (10.4)	0.131	0.035
Education level, *n* (%)								
Elementary or below	375 (49.7)	527 (61.3)	766 (70.5)	761 (68.7)	1, 825 (76.4)	4, 254 (68.6)	< 0.001	< 0.001
Junior high school	173 (23.0)	201 (23.4)	193 (17.8)	216 (19.5)	380 (15.9)	1, 163 (18.8)		< 0.001
High school or above	206 (27.3)	132 (15.3)	127 (11.7)	131 (11.8)	185 (7.7)	781 (12.6)		< 0.001
Alcohol drinking, *n* (%)	65 (8.6)	40 (4.7)	38 (3.5)	66 (6)	134 (5.6)	343 (5.5)	< 0.001	0.229
Smoking, *n* (%)	31 (4.1)	32 (3.7)	36 (3.3)	54 (4.9)	85 (3.6)	238 (3.8)	0.203	0.952
Hypertension, *n* (%)	380 (50.4)	435 (50.6)	589 (54.2)	582 (52.5)	1, 222 (51.1)	3, 208 (51.8)	0.361	0.871
Diabetes, *n* (%)	123 (16.3)	108 (12.6)	135 (12.4)	139 (12.5)	290 (12.1)	795 (12.8)	0.050	0.021
Dyslipidemia, *n* (%)	288 (38.2)	267 (31)	404 (37.2)	397 (35.8)	814 (34.1)	2, 170 (35)	0.012	0.346
Comorbidity, *n* (%)	230 (30.5)	216 (25.1)	299 (27.5)	290 (26.2)	609 (25.5)	1, 644 (26.5)	0.062	0.040
Have pharmacological treatment, *n* (%)	278 (36.9)	285 (33.1)	412 (37.9)	381 (34.4)	830 (34.7)	2, 186 (35.3)	0.157	0.438
Ever pregnant, *n* (%)	750 (99.5)	853 (99.2)	1, 076 (99.1)	1, 099 (99.2)	2, 366 (99.0)	6, 144 (99.1)	0.807	0.276
Ever use of contraceptives, *n* (%)	67 (8.9)	78 (9.1)	85 (7.8)	92 (8.3)	175 (7.3)	497 (8.0)	0.433	0.086
Have breastfeeding experience, *n* (%)	693 (91.9)	825 (95.9)	1, 038 (95.6)	1, 077 (97.2)	2, 330 (97.5)	5, 963 (96.2)	< 0.001	< 0.001
Parity								
Parity, mean (SD)	2.6 (1.5)	2.9 (3.6)	3.0 (1.7)	3.0 (3.3)	3.1 (1.5)	3.0 (2.3)	0.345	< 0.001
0–1, *n* (%)	199 (26.4)	150 (17.4)	169 (15.6)	156 (14.1)	239 (10)	913 (14.7)	< 0.001	< 0.001
2, *n* (%)	236 (31.3)	275 (32)	325 (29.9)	380 (34.3)	705 (29.5)	1, 921 (31)		0.354
≥3, *n* (%)	319 (42.3)	435 (50.6)	592 (54.5)	572 (51.6)	1, 446 (60.5)	3, 364 (54.3)		< 0.001
Age at menopause, mean (SD)	48.4 (3.6)	48.5 (3.6)	48.9 (3.3)	48.7 (3.3)	48.9 (3.5)	48.8 (3.5)	0.002	< 0.001
Reproductive lifespan, mean (SD)	35.8 (3.7)	34.5 (3.6)	33.9 (3.3)	32.7 (3.3)	31.0 (3.7)	32.9 (3.9)	< 0.001	< 0.001
Family history of CVD, n (%)	176 (23.3)	148 (17.2)	212 (19.5)	212 (19.1)	478 (20.0)	1, 226 (19.8)	0.041	0.526
Follow-up event								
CVD, *n* (%)	15 (2.0)	19 (2.2)	29 (2.7)	30 (2.7)	83 (3.5)	176 (2.8)	0.143	0.011

Percentages were calculated based on women with complete information for that specific variable; SD, standard deviation; BMI, body mass index.

TABLE 2 | Characteristics of study participants by age at menopause.

Characteristics	Age at menopause						P_{value}	P_{trend}
	≤44	45–46	47–48	49–50	≥51	All		
Number (%)	647 (10.4)	761 (12.3)	1, 127 (18.2)	2, 068 (33.4)	1, 595 (25.7)	6, 198 (100.0)		
Age at recruitment								
Age, mean (SD)	61.9 (11.3)	63.0 (10.7)	63.0 (10.2)	64.7 (9.8)	63.7 (8.7)	63.6 (9.9)	< 0.001	< 0.001
<60, *n* (%)	278 (43.0)	302 (39.7)	441 (39.1)	704 (34)	625 (39.2)	2, 350 (37.9)	< 0.001	0.015
60–70, *n* (%)	192 (29.7)	237 (31.1)	395 (35.0)	707 (34.2)	557 (34.9)	2, 088 (33.7)		0.011
≥70, *n* (%)	177 (27.4)	222 (29.2)	291 (25.8)	657 (31.8)	413 (25.9)	1, 760 (28.4)		0.956
Baseline characteristics								
Urban resident, *n* (%)	234 (36.2)	301 (39.6)	470 (41.7)	1, 038 (50.2)	688 (43.1)	2, 731 (44.1)	< 0.001	< 0.001
Han ethnicity, *n* (%)	555 (85.8)	655 (86.1)	981 (87)	1, 854 (89.7)	1, 459 (91.5)	5, 504 (88.8)	< 0.001	0.001
Unmarried or widowed, n (%)	141 (21.8)	160 (21.1)	218 (19.4)	437 (21.2)	295 (18.6)	1, 251 (20.2)	0.231	0.134
BMI								
BMI (kg/m^2), mean (SD)	24.4 (3.5)	24.8 (3.6)	24.6 (3.6)	24.8 (3.8)	25.0 (3.7)	24.8 (3.7)	0.001	< 0.001
<24 kg/m^2, *n* (%)	300 (46.4)	320 (42)	509 (45.2)	922 (44.6)	662 (41.5)	2, 713 (43.8)	0.050	0.128
24–28 kg/m^2, *n* (%)	252 (38.9)	311 (40.9)	419 (37.2)	751 (36.3)	624 (39.1)	2, 357 (38)		0.486
≥28 kg/m^2, *n* (%)	95 (14.7)	130 (17.1)	199 (17.7)	395 (19.1)	309 (19.4)	1, 128 (18.2)		0.005
Waist circumference (cm), mean (SD)	82.7 (10.2)	83.3 (10.1)	83.7 (10.2)	84.0 (10.7)	84.8 (10.2)	83.9 (10.4)	< 0.001	< 0.001
Education level, *n* (%)								
Elementary or below	466 (72.0)	533 (70.0)	752 (66.7)	1, 426 (69.0)	1, 077 (67.5)	4, 254 (68.6)	0.038	0.074
Junior high school	117 (18.1)	136 (17.9)	243 (21.6)	377 (18.2)	290 (18.2)	1, 163 (18.8)		0.722
High school or above	64 (9.9)	92 (12.1)	132 (11.7)	265 (12.8)	228 (14.3)	781 (12.6)		0.004
Alcohol drinking, *n* (%)	49 (7.6)	42 (5.5)	63 (5.6)	102 (4.9)	87 (5.5)	343 (5.5)	0.158	0.073
Smoking, *n* (%)	36 (5.6)	34 (4.5)	38 (3.4)	80 (3.9)	50 (3.1)	238 (3.8)	0.065	0.011
Hypertension, *n* (%)	298 (46.1)	373 (49.0)	556 (49.3)	1, 100 (53.2)	881 (55.2)	3, 208 (51.8)	< 0.001	< 0.001
Diabetes, *n* (%)	86 (13.3)	83 (10.9)	141 (12.5)	260 (12.6)	225 (14.1)	795 (12.8)	0.268	0.190
Dyslipidemia, *n* (%)	208 (32.1)	243 (31.9)	419 (37.2)	724 (35.0)	576 (36.1)	2, 170 (35.0)	0.070	0.047
Comorbidity, *n* (%)	147 (22.7)	187 (24.6)	301 (26.7)	545 (26.4)	464 (29.1)	1, 644 (26.5)	0.019	0.001
Have pharmacological treatment, *n* (%)	210 (32.5)	240 (31.5)	373 (33.1)	755 (36.5)	608 (38.1)	2, 186 (35.3)	0.003	< 0.001
Ever pregnant, *n* (%)	643 (99.4)	755 (99.2)	1, 115 (98.9)	2, 047 (99)	1, 584 (99.3)	6, 144 (99.1)	0.711	0.907
Ever use of contraceptives, *n* (%)	44 (6.8)	69 (9.1)	107 (9.5)	137 (6.6)	140 (8.8)	497 (8.0)	0.014	0.908
Have breastfeeding experience, *n* (%)	619 (95.7)	725 (95.3)	1, 090 (96.7)	1, 982 (95.8)	1, 547 (97.0)	5, 963 (96.2)	0.159	0.102
Parity, *n* (%)								
Parity, mean (SD)	3.1 (4.1)	3.0 (1.6)	2.9 (1.5)	3.0 (2.6)	2.9 (1.5)	3.0 (2.3)	0.367	0.226
0–1	92 (14.2)	111 (14.6)	175 (15.5)	300 (14.5)	235 (14.7)	913 (14.7)	0.281	0.929
2	219 (33.8)	236 (31.0)	357 (31.7)	597 (28.9)	512 (32.1)	1, 921 (31.0)		0.326
≥3	336 (51.9)	414 (54.4)	595 (52.8)	1, 171 (56.6)	848 (53.2)	3, 364 (54.3)		0.396
Age at menarche, mean (SD)	15.8 (2.1)	15.7 (2.0)	15.8 (2.0)	16.0 (2.0)	16.0 (2.0)	15.9 (2.0)	0.001	< 0.001
Reproductive lifespan, mean (SD)	25.9 (2.6)	29.7 (2.0)	31.8 (2.0)	33.7 (2.1)	36.8 (2.4)	32.9 (2.2)	< 0.001	< 0.001
Family history of CVD, n (%)	127 (19.6)	123 (16.2)	229 (20.3)	384 (18.6)	363 (22.8)	1, 226 (19.8)	0.002	< 0.001
Follow-up event								
CVD, *n* (%)	24 (3.7)	17 (2.2)	31 (2.8)	54 (2.6)	50 (3.1)	176 (2.8)	0.446	0.907

Percentages were calculated based on women with complete information for that specific variable; SD, standard deviation; BMI, body mass index.

pharmacological treatment (yes or no), comorbidity (yes or no), family history of CVD (yes or no), ever pregnant (yes or no), contraceptive use (yes or no), breastfeeding experience (yes or no), and parity (0–1, 2, ≥3). We also examined the CVD risk by age at menarche and menopause and reproductive lifespan in subgroups of women defined by region, age at recruitment, marital status, BMI, education level, comorbidity, pharmacological treatment, alcohol drinking status, and family history of CVD, use of contraceptives, parity.

R 3.6.2 software were used to conduct analyses. The threshold of statistical significance was set at $p < 0.05$.

RESULTS

The characteristics of the study participants by age at menarche and menopause, and reproductive lifespan were listed in **Tables 1**–**3**, respectively. The mean (SD) age of study participants at recruitment was 63.6 (9.9) years, and the mean age at

TABLE 3 | Characteristics of study participants by reproductive lifespan.

Characteristics	Reproductive lifespan						P_{value}	P_{trend}
	≤28	29–31	32–34	35–37	≥38	All		
Number (%)	814 (13.1)	1, 263 (20.4)	1, 897 (30.6)	1, 584 (25.6)	640 (10.3)	6, 198 (100.0)		
Age at recruitment								
Age, mean (SD)	63.4 (10.8)	63.4 (10.2)	63.8 (10.1)	63.6 (9.4)	63.7 (8.7)	63.6 (9.9)	< 0.001	0.429
<60, n (%)	296 (36.4)	449 (35.6)	716 (37.7)	620 (39.1)	269 (42.0)	2, 350 (37.9)	< 0.001	0.005
60–70, n (%)	276 (33.9)	460 (36.4)	628 (33.1)	523 (33.0)	201 (31.4)	2, 088 (33.7)		0.077
≥70, *n* (%)	242 (29.7)	354 (28.0)	553 (29.2)	441 (27.8)	170 (26.6)	1, 760 (28.4)		0.240
Baseline characteristics								
Urban resident, *n* (%)	261 (32.1)	482 (38.2)	881 (46.4)	779 (49.2)	328 (51.2)	2, 731 (44.1)	< 0.001	< 0.001
Han ethnicity, *n* (%)	703 (86.4)	1, 123 (88.9)	1, 673 (88.2)	1, 432 (90.4)	573 (89.5)	5, 504 (88.8)	0.040	0.0129
Unmarried or widowed, *n* (%)	186 (22.9)	274 (21.8)	382 (20.2)	310 (19.6)	99 (15.5)	1, 251 (20.2)	0.006	0.001
BMI								
BMI (kg/m^2), mean (SD)	24.3 (3.4)	24.6 (3.6)	24.8 (3.8)	24.9 (3.6)	25.3 (3.7)	24.8 (3.7)	< 0.001	< 0.001
<24 kg/m^2, *n* (%)	375 (46.1)	578 (45.8)	823 (43.4)	681 (43.0)	256 (40.0)	2, 713 (43.8)	0.009	0.008
24–28 kg/m^2, *n* (%)	328 (40.3)	465 (36.8)	716 (37.7)	600 (37.9)	248 (38.8)	2, 357 (38.0)		0.744
≥28 kg/m^2, *n* (%)	111 (13.6)	220 (17.4)	358 (18.9)	303 (19.1)	136 (21.2)	1, 128 (18.2)		< 0.001
Waist circumference (cm), mean (SD)	82.5 (10.0)	83.4 (10.4)	84.0 (10.7)	84.5 (10.1)	85.0 (10.2)	83.9 (10.3)	< 0.001	< 0.001
Education level, *n* (%)								
Elementary or below	644 (79.1)	895 (70.8)	1, 314 (69.3)	1, 013 (64.0)	388 (60.6)	4, 254 (68.6)	< 0.001	< 0.001
Junior high school	116 (14.3)	242 (19.2)	375 (19.7)	298 (18.8)	132 (20.6)	1, 163 (18.8)		0.010
High school or above	54 (6.6)	126 (10.0)	208 (11.0)	273 (17.2)	120 (18.8)	781 (12.6)		< 0.001
Alcohol drinking, *n* (%)	51 (6.3)	74 (5.9)	101 (5.3)	70 (4.4)	47 (7.3)	343 (5.5)	0.061	0.622
Smoking, *n* (%)	41 (5.0)	58 (4.6)	67 (3.5)	51 (3.2)	21 (3.3)	238 (3.8)	0.100	0.010
Hypertension, *n* (%)	384 (47.2)	617 (48.9)	1, 000 (52.7)	842 (53.2)	365 (57.0)	3, 208 (51.8)	< 0.001	< 0.001
Diabetes, *n* (%)	100 (12.3)	139 (11.0)	232 (12.2)	227 (14.3)	97 (15.2)	795 (12.8)	0.028	0.006
Dyslipidemia, *n* (%)	258 (31.7)	418 (33.1)	694 (36.6)	563 (35.5)	237 (37.0)	2, 170 (35.0)	0.052	0.011
Comorbidity, *n* (%)	185 (22.7)	300 (23.8)	512 (27.0)	458 (28.9)	189 (29.5)	1, 644 (26.5)	0.001	< 0.001
Have pharmacological treatment, *n* (%)	263 (32.3)	410 (32.5)	673 (35.5)	571 (36.0)	269 (42.0)	2, 186 (35.3)	< 0.001	< 0.001
Ever pregnant, *n* (%)	807 (99.1)	1, 251 (99)	1, 877 (98.9)	1, 571 (99.2)	638 (99.7)	6, 144 (99.1)	0.527	0.311
Ever use of contraceptives, *n* (%)	57 (7.0)	94 (7.4)	169 (8.9)	126 (8.0)	51 (8.0)	497 (8.0)	0.440	0.381
Have breastfeeding experience, *n* (%)	786 (96.6)	1, 213 (96.0)	1, 842 (97.1)	1, 514 (95.6)	608 (95.0)	5, 963 (96.2)	0.067	0.103
Parity, *n* (%)								
Parity, mean (SD)	3.1 (3.7)	3.0 (1.5)	3.1 (2.7)	2.9 (1.6)	2.7 (1.5)	3.0 (2.3)	0.490	0.002
0–1	103 (12.7)	141 (11.2)	256 (13.5)	296 (18.7)	117 (18.3)	913 (14.7)	< 0.001	< 0.001
2	248 (30.5)	413 (32.7)	588 (31.0)	457 (28.9)	215 (33.6)	1, 921 (31.0)		0.752
≥3	463 (56.9)	709 (56.1)	1, 053 (55.5)	831 (52.5)	308 (48.1)	3, 364 (54.3)		< 0.001
Age at menarche, mean (SD)	17 (2.0)	16.8 (1.9)	16.1 (1.7)	15 (1.7)	14.1 (1.6)	15.9 (2.0)	< 0.001	< 0.001
Age at menopause, mean (SD)	42.9 (2.4)	47 (2.0)	49.1 (1.7)	50.8 (1.7)	53.3 (1.8)	48.7 (3.5)	< 0.001	< 0.001
Family history of CVD, *n* (%)	154 (18.9)	223 (17.7)	373 (19.7)	324 (20.5)	152 (23.8)	1, 226 (19.8)	0.029	0.006
Follow-up event								
CVD, *n* (%)	30 (3.7)	37 (2.9)	53 (2.8)	37 (2.3)	19 (3.0)	176 (2.8)	0.454	0.170

Percentages were calculated based on women with complete information for that specific variable; SD, standard deviation; BMI, body mass index.

menarche and menopause, and reproductive lifespan were 15.9 (2.0), 48.7 (3.5), and 32.9 (3.9) years, respectively. The mean (SD) BMI, waist circumference, and parity were 24.8 (3.7) kg/m^2, 83.9 (10.4) cm, and 3.0 (2.3), respectively. A minority of women were smokers (3.8%), alcohol drinkers (5.5%), and users of contraceptives (8.0%). Most women had previously pregnant (99.1%) and breastfeeding experience (96.2%). Women with earlier age at menarche had higher educational level, had lower BMI, waist circumference and parity, had higher percent of urban resident. Women with later age at menopause had higher educational level, BMI, and waist circumference, had higher percent of comorbidity, Women with lower reproductive lifespan had higher parity, had lower educational level, BMI and waist circumference, had lower percent of comorbidity.

Figure 2 showed the HRs for CVD events by age at menarche, age at menopause, and reproductive lifespan amongst postmenopausal women. In model 1, the association between age at menarche and CVD was significant, and the association between age menopause, reproductive lifespan and CVD was

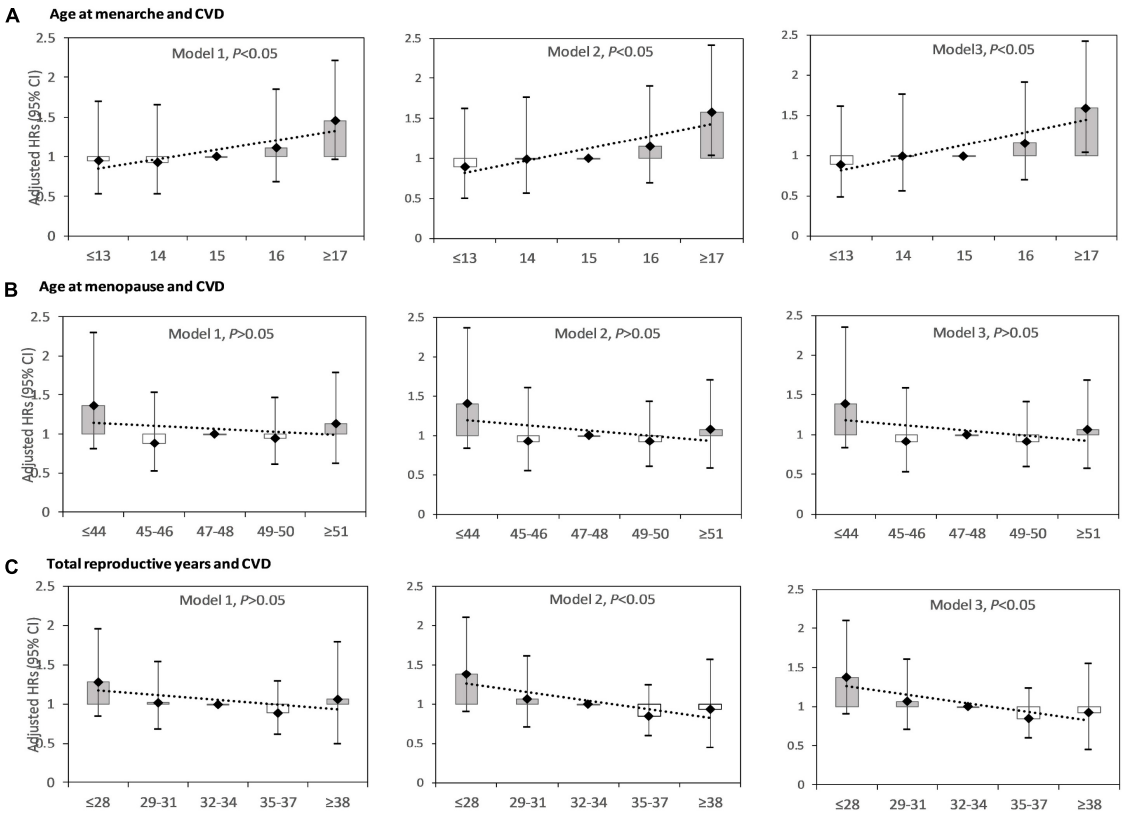

FIGURE 2 | Hazard ratios (HRs) for cardiovascular disease (CVD) by age at menarche, age at menopause, and reproductive lifespan among postmenopausal women. **(A)** HRs for CVD by age at menarche; **(B)** HRs for CVD by age at menopause; **(C)** HRs for CVD by reproductive lifespan. Model 1: adjusted for age at recruitment. Model 2: model 1 plus region, ethnicity, marital status, body mass index, waist circumference, education level, alcohol drinking, smoking, comorbidity, pharmacological treatment, family history of CVD. Model 3: model 2 plus pregnant, contraceptive use status, and breastfeeding experience, parity.

not significant. In model 2 and 3, the association between age at menarche, reproductive lifespan and CVD was significant, and the association between age menopause and CVD was not significant. Model 3 showed that for those with age at menarche $\leq$ 13, 14, 15 (reference), 16, and $\geq$ 17 years, the HRs (95%CIs) were respectively 0.887 (0.489–1.609), 0.993 (0.560–1.762) 1.000 (reference), 1.157 (0.699–1.915), and 1.589 (1.041–2.424), for those with age at menopause $\leq$44, 45–46, 47–48 (reference), 49–50, and $\geq$51 years, the HRs (95%CIs) were respectively 1.388n(0.821–2.346), 0.861 (0.482–1.537), 1.000 (reference), 0.909 (0.587–1.405), and 1.111. (0.716–1.726), for those with reproductive lifespan $\leq$28, 29–31, 32–34 (reference), 35–37, and $\geq$38, the HRs (95%CIs) were respectively 1.368 (0.896–2.090), 1.059 (0.700–1.602), 1.000 (reference), 0.746 (0.492–1.132), and 0.926 (0.538–1.549). The highest risk was seen in those with menarche at age $\geq$17 years, and those with reproductive lifespan $\leq$28 years.

Age at menarche was positively associated with CVD events, with an adjusted HR (95%CI) of 1.106 (1.047–1.167) per year. For every 1-year increase in age at menarche, the risk of CVD increased by 10.6%. The association between age at menopause and risk of CVD was not significant, with an adjusted HR (95%CI) of 0.982 (0.943–1.024) per year. Reproductive lifespan was negatively associated with CVD events, with an adjusted HR (95%CI) of 0.962 (0.929–0.996) per year. For every 1-year increase in reproductive lifespan, the risk of CVD was reduced by 3.8%.

Subgroup analyses were also conducted according to region, age at recruitment, marital status, BMI, education level, pharmacological treatment, comorbidity, alcohol drinking status, use of contraceptives, parity, and family history of CVD (**Figure 3**). There was a positive association between age at menarche and risk of CVD events in postmenopausal women within the following subgroups: living in urban areas, 70 years old and above, low BMI, low education level, have no comorbidity, have pharmacological treatment, non-drinkers, no previous contraceptive use, and 0–2 live births. There was a negative association between reproductive lifespan and risk of CVD events among the following subgroups: married, 60–70 years old, low BMI, low education level, have comorbidity, have pharmacological treatment, non-drinkers, no previous contraceptive use, and 2 live births. There was a negative association between age at menopause and CVD risk in postmenopausal women with comorbidity, with an adjusted HR (95%CI) of 0.938 (0.880–0.999) per year. The risk of CVD reduced by 6.2% for every 1-year

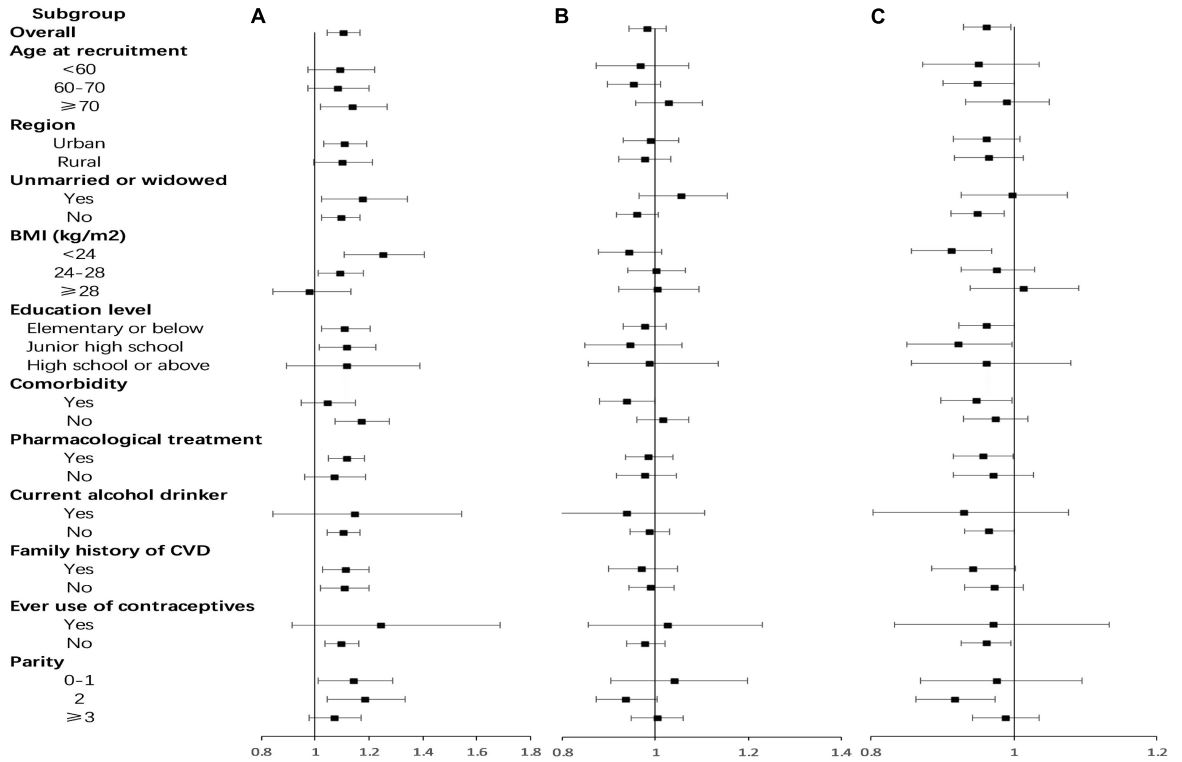

FIGURE 3 | Adjusted hazard ratios (HRs) for cardiovascular disease (CVD) per year by age at menarche, age at menopause, and reproductive lifespan within various subgroups. **(A)** Age at menarche; **(B)** age at menopause; **(C)** reproductive lifespan. Analyses were adjusted for age at recruitment, region, ethnicity, marital status, body mass index, waist circumference, education level, alcohol drinking, smoking, comorbidity, pharmacological treatment, family history of CVD, pregnant, contraceptive use status, and breastfeeding experience, parity.

increase in age at menopause in postmenopausal women with comorbidity.

DISCUSSION

To our knowledge, this was the first large prospective study that comprehensively investigated the associations between age at menarche and menopause, reproductive lifespan, and risk of CVD events in Chinese postmenopausal women using a nationally representative sample and evaluating multiple subgroups. Based on 6,198 Chinese postmenopausal women without prior history of CVD, we found that late age at menarche and shorter reproductive span is significantly associated with increased risk in CVD events among women. These associations also appeared to be similar amongst subgroups. There was also a negative association between age at menopause and CVD risk in postmenopausal women with comorbidity. For every 1-year increase in age at menarche, the risk of CVD increased by 10.6%, and for every 1-year increase in reproductive lifespan, the risk of CVD reduced by 3.8%. The risk of CVD reduced by 6.2% for every 1-year increase in age at menopause in women with comorbidity.

Several studies have previously investigated the relationship of age of menarche and CVD events, but reported inconsistent findings. A systematic review revealed that for Caucasian populations, eight out of twelve studies show a generally linear association between a decrease in age at menarche with an increase in CVD risk (11). But the UK Million Women Study showed a significant U-shaped relationship between age at menarche and the outcomes CHD (6). This discrepancy may be due in part to small sample sizes, geographic limits to one city or province, or only rural areas, age or ethnic differences, or residual confounding from unmeasured or other potential risk factors. The results from studies with Asian populations are inconclusive, with either early or late menarche increasing the CVD risk. One cohort study reported an increased risk of ischemic stroke for women with an age at menarche $\leq$13 years compared to those with 15 years, but the participants were selected from a rural town in northern Japan and therefore not representativeness of the general population (27). The same U-shape between age at menarche and CVD risk was found in data from the Chinese Kadoori Biobank (CKB), but the associations seemed to differ by birth cohort (28). A case-control study reported that higher age at menarche was associated with an increased ischemic stroke risk, which was consistent with our study (29).

Some mechanisms may explain the positive correlation between age of menarche and risk of CVD events in our results. Studies have shown that late menarche is associated with low

estrogen levels (30, 31). Estrogen affects the elasticity of blood vessels and regulates the level of metabolic mediators such as lipids, inflammatory markers and the coagulation system (4). Estrogen has a protective effect on CVD in women by stimulating endothelial nitric oxide synthase, which mediates vasodilation and maintains cardiovascular health (32, 33). Women with early age at menarche are more likely to have higher levels of ovarian hormone, which can protect women from hypertension and atherosclerosis (34). Several studies agree about the different impact of testosterone on males and females (35, 36). Low endogen levels of this hormone in males can be associated with CVD and coronary stenosis severity. High levels of circulating androgens in women appear to be associated with higher cardiovascular risk (37, 38). In addition, age at menarche is associated with the higher adiposity both in childhood and in adulthood (39, 40). Adiposity indicators mediated the relationship between age at menarche and blood pressure in women. Adiposity is a risk factor of CVD, so the association between age at menarche and CVD could a result of higher estrogen levels or higher adiposity in early maturing women (40).

Additionally, the relationships between age at menopause and CVD risk in previous research are contradictory. Two meta-analysis indicated women with early menopausal age have a higher risk of incident CVD (16, 41). However, the result might have introduced some heterogeneity or has certain limitations about extrapolation due to the limited racial population included. Results of UK Biobank on early natural menopause were associated with a increased risk for a composite of CVD may have a "healthy participant" selection bias (42). The following studies are consistent with our findings on no convincing relationship between early menopausal age and cardiovascular disease (12, 43–47). Differences in population and study design and the influence of confounding factors may be the main reasons for the inconsistent results.

Persuasive evidence demonstrated that bilateral oophorectomy in premenopausal women increases the risk of CHD unless exogenous hormones are administered (48). However, there is no convincing evidence to support the hypothesis that natural menopause is a risk factor for CHD. When women with natural, surgical, and medicated menopause were analyzed together, the risk increased significantly with decreasing age at menopause, but this inverse association was limited to current non-smokers and not statistically significant amongst women with natural menopause (49). In a previous report from the Nurses' Health Study, with further adjustment for smoking and age the relative risk of CHD in postmenopausal women diminished from significantly elevated to insignificant (48). These results might reflect the need to closely control the residual confounding factors of smoking and age, which have been adjusted for in our study. Furthermore, we found that there was a negative association between age at menopausal and CVD risk in postmenopausal women with comorbidity. As far as we know, diabetes, hypertension and dyslipidemia are independent risk factors for CVD events and show a additive association with the risk of CVD (50). Our finding suggests that this association may be more striking to particularly attention in postmenopausal women.

Previous studies investigating the association between reproductive lifespan and CVD risk were inconsistent. A systematic review and meta-analysis found that women with a shorter reproductive lifespan was associated with a higher risk of CVD events, with a 31% increased risk of stroke in particular (19). The Nurse's Health Study found that the CVD risk was 25% higher amongst those with <30 years of reproductive lifespan compared to 34–37 years (51). One cross-sectional study from the United States showed that each yearly increase in reproductive lifespan was associated with 3% reduction in the risk for overall CVD and stroke events (20). The findings from this and other studies were consistent for CHD (34, 51, 52). A cohort study from the Women's Health Initiative manifested that a shorter total reproductive duration in postmenopausal women resulted in a modestly increased risk of any heart failure (53). In Asia, the study of CKB found that total reproductive years were inversely associated with risks of both fatal and non-fatal CVD events, with 1.4% lower risk of CVD events death per each additional reproductive year (52). For stroke mortality, a large prospective study from Japan showed a decreased risk for longer reproductive lifespan (54). The above relationship between reproductive lifespan and CVD risk is consistent with our current study. However, some studies have found that there is no statistically significant association between the number of reproductive years and CVD mortality (9, 46, 55, 56). In addition, Jung et al. found a U-shaped association between reproductive lifespan and ischemic heart disease; the risk of which increased in both reproductive lifespan <30 and 40 years when 36–39 years were used as a reference (34). In one prospective study, it was significantly associated with 5% higher mortality for every additional year of reproductive lifespan (57).

Timing of menarche and menopause were correlated in that women who experienced early menarche were at higher risk of early menopause (51). In addition, reproductive lifespan can serve as a simple way to estimate estrogen exposure (51). Therefore, the underlying mechanism linking a longer reproductive lifespan with reduced risk of CVD events can be attributed to prolonged exposure to endogenous estrogen, which is accordant with our previous explanatory mechanism. These findings suggest that reproductive factors may play an important role in maintaining and improving cardiovascular health, which can be used to assess populations with poor cardiovascular health for targeted interventions.

STRENGTHS AND LIMITATIONS

Important strengths of our study are the prospective design and nationally representative sample. The study has several other strengths, including the standardized approaches and stringent quality control measures taken to ensure data quality and reliability. We adjusted for potential risk factors for CVD and conducted a detailed subgroup analysis to improve the reliability of our results, which allowed us to simultaneously adjust for potential confounders and reliably assess the associations.

Several limitations need to be taken into account. First, CVD is composed of multiple diseases, so it is unclear whether role in our study is specific for certain CVD. Second, age at menarche is known to vary by ethnicity, with girls of African and Asian descent experiencing earlier menarche than Caucasian girls (58, 59). However, it is unknown whether ethnicity plays a role in the association between age at menarche and CVD events. Furthermore, our study participants were Chinese women, which minimized the confounding effects by ethnic background, but might reduce the generalization of our results to other ethnic groups. Thirdly, ages at the time of menarche and menopause were self-reported which raises the possibility of misclassification due to recall bias. However, previous studies have reported that the recall of age at menarche (60, 61) and menopause is relatively accurate (62, 63). Therefore, self-reported age at menarche and menopause were reasonably valid and reproducible. If recall bias existed, it would be non-differential, tending to attenuate the real strengths of the associations that we observed. Lastly, although we have adjusted for a comprehensive range of potential confounders, the possibility of residual confounding from other known or unknown risk factors cannot be completely ruled out.

CONCLUSION

Based on 6,198 Chinese postmenopausal women who had no prior history of CVD, we found that late age at menarche and shorter reproductive span are both significantly associated with increased risk of CVD events. These associations also appeared to be similar amongst subgroups. In addition, there was a negative association between age at menopause and CVD risk in postmenopausal women with comorbidity. Our findings have important public health implications for early detection and timely implementation of appropriate interventions in women at high risk of CVD.

DATA AVAILABILITY STATEMENT

Data from this study cannot be used publicly. Requests to access these datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital (Beijing, China). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC: methodology, formal analysis, software, and writing – original draft preparation partly. ZH: conceptualization and writing – original draft preparation partly. XW and YS: investigation and writing – original draft preparation partly. ZC, LZ, and CZ: data curation, formal analysis, and software. HZ, XC, YT, JC, RG, and YH: investigation. JV: language polishing. ZW: conceptualization, funding acquisition, and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global burden of disease study 2010. *Lancet.* (2013) 381:1987–2015. doi: 10.1016/S0140-6736(13)61097-1
2. Abubakar I, Tillmann T, Banerjee A. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* (2015) 385:117–71. doi: 10.1016/S0140-6736(14)61682-2
3. World Health Organization [WHO]. *Noncommunicable Diseases. Country Profiles 2018.* (2018). Available online at: https://www.who.int/publications/i/item/9789241514620 (accessed March 29, 2022).
4. Maas AH, Appelman YE. Gender differences in coronary heart disease. *Neth Heart J.* (2010) 18:598–603.
5. DiVall SA, Radovick S. Pubertal development and menarche. *Ann N Y Acad Sci.* (2008) 1135:19–28.
6. Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, et al. Age at menarche and risks of coronary heart and other vascular diseases in a large UK

Cohort. *Circulation.* (2015) 131:237–44. doi: 10.1161/CIRCULATIONAHA.114.010070
7. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK, et al. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. *Am J Epidemiol.* (2014) 180:29–40. doi: 10.1093/aje/kwu113
8. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. A prospective study of age at menarche, parity, age at first birth, and coronary heart disease in women. *Am J Epidemiol.* (1987) 126:861–70.
9. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al. Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. *J Epidemiol.* (2006) 16:177–84. doi: 10.2188/jea.16.177
10. Zhu D, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health.* (2019) 4:e553–64. doi: 10.1016/S2468-2667(19)30155-0
11. Luijken J, van der Schouw YT, Mensink D, Onland-Moret NC. Association between age at menarche and cardiovascular disease: a systematic review on risk and potential mechanisms. *Maturitas.* (2017) 104:96–116.
12. Snowdon DA, Kane RL, Beeson WL, Burke GL, Sprafka JM, Potter J, et al. Is early natural menopause a biologic marker of health and aging?. *Am J Public Health.* (1989) 79:709–14.
13. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab.* (2003) 88:2404–11.
14. Agrinier A, Cournot M, Dallongeville J, Arveiler D, Ducimetière P, Ruidavets JB, et al. Menopause and modifiable coronary heart disease risk factors: a population based study - ScienceDirect. *Maturitas.* (2010) 65:237–43. doi: 10.1016/j.maturitas.2009.11.023
15. Toth MJ, Chernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. *Int J Obes Relat Metab Disord.* (2000) 24:226–31.
16. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol.* (2016) 1:767–76. doi: 10.1001/jamacardio.2016.2415
17. Kim SH, Sim MY, Park SB. Association between duration of reproductive lifespan and Framingham risk score in postmenopausal women. *Maturitas.* (2015) 82:431–5. doi: 10.1016/j.maturitas.2015.07.011
18. Mishra SR, Waller M, Chung HF, Mishra GD. Association of the length of oestrogen exposure with risk of incident stroke in postmenopausal women: insights from a 20-year prospective study. *Int J Cardiol.* (2021) 328:206–14. doi: 10.1016/j.ijcard.2020.12.022
19. Mishra SR, Hung HF, Waller M, Mishra GD. Duration of estrogen exposure during reproductive years, age at menarche and age at Menopause, and risk of cardiovascular disease events, all−cause and cardiovascular mortality: a systematic review and meta−analysis. *BJOG.* (2021) 128:809–21. doi: 10.1111/1471-0528.16524
20. Mansoor H, Elgendy IY, Segal R, Hartzema A. Duration of reproductive years and the risk of cardiovascular and cerebrovascular events in older women: insights from the national health and nutrition examination survey. *J Womens Health.* (2017) 26:1047–52. doi: 10.1089/jwh.2016.6013
21. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. *Diabetes Care.* (2005) 28:391–7.
22. Dong Y, Wang X, Zhang L, Chen Z, Zheng C, Wang J, et al. High-sensitivity C reactive protein and risk of cardiovascular disease in China-CVD study. *J Epidemiol Community Health.* (2019) 73:188–92.
23. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, et al. Status of hypertension in china: results from the China hypertension survey, 2012-2015. *Circulation.* (2018) 137:2344–56.
24. Joint Committee on Guidelines for Prevention and Treatment of dyslipidemia in adults in China. Chinese guidelines for prevention and treatment of dyslipidemia in adults [J]. *Chin J cardiol.* (2007) 35:390–419.
25. Zhang D, Tang X, Shen P, Si Y, Liu X, Xu Z, et al. Multimorbidity of cardiometabolic diseases: prevalence and risk for mortality from one million Chinese adults in a longitudinal cohort study. *BMJ Open.* (2019) 9:e024476. doi: 10.1136/bmjopen-2018-024476
26. Liu G. *Relationship between Age of Menarche and Live Birth and Obesity and Hypertension in Women*. Chongqing: Chongqing Medical University (2019).
27. Murakami K, Metoki H, Satoh M, Asayama K, Hosaka M, Matsuda A, et al. Menstrual factors and stroke incidence in Japanese postmenopausal women: the Ohasama study. *Neuroepidemiology.* (2016) 2016:109–16. doi: 10.1159/000452220
28. Yang L, Li L, Millwood IY, Peters SAE, Chen Y, Guo Y, et al. Age at menarche and risk of major cardiovascular diseases: evidence of birth cohort effects from a prospective study of 300,000 Chinese women. *Int J Cardiol.* (2017) 227:497–502. doi: 10.1016/j.ijcard.2016.10.115
29. Hsieh YC, Hwang L-C, Hsieh F-I, Lien LM, Lin H-J, Hu C-J, et al. Early menarche and ischemic stroke risk among postmenopausal women. *Int J Gerontol.* (2010) 4:16–22. doi: 10.1212/01.wnl.0000250238.69938.f5
30. Qiu C, Chen H, Wen J, Zhu P, Lin F, Huang B, et al. Associations between age at menarche and menopause with cardiovascular disease, diabetes, and osteoporosis in Chinese women. *J Clin Endocrinol Metab.* (2013) 98:1612–21. doi: 10.1210/jc.2012-2919
31. Kleijn MJJD, Schouw YTVD, Graaf YVD. Reproductive history and cardiovascular disease risk in postmenopausal women - A review of the literature. *Maturitas.* (1999) 33:7–36.
32. Chen Z, Yuhanna IS, Galcheva-Gargova Z, Karas RH, Mendelsohn ME, Shaul PW. Estrogen receptor a mediates the nongenomic activation of endothelial nitric oxide synthase by estrogen. *J Clin Invest.* (1999) 103:401–6.
33. Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. *Cardiovasc Res.* (2002) 53:688–708.
34. Jung KJ, Kim MR, Yun YD, Kim HC, Jee SH. Duration of ovarian hormone exposure and atherosclerotic cardiovascular disease in Korean women: the Korean Heart Study. *Menopause.* (2016) 23:60–6. doi: 10.1097/GME.0000000000000489
35. Wu FC, von Eckardstein A. Androgens and coronary artery disease. *Endocr Rev.* (2003) 24:183–217.
36. Hu X, Rui L, Zhu T, Xia H, Yang X, Wang X, et al. Low testosterone level in middle-aged male patients with coronary artery disease. *Eur J Intern Med.* (2011) 22:e133–6.
37. Alexander CJ, Tangchitnob EP, Lepor NE. Polycystic ovary syndrome: a major unrecognized cardiovascular risk factor in women. *Rev Cardiovasc Med.* (2009) 10:83–90.
38. Christakou CD, Diamanti-Kandarakis E. Role of androgen excess on metabolic aberrations and cardiovascular risk in women with polycystic ovary syndrome. *Womens Health.* (2008) 4:583–94. doi: 10.2217/17455057.4.6.583
39. Castilho SD, Nucci LB. Age at menarche in schoolgirls with and without excess weight. *J Pediatr.* (2015) 91:75–80. doi: 10.1016/j.jped.2014.05.008
40. Werneck AO, Oyeyemi AL, Cyrino ES, Ronque ERV, Szwarcwald CL, et al. Association between age at menarche and blood pressure in adulthood: is obesity an important mediator?. *Hypertens Res.* (2018) 41:856–64.
41. Roeters van Lennep JE, Heida KY, Bots ML, Hoek A, Collaborators Dutch. Cardiovascular disease risk in women with premature ovarian insufficiency: a systematic review and meta-analysis. *Eur J Prev Cardiol.* (2016) 23:178–86.
42. Honigberg MC, Zekavat SM, Aragam K, Finneran P, Klarin D, Bhatt DL, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA.* (2019) 322:2411–21.
43. Huan L, Deng X, He M, Chen S, Niu W. Meta-analysis: early age at natural menopause and risk for all-cause and cardiovascular mortality. *Biomed Res Int.* (2021) 2021:6636856.
44. Gong D, Sun J, Zhou Y, Zou C, Fan Y. Early age at natural menopause and risk of cardiovascular and all-cause mortality: a meta-analysis of prospective observational studies. *Int J Cardiol.* (2016) 203:115–9. doi: 10.1016/j.ijcard.2015.10.092
45. Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause.* (2006) 13:265–79. doi: 10.1097/01.gme.0000218683.97338.ea
46. Wu X, Cai H, Kallianpur A, Gao YT, Yang G, Chow WH, et al. Age at menarche and natural menopause and number of reproductive years in association

with mortality: results from a median follow-up of 11.2 years among 31,955 naturally menopausal Chinese women. *PLoS One.* (2014) 9:e103673. doi: 10.1371/journal.pone.0103673
47. Gallagher LG, Davis LB, Ray RM, Psaty BM, Gao DL, Checkoway H, et al. Reproductive history and mortality from cardiovascular disease among women textile workers in Shanghai, China. *Int J Epidemiol.* (2011) 40:1510–8. doi: 10.1093/ije/dyr134
48. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the risk of coronary heart disease in women. *N Engl J Med.* (1987) 316:1105–10.
49. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. *Lancet.* (1996) 347:714–8.
50. Wang J, Wang Z, Guo F, Zhang Y, Ji H, Chen G, et al. Individual and Combined Cardiometabolic Morbidities and the Subsequent Risk of Cardiovascular Events in Chinese Adults. *J Clin Endocrinol Metab.* (2022) 107:e84–94. doi: 10.1210/clinem/dgab609
51. Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, et al. Duration of reproductive life span, age at menarche, and age at menopause are associated with risk of cardiovascular disease in women. *J Am Heart Assoc.* (2017) 6:e006713.
52. Ling Y, Lin L, Kartsonaki C, Guo Y, Chen Y, Bian Z, et al. Menopause characteristics, total reproductive years, and risk of cardiovascular disease among Chinese women. *Circ Cardiovasc Qual Outcomes.* (2017) 10:e004235.
53. Hall PS, Nah G, Howard BV, Lewis CE, Allison MA, Sarto GE, et al. Reproductive factors and incidence of heart failure hospitalization in the Women's Health Initiative. *J Am Coll Cardiol.* (2017) 69:2517–26.
54. Otsuki S, Saito E, Sawada N, Abe SK, Hidaka A, Yamaji T, et al. Female reproductive factors and risk of all-cause and cause-specific mortality among women: the Japan public health center–based prospective study (JPHC study). *Ann Epidemiol.* (2018) 28:597–604.e6. doi: 10.1016/j.annepidem.2018.06.001
55. Chang HS, Odongua N, Ohrr H, Sull JW, Nam CM. Reproductive risk factors for cardiovascular disease mortality among postmenopausal women in Korea: the Kangwha Cohort Study, 1985-2005. *Menopause.* (2011) 18:1205–12. doi: 10.1097/gme.0b013e31821adb43
56. Jansen SC, Temme EH, Schouten EG. Lifetime estrogen exposure versus age at menopause as mortality predictor. *Maturitas.* (2002) 43:105–12. doi: 10.1016/s0378-5122(02)00183-4
57. Jaspers L, Kavousi M, Erler NS, Hofman A, Laven JS, Franco OH. Fertile lifespan characteristics and all-cause and cause-specific mortality among postmenopausal women: the Rotterdam Study. *Fertil Steril.* (2017) 107:448–456.e1 doi: 10.1016/j.fertnstert.2016.11.006
58. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. *Pediatrics.* (2002) 110:e43. doi: 10.1542/peds.110.4.e43
59. Yermachenko A, Dvornyk V. Nongenetic determinants of age at menarche: a systematic review. *BioMed Res Int.* (2014) 2014:371583. doi: 10.1155/2014/371583
60. Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, et al. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember?. *Am J Epidemiol.* (2002) 155:672–9. doi: 10.1093/aje/155.7.672
61. Casey V, Dwyer JT, Coleman KA, Krall EA, Gardner J, Valadian I, et al. Accuracy of recall by middle-aged participants in a longitudinal study of their body size and indices of maturation earlier in life. *Ann Hum Biol.* (1991) 18:155–66. doi: 10.1080/03014469100001492
62. Colditz GA, Stampfer MJ, Willett WC, Stason WB, Rosner B, Hennekens CH, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am J Epidemiol.* (1987) 126:319–25. doi: 10.1093/aje/126.2.319
63. Den Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. *Maturitas.* (1997) 27:117–23. doi: 10.1016/s0378-5122(97)01122-5

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The prevalence of cardiometabolic multimorbidity and its associations with health outcomes among women in China

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Objective: In China, a limited number of studies focus on women and examine the effect of cardiometabolic multimorbidity (defined as the presence of two or more cardiometabolic diseases) on health outcomes. This research aims to investigate the epidemiology of cardiometabolic multimorbidity and the association of cardiometabolic multimorbidity with long-term mortality.

Methods: This study used data from the China Health and Retirement Longitudinal Study between 2011 and 2018, which includes 4,832 women aged 45 years and older in China. Poisson-distributed Generalized Linear Models (GLM) were applied to examine the association of cardiometabolic multimorbidity with all-cause mortality.

Results: Overall, the prevalence of cardiometabolic multimorbidity was 33.1% among the total sample of 4,832 Chinese women, and increased with age, ranging from 28.5% (22.1%) for those aged 45–54 years to 65.3% (38.2%) for those aged ≥75 years in urban (rural) areas. Compared with the group of none and single disease, cardiometabolic multimorbidity was positively associated with all-cause death (RR = 1.509, 95% CI = 1.130, 2.017), after adjusting socio-demographic and lifestyle behavioral covariates. Stratified analyses revealed that the association between cardiometabolic multimorbidity and all-cause death was only statistically significant (RR = 1.473, 95% CI = 1.040, 2.087) in rural residents, but not significant in urban residents.

Conclusion: Cardiometabolic multimorbidity is common among women in China and has been associated with excess mortality. Targeted strategies and people-centered integrated primary care models must be considered to more effectively manage the cardiometabolic multimorbidity shift from focusing on single-disease.

KEYWORDS

cardiometabolic disease, multimorbidity, health outcomes, women, Chinese adults

1. Introduction

Metabolic disease is associated with the high risk of cardiovascular diseases (1, 2) and all-cause mortality (3–5) has been a major global challenge. In 2019, one-third of all deaths worldwide were due to cardiovascular disease and the cardiovascular diseases, especially coronary heart disease and stroke, is the leading cause of death worldwide (3). The disease burden of cardiometabolic multimorbidity (defined as the coexistence of two or more cardiometabolic diseases) is rising rapidly. In China and low-and middle income countries (LMICs), the number of people experiencing cardiometabolic multimorbidity has increased rapidly over the past few decades (6–8). In European countries and the United States, multimorbidity is associated with higher healthcare service utilization, poorer health outcomes, and mortality, challenging the single-disease framework of most healthcare configurations (9, 10).

Although several studies have been conducted in high-income countries (HICs) on the burden and effect of multimorbidity, this topic remains an emerging research area of research in LMICs (11–13). Recently, only a few studies in certain regions of China have explored this topic (14–16). For example, the Chinese Electronic Health Records Research in Yinzhou (CHERRY) study focusing on Yinzhou County, which examined the burden of cardiometabolic multimorbidity and mortality risk among 1 million subjects in China (16).

Most of previous studies investigated the relationships between some single chronic conditions alone and health outcomes. There is limited evidence on the long-term changes of health related outcomes in individuals who are suffering from cardiometabolic multimorbidity (3–5). In China, there is no study focusing on females and estimated the impact of cardiometabolic multimorbidity on long-term mortality using nationally representative data (17–21). Therefore, the objective of this research is to investigate the prevalence of cardiometabolic multimorbidity among Chinese women and the association of cardiometabolic multimorbidity with all-cause mortality, using nationally representative population-based cohort data.

2. Materials and methods

2.1. Data source

A nationally representative population-based cohort study was designed, using longitudinal data from the baseline and newest wave of China Health and Retirement Longitudinal Study (CHARLS) conducted from 2011 to 2018. The aim of CHARLS is to collect a set of high-quality micro-data representing families and individuals of middle-aged and elderly people aged 45 and above in China. The CHARLS baseline survey was launched in 2011, covering 150 counties, 450 villages/communities as primary sampling units (PSUs), and over 17,000 individuals in about 10,000 households. These samples will then be tracked every 2 to 3 years. Data were collected in a survey in which four-stage stratified cluster sampling was used to select eligible individuals. Details of the procedures involved in CHARLS and its multistage stratified sampling are described elsewhere (22). The CHARLS questionnaire includes: basic socio-demographic information, family structure and income, health status, health service utilization and expenditure, retirement and pensions, anthropometric measurements and biomarkers. Written informed consent was obtained from all participants (22).

The baseline of CHARLS collected a total of 17,708 participants, including 9,230 adult women, with the respondent rate above 80%. The fourth wave of CHARLS survey successfully re-interviewed 7,593 females in 2018. This study identified 5,538 participants with biomarker information and blood test. After deleting the individuals aged below 45 years and those respondents with missing values for the outcome variable and covariates of interest, 4,832 individuals who performed the two wave surveys were included (The sample selection flowchart was shown in **Supplementary Figure 1**).

2.2. Measures

We counted the number of chronic diseases for each participant, identifying those with multimorbidity (23, 24). Cardiometabolic multimorbidity was defined as the presence of two or more cardiometabolic diseases included for each participant (17, 20, 21). A total of seven cardiovascular and metabolic diseases were used to measure multimorbidity. Hypertension, diabetes, dyslipidaemia, hyperuricemia and central obesity were measured by biomarkers or blood test information. Another two non-fatal cardiometabolic diseases, including heart disease and stroke, were ascertained *via* self-reports of a physician or health professional diagnosis of heart disease or stroke.

In this study, the hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, and/or taking antihypertensive drugs for elevated blood pressure (25). The diabetes was defined as (1) fasting blood glucose level ≥126 mg/dL (7.0 mmol/L); and/or (2) HbA1c concentration ≥6.5%; and/or (3) insulin therapy and/or medication for elevated blood glucose (26). The dyslipidemia was defined as (1) total cholesterol ≥240 mg/dL (6.22 mmol/L); and/or (2) low-density lipoprotein cholesterol ≥160 mg/dL (4.14 mmol/L); and/or (3) high-density lipoprotein cholesterol Protein cholesterol <40 mg/dL (1.04 mmol/L); and/or (4) triglycerides ≥200 mg/dL (2.26 mmol/L); and/or (5) taking anti-dyslipidemic drugs (27). The hyperuricemia is defined as a serum uric acid concentration greater than 7.0 mg/dL in men and greater than 6.0 mg/dL in women (28). The central obesity was defined as a waist circumference greater than 85 cm in female participants with a body mass index (BMI) ≥30 kg/m^2 (29). The presence of heart disease and stroke, respectively, was determined by two questions in CHARLS survey: the participants were asked "Have you been diagnosed with heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems by a doctor" and "Have you been diagnosed with stroke by a doctor?"

Regarding the health related outcome variable, all-cause mortality during the period of 2011–2018 was used as the primary outcome. The death information of participants at baseline was collected in sequential surveys and the last follow-up was conducted in 2018.

2.3. Statistical analysis

Poisson-distributed Generalized Linear Models (GLM) were conducted to determine the longitudinal association of Cardiometabolic multimorbidity with all-cause mortality. Models

are adjusted on age, marital status, educational level, residence place, region, and social health insurance at baseline (model 1) and other confounding factors (smoking, drinking alcohol, other non-communicable diseases (NCDs), and depression) (model 2). Depressive disorder was measured by the 10-item Center for Epidemiologic Studies Depression Scale (CES-D 10), which has been identified as a valid and reliable useful mental health assessment tool in China (30).

We performed stratified analyses to further investigate urban-rural differences of the association of cardiometabolic multimorbidity with all-cause death. In terms of the multivariable regression analyses, relative risk ratios (RR) and 95% confidence intervals (CI) were reported. We performed the sensitivity analysis on relationships between the single components of cardiometabolic syndrome and all-cause mortality. We also conducted the regression analyses by using a newer cut-off of 5.1 mg/dl for the definition of

TABLE 1 Characteristics of participants, the prevalence of single condition and CMD multimorbidity.

Variables	*N* (Percentage)[a]		Prevalence of single disease[b] (95% CI)			Prevalence of CMD multimorbidity (95% CI)		
All	4,832	100.0	34.1%	32.2%	36.0%	33.7%	31.6%	35.9%
Age, years								
45–55	1,900	39.3	32.4%	29.2%	35.8%	25.1%	21.3%	29.4%
55–65	1,903	39.4	34.9%	32.3%	37.6%	35.7%	33.1%	38.4%
65–75	786	16.3	35.2%	30.8%	39.8%	44.9%	40.5%	49.5%
≥ 75	243	5.0	37.2%	29.0%	46.1%	50.4%	41.0%	59.7%
Marital status								
Married and partnered	4,200	86.9	33.6%	31.6%	35.7%	32.5%	30.2%	35.0%
Unmarried and others	632	13.1	36.6%	31.9%	41.6%	40.7%	35.9%	45.7%
Education level								
Illiterate	2,901	60.0	36.5%	34.3%	38.7%	33.8%	31.6%	36.0%
Primary school	858	17.8	31.2%	27.3%	35.3%	37.5%	32.9%	42.3%
Secondary school	726	15.0	31.0%	25.8%	36.7%	30.1%	25.0%	35.7%
College and above	347	7.2	31.7%	24.1%	40.4%	33.5%	22.6%	46.5%
Residence place								
Urban	1,685	34.9	30.7%	27.4%	34.3%	39.2%	35.0%	43.5%
Rural	3,147	65.1	36.8%	34.9%	38.7%	29.2%	27.5%	31.0%
Region								
East	1,780	36.8	33.9%	30.4%	37.5%	33.0%	28.9%	37.3%
Central	1,852	38.3	34.5%	31.7%	37.3%	35.8%	33.2%	38.5%
West	1,200	24.8	33.7%	30.4%	37.2%	32.0%	28.0%	36.2%
Social health insurance								
No	311	6.4	35.2%	28.6%	42.4%	31.9%	24.9%	39.9%
Yes	4,521	93.6	34.0%	32.0%	36.0%	33.9%	31.7%	36.2%
Smoking								
No	4,549	94.1	34.0%	32.1%	36.1%	33.5%	31.3%	35.8%
Yes	283	5.9	34.2%	27.6%	41.5%	38.1%	31.0%	45.8%
Alcohol drinking								
No	4,241	87.8	33.6%	31.6%	35.7%	34.9%	32.6%	37.4%
Yes	591	12.2	37.4%	32.5%	42.5%	24.8%	20.8%	29.3%
Other NCDs								
No	1,958	40.5	33.2%	29.9%	36.7%	31.3%	27.4%	35.5%
Yes	2,874	59.5	34.7%	32.5%	36.9%	35.5%	33.3%	37.8%
Depression								
No	2,690	55.7	33.7%	31.0%	36.5%	32.4%	29.2%	35.7%
Yes	2,142	44.3	34.6%	32.2%	37.1%	35.7%	33.2%	38.3%

a, *N* and percentages were based on study samples (unweighted); b, weighted prevalence of single disease and cardiometabolic multimorbidity. CMD, cardiometabolic disease.

TABLE 2 The proportion of cardiometabolic diseases and multimorbidity among Chinese adults by age group and residence place (N = 4,832).

CMD and multimorbidity	Total		Rural				Urban			
	n	%	45–55	55–65	65–75	≥ 75	45–55	55–65	65–75	≥ 75
Single disorder										
Hypertension	1,641	34.0	22.0	33.2	49.5	59.7	24.0	37.5	49.5	61.2
Hyperlipidemia	1,986	41.1	34.9	40.5	40.9	42.4	40.1	51.2	51.9	57.7
Diabetes	708	14.7	11.2	15.3	14.0	16.7	12.4	19.3	21.3	26.3
Hyperuricemia	216	4.5	2.3	3.6	8.2	11.6	3.7	8.4	8.5	6.4
Concentric obesity	267	5.5	4.4	4.8	3.5	2.6	5.5	7.9	7.3	8.0
Heart disease	768	15.9	12.2	14.9	15.4	8.3	10.5	20.7	29.5	29.1
Stroke	127	2.	1.9	3.3	3.6	1.4	1.5	3.0	3.3	6.4
Overall multimorbidity	1,601	33.1	22.1	31.1	39.0	38.2	28.5	41.8	52.0	65.3

Values are unweighted counts and weighted percentages unless otherwise indicated. Overall multimorbidity refers to any two or more cardiometabolic diseases included in this study. CMD, cardiometabolic disease.

hyperuricemia for females (31). All analyses were weighted to account for the multi-stage probability-proportionate-to-size sampling (PPS) design of CHARLS, and conducted using Stata Version 16.0 (Stata Corp., College Station, TX, USA). P-values < 0.05 were deemed statistically significant.

3. Results

Our analysis included 4,832 females from the CHARLS in China. The mean age of respondents was 57.7 years at the baseline survey. Among the participants, 60.1% of the respondents were illiterate, 65.1% of individuals living in rural areas and 93.6% of individuals with social medical insurances. Among Chinese women, the proportion of current smoking and alcohol drinking was 5.9 and 12.2%, respectively. The prevalence of depression disorder was 44.3% (**Table 1**).

Table 2 showed the prevalence of main cardiometabolic diseases and multimorbidity across age group and residence place. Among the Chinese women, the prevalence of cardiometabolic multimorbidity was 33.1%, and raised with age, ranging from 28.5% (22.1%) for those aged 45–54 years to 65.3% (38.2%) for those aged 75 years and above in urban (rural) areas. Over 30% of Chinese women experiencing hypertension and hyperlipidemia. The prevalence of heart disease, diabetes, concentric obesity, hyperuricemia and stroke was 15.9, 14.7 5.5, 4.5, and 2.6%, respectively. The prevalence of hypertension, hyperlipidemia, diabetes as well as stroke increased with age among urban citizens and was commonly higher than those of rural residents. **Figure 1** showed a higher proportions of all-cause death among individuals in rural areas compared to individuals in urban areas.

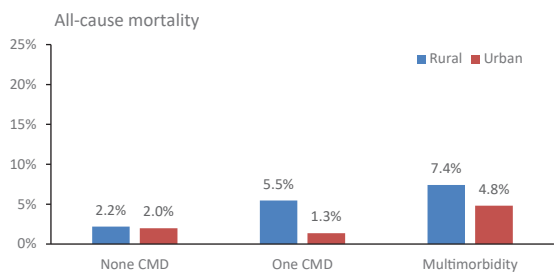

FIGURE 1
The all-cause mortality from 2011 to 2018 by the number of disease and residence place. CMD, cardiometabolic disease.

Table 3 revealed the relationship between cardiometabolic multimorbidity and health-related outcomes. Cardiometabolic multimorbidity was positively associated with all-cause death (RR = 1.509, 95% CI = 1.130, 2.017), after adjusting socio-demographic and lifestyle behavioral covariates. In women with ages above 65 years, depression and those without social health insurance were more likely to have the risk of death (**Table 3**). The stratified analysis showed that he association of cardiometabolic multimorbidity with all-cause death was only statistically significant (RR = 1.473, 95% CI = 1.040, 2.087) in rural residents, but not significant in urban residents (**Table 4**). The sensitivity analyses suggested consistent results (**Supplementary Tables 1**, **2**). For the single disorders, stroke, heart disease and diabetes showed a statistically significant association with all-cause mortality, after adjusting socio-demographic and lifestyle behavioral covariates (**Supplementary Table 3**).

4. Discussion

This research analyzed nationally representative longitudinal data from the CHARLS to examine the prevalence of cardiometabolic multimorbidity and its association of cardiometabolic multimorbidity with all-cause death among middle-aged and elderly Chinese females. This study revealed that cardiometabolic multimorbidity is common among Chinese women, especially among the elderly and urban citizens. We found that cardiometabolic multimorbidity was associated with excess mortality. Furthermore, the association between cardiometabolic multimorbidity and all-cause death was only statistically significant in rural residents, but not significant in urban residents.

The cardiometabolic multimorbidity prevalence estimated by this study was 33.1% among middle-aged and older Chinese women

TABLE 3 Association of CMD multimorbidity with all-cause death.

Variable (reference)	Model 1				Model 2			
	RR	95% CI		*P*-value	RR	95% CI		*P*-value
CMD multimorbidity (single disorder)	1.529	1.146	2.039	0.004	1.509	1.130	2.017	0.005
Age (45–59 years)								
55–65	1.539	0.887	2.672	0.125	1.514	0.872	2.630	0.140
65–75	6.035	3.592	10.140	<0.001	5.970	3.552	10.036	<0.001
≥ 75	13.694	7.751	24.193	<0.001	13.362	7.566	23.599	<0.001
Marital status (married)	1.340	0.963	1.863	0.082	1.312	0.944	1.824	0.106
Education level (Illiterate)								
Primary school	0.837	0.536	1.307	0.435	0.851	0.544	1.330	0.479
Secondary school	1.167	0.677	2.013	0.578	1.209	0.701	2.086	0.496
College and above	0.297	0.072	1.228	0.094	0.317	0.077	1.315	0.114
Residence place (urban)	1.164	0.850	1.595	0.345	1.137	0.828	1.561	0.428
Region (east)								
Central	1.094	0.783	1.528	0.600	1.066	0.762	1.492	0.708
West	1.278	0.893	1.829	0.180	1.265	0.877	1.826	0.209
Social health insurance (no)	0.602	0.393	0.922	0.020	0.597	0.390	0.914	0.018
Smoking (no)	–	–	–	–	1.274	0.758	2.143	0.360
Alcohol drinking (no)	–	–	–	–	0.966	0.618	1.511	0.880
Other NCDs (no)	–	–	–	–	0.916	0.677	1.239	0.569
Depression (no)	–	–	–	–	1.406	1.044	1.894	0.025

Models are adjusted on age, marital status, educational level, residence place, region, and social health insurance at baseline (model 1) and other confounding factors (smoking, alcohol drinking, other NCDs, and depression) (model 2). CMD, cardiometabolic disease; RR, relative risk ratio; CI, confidence interval; Other NCDs, other non-communicable diseases excluding the seven cardiometabolic diseases in this study.

in 2011. For general adults in China, there were studies showing a lower prevalence of metabolic disorder (16.5% in 2000 and 23.3% in 2009) (7). A meta-analysis in the basis of studies from mainland China also showed that the pooled prevalence of metabolic syndrome was 24.5% (32). Those evidence suggested that China is experiencing an emerging cardiometabolic disease epidemic, which may be related to the accelerated changes in dietary patterns and lifestyle behaviors due to demographic and socioeconomic transitions during the past decades (33). Moreover, there are many studies revealing a high prevalence of cardiometabolic syndromes in western developed countries and other regions in Asia, such as the United States (35%), Iran (37%), and Turkey (44%) (34–36). Variations in cardiometabolic syndrome prevalence between LMICs and HICs could be because of real differences across countries, and might also be due to potentially different definitions and sampling methods (36, 37).

The results from this research also suggested that cardiometabolic multimorbidity increased with the individual's age and the people living in urban areas had a higher proportion of cardiometabolic multimorbidity than those rural persons in China. In line with previous findings, the burden of cardiometabolic disease increases with age due to the declining trends in cardiometabolic function (34, 38). Urban residents experiences a higher proportion of cardiometabolic multimorbidity than rural residents (32, 39), which could be attributed to physical inactivity, sedentary, unhealthy diet (such as excessive intake of high-calorie food, fat and salt) during the process of urbanization and economic development (39–41).

A few of studies have suggested that multiple chronic diseases have a significant impact on health related outcomes and mortality (10, 16–18). These findings are consistent with our previous studies in China (16, 19–21), United States (10, 42, 43), Japan (44), and Europe (45), where multimorbidity presented in health-related outcomes and deaths (10, 16). Cardiovascular and metabolic diseases have been revealed by several studies to play a dominant role in multiple multimorbidity patterns (41). The association between single cardiometabolic disease and negative health outcomes and mortality has also been documented (46). This research further provides new evidence that significant relationship between cardiometabolic multimorbidity and long-term mortality among adult women in China. We also performed the regression analyses by using a recently lower cut-off of 5.1 mg/dl for the definition of hyperuricemia for females (31), which also suggested consistent results.

Stratified analyses of this study revealed a significant association between cardiometabolic multimorbidity and all-cause death in rural residents, but there was not a significant association in urban residents while they had a high prevalence of cardiometabolic multimorbidity. Previous studies from China have documented disparities in the healthcare access and service utilization between residents living in rural and urban areas (47). Patients in rural areas have less geographic access to health-care than those patients living in urban areas. Rural areas in China could be more prone to healthcare provider shortages and lack of medical resources (48, 49). Rural residents usually face greater financial barriers and relatively low-quality

TABLE 4 Association of CMD multimorbidity with all-cause death among participants living the rural and urban area.

Variable (reference)	Rural				Urban			
	RR	95% CI		*P*-value	RR	95% CI		*P*-value
CMD Multimorbidity (single disorder)	1.473	1.040	2.087	0.029	1.571	0.920	2.681	0.098
Age (45–59 years)								
55–65	1.404	0.699	2.819	0.340	1.649	0.657	4.139	0.28
65–75	6.638	3.520	12.516	<0.001	4.606	1.833	11.571	0.001
≥ 75	14.157	7.077	28.322	<0.001	11.690	4.196	32.570	<0.001
Marital status (married)	1.331	0.893	1.982	0.160	1.257	0.694	2.277	0.450
Education level (Illiterate)								
Primary school	0.732	0.398	1.347	0.316	1.128	0.570	2.233	0.729
Secondary school	1.076	0.477	2.426	0.860	1.355	0.631	2.910	0.436
College and above	0.674	0.091	4.976	0.699	0.248	0.033	1.874	0.177
Region (east)								
Central	0.965	0.642	1.449	0.862	1.265	0.689	2.324	0.449
West	1.175	0.755	1.828	0.476	1.607	0.821	3.142	0.166
Social health insurance (no)	0.611	0.356	1.047	0.073	0.623	0.305	1.274	0.195
Smoking (no)	1.089	0.548	2.163	0.807	1.645	0.732	3.693	0.228
Alcohol drinking (no)	1.193	0.739	1.927	0.471	0.358	0.087	1.476	0.155
Other NCDs (no)	0.774	0.537	1.113	0.167	1.321	0.761	2.292	0.323
Depression (no)	1.290	0.901	1.847	0.165	1.711	1.009	2.902	0.046

Models are adjusted on age, marital status, educational level, region, social health insurance, smoking, alcohol drinking, other NCDs, and depression. CMD, cardiometabolic disease; RR, relative risk ratio; CI, confidence interval; Other NCDs, other non-communicable diseases excluding the seven cardiometabolic diseases in this study.

health care (50). Thus, early screening of high-risk groups of cardiometabolic multimorbidity should be strengthened, and targeted preventive measures should be taken further. A strong people-centered primary care system needs to be oriented toward cardiometabolic diseases and multimorbidity, which has been shown to be the most cost-effective way to manage chronic diseases (51–54).

Establishing a multidisciplinary team composed of clinical physicals, geriatricians, pharmacists, nurses, nutritionists, rehabilitation physiotherapists, social workers, patients and their families is a potential model for dealing with multimorbidity issues, following the "people-centered principle" of managing multimorbidity. In the process of achieving the "Healthy China 2030" strategic goals (55) and Sustainable Development Goals, considering the increasing burden of multimorbidity populations and its long-term impact in future, it need more attention from clinicians, researchers and health policy makers from China as well as other countries with economies in transition.

To our best knowledge, this is the first nationally representative cohort study that focused on adult women and investigated associations of cardiometabolic multimorbidity with long-term mortality in China that examined the rural-urban differences in the relationships, by using longitudinal data with cardiometabolic biomarkers for the disease diagnosis. This study also has some limitations. First, while we identify several cardiometabolic diseases on the basis of biomarkers, the partial use of self-reported measures of heart disease and stroke could underestimate the prevalence of these chronic diseases. Second, we estimated the prevalence of cardiometabolic multimorbidity and its association with health outcomes by simply counting the number of chronic conditions, hence the accuracy of findings may be affected by the types of cardiometabolic multimorbidity. CHARLS only collected the data for calculating all-cause mortality and we could not further analyze the association between multimorbidity and mortality due to stroke or cardiovascular diseases. Third, there was only a 7-year follow-up period of CHARLS data and long-term impacts on health-related outcomes due to multimorbidity should be examined further. Finally, this study only analyzed the middle-aged and older Chinese women due to the CHARLS data collection, which may affect the generalizability of the findings from this study. The prevalence of cardiometabolic multimorbidity and its relationships with more health related outcomes among younger populations should be considered for future studies.

5. Conclusion

Cardiometabolic multimorbidity is common among women in China and has been associated with excess mortality. Health-care delivery models need to shift from focusing on single-disease to effectively managing cardiometabolic multimorbidity. Targeted strategies and people-centered integrated primary care models must be considered to more effectively manage the cardiometabolic multimorbidity shift from focusing on single-disease. Medical resources need to be prioritized to screen, prevent and treat cardiometabolic diseases as well as multimorbidity, especially in rural areas.

Data availability statement

The original contributions presented in this study are included in this article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by The Biomedical Ethics Review Committee of Peking University approved the CHARLS study (approval number: IRB00001052–11015), and all interviewees were required to provide informed consent. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZ conceived and designed the study and did the initial analysis. LS supervised data analysis. YZ and SZ wrote the first draft of the manuscript. HZ, XL, AD, QW, LS, and IT critically revised the first draft. All authors reviewed, edited and commented on multiple versions of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.922932/full#supplementary-material

References

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* (2009) 120:1640–5. doi: 10.1161/CIRCULATIONAHA.109.192644

2. Meigs JB. Invited commentary: insulin resistance syndrome? Syndrome X? Multiple metabolic syndrome? A syndrome at all? Factor analysis reveals patterns in the fabric of correlated metabolic risk factors. *Am J Epidemiol.* (2000) 152:908–11. doi: 10.1093/aje/152.10.908

3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol.* (2020) 76:2982–3021. doi: 10.1016/j.jacc.2020.11.010

4. Rutter MK, Meigs JB, Wilson PW. Cardiovascular risk and the metabolic syndrome. *Metab Syndr Relat Disord.* (2006) 4:252–60. doi: 10.1089/met.2006.4.252

5. Kivimaki M, Kuosma E, Ferrie JE, Luukkonen R, Nyberg ST, Alfredsson L, et al. Overweight, obesity, and risk of cardiometabolic multimorbidity: pooled analysis of individual-level data for 120813 adults from 16 cohort studies from the USA and Europe. *Lancet Public Health.* (2017) 6:e277–85. doi: 10.1016/S2468-2667(17)30074-9

6. Gu D, Reynolds K, Wu X, Chen J, Duan X, Reynolds RF, et al. Prevalence of the metabolic syndrome and overweight among adults in China. *Lancet.* (2005) 365:1398–405. doi: 10.1016/S0140-6736(05)66375-1

7. Xi B, He D, Hu Y, Zhou D. Prevalence of metabolic syndrome and its influencing factors among the Chinese adults: the China Health and Nutrition Survey in 2009. *Prev Med.* (2013) 57:867–71. doi: 10.1016/j.ypmed.2013.09.023

8. Boyd CM, Fortin M. Future of multimorbidity research: how should understanding of multimorbidity inform health system design? *Public Health Rev.* (2010) 32:451–74. doi: 10.1007/BF03391611

9. Palladino R, Lee JT, Millett C. Associationbetween multimorbidity and healthcareutilisation and health outcomesamong elderly people in Europe. *Eur J Public Health.* (2014) 24:49. doi: 10.1093/eurpub/cku151.118

10. Angelantonio ED, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA.* (2015) 314:52–60.

11. Glynn LG, Valderas JM, Healy P, Burke E, Newell J, Gillespie P, et al. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. *Family Pract.* (2011) 28:516–23. doi: 10.1093/fampra/cmr013

12. Lehnert T, Heider D, Leicht H, Heinrich S, Corrieri S, Luppa M, et al. Health care utilization and costs of elderly persons with multiple chronic conditions. *Med Care Res Rev.* (2011) 68:387–420. doi: 10.1177/1077558711399580

13. Lee JT, Hamid F, Pati S, Atun R, Millett C. Impact of noncommunicable disease multimorbidity on health care utilisation and out-of-pocket expenditures in middle-income countries: cross sectional analysis. *PLoS One.* (2015) 10:e0127199. doi: 10.1371/journal.pone.0127199

14. Chen H, Cheng M, Zhuang Y, Broad JB. Multimorbidity among middle-aged and older persons in urban China: prevalence, characteristics and health service utilization. *Geriatr Gerontol Int.* (2018) 18:1447–52. doi: 10.1111/ggi.13510

15. Chen H, Chen Y, Cui B. The association of multimorbidity with health care expenditure among the elderly patients in Beijing, China. *Arch Gerontol Geriat.* (2018) 79:32–8. doi: 10.1016/j.archger.2018.07.008

16. Zhang D, Tang X, Shen P, Si Y, Liu X, Xu Z, et al. Multimorbidity of cardiometabolic diseases: prevalence and risk for mortality from one million Chinese adults in a longitudinal cohort study. *BMJ Open.* (2019) 9:e024476. doi: 10.1136/bmjopen-2018-024476

17. Archana SM, Aurore F, Séverine S, Tabak A, Shipley M, Dugravot A, et al. Clinical, socioeconomic, and behavioural factors at age 50 years and risk of cardiometabolic multimorbidity and mortality: a cohort study. *PLoS Med.* (2018) 15:e1002571. doi: 10.1371/journal.pmed.1002571

18. Arokiasamy P, Uttamacharya U, Jain K, Biritwum RB, Yawson AE, Wu F, et al. The impact of multimorbidity on adult physical and mental health in low- and middle-income countries: what does the study on global ageing and adult health (SAGE) reveal? *BMC Med.* (2015) 13:178. doi: 10.1186/s12916-015-0402-8

19. Zhao Y, He L, Han C, Oldenburg B, Sum G, Haregu TN, et al. Urban-rural differences in the impacts of multiple chronic disease on functional limitations and work productivity among Chinese adults. *Glob Health Action.* (2021) 14:1975921. doi: 10.1080/16549716.2021.1975921

20. Zhao Y, Zhang P, Lee JT, Oldenburg B, van Heusden A, Haregu TN, et al. The prevalence of metabolic disease multimorbidity and its associations with spending and health outcomes in middle-aged and elderly Chinese adults. *Front Public Health.* (2021) 9:658706. doi: 10.3389/fpubh.2021.658706

21. Emerging Risk Factors Collaboration, Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA.* (2015) 314:52–60. doi: 10.1001/jama.2015.7008

22. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). *Int J Epidemiol.* (2014) 43:61–8. doi: 10.1093/ije/dys203

23. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet.* (2012) 380:37–43. doi: 10.1016/S0140-6736(12)60240-2

24. Zhao Y, Atun R, Oldenburg B, McPake B, Tang S, Mercer SW, et al. Physical multimorbidity, health service use, and catastrophic health expenditure by socioeconomic groups in China: an analysis of population-based panel data. *Lancet Glob Health.* (2020) 8:e840-9. doi: 10.1016/S2214-109X(20)30127-3

25. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., et al. National heart, lung, and blood institute joint national committee on prevention, detection, evaluation, and treatment of high blood pressure; national high blood pressure education program coordinating committee: the seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA.* (2003) 289:2560–72. doi: 10.1001/jama.289.19.2560

26. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, et al. Prevalence and control of diabetes in Chinese adults. *JAMA.* (2013) 310:948–59. doi: 10.1001/jama.2013.168118

27. Zhang M, Deng Q, Wang L, Huang Z, Zhou M, Li Y, et al. Prevalence of dyslipidemia and achievement of low-density lipoprotein cholesterol targets in Chinese adults: a nationally representative survey of 163,641 adults. *Int J Cardiol.* (2018) 260:196–203. doi: 10.1016/j.ijcard.2017.12.069

28. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med.* (2008) 359:1811–21. doi: 10.1016/S1471-4892(02)00143-1

29. Association CDSoM. Guideline to the prevention and treatment of type 2 diabetes in China (2013 Edition). *Chin J Endocrinol Metab.* (2014) 10:893–942. doi: 10.3760/cma.j.issn.1000-6699.2014.10.02031

30. Boey KW. Cross-validation of a short form of the CES-D in Chinese elderly. *Int J Geriatr Psychiatry.* (1999) 14:608–17. doi: 10.1002/(sici)1099-1166(199908)14:8<608::aid-gps991>3.0.co;2-z

31. Maloberti A, Giannattasio C, Bombelli M, Desideri G, Cicero AFG, Muiesan ML, et al. Hyperuricemia and risk of cardiovascular outcomes: the experience of the URRAH (Uric Acid Right for Heart Health) project. *High Blood Press Cardiovasc Prev.* (2020) 27:121–8. doi: 10.1007/s40292-020-00368-z

32. Li R, Li W, Lun Z, Zhang H, Sun Z, Kanu JS, et al. Prevalence of metabolic syndrome in mainland china: a meta-analysis of published studies. *BMC Public Health.* (2016) 16:296. doi: 10.1186/s12889-016-2870-y

33. Lao XQ, Ma WJ, Sobko T, Zhang YH, Xu YJ, Xu XJ, et al. Dramatic escalation in metabolic syndrome and cardiovascular risk in a Chinese population experiencing rapid economic development. *BMC Public Health.* (2014) 14:983. doi: 10.1186/1471-2458-14-983

34. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003-2012. *JAMA.* (2015) 313:1973–4. doi: 10.1001/jama.2015.4260

35. Gundogan K, Bayram F, Gedik V, Kaya A, Karaman A, Demir O, et al. Metabolic syndrome prevalence according to ATP III and IDF criteria and related factors in Turkish adults. *Arch Med Sci.* (2013) 9:243–53. doi: 10.5114/aoms.2013.34560

36. Amirkalali B, Fakhrzadeh H, Sharifi F, Kelishadi R, Zamani F, Asayesh H, et al. Prevalence of metabolic syndrome and its components in the iranian adult population: a systematic review and meta-analysis. *Iran Red Crescent Med J.* (2015) 17:e24723. doi: 10.5812/ircmj.24723

37. Santos A, Barros H. Impact of metabolic syndrome definitions on prevalence estimates: a study in a Portuguese community. *Diabetes Vasc Dis Res.* (2007) 4:320–7. doi: 10.3132/dvdr.2007.059

38. Agborsangaya CB, Lau D, Lahtinen M, Cooke Tim, Johnson JA. Multimorbidity prevalence and patterns across socioeconomic determinants: a cross-sectional survey. *BMC Public Health.* (2012) 12:201. doi: 10.1186/1471-2458-12-201

39. Lu J, Wang L, Li M, Xu Y, Jiang Y, Wang W, et al. Metabolic syndrome among adults in China - The 2010 China noncommunicable disease surveillance. *J Clin Endocrinol Metab.* (2016) 102:507–15. doi: 10.1210/jc.2016-2477

40. Wikstrom K, Lindstrom J, Harald K, Peltonen M, Laatikainen T. Clinical and lifestyle-related risk factors for incident multimorbidity: 10-year follow-up of Finnish population-based cohorts 1982-2012. *Eur J Intern Med.* (2015) 26:211–6. doi: 10.1016/j.ejim.2015.02.012

41. Noe G, Ai K, Somnath C, Tyrovolas S, Olaya B, Leonardi M, et al. Global multimorbidity patterns: a cross-sectional, population-based, multi-country study. *J Gerontol.* (2016) 71:205–14. doi: 10.1093/gerona/glv128

42. Bowling CB, Deng L, Sakhuja S, Morey MC, Jaeger BC, Muntner P. Prevalence of activity limitations and association with multimorbidity among US adults 50 to 64 years old. *J Gen Intern Med.* (2019) 34:2390–6.

43. Jindai K, Nielson CM, Vorderstrasse BA, Quiñones AR. Multimorbidity and functional limitations among adults 65 or older, NHANES 2005-2012. *Prev Chronic Dis.* (2016) 13:E151–151. doi: 10.5888/pcd13.160174

44. Jiao D, Watanabe K, Sawada Y, Tanaka E, Watanabe T, Tomisaki E, et al. Multimorbidity and functional limitation: the role of social relationships. *Arch Gerontol Geriatr.* (2021) 92:104249–104249. doi: 10.1016/j.archger.2020.104249

45. Singer L, Green M, Rowe F, Ben-Shlomo Y, Kulu H, Morrissey K. Trends in multimorbidity, complex multimorbidity and multiple functional limitations in the ageing population of England, 2002–2015. *J Comorb.* (2019) 9:2235042X19872030. doi: 10.1177/2235042X19872030

46. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol.* (2010) 56:1113–32. doi: 10.1016/j.jacc.2010.05.034

47. Chen Y, Yin Z, Xie Q. Suggestions to ameliorate the inequity in urban/rural allocation of healthcare resources in China. *Int J Equity Health.* (2014) 13:34. doi: 10.1186/1475-9276-13-34

48. Wu RX, Cai Y, Lan L, Fan ZW, Xue M. Trend analysis on the allocation of primary health care resources between urban and rural areas in China from 2008 to 2015. *Chin Health Resour.* (2017) 3:20–3.

49. Sibley LM, Weiner JP. An evaluation of access to health care services along the rural-urban continuum in Canada. *BMC Health Serv Res.* (2011) 11:20. doi: 10.1186/s12913-017-1983-z

50. Yongjian X, Jie M, Na W, Fan X, Zhang T, Zhou Z, et al. Catastrophic health expenditure in households with chronic disease patients: a pre-post comparison of the New Health Care Reform in Shaanxi Province, China. *PLoS One.* (2018) 13:e0194539. doi: 10.1371/journal.pone.0194539

51. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. *BMJ.* (2012) 345:809–e5205. doi: 10.1136/bmj.e5205

52. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. *Eur J Gen Pract.* (2008) 14(Suppl 1):28–32. doi: 10.1080/13814780802436093

53. Smith SM, Wallace E, O'Dowd T, Fortin M, Smith SM. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev.* (2016) 2017(9):CD006560.

54. Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care. *BMJ.* (2015) 350:h176.

55. Tan X, Liu X, Shao H. Healthy China 2030: a vision for health care. *Value Health Reg Issues.* (2017) 12:112–4. doi: 10.1016/j.vhri.2017.04.001

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Non-dipping pulse rate and chronic changes of the kidney in patients with chronic kidney disease

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Introduction: An insufficient decrease in nocturnal pulse rate (PR), non-dipping PR, reflects autonomic imbalance and is associated with cardiovascular events and all-cause mortality. We aimed to investigate the clinical and microanatomical structural findings associated with the non-dipping PR status in patients with chronic kidney disease (CKD).

Methods: This cross-sectional study included 135 patients who underwent ambulatory blood pressure monitoring and kidney biopsy concurrently at our institution between 2016 and 2019. Non-dipping PR status was defined as (daytime PR-nighttime PR)/daytime PR <0.1. We compared clinical parameters and microstructural changes in the kidney between patients with and without non-dipping PR, including 24 h proteinuria, glomerular volume, and Mayo Clinic/Renal Pathology Society Chronicity Score.

Results: The median age was 51 years (interquartile range: 35–63), 54% of which were male, and the median estimated glomerular filtration rate was 53.0 (30.0–75.0) mL/min/1.73 m^2. Non-dipping PR status was observed in 39 patients. Patients with non-dipping PR were older and had worse kidney function, higher blood pressure, greater prevalence of dyslipidemia, lower hemoglobin levels, and a larger amount of urinary protein excretion than patients with dipping PR. Patients with non-dipping PR had more severe glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis. In the multivariable analysis, the severe chronic changes of the kidney were associated with non-dipping PR status after adjusting for age, sex, and other clinical parameters (odds ratio = 20.8; 95% confidence interval, 2.82–153; $P = 0.003$).

Conclusion: This study is the first to indicate that non-dipping PR is significantly associated with chronic microanatomical changes in the kidneys of patients with CKD.

KEYWORDS

autonomic imbalance, ambulatory blood pressure monitoring, cardiorenal syndrome, chronic kidney disease, microanatomical structure, non-dipping pulse rate

1. Introduction

Blood pressure (BP) and pulse rate (PR) physiologically decrease by 10–20% at night due to the relative dominance of the parasympathetic nervous system (1, 2). Non-dipping, the phenomenon of insufficient nocturnal BP and PR decline (defined as less than 10% from day to night), reflects autonomic imbalance.

Abnormal circadian rhythms of BP, including non-dipping and nocturnal rising BP, are established risk factors for hypertensive target organ damage and cardiovascular events (3–5). In this regard, ambulatory blood pressure monitoring (ABPM) is useful for predicting long-term kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD) (6, 7). We reported cross-sectional studies using ABPM and kidney biopsy specimens, which showed that chronic kidney biopsy findings were significantly associated with both daytime and nighttime hypertension in patients with CKD (8) and patients with IgA nephropathy (9). In addition, several experimental models have demonstrated that tubulointerstitial damage induces salt-sensitive hypertension (10, 11). These studies suggest the possibility that intrarenal mechanisms regulate systemic BP.

Likewise, recent studies have reported that non-dipping PR is associated with cardiovascular events and all-cause mortality in the general population and in patients with hypertension, acute myocardial infarction, and type 2 diabetes (2, 12–16). These studies have shown that non-dipping PR status is associated with several clinical factors, including age, sex, body mass index (BMI), hypertension (HTN), and diabetes mellitus (DM) (12, 14). However, little is known about non-dipping PR in patients with CKD. A recent cross-sectional study showed that the prevalence of non-dipping PR was higher in CKD and hemodialysis patients than in the general population (14, 17). Previous clinical and experimental studies have suggested that autonomic cardiovascular alterations occur in the presence of CKD, contributing to cardiovascular morbidity and mortality (18, 19). Although ABPM recordings provide PR together with BP measurements, studies regarding ambulatory PR data are limited, and the association between non-dipping PR and microanatomical structural changes in kidney biopsies is unclear.

In the present study, we investigated the clinical and microanatomical characteristics of non-dipping PR in Japanese patients with CKD using both ABPM and kidney biopsy specimens and aimed to identify pathophysiological factors associated with non-dipping PR status.

2. Materials and methods

2.1. Subjects

Patients who underwent both ABPM and kidney biopsy during the same admission period from March 2016 to March 2019 at Jikei University Hospital, Tokyo, Japan, were included in the present cross-sectional study. A kidney biopsy was performed at the time of diagnosis and, in case of repetition, only the first diagnostic biopsy was included. All subjects were diagnosed with primary or secondary glomerular disease by kidney biopsy. We excluded patients who fall within the following criteria: aged <20 years, end-stage kidney disease, kidney transplant recipients, patients taking β-blockers, those with less than 5 glomeruli in the kidney biopsy (8, 20), and those with no histopathological data available (**Figure 1**).

This study was approved by the Ethics Review Board of The Jikei University School of Medicine (33–265, 10,883) and was carried out according to the Declaration of Helsinki. Because this was a cross-sectional study, information on the research plan was proposed and an opportunity to opt out was provided; therefore, individual informed consent was waived for this study. All patients provided their written informed consent for kidney biopsy.

2.2. Clinical measurements

General demographic data, including age, sex, height, body weight, type of antihypertensive medication, frequency of DM and frequency of dyslipidemia, were obtained from medical records at the time of diagnostic kidney biopsy. Laboratory measurements included hemoglobin, creatinine, estimated glomerular filtration rate (eGFR), uric acid, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), urinary β2-microglobulin, and 24 h proteinuria. Urine was collected for 24 h, and dietary sodium intake was assessed using 24 h urinary sodium excretion. Estimated protein intake was estimated from 24 h urinary urea excretion according to Maroni's formula (21), normalized to ideal body weight, and expressed as g/kg/day. Ideal body weight was defined as a BMI of 22 kg/m^2, as previously reported (22).

Diabetes mellitus was defined as a HbA1c value > 6.5% (National Glycohemoglobin Standardization Program) or the use

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; dBP, diastolic BP; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GS%, percentage of segmental and/or global glomerulosclerosis; GV, mean glomerular volume; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IQRs, interquartile ranges; IF, interstitial fibrosis; IF/TA, interstitial fibrosis and/or tubular atrophy; JSH, 2019 japanese society of hypertension guidelines for the management of hypertension; KDIGO, kidney disease improving global outcomes; LDL-C, low-density lipoprotein cholesterol; MAP, mean arterial pressure; PR, pulse rate; RAS, renin-angiotensin system; sBP, systolic BP; TA, tubular atrophy; TG, triglyceride.

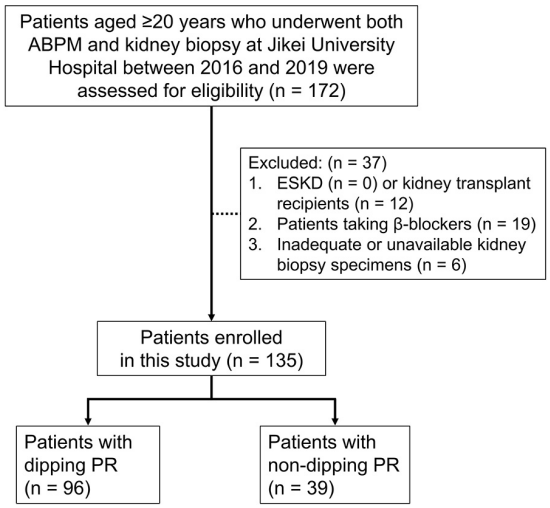

FIGURE 1
Flow diagram of study participants. One hundred and seventy-two patients aged ≥20 years who underwent ABPM and kidney biopsy at our institution between March 2016 and March 2019 were assessed for eligibility. Of these patients, 37 were excluded from this study due to the exclusion criteria. ABPM, ambulatory blood pressure monitoring; ESKD, end-stage kidney disease; PR, pulse rate.

of antidiabetic medications. Dyslipidemia was defined as LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, TG ≥ 150 mg/dL, or the use of antihyperlipidemic agents (23). BMI was defined as body weight divided by the square of height, and eGFR was calculated using the following formula for Japanese subjects: eGFR (mL/min/1.73 m^2) = 194 × $Cr^{-1.094}$ × $age^{-0.287}$ (× 0.739 for women) (24).

In addition, patients were classified into four CKD prognostic groups (low risk, moderately increased risk, high risk and very high risk) by glomerular filtration rate (GFR) and proteinuria categories according to the KDIGO (Kidney Disease Improving Global Outcomes) 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease (**Supplementary Figure 1**) (25).

2.3. ABPM measurements and definition of non-dipping status

Ambulatory blood pressure monitoring analyses were performed using a TM-243 device (A&D, Tokyo, Japan). Measurements were taken at 30-min intervals from 06:00 to 22:00, whereas measurements were taken at 1-h intervals from 22:00 to 06:00. The daytime and nighttime were defined as the awake and sleeping periods, respectively, which were determined by the activity records of the patients (26). According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019) (27), 24 h hypertension was defined as an average 24 h systolic BP (sBP) of ≥130 mmHg and/or an average 24 h diastolic BP (dBP) of ≥80 mmHg. Daytime hypertension was defined as an average diurnal sBP ≥135 mmHg and/or an average diurnal dBP ≥85 mmHg. Nighttime hypertension was defined as an average nocturnal sBP ≥120 mmHg and/or an average nocturnal dBP ≥70 mmHg. Mean arterial pressure (MAP) was defined as dBP plus pulse pressure divided by three. The PR and BP drop rates were defined as (daytime PR-nighttime PR)/daytime PR and (daytime sBP-nighttime sBP)/daytime sBP, respectively. Non-dipping PR status was defined as a PR drop rate <0.1, whereas non-dipping BP status was defined as a BP drop rate <0.1 (12–15, 17, 28).

2.4. Microanatomical structural findings

Kidney biopsy specimens were obtained using percutaneous needle biopsy, after which tissues were embedded in paraffin, cut into 3-μm sections, and stained with hematoxylin and eosin, periodic acid–Schiff, Masson's trichrome, and periodic acid silver–methenamine. These specimens were evaluated by light microscopy, immunostaining, and electron microscopy in routine diagnostic pathological assessments. The number and percentage of glomeruli with segmental and/or global sclerosis were also recorded. In addition, the mean glomerular volume (GV) was estimated from the measured mean glomerular tuft area as follows: GV = (glomerular tuft area)$^{3/2}$ × β/d, where β is a dimensionless shape coefficient (β = 1.382 for spheres), and d is the size distribution coefficient used to adjust for variations in glomerular size (d = 1.01) (29). The severity of arteriosclerosis was graded based on the most severe lesions by comparing the thickness of the intima with that of the media in the same segment of the vessel; it was graded on a scale of 0 to 2 (grade 0: absence of intimal thickening, 1: intimal thickening <thickness of media, 2: intimal thickening ≥ thickness of media) (8, 30). The percentage of segmental and/or global glomerulosclerosis (GS%) and interstitial fibrosis and/or tubular atrophy (IF/TA) was semiquantitatively scored on a scale of 0 to 3 (score 0 for <10%, 1 for 10% to 25%, 2 for 26% to 50%, and 3 for >50%). From these scores, the total renal chronicity score was determined according to the Mayo Clinic/Renal Pathology Society Chronicity Score (31) to grade the overall severity of chronic lesions as minimal (0–1 total score), mild (2–4 total score), moderate (5–7 total score), and severe (≥8 total score). Arteriosclerosis was scored from 0 to 1 (0: intimal thickening <thickness of media; 1: intimal thickening ≥ media thickness) in this scoring system. Interstitial fibrosis (IF) and tubular atrophy (TA) usually occur together, but rarely develop independently of each other (31). IF and TA scores are considered equal to the IF/TA score in this study.

2.5. Statistical analyses

Continuous variables are presented as medians and interquartile ranges (IQRs) or numbers with percentages in parentheses. Differences in continuous variables were analyzed using the Mann–Whitney U test or Kruskal–Wallis test, as appropriate, and those in categorical variables were analyzed using the chi-square test or Fisher's exact test according to the sample size. The Dunn–Bonferroni test was used as a *post hoc* analysis for the Kruskal–Wallis test. Spearman's correlation analysis was used to analyze the correlations among the variables. Multivariable logistic regression analysis was performed to identify independent determinants of non-dipping PR status in patients with CKD. All covariates except sex, the presence of DM, the renal chronicity score grades and the use of antihypertensive medications were treated as

continuous variables in the multivariable analyses. Missing values are excluded and addressed for each variable. Statistical significance was defined as a two-sided $P < 0.05$. All statistical analyses were performed with SPSS v.25.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Subject selection

A total of 172 patients aged ≥20 years underwent both ABPM and kidney biopsy at our institution between March 2016 and March 2019. Of these patients, 37 were excluded from this study due to the following exclusion criteria: kidney transplant recipients, taking β-blockers, inadequate glomerular number or unavailable kidney biopsy specimens. After exclusion, 135 patients were enrolled, of which 39 (28.9%) patients were in the non-dipping PR group and 96 (71.1%) patients were in the dipping PR group (**Figure 1**).

3.2. Baseline demographic and clinical characteristics

Tables 1, **2** summarize the demographic, clinical and laboratory data of the patients. The median age was 51 years (IQR: 35–63), 54% of which were male, and the median eGFR at diagnosis was 53.0 (30.0–75.0) mL/min/1.73 m^2. The proportions of each GFR category were as follows: G1 7.4%, G2 32.6%, G3a 16.3%, G3b 20.0%, G4 13.3%, and G5 10.4%.

Patients with non-dipping PR were significantly older and had worse kidney function at baseline. Dyslipidemia was more prevalent among patients with non-dipping PR than among those with dipping PR. Patients with non-dipping PR had significantly lower levels of hemoglobin, a greater amount of urinary protein excretion, and a greater amount of urinary β2-microglobulin than patients with dipping PR. Twenty-nine out of 39 (74%) patients with non-dipping PR were classified as "very high risk" in the CKD prognostic categories, whereas 42 out of 96 (44%) patients with dipping PR were classified in the same category. Of note, other characteristics, including sex, frequencies of DM,

TABLE 1 Clinical and demographic characteristics of the subjects according to the dipping and non-dipping pulse rate pattern.

	All (*n* = 135)	Dipping (*n* = 96)	Non-dipping (*n* = 39)	*P*-value
Age (years)	51 (35–63)	46 (33–59)	62 (49–74)	<**0.001**
Male, *n* (%)	73 (54)	50 (52)	23 (59)	0.47
eGFR (mL/min/1.73 m^2)	53.0 (30.0–75.0)	59.0 (36.0–79.0)	36.0 (14.0–53.0)	<**0.001**
Diabetes, *n* (%)	23 (17)	14 (15)	9 (23)	0.23
Dyslipidemia, *n* (%)	90 (67)	58 (60)	32 (82)	**0.02**
BMI (kg/m^2)	22.2 (20.4–24.7)	22.0 (20.2–24.6)	22.9 (20.8–25.3)	0.43
Hb (g/dL)	13.0 (11.1–14.7)	13.6 (11.8–14.9)	11.2 (10.1–13.1)	<**0.001**
Anemia, *n* (%)	56 (41)	29 (30)	27 (69)	< **0.001**
UA (mg/dL)	6.3 (5.1–7.3)	6.1 (5.0–7.1)	7.0 (5.2–7.5)	0.05
HbA1c (%)[a]	5.6 (5.4–6.0)	5.6 (5.4–6.0)	5.7 (5.4–6.1)	0.90
LDL-C (mg/dL)[b]	121 (101–142)	121 (101–137)	120 (94–165)	0.53
HDL-C (mg/dL)[c]	60 (50–73)	60 (49–75)	62 (51–70)	0.63
TG (mg/dL)[d]	134 (102–183)	136 (104–196)	117 (95–164)	0.10
EPI/IBW (g/kg/day)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.6–1.0)	0.13
NaCl (g/day)	6.1 (4.4–8.5)	5.8 (4.4–7.8)	7.0 (4.3–9.8)	0.18
UPE (g/day)	0.9 (0.4–2.1)	0.7 (0.3–1.6)	1.8 (0.6–4.3)	**0.002**
u-β2MG (μg/L)[e]	128 (55–2,465)	84 (0–452)	1,363 (119–12,095)	<**0.001**
Prognosis of CKD by GFR and proteinuria categories				<**0.001**
Low risk, *n* (%)	9 (6)	9 (9)	0 (0)	–
Moderately increased risk, *n* (%)	15 (11)	12 (13)	3 (8)	–
High risk, *n* (%)	40 (30)	33 (34)	7 (18)	–
Very high risk, *n* (%)	71 (53)	42 (44)	29 (74)	–

eGFR, estimated glomerular filtration rate; BMI, body mass index; Hb, hemoglobin; UA, uric acid; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; EPI/IBW, estimated protein intake divided by ideal body weight; NaCl, sodium intake; UPE, urinary protein excretion; u-β2MG, urinary β2-microglobulin; CKD, chronic kidney disease; GFR, glomerular filtration rate. Values are presented as medians and interquartile ranges (IQRs) or numbers with percentages in parentheses. The bold values indicate statistically significant.

[a]11 cases are missing.

[b]2 cases are missing.

[c]4 cases are missing.

[d]2 cases are missing.

[e]22 cases are missing.

BMI, serum uric acid, cholesterol levels, estimated protein intake, and sodium intake were not statistically different between the two groups (**Table 1**). Patients with non-dipping PR had higher 24 h/diurnal/nocturnal BP parameters and a higher prevalence of 24 h/diurnal/nocturnal HTN. 24 h PR and diurnal PR were not statistically different between the groups. In addition, the presence of non-dipping BP was not associated with non-dipping PR (P = 0.24, **Table 2**).

3.3. Association between non-dipping PR and kidney function

As shown in **Table 1**, patients with non-dipping PR had worse kidney function than those with dipping PR; however, there were no differences in baseline eGFR between patients with and without non-dipping BP. When we analyzed the association between PR or BP drop rate and kidney function as continuous variables, the PR drop rate exhibited a positive linear correlation with baseline eGFR (r_s = 0.40, P < 0.001, **Figure 2A**), whereas the BP drop rate was not significantly correlated with baseline eGFR (r_s = 0.04, P = 0.67, **Figure 2B**).

3.4. Comparison of microanatomical characteristics

Table 3 lists the characteristics of microanatomical structural changes in the kidney. Kidney biopsies contained a median of 29 (21–39) glomeruli, and the median GS% and IF/TA were 20.0% (5.9–46.2) and 10.0% (5.0–30.0), respectively. Patients with non-dipping PR had significantly higher GS%, IF/TA, and more severe arteriosclerosis (P < 0.001, P < 0.001, and P = 0.02, respectively) than patients with dipping PR; therefore, patients with non-dipping PR had a higher renal chronicity score than those without it (P < 0.001). GV was not significantly different between the groups. The proportion of the histopathological diagnosis was as follows: IgA nephropathy, 54 patients (40%); nephrosclerosis, 13 patients (9.6%); focal segmental glomerulosclerosis, 13 patients (9.6%); membranous nephropathy, 10 patients (7.4%); minimal change disease, 8 patients (5.9%); diabetic nephropathy, 7 patients (5.2%); tubulointerstitial nephritis, 6 patients (4.5%); membranoproliferative glomerulonephritis, 3 patients (2.2%); and others, 21 patients (15.6%) (**Supplementary Table 1**).

3.5. Comparison of four categories regarding PR and BP dipping status

When we classified subjects as having or not having BP and/or PR non-dipping into four categories (**Table 4**), the proportion of very high risk CKD prognostic categories increased in the following order: BP/PR dipping, BP non-dipping/PR dipping, BP dipping/PR non-dipping, and BP/PR non-dipping. The BP/PR non-dipping group had significantly lower eGFR than the BP/PR dipping and BP non-dipping/PR dipping groups (adjusted P = 0.004 and P = 0.002, respectively). The GS% was significantly higher in the BP/PR non-dipping group than in the BP/PR dipping and BP non-dipping/PR dipping groups (adjusted P = 0.006 and P < 0.001, respectively). The IF/TA ratio was significantly higher in the BP/PR non-dipping group than in the BP/PR dipping group (adjusted P = 0.02).

3.6. Clinical and microanatomical factors associated with non-dipping PR status

Univariable and multivariable adjusted logistic regression analyses were performed to identify the independent determinants of non-dipping PR status in this population (**Table 5**). As per univariable analysis, non-dipping PR status was associated with age, baseline eGFR, urinary protein excretion, MAP, and moderate and severe renal chronicity score groups. As per multivariable analysis, the severe chronic changes of the kidney were significantly associated with non-dipping PR status after adjustment for age, sex, and previously reported covariates, including eGFR, 24 h proteinuria, the presence of DM, BMI, and MAP (odds ratio = 20.8; 95% confidence interval, 2.82–153; P = 0.003). Moreover, we added the use of antihypertensive agents to the age/sex-adjusted multivariable model to adjust for each effect of antihypertensive agents, which did not change the association between the renal chronicity score and non-dipping PR status (**Supplementary Table 2**).

4. Discussion

Two major findings novel to the present study are as follows. First, the non-dipping PR status was observed in approximately 30% of patients with CKD, and the highest proportion of patients with CKD with non-dipping PR was in the "very high risk" category by the KDIGO GFR and proteinuria categories. Second, even after adjustment for clinical parameters, severe chronic changes in kidney microanatomical structure were significantly associated with insufficient decline in nocturnal PR, which is reported to indicate autonomic nervous system dysfunction. To our knowledge, this is the first study to investigate the association between non-dipping PR and clinical and microanatomical factors in patients with CKD. We identified microanatomical structural changes in the kidney responsible for non-dipping PR; therefore, it may contribute to understanding the pathophysiology behind the autonomic imbalance in patients with CKD.

Although the pathophysiology of the development / progression of CKD and autonomic disorders has not been fully elucidated, a CKD animal model showed that central and peripheral circadian clocks were disrupted in mice with CKD, and the study suggested that circadian disruption accelerated CKD progression, resulting in a vicious cycle (32). In addition, cardiovascular autonomic dysfunction is an important complication of CKD (18, 33). There is a bidirectional interaction between the heart and kidneys, and the dysfunction of one organ may induce the dysfunction of the other, which is called cardiorenal syndrome. Cardiorenal syndrome is frequently complicated by anemia, which is also called cardiorenal anemia syndrome (34). Anemia was more prevalent among patients with non-dipping PR than among those with dipping PR in this study. Several mechanisms, including autonomic, neural, hormonal, and vascular mechanisms, have been implicated in its pathogenesis (35). A high nocturnal heart rate increases the mechanical load and shear stress on the endothelium, leading to endothelial dysfunction and predisposition to arteriosclerosis (17, 36). In accordance with this

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TABLE 2 Ambulatory blood pressure monitoring measurements of the subjects according to the dipping and non-dipping pulse rate pattern.

	All (*n* = 135)	Dipping (*n* = 96)	Non-dipping (*n* = 39)	*P*-value
Antihypertensive agent	72 (53)	47 (49)	25 (64)	0.11
Ca channel blocker, *n* (%)	41 (30)	21 (22)	20 (51)	**0.003**
ACE-I/ARB, *n* (%)	55 (41)	35 (36)	20 (51)	0.11
Diuretics, *n* (%)	15 (11)	7 (7.3)	8 (21)	**0.03**
Alfa blocker, *n* (%)	1 (0.7)	0 (0.0)	1 (2.6)	0.29
24 h sBP (mmHg)	125 (114–141)	122 (113–135)	141 (125–152)	<**0.001**
Diurnal sBP (mmHg)	128 (116–143)	124 (115–138)	142 (125–155)	<**0.001**
Nocturnal sBP (mmHg)	118 (108–133)	113 (107–128)	133 (114–146)	<**0.001**
24 h dBP (mmHg)	76 (70–84)	75 (69–83)	81 (72–92)	**0.03**
Diurnal dBP (mmHg)	77 (71–87)	76 (71–84)	80 (73–93)	0.05
Nocturnal dBP (mmHg)	70 (64–78)	68 (62–75)	78 (66–88)	**0.001**
24 h MAP (mmHg)	93 (85–102)	90 (84–100)	102 (90–112)	**0.001**
Diurnal MAP (mmHg)	94 (86–105)	91 (86–102)	99 (92–115)	**0.003**
Nocturnal MAP (mmHg)	86 (78–96)	84 (77–91)	99 (81–109)	<**0.001**
24 h PR (bpm)	72 (66–78)	72 (66–78)	72 (67–78)	0.95
Diurnal PR (bpm)	74 (68–79)	74 (68–80)	72 (68–79)	0.34
Nocturnal PR (bpm)	63 (57–69)	60 (55–66)	68 (63–74)	<**0.001**
PR drop (%)	14.3 (8.6–19.4)	17.0 (13.0–21.0)	6.8 (5.8–8.1)	<**0.001**
BP drop (%)	7.9 (1.8–12.1)	8.3 (2.5–12.4)	5.7 (0.0–11.7)	0.12
24 h HTN, *n* (%)	66 (49)	38 (40)	28 (72)	<**0.001**
Diurnal HTN, *n* (%)	59 (44)	31 (32)	28 (72)	<**0.001**
Nocturnal HTN, *n* (%)	80 (59)	51 (53)	29 (74)	**0.02**
BP non-dipping, *n* (%)	83 (61)	56 (58)	27 (69)	0.24

Ca, calcium; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; sBP, systolic blood pressure; dBP, diastolic blood pressure; MAP, mean arterial pressure; PR, pulse rate; HTN, hypertension; BP, blood pressure. Values are presented as medians and interquartile ranges (IQRs) or numbers with percentages in parentheses. BP drop rate was defined as (daytime sBP-nighttime sBP)/daytime sBP. The bold values indicate statistically significant.

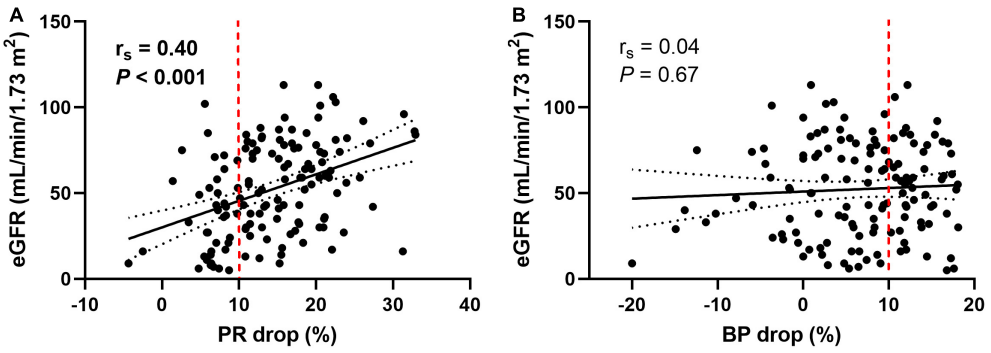

FIGURE 2
Pulse rate and blood pressure drop in relation to the baseline eGFR. The pulse rate drop rate showed a positive linear correlation with baseline eGFR **(A)**, whereas the blood pressure drop rate did not show a significant correlation with baseline eGFR **(B)**. Measures of association were tested by Spearman's correlation analysis. Solid lines indicate lines of best fit. Dotted lines show 95% confidence intervals. The dashed red line represents 10% of the pulse rate drop **(A)** and the blood pressure drop **(B)**. eGFR, estimated glomerular filtration rate; PR, pulse rate; BP, blood pressure.

vascular mechanism, we observed more severe chronic microvascular changes, including arteriosclerosis, IF/TA, and glomerulosclerosis, in kidney biopsies of patients with non-dipping PR than in those with dipping PR.

Moreover, we hypothesize that intrarenal renin-angiotensin system (RAS) activation may be one of the underlying mechanisms of the association between non-dipping PR and chronic changes (GS% and IF/TA) in this study. Urinary angiotensinogen is an established surrogate marker for intrarenal RAS activity, and a previous pathological study showed that urinary angiotensinogen levels were correlated with the severity of GS% and IF/TA (37). Another study reported that urinary angiotensinogen levels had

TABLE 3 Microanatomical structural characteristics of the subjects according to the dipping and non-dipping pulse rate pattern.

	All (*n* = 135)	Dipping (*n* = 96)	Non-dipping (*n* = 39)	*P*-value
GV ($\times 10^6 \mu m^3$)	2.3 (1.8–3.4)	2.3 (1.8–3.3)	2.6 (1.7–3.8)	0.43
GS (%)	20.0 (5.9–46.2)	13.1 (5.0–31.0)	46.2 (13.9–64.5)	<**0.001**
IF/TA (%)	10.0 (5.0–30.0)	10.0 (5.0–20.0)	30.0 (10.0–60.0)	<**0.001**
Arteriosclerosis grade				**0.02**
0: No intimal thickening	29 (21)	23 (24)	6 (15)	–
1: Intima < Media	34 (25)	29 (30)	5 (13)	–
2: Intima > Media	72 (53)	44 (46)	28 (72)	–
Renal chronicity score				<**0.001**
Minimal (score 0–1)	40 (30)	36 (38)	4 (10)	–
Mild (score 2–4)	36 (26)	29 (30)	7 (18)	–
Moderate (score 5–7)	39 (29)	25 (26)	14 (36)	–
Severe (score ≥ 8)	20 (15)	6 (6)	14 (36)	–

GV, mean glomerular volume; GS, segmental and/or global glomerulosclerosis; IF/TA, interstitial fibrosis and/or tubular atrophy. Values are presented as medians and interquartile ranges (IQRs) or numbers with percentages in parentheses. The bold values indicate statistically significant.

a significant positive association with an increase in nighttime heart rate in patients with CKD (38). Intrarenal RAS activation increases intraglomerular pressure and induces proteinuria, followed by progressive kidney damage and activation of the sympathetic nervous system (38). We observed an association between non-dipping PR and chronic changes irrespective of patient age, kidney function, and use of antihypertensives. In the participants of this study with circadian disruption, intrarenal RAS may be activated, leading to the further formation of chronic microvascular changes.

The renal chronicity score, which is derived from the sum of semiquantitative assessments of chronic changes, has been proposed as a uniform approach to grade chronic changes in kidney biopsy specimens (31). Chronic changes are generally irreversible and are important for predicting the prognosis and response to treatment. A prospective cohort study including native kidney biopsies with various kidney diseases showed that each component of the renal chronicity score was associated with the progression of kidney disease, even after adjusting for clinical predictors, including eGFR and proteinuria. In addition, this study validated that the renal chronicity score was independently associated with kidney failure (39). In this study, we observed a significant association between renal chronicity score and non-dipping PR after adjustments for clinical covariates. Patients with non-dipping PR had higher renal chronicity scores, and the largest proportion belonged to the very high risk group of the KDIGO categories in this study. We speculate that patients with non-dipping PR may exhibit poorer kidney outcomes than those without dipping PR, although this cannot be proven from our study. Future longitudinal studies are needed.

Notably, there was no association between non-dipping PR and non-dipping BP, which is consistent with previous studies (12, 14, 15). A randomized double-blind study investigating the effects of melatonin suggested that BP and PR are regulated by different mechanisms (40). In addition, when we divided subjects into the abovementioned four categories according to BP/PR non-dipping status, the proportion of very high risk CKD prognostic categories tended to increase in the following order: BP/PR dipping, BP non-dipping/PR dipping, BP dipping/PR non-dipping, and BP/PR non-dipping (**Table 4**). The risk of all-cause mortality is reported to increase in the following order: sole non-dipping BP, sole non-dipping PR, and a combination of non-dipping BP and non-dipping PR when a combination of dipping BP and dipping PR is a reference group (12). Another study showed that the combination of BP and PR non-dipping resulted in a significant synergistic increase in the risk of cardiovascular events (13). However, in this study we did not investigate cardiovascular or all-cause mortality.

This study had several limitations. First, the study design was cross-sectional, and the causal relationship between non-dipping PR and microanatomical parameters could not be proven. In this regard, we assessed non-dipping PR status in relation to CKD prognostic categories by KDIGO and renal chronicity score, as these parameters are established prognostic factors. Second, ABPM was performed once during the hospitalization period, and these results might be different from ABPM performed in outpatient clinics; however, restricted diet and physical activity during hospitalization can minimize the effect of interpersonal differences, which could be an advantage at the same time. Third, we did not consider the physical activity of the patients, smoking habits, food intake, and sleep quality. Finally, the present study was limited to a single center with Japanese patients with CKD who underwent kidney biopsies, making it difficult to generalize these results to all patients with CKD.

Despite these limitations, this study is the first to investigate the association between a flattened PR circadian rhythm and microanatomical structural findings of the kidney. This study supported the hypothesis that the bidirectional interactions between chronic changes in the kidney and circadian disruption fall into a vicious cycle in patients with CKD. We speculate that patients with CKD and non-dipping PR have an additional risk of cardiovascular events and poor kidney outcomes compared to patients with CKD and dipping PR. Non-dipping PR is an important but neglected parameter, and only limited studies focusing on this topic have emerged in recent decades (41). A new attempt to monitor non-dipping PR with wearable devices has been proposed in a recent review (41). Therefore, we await future studies with these new devices to further investigate the effects of non-dipping PR on CKD.

TABLE 4 Clinical and microanatomical characteristics of the subjects according to the dipping and non-dipping blood pressure/pulse rate pattern.

	DBP/DPR (*n* = 40)	NBP/DPR (*n* = 56)	DBP/NPR (*n* = 12)	NBP/NPR (*n* = 27)	*P*-value
Clinical parameters					
Age (years)	44 (33–55)	51 (33–60)	64 (49–73)	60 (49–76)	**0.001**[abcd]
Male, *n* (%)	25 (63)	25 (45)	4 (33)	19 (70)	**0.04**
eGFR (mL/min/1.73 m^2)	59.0 (39.0–78.8)	61.0 (35.0–80.5)	42.5 (16.3–56.0)	33.0 (13.0–53.0)	<**0.001**[abd]
Prognosis of CKD by GFR and proteinuria categories					**0.01**[abd]
Low risk, *n* (%)	3 (7)	6 (11)	0 (0)	0 (0)	–
Moderately increased risk, *n* (%)	8 (20)	4 (7)	2 (17)	1 (4)	–
High risk, *n* (%)	12 (30)	21 (37)	2 (17)	5 (18)	–
Very high risk, *n* (%)	17 (43)	25 (45)	8 (66)	21 (78)	–
Microanatomical structural parameters					
GV ($\times 10^6 \mu m^3$)	2.4 (1.9–3.4)	2.2 (1.6–3.1)	2.0 (1.6–3.4)	2.7 (1.9–3.9)	0.34
GS (%)	15.5 (5.2–36.9)	13.1 (3.8–30.1)	39.4 (11.8–53.6)	54.5 (20.0–73.0)	<**0.001**[abd]
IF/TA (%)	10.0 (5.0–20.0)	10.0 (5.0–25.0)	30.0 (11.3–47.5)	30.0 (5.0–60.0)	**0.004**[ab]
Arteriosclerosis grade					0.11
0: No intimal thickening	10 (25)	13 (23)	1 (8)	5 (19)	–
1: Intima < Media	13 (32)	16 (29)	2 (17)	3 (11)	–
2: Intima > Media	17 (43)	27 (48)	9 (75)	19 (70)	–
Renal chronicity score					<**0.001**[abd]
Minimal (score 0–1)	14 (35)	22 (39)	0 (0)	4 (15)	–
Mild (score 2–4)	15 (38)	14 (25)	3 (25)	4 (15)	–
Moderate (score 5–7)	7 (17)	18 (32)	8 (67)	6 (22)	–
Severe (score ≥ 8)	4 (10)	2 (4)	1 (8)	13 (48)	–

DBP, dipping blood pressure; DPR, dipping pulse rate; NBP, non-dipping blood pressure; NPR, non-dipping pulse rate; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; GV, mean glomerular volume; GS, segmental and/or global glomerulosclerosis; IF/TA, interstitial fibrosis and/or tubular atrophy. Values are presented as medians and interquartile ranges (IQRs) or numbers with percentages in parentheses. BP drop rate was defined as (daytime systolic BP-nighttime systolic BP)/daytime systolic BP. The bold values indicate statistically significant.

[a] Kruskal–Wallis test with Dunn–Bonferroni test.

[b] Adjusted $P < 0.05$, DBP/DPR vs. NBP/NPR.

[c] Adjusted $P < 0.05$, DBP/DPR vs. DBP/NPR.

[d] Adjusted $P < 0.05$, NBP/DPR vs. NBP/NPR.

TABLE 5 Univariable and multivariable logistic regression analysis for determinants of non-dipping pulse rate.

	Univariable		Multivariable	
	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Age (years)	1.05 (1.03–1.08)	<**0.001**	**1.05 (1.02–1.08)**	**0.003**
Sex (Male)	1.32 (0.62–2.81)	0.47	0.90 (0.33–2.46)	0.84
eGFR (mL/min/1.73 m^2)	0.97 (0.95–0.98)	<**0.001**	1.00 (0.98–1.03)	0.76
UPE (g/day)	1.15 (1.01–1.31)	**0.03**	1.09 (0.92–1.30)	0.31
Diabetes	1.76 (0.69–4.48)	0.24	0.61 (0.18–2.14)	0.44
BMI (kg/m^2)	1.02 (0.94–1.11)	0.59	0.96 (0.86–1.06)	0.40
24 h MAP (mmHg)	1.05 (1.02–1.08)	**0.001**	1.04 (0.99–1.09)	0.06
Renal chronicity score				
Minimal (score 0–1)	Reference	-	Reference	-
Mild (score 2–4)	2.17 (0.58–8.15)	0.25	1.63 (0.35–7.56)	0.54
Moderate (score 5–7)	5.04 (1.48–17.1)	**0.01**	3.06 (0.55–17.0)	0.20
Severe (score ≥8)	21.0 (5.14–85.8)	<**0.001**	**20.8 (2.82–153)**	**0.003**

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; UPE, urinary protein excretion; BMI, body mass index; MAP, mean arterial pressure. All covariates except sex, the renal chronicity score and the presence of diabetes were treated as continuous variables. The bold values indicate statistically significant.

5. Conclusion

Non-dipping PR status was observed in 28.9% of patients with CKD, and the majority of patients with non-dipping PR belonged to the "very high risk" category by the KDIGO GFR and proteinuria categories. In conclusion, this study indicates that a flattened PR circadian rhythm is associated with chronic changes in kidney microanatomical structure.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Board of The Jikei University School of Medicine (33–265, 10,883). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

RO and GK: conceptualization, formal analysis, investigation, data curation, and writing—original draft preparation. RO, KH, and GK: methodology. TY: resources and supervision. RO, GK, KH, TS, YO, KK, NT, and TY: writing—review and editing. RO: visualization. GK: project administration. All authors contributed to data interpretation and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.911773/full#supplementary-material

References

1. Kantharia B. Non-dipping heart rate, microalbuminuria and thrombocytosis in type 2 diabetes mellitus: can we connect the dots? *Cardiology.* (2014) 129:25–7. doi: 10.1159/000363283

2. Baka T, Simko F. Nondipping heart rate: a neglected cardiovascular risk factor based on autonomic imbalance? *Auton Neurosci.* (2018) 210:83–4. doi: 10.1016/j.autneu.2018.02.001

3. Kario K, Pickering T, Matsuo T, Hoshide S, Schwartz J, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension.* (2001) 38:852–7.

4. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the ohasama study. *J Hypertens.* (2002) 20:2183–9. doi: 10.1097/00004872-200211000-00017

5. Kario K, Shimada K. Risers and extreme-dippers of nocturnal blood pressure in hypertension: antihypertensive strategy for nocturnal blood pressure. *Clin Exp Hypertens.* (2004) 26:177–89. doi: 10.1081/ceh-120028556

6. Agarwal R, Andersen M. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. *Kidney Int.* (2006) 69:1175–80.

7. Minutolo R, Agarwal R, Borrelli S, Chiodini P, Bellizzi V, Nappi F, et al. Prognostic role of ambulatory blood pressure measurement in patients with nondialysis chronic kidney disease. *Arch Intern Med.* (2011) 171:1090–8.

8. Haruhara K, Tsuboi N, Koike K, Fukui A, Miyazaki Y, Kawamura T, et al. Renal histopathological findings in relation to ambulatory blood pressure in chronic kidney disease patients. *Hypertens Res.* (2015) 38:116–22. doi: 10.1038/hr.2014.140

9. Haruhara K, Tsuboi N, Koike K, Kanzaki G, Okabayashi Y, Miyazaki Y, et al. Ambulatory blood pressure and tubulointerstitial injury in patients with IgA nephropathy. *Clin Kidney J.* (2015) 8:716–21.

10. Alvarez V, Quiroz Y, Nava M, Pons H, Rodríguez-Iturbe B. Overload proteinuria is followed by salt-sensitive hypertension caused by renal infiltration of immune cells. *Am J Physiol Ren Physiol.* (2002) 283:F1132–41. doi: 10.1152/ajprenal.00199.2002

11. Vanegas V, Ferrebuz A, Quiroz Y, Rodríguez-Iturbe B. Hypertension in page (cellophane-wrapped) kidney is due to interstitial nephritis. *Kidney Int.* (2005) 68:1161–70. doi: 10.1111/j.1523-1755.2005.00508.x

12. Ben-Dov I, Kark J, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Blunted heart rate dip during sleep and all-cause mortality. *Arch Intern Med.* (2007) 167:2116–21.

13. Kabutoya T, Hoshide S, Ishikawa J, Eguchi K, Shimada K, Kario K. The effect of pulse rate and blood pressure dipping status on the risk of stroke and cardiovascular disease in Japanese hypertensive patients. *Am J Hypertens.* (2010) 23:749–55. doi: 10.1038/ajh.2010.45

14. Cuspidi C, Facchetti R, Bombelli M, Sala C, Tadic M, Grassi G, et al. Night-time heart rate nondipping: clinical and prognostic significance in the general population. *J Hypertens.* (2018) 36:1311–7. doi: 10.1097/HJH.0000000000001703

15. Magri C, Xuereb R, Fava S. Non-dipping heart rate and microalbuminuria in type 2 diabetes mellitus. *Cardiology.* (2014) 129:28–35.

16. Carney R, Steinmeyer B, Freedland K, Stein P, Hayano J, Blumenthal J, et al. Nocturnal patterns of heart rate and the risk of mortality after acute myocardial infarction. *Am Heart J.* (2014) 168:117–25. doi: 10.1016/j.ahj.2014.04.012

17. Biyik Z, Yavuz Y, Altintepe L, Celik G, Guney I, Oktar S. Nondipping heart rate and associated factors in patients with chronic kidney disease. *Clin Exp Nephrol.* (2019) 23:1298–305.

18. Salman I. Cardiovascular autonomic dysfunction in chronic kidney disease: a comprehensive review. *Curr Hypertens Rep.* (2015) 17:59.

19. Quarti-Trevano F, Seravalle G, Dell'Oro R, Mancia G, Grassi G. Autonomic cardiovascular alterations in chronic kidney disease: effects of dialysis, kidney transplantation, and renal denervation. *Curr Hypertens Rep.* (2021) 23:10.

20. Hoy W, Samuel T, Hughson M, Nicol J, Bertram J. How many glomerular profiles must be measured to obtain reliable estimates of mean glomerular areas in human renal biopsies? *J Am Soc Nephrol.* (2006) 17:556–63. doi: 10.1681/ASN.2005070772

21. Maroni B, Steinman T, Mitch WE. A method for estimating nitrogen intake of patients with chronic renal failure. *Kidney Int.* (1985) 27:58–65.

22. Tokunaga K, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Fujioka S, et al. Ideal body weight estimated from the body mass index with the lowest morbidity. *Int J Obes.* (1991) 15:1–5.

23. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. *J Atheroscler Thromb.* (2018) 25:846–984.

24. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis.* (2009) 53:982–92. doi: 10.1053/j.ajkd.2008.12.034

25. Kidney International Supplements. Chapter 1: definition and classification of CKD. *Kidney Int Suppl (2011).* (2013) 3:19–62.

26. Agarwal R, Pappas M, Sinha A. Masked uncontrolled hypertension in CKD. *J Am Soc Nephrol.* (2016) 27:924–32.

27. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese society of hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res.* (2019) 42:1235–481.

28. Ogoyama Y, Kabutoya T, Hoshide S, Kario K. The combination of non-dipper heart rate and high brain natriuretic peptide predicts cardiovascular events: the Japan morning surge-home blood pressure (J-HOP) study. *Am J Hypertens.* (2020) 33:430–8. doi: 10.1093/ajh/hpaa025

29. Weibel E, Gomez DM. A principle for counting tissue structures on random sections. *J Appl Physiol.* (1962) 17:343–8.

30. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int.* (2009) 76:546–56.

31. Sethi S, D'Agati V, Nast C, Fogo A, De Vriese A, Markowitz G, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. *Kidney Int.* (2017) 91:787–9. doi: 10.1016/j.kint.2017.01.002

32. Motohashi H, Tahara Y, Whittaker D, Wang H, Yamaji T, Wakui H, et al. The circadian clock is disrupted in mice with adenine-induced tubulointerstitial nephropathy. *Kidney Int.* (2020) 97:728–40. doi: 10.1016/j.kint.2019.09.032

33. Hildreth C. Prognostic indicators of cardiovascular risk in renal disease. *Front Physiol.* (2011) 2:121. doi: 10.3389/fphys.2011.00121

34. McCullough P. Anemia of cardiorenal syndrome. *Kidney Int Suppl.* (2021) 11:35–45.

35. Rangaswami J, Bhalla V, Blair J, Chang T, Costa S, Lentine K, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American heart association. *Circulation.* (2019) 139:e840–78. doi: 10.1161/CIR.0000000000000664

36. Bai Y, Xiao H, Liu Z, Huang X, Tian X, Wang T, et al. Increased night heart rate is associated with worse large artery elasticity in chronic kidney disease patients. *Int Urol Nephrol.* (2013) 45:1621–7. doi: 10.1007/s11255-013-0431-1

37. Kim S, Jang H, Lee Y, Lee J, Huh W, Kim D, et al. Urinary angiotensinogen levels reflect the severity of renal histopathology in patients with chronic kidney disease. *Clin Nephrol.* (2011) 76:117–23. doi: 10.5414/cn107045

38. Ohashi N, Isobe S, Ishigaki S, Aoki T, Matsuyama T, Sato T, et al. Increased heart rate is associated with intrarenal renin-angiotensin system activation in chronic kidney disease patients. *Clin Exp Nephrol.* (2019) 23:1109–18.

39. Srivastava A, Palsson R, Kaze A, Chen M, Palacios P, Sabbisetti V, et al. The prognostic value of histopathologic lesions in native kidney biopsy specimens: results from the Boston kidney biopsy cohort study. *J Am Soc Nephrol.* (2018) 29:2213–24. doi: 10.1681/ASN.2017121260

40. Cagnacci A, Cannoletta M, Renzi A, Baldassari F, Arangino S, Volpe A. Prolonged melatonin administration decreases nocturnal blood pressure in women. *Am J Hypertens.* (2005) 18:1614–8. doi: 10.1016/j.amjhyper.2005.05.008

41. Baka T, Simko F. Monitoring non-dipping heart rate by consumer-grade wrist-worn devices: an avenue for cardiovascular risk assessment in hypertension. *Front Cardiovasc Med.* (2021) 8:711417. doi: 10.3389/fcvm.2021.711417

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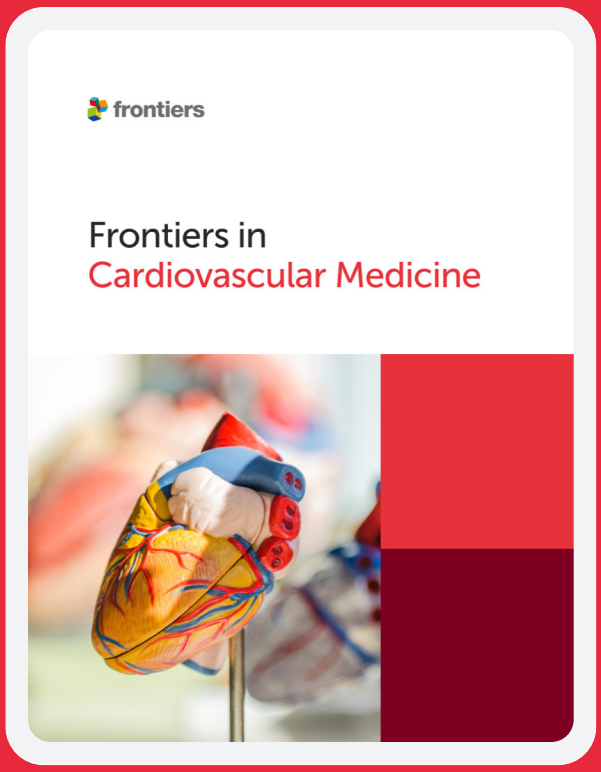

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