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The role of metabolic syndrome and disorders in cardiovascular disease, volume II

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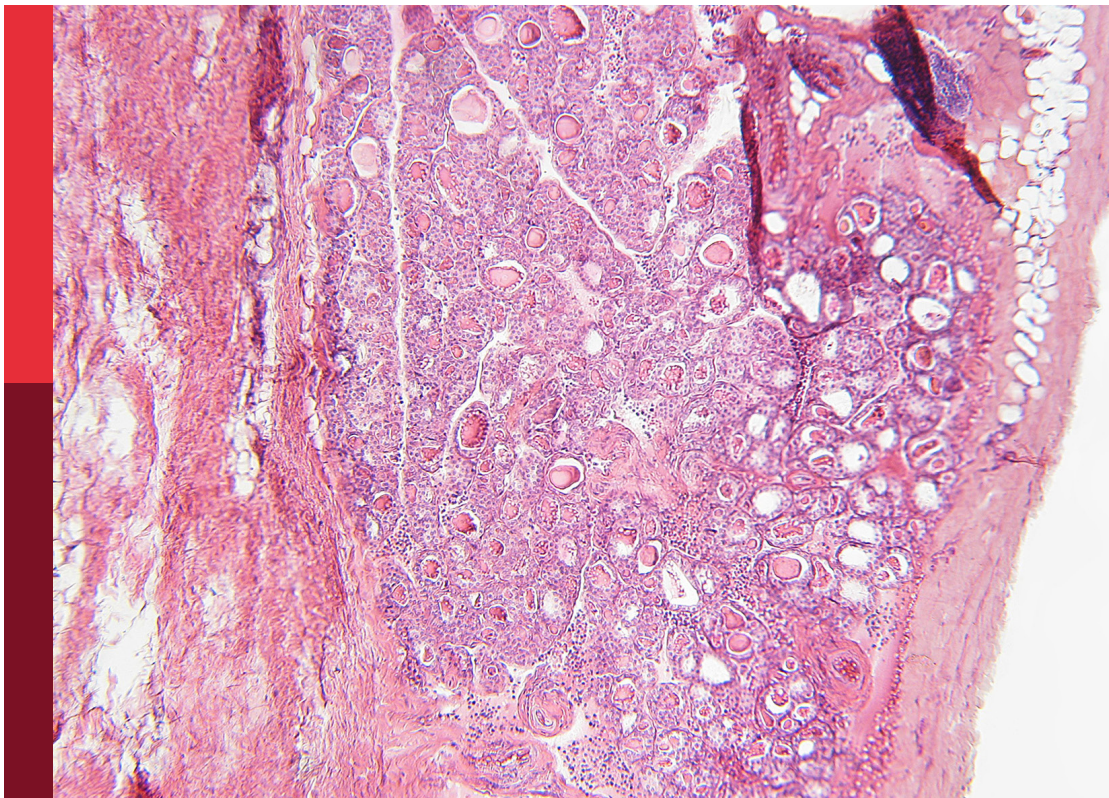

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The role of metabolic syndrome and disorders in cardiovascular disease, volume II

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Editorial: The role of metabolic syndrome and disorders in cardiovascular disease, volume II

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metabolic syndrome, risk factors, cardiovascular disease, biomarkers, cardiovascular complications

Editorial on the Research Topic
The role of metabolic syndrome and disorders in cardiovascular disease, volume II

The global burden of cardiovascular disease (CVD) remains persistently high, with a marked increase in incidence attributable to metabolic disorders such as obesity, insulin resistance, and dyslipidemia. Metabolic syndrome (MetS), characterized by a cluster of risk factors including central obesity, hyperglycemia, dyslipidemia, and hypertension, plays a pivotal role in the pathogenesis and progression of CVD. This second volume of the Research Topic "*The Role of Metabolic Syndrome and Disorders in Cardiovascular Disease*" builds upon prior knowledge, further elucidating the complex interplay between metabolic dysfunction and cardiovascular outcomes. The contributions in this Research Topic explore diverse mechanistic, clinical, and epidemiological perspectives, offering new insights with translational and preventive relevance.

A prominent theme across the studies is the prognostic value of metabolic indices and biomarkers in cardiovascular risk stratification. In a retrospective cohort, Zhao et al. demonstrated that the triglyceride-glucose (TyG) index, a marker of insulin resistance, independently predicted major adverse cardiovascular and cerebrovascular events (MACCE) in patients with coronary heart disease (CHD) and coexisting depression. Similarly, the ankle-brachial index (ABI) was examined in two complementary studies. Wu et al. found an inverse association between ABI and erectile dysfunction (ED), suggesting vascular dysfunction as a key mediator, while Wang and Ni confirmed that ED may serve as a clinical indicator of peripheral arterial disease (PAD), reinforcing the shared vascular basis of these conditions.

Several articles evaluated novel risk markers and indices with cardiometabolic relevance. Non-HDL-cholesterol to HDL-cholesterol ratio was strongly associated with arterial stiffness and may outperform traditional lipid measures in predicting vascular

damage (Guo et al.). In another population-based study, Zhou et al. identified a positive association between blood ethylene oxide levels and MetS, underlining the possible contribution of environmental toxins to metabolic dysfunction.

The impact of cardiometabolic risk on mortality was comprehensively analyzed in heart failure populations. Zhou et al. categorized patients with chronic heart failure into distinct metabolic obesity phenotypes and demonstrated that metabolically unhealthy individuals, regardless of BMI, faced elevated mortality risks. Interestingly, the so-called "obesity paradox" appeared to be modified by age and sex. This nuanced analysis underscores the importance of metabolic profiling beyond body weight alone.

Cardiorenal and cerebrovascular interactions also emerged as important considerations. Wang et al. conducted a meta-analysis of sodium-glucose cotransporter 2 inhibitors (SGLT2i), confirming their efficacy in reducing heart failure, stroke, and all-cause mortality—further validating their role in high-risk patients with type 2 diabetes. Complementing these findings, Wang and Meng showed that higher scores on the Life's Essential 8 cardiovascular health metrics correlated with lower uric acid levels, suggesting a link between lifestyle-driven CV health and risk for hyperuricemia —a known contributor to both renal and vascular complications.

Sex-specific and hormonal influences on metabolic and vascular outcomes were another central focus. Testosterone deficiency impacts inflammatory markers in obese male mice, revealing increased IL-6 expression and potential implications for male-specific CVD risk (Malagon-Soriano et al.). In a related experimental study, physical exercise improved lipid metabolism and gut microbiota composition in ovariectomized rats, highlighting a protective role in postmenopausal women (Song et al.).

Psychosocial and cognitive dimensions of cardiometabolic disease were examined by Chen et al., who found that MetS was significantly associated with cognitive impairment among patients with bipolar disorder, emphasizing the need for holistic care approaches. Similarly, Mehran et al. explored the predictive value of TyG-related indices for MACCE in hypertensive patients with CHD, suggesting their utility in behavioral and pharmacologic risk stratification.

The importance of precision medicine was highlighted in studies exploring phenotype stratification. Huang et al. examined metabolically healthy and unhealthy obesity in adolescents, finding that BMI alone is insufficient to assess metabolic risk. Complementing this, Zeng et al. described the independent contributions of visceral adiposity to subclinical atherosclerosis in Chinese adults, regardless of overall obesity.

Clinical management perspectives were advanced in multiple articles. Zhou et al. found that serum uric acid was positively associated with pulse wave velocity, adding evidence to its role as a modifiable vascular risk marker. Wang et al. also explored the relationship between C-peptide levels and stroke in diabetic individuals, finding a nonlinear association that might inform future therapeutic thresholds.

From a population health standpoint, Wang and Meng used NHANES data to establish a robust inverse relationship between cardiovascular health (assessed by LE8) and hyperuricemia, supporting the use of preventive lifestyle metrics to mitigate metabolic burden. In a related NHANES-based analysis, Wu et al. and Wang et al. provided complementary evidence on the link between ABI, ED, and PAD, reinforcing the systemic nature of metabolic vascular damage.

Lastly, Wang et al. contributed an innovative study on the bidirectional relationship between serum 25(OH)D levels and CVD, applying Mendelian randomization and reinforcing the vitamin D hypothesis in cardiovascular prevention.

Taken together, the articles in this volume offer a comprehensive and multidimensional perspective on how metabolic syndrome and its components intersect with cardiovascular pathophysiology. They reinforce the critical need for early detection, personalized risk profiling, and integrated therapeutic approaches that bridge endocrinology and cardiology. We extend our gratitude to the contributing authors, peer reviewers, and editorial team for enriching this Research Topic with robust and impactful science. We hope this Research Topic stimulates further interdisciplinary collaboration and informs future research and clinical innovation in cardiometabolic health.

Author contributions

CI: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. PP: Investigation, Writing – review & editing. JG: Data curation, Writing – review & editing. AC: Supervision, Writing – review & editing.

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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Age differences in the association of body mass index-defined obesity with abdominal aortic calcification

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Objectives: In cardiovascular disease, previous studies have suggested young age as one of the reasons to explain the obesity paradox. This study attempts to provide a different opinion on this claim through unexpected findings.

Methods: We used a cross-sectional analysis of the US nationally representative data, total of 10,175 participants were recruited in 2013-2014 from NHANES. A total of 947 participants were selected to be included in this study through inclusion criteria and exclusion criteria for statistical analysis of the relationship between obesity and abdominal aortic calcification(AAC). Smooth curve fitting and multivariate regression analyses were conducted to examine the associations of obesity with AAC after adjusting for age, gender and associated variates.

Results: Depending on the age of the population, the relationship between obesity and AAC showed the different outcome. Obesity was associated with the lower risk of AAC among individuals older than 52 years of age. According to the difference of adjusted covariates, the AAC scores in the obesity group decreased by 0.92, 0.87, and 1.11 for 52 years old or older individuals. In particular, the risk of AAC was lower for patients with obesity with the following characteristics: male, low LDL, low triglyceride, DM, non-cancer patient, smoking, drinking, vigorous work activity, low annual household income, education of 9 – 11th grades and non-Hispanic white.

Conclusions: In US, adults aged 52 years or older, obesity was associated with decreased AAC risk. Older age may be one potential reason for the obesity paradox.

KEYWORDS

age, obesity, abdominal vascular calcification, NHANES, body mass index

Introduction

Cardiovascular disease (CVD) remains the leading cause of death globally (1). Abdominal aortic calcification (AAC) is significantly associated with CVD, and the circularity of the calcification independently adds to the cardiovascular risk (2–4). Previous studies have found that AAC results in increased aortic stiffness, isolated systolic hypertension, decreased organ perfusion, left ventricular hypertrophy, diastolic dysfunction, and heart failure with preserved ejection fraction (5–8). In addition, AAC can measure advanced atherosclerosis, which predicts CVD morbidity and mortality independently of traditional CVD risk factors (9).

A recent study found that obesity accelerated vascular calcification (VC) *in vivo*, which plays an important role in VC response to cholecalciferol *in vivo*, resulting in increased ectopic mineralization signaled by specific osteochondrogenic program activation and associated positive, hypotrophic vascular remodeling (10). Various measures of obesity were associated with increased progression of coronary artery calcification (CAC) (11–14). However, over the past 25 years, quite a few studies have demonstrated a strong "obesity paradox." This paradox suggests that although obesity has a detrimental effect on risk factors associated with cardiovascular disease and many other chronic diseases, patients with cardiovascular disease and who are overweight or obese tend to have a better prognosis than thinner patients (15). One study has suggested young age as one of the reasons to explain the obesity paradox (16). Therefore, it is necessary to study the association between obesity and AAC by age stratification.

To fill these knowledge gaps, it is necessary to reveal the relationship between obesity and AAC with data based on population epidemiology. This study analyzed the association of obesity and AAC from National Health and Nutrition Examination Survey (NHANES) in a nationally representative sample of U.S. adults. The study's strengths include its large, representative national sample and its consistent use of standardized methods.

Methods

Study participants

NHANES was a stratified, multistage probability sampling method to select a series of cross-sectional, nationally representative samples. It was designed to assess the health and nutritional status of the US general population (17). The current analyses were limited to participants aged 40 years or older who completed the lateral spine scan of instant vertebral assessment and whose L1-L4 vertebrae are valid in 2013–2014. The people who had one or more invalid L1-L4 vertebrae were excluded. After exclusion, 947 participants with AAC scores of 1 or more were included in the final sample for analysis. The AAC total scores were used to assess the severity of AAC. The institutional review board approved the National Center for Health Statistics study protocols. No informed consent was required because the data were anonymized. Figure 1 depicts the flow chart of the participants' selection process in the studies.

Data collection

Participants completed in-home interviews and visited a mobile examination center where they underwent a physical examination and blood sample collection. A standardized questionnaire was used to collect information on age, gender, smoking history, drinking, hypertension, diabetes mellitus (DM), renal dysfunction, cancer,

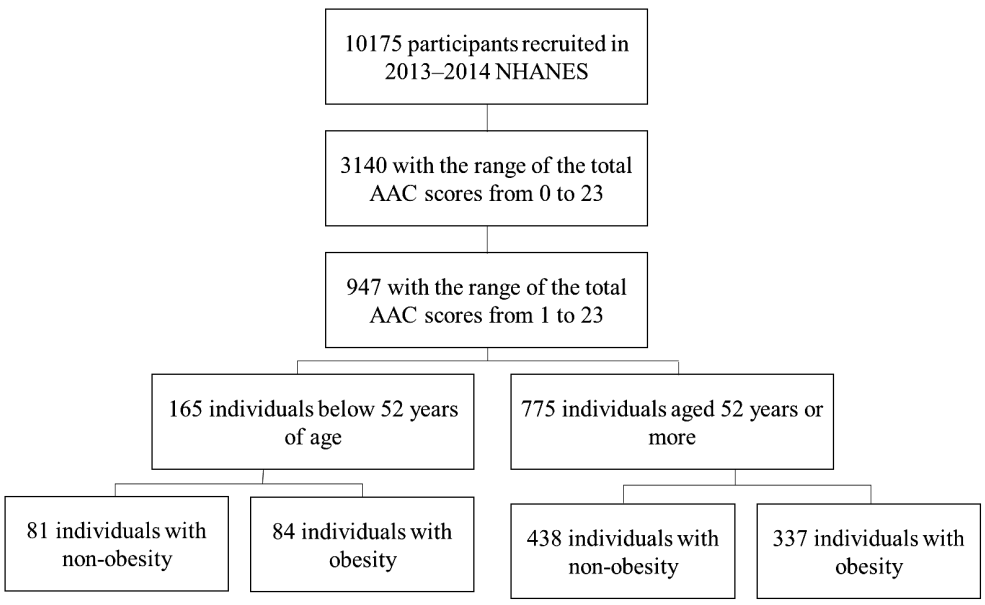

FIGURE 1
Flow-chart of study participants.

vigorous work activity, annual household income, education, and race/ethnicity. According to the standard questionnaire, participants were asked whether they had received a diagnosis of DM, hypertension, renal dysfunction or cancer. Race/ethnicity was categorized into Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other races, including "multi-racial." Caregiver education was categorized as less than grade 9, grades 9–11 (including grade 12 with no diploma), high school graduate/general equivalency diploma or equivalent, some college, and college graduate or above. Smoking history was defined as answering "yes" to the question, "Have you smoked at least 100 cigarettes in your entire life?" Drinking history was defined as answering "yes" to the question, "Have you drunk at least 12 alcohol drinks in one year?"

During the physical examination, body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared according to the measured weight and height. Obesity was defined as BMI ≥ 28.0 kg/m^2, which was cited from the working group on obesity (18). An examination of AAC with dual-energy X-ray absorptiometry (DXA) was performed. In the scoring method for AAC, the anterior and posterior aortic walls were divided into four segments, corresponding to the areas in front of the lumbar vertebrae L1-L4. Within these eight segments, aortic calcification was recognized visually as either a diffused white stippling of the aorta extending out to the anterior and posterior aortic walls or as white linear calcification of the anterior and posterior walls. In addition, aortic calcification was scored as "0" if there was no calcification; "1" if one-third or less of the aortic wall in that segment was calcified; "2" if more than one-third but less than two-thirds was calcified; or "3" if more than two-thirds was calcified. The scores were obtained separately for the anterior and posterior aortic walls, ranging from "0" to "24" for the total score (19).

Blood pressure was measured using a mercury sphygmomanometer after the participant rested quietly in a seated position for at least 5 min by trained staff. Blood samples were collected and sent to central laboratories to determine LDL-cholesterol, triglyceride and 25-hydroxyvitamin D3 (25OHD3) using standard methods.

Statistical analysis

The survey examination weights were used for analysis to obtain nationally representative estimates following National Center for Health Statistics guidelines (20).

All statistical tests were two-sided, and P <0.05 was considered statistically significant. Mean +/− SD for continuous variables. P-value was calculated by a weighted linear regression model. Percentages were used for categorical data. The weighted chi-squared test calculated the P-value. Smooth curve fitting was used to examine the associations of age with AAC scores when the individuals were divided into two group as obesity and non-obesity. Multivariate regression analyses were conducted to examine the associations of obesity with AAC after adjusting for age, gender, 25OHD3, LDL-cholesterol, triglyceride, SBP, DBP, smoking history, drinking, hypertension, DM, renal dysfunction, cancer, vigorous work activity, annual household income, education, and race/ethnicity. Data on LDL-cholesterol and triglyceride level were missing in 49.9% and 49.4%, respectively. We used multivariate multiple imputation analysis to impute missing values (21). Otherwise, less than 0.1% of values were missing. If ≤10% of data for the main outcome variable were missing for eligible examinees, it is usually acceptable to continue the analysis without further evaluation or adjustment as a general rule (22). All analyses were conducted using Empower (R) (www.empowerstats.com, X&Y Solutions, Inc., Boston MA) and R (http://www.R-project.org).

Results

We defined obesity as BMI ≥ 28.0 kg/m^2 and non-obesity as BMI<28 kg/m^2 according to the working group on obesity in China (18). In Table 1, all participants were assigned into two groups, namely, obesity and non-obesity, based on their BMI values. The participants in the obesity group showed lower ages, calcification scores and 25OHD3 levels, but higher triglyceride levels and ratio of female, Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, hypertension, DM, education background of 9–11th grades, high school graduate and some college or AA degree (P<0.05). The smoking history, drinking history, vigorous work activity, annual household income and diseases of renal dysfunction and cancer were not significantly different (P>0.05).

We used smooth curve fitting to examine the association of AAC scores and age in the individuals who were divided into two groups: obesity and non-obesity (Figure 2A). It could be clearly seen that, with the increase of age, the AAC scores of the non-obesity group increased gradually. The obese group showed similar results after reaching the age of 52 or older. The values of AAC scores between obesity and non-obesity group were reversed when the age was around 52 years old. The obesity group maintained higher AAC scores before 52 years old, but it was overtaken by the non-obesity group for individuals older than 52 years of age. In the Figure 2B, we can see that for people aged 52 and older, a BMI of about 24 is a turning point. When BMI was greater than 24, the AAC score showed a decreasing trend. The results support the obesity paradox.

Generalized additive models were used to visually assess functional relationships between the age/BMI and the risk of AAC (Figure 2). The stratified AAC scores by obesity or non-obesity were presented in the Figure 2A. The stratified AAC scores by age were presented in the Figure 2B. Adjusted for age, gender, 25OHD3, LDL-cholesterol, triglyceride, SBP, DBP, smoking history, drinking, hypertension, DM, renal dysfunction, cancer, vigorous work activity, annual household income, education, and race/ethnicity. Abbreviations: AAC, abdominal aortic calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; 25OHD3, 25-hydroxyvitamin D3; DM, diabetes mellitus.

Next, we used multivariate regression analyses to identify the association between obesity and AAC risk. The analysis revealed that obesity was associated with AAC scores. In people under 52 years of age, the risk of AAC appears to be higher in obesity people than in non-obesity people, although the association did not reach statistical significance (P= 0.09). When the individuals were 52

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TABLE 1 Characteristics of abdominal aortic calcification in individuals with obesity vs. non-obesity.

	Non-obesity	Obesity	P-value
Age, years	66.01 ± 11.94	63.22 ± 11.59	<0.01
Gender			0.02
Male	53.6	45.6	
Female	46.4	54.4	
AAC scores	5.83 ± 4.73	4.91 ± 4.10	<0.01
25OHD3, nmol/L	67.53 ± 26.20	63.79 ± 25.59	0.03
LDL-cholesterol, mmol/L	2.79 ± 1.00	2.87 ± 0.93	0.20
Triglyceride, mmol/L	1.44 ± 0.86	1.66 ± 0.95	<0.01
SBP, mmHg	132.22 ± 21.18	130.56 ± 17.92	0.21
DBP, mmHg	65.59 ± 17.10	68.62 ± 13.85	<0.01
Hypertension			0.01
Yes	56.8	65.3	
No	43.2	34.7	
DM			<0.01
Yes	20.4	32.5	
No	79.6	67.5	
Renal dysfunction			0.07
Yes	4.8	7.6	
No	95.2	92.4	
Cancer			0.31
Yes	20.4	17.8	
No	79.6	82.2	
Smoking (at least 100 cigarettes in life)			0.32
Yes	55.5	52.3	
No	44.5	47.7	
Drinking (at least 12 alcohol drinks/1 year)			0.12
Yes	73.9	69.2	
No	26.1	30.8	
Vigorous work activity			0.95
Yes	13.9	14	
No	86.1	86	
Annual household income			0.28
Low	41.9	46.5	
Medium	39.3	38	
High	18.8	15.4	
Education			0.01
Less than 9th grade	9.6	9	
9–11th grades	13.7	14.3	
High school graduate	23.1	26.7	
Some college or AA degree	25	31.7	
College graduate or above	28.5	18.3	
Race/ethnicity			<0.01
Mexican American	7.3	13.5	
Other Hispanic	6.9	8.8	
Non-Hispanic white	52.4	54.4	
Non-Hispanic black	15.6	17.6	
Other Race - Including Multi-Racial	17.7	5.7	

AAC, abdominal aortic calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; 25OHD3, 25-hydroxyvitamin D3; DM, diabetes mellitus. Mean +/− SD for: age, AAC scores, 25OHD3, LDL-cholesterol, triglyceride, SBP and DBP. Percentage for: gender, smoking history, drinking, hypertension, DM, renal dysfunction, cancer, vigorous work activity, annual household income, education and race/ethnicity.

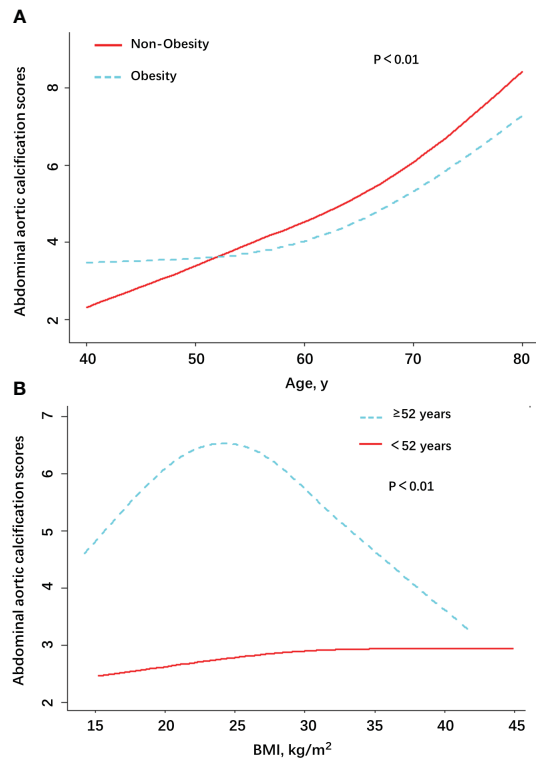

FIGURE 2
Association between AAC scores and age/BMI among patients with AAC in NHANES, by Obesity **(A)** and age **(B)**.

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years or older, obesity was significantly negatively associated with risk of AAC (P ≤ 0.01) (Table 2). According to the difference of adjusted covariates, the AAC scores of the obesity group decreased by 0.92, 0.87, and 1.11, compared with those of the non-obesity group of older individuals. Table 2 showed that the maximum effect value of obesity on AAC scores was 1.11 in the older group after adjusting for age, gender, 25OHD3, LDL-cholesterol, triglyceride, SBP, DBP, smoking history, drinking, hypertension, DM, renal dysfunction, cancer, vigorous work activity, annual household income, education, and race/ethnicity.

Finally, we further analyzed the relationship between obesity and AAC score by stratification method (Table 3). Overall, the results were statistically significant in the age group ≥52 years, suggesting a negative correlation between obesity and AAC scores. In particular, the risk of AAC was lower for patients with obesity with the following characteristics: male, low LDL, low triglyceride, DM, non-cancer patient, smoking, drinking, vigorous work activity, low annual household income, education of 9 – 11th grades and non-Hispanic white.

Discussion

In our study, we found AAC became more common after the age of 50 years old. The average age of AAC individuals in our study was 59.3 years. The AAC scores were increased with age which was

TABLE 2 Multivariate regression analyses of the association between obesity and AAC risk in NHANES.

	Age <52 years	Age >=52 years	Total
Non-adjusted			
Non-Obesity	0	0	0
Obesity	0.45 (−0.06, 0.95) 0.09	−0.92 (−1.55, −0.28) <0.01	−0.65 (−1.18, −0.12) 0.02
Adjust I			
Non-Obesity	0	0	0
Obesity	0.40 (−0.16, 0.97) 0.17	−0.87 (−1.55, −0.20) 0.01	−0.63 (−1.20, −0.07) 0.03
Adjust II			
Non-Obesity	0	0	0
Obesity	0.30 (−0.36, 0.86) 0.42	−1.11 (−1.78, −0.25) <0.01	−0.78 (−1.36, −0.08) 0.02

Data are presented as β (95% CI) unless indicated otherwise.
Outcome: AAC scores.
Exposure: obesity or non-obesity
Non-adjusted model adjusts for: none.
Adjust I model adjust for: gender, smoking history, drinking, vigorous work activity, annual household income, education, and race/ethnicity.
Adjust II model adjust for: age, gender, 25OHD3, LDL-cholesterol, triglyceride, SBP, DBP, smoking history, drinking, hypertension, DM, renal dysfunction, cancer, vigorous work activity, annual household income, education, and race/ethnicity. Abbreviations: AAC, abdominal aortic calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; 25OHD3, 25-hydroxyvitamin D3; DM, diabetes mellitus.

TABLE 3 Association of obesity and AAC score in strata defined by sample characteristics.

	Age <52 years	Age >=52 years
Gender		
Male	0.60 (-0.07, 1.26) 0.08	-1.60 (-2.52, -0.68) 0.001
Female	0.35 (-0.53, 1.22) 0.44	-0.65 (-1.61, 0.31) 0.19
25OHD3, nmol/L		
Low	0.77 (0.01, 1.53) 0.05	-1.12 (-2.09, -0.15) 0.02
High	-0.06 (-0.76, 0.64) 0.87	-0.94 (-1.89, 0.00) 0.05
LDL-cholesterol, mmol/L		
Low	0.99 (0.10, 1.89) 0.03	-1.50 (-2.42, -0.58) 0.002
High	0.12 (-0.55, 0.79) 0.73	-0.51 (-1.45, 0.44) 0.29
Triglyceride, mmol/L		
Low	0.54 (-0.16, 1.24) 0.13	-1.41 (-2.47, -0.35) 0.01
High	0.31 (-0.66, 1.29) 0.53	-0.91 (-1.81, -0.01) 0.05
Hypertension		
Yes	0.06 (-1.08, 1.21) 0.92	-1.22 (-2.07, -0.37) 0.005
No	0.63 (0.02, 1.24) 0.04	-1.32 (-2.30, -0.34) 0.01
DM		
Yes	1.30 (-0.70, 3.31) 0.22	-2.29 (-3.56, -1.01) 0.0005
No	0.27 (-0.27, 0.81) 0.33	-0.85 (-1.62, -0.07) 0.03
Renal dysfunction		
Yes	-[#]	
No	0.47 (-0.07, 1.02) 0.09	-1.85 (-4.69, 0.98) 0.21
Cancer		-1.04 (-1.73, -0.36) 0.003
Yes	1.93 (-0.46, 4.32) 0.15	-0.24 (-1.70, 1.21) 0.74
No	0.39 (-0.17, 0.94) 0.18	-1.27 (-2.01, -0.52) 0.0009
Smoking (at least 100 cigarettes in life)		
Yes	0.34 (-0.34, 1.02) 0.33	-1.40 (-2.30, -0.51) 0.002
No	0.57 (-0.28, 1.43) 0.19	-0.61 (-1.59, 0.37) 0.22
Drinking (at least 12 alcohol drinks/1 year)		
Yes	0.71 (0.06, 1.36) 0.03	-1.10 (-1.89, -0.31) 0.006

(Continued)

TABLE 3 Continued

	Age <52 years	Age >=52 years
Drinking (at least 12 alcohol drinks/1 year)		
No	-0.02 (-1.30, 1.25) 0.97	-0.79 (-2.08, 0.50) 0.23
Vigorous work activity		
Yes	0.06 (-1.08, 1.21) 0.92	-1.34 (-2.66, -0.03) 0.05
No	0.63 (0.02, 1.24) 0.04	-0.92 (-1.69, -0.15) 0.02
Annual household income		
Low	-0.57 (-1.54, 0.40) 0.26	-1.33 (-2.29, -0.36) 0.007
Medium	1.28 (0.39, 2.17) 0.01	-1.10 (-2.29, 0.08) 0.07
High	0.92 (-0.13, 1.97) 0.09	-0.41 (-2.11, 1.30) 0.64
Education		
Less than 9th grade	1.00 (-1.64, 3.64) 0.47	-1.14 (-3.35, 1.07) 0.32
9–11th grades	1.05 (-0.67, 2.76) 0.24	-1.87 (-3.59, -0.15) 0.04
High school graduate	0.06 (-0.99, 1.11) 0.91	-0.53 (-1.93, 0.88) 0.46
Some college or AA degree	0.52 (-0.61, 1.66) 0.37	-1.02 (-2.17, 0.13) 0.08
College graduate or above	0.17 (-0.69, 1.04) 0.70	-1.22 (-2.76, 0.31) 0.12
Race/ethnicity		
Mexican American	0.72 (-1.18, 2.61) 0.46	-0.06 (-1.87, 1.74) 0.94
Other Hispanic	0.33 (-1.70, 2.36) 0.75	-1.78 (-4.06, 0.50) 0.13
Non-Hispanic white	0.40 (-0.24, 1.04) 0.23	-1.11 (-2.04, -0.18) 0.02
Non-Hispanic black	0.36 (-1.37, 2.08) 0.69	-1.06 (-2.58, 0.46) 0.17
Other Race - Including Multi-Racial	-0.47 (-2.26, 1.33) 0.62	-1.73 (-3.88, 0.42) 0.12

Data are presented as β (95% CI) unless indicated otherwise.
Outcome: AAC scores.
Exposure: obesity or non-obesity.
AAC, abdominal aortic calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; 25OHD3, 25-hydroxyvitamin D3; DM, diabetes mellitus. Mean +/− SD for: age, AAC scores, 25OHD3, LDL-cholesterol, triglyceride, SBP and DBP. Percentage for: gender, smoking history, drinking, hypertension, DM, renal dysfunction, cancer, vigorous work activity, annual household income, education and race/ethnicity. # means less data, not calculated.

consistent to other reports as an age-related disease (23). The prevalence of AAC increased to 100% in both males and females when they were over 75 years of age (2).

As far as we know, this is the first report showing that obesity was negative association with the AAC. This conclusion is contrary to the finding of recent reports showing that obesity was associated with higher risk of AAC (24–27). After comparison, it was found that the reason for the difference between our study and other studies was due to the different ways of evaluating obesity. We define obesity using BMI, other studies have used weight-adjusted waist index (WWI) and a body shape index (ABSI). WWI and ABSI are a newly-developed parameter of obesity that more accurately estimates whole-body fat percentage (28, 29). The mechanism underlying the positive association between WWI/ABSI and AAC may be correlated with metabolic abnormalities. It is also possible that WWI/ABSI and AAC are a concomitant relationship related to age, and there is no inherent correlation (30).

Controversies about the obesity paradox have a long history (31). It has become increasingly apparent during the past half century that a relationship exists between obesity and CVD (32). The obesity paradox could be explained by the inherent limitations of both BMI and clinical studies (33). BMI does not differentiate between muscle mass and fat mass. Its assessment of body fat in older adults is not as accurate as that in younger adults (34). Perhaps it is precisely because of the difference in the accuracy of BMI in evaluating fat content between young and old people that the different results of this study appear. A limited number of previous studies have assessed the severity of CAC among those with obesity compared with those without obesity (14). Obesity was associated with increased progression of CAC in those at lower risk of CVD. But no baseline obesity measure was significantly associated with progression of CAC among those at higher risk for CVD. We found that the mean age of the group with high-risk of CVD was 57.9 years old, which is significantly higher than the mean age of the low-risk group (48.8 years old). Older age may be one reason why obesity is not positively associated with CAC progression in patients at high risk for CVD. Therefore, age stratification is necessary when analyzing the relationship between BMI and cardiovascular events. We did find an unusual relationship between BMI and AAC in relatively old age. Obese people aged 52 years and older were associated with a lower risk of AAC. This seems to provide new evidence for the obesity paradox.

How to explain the obesity paradox in the elderly? One finding show that obesity is often associated with increased survival time among people who have some serious injury or illness (35). In general, older people have a higher risk of disease than younger people. In this sense, it seems that our study as well as this one supports the obesity paradox. Beyond that, the obesity paradox is not entirely devoid of internal mechanisms. Some studies have summarized the molecular mechanisms by which adipose tissue protects against cardiovascular disease, such as efficient fat storage and lipid droplet formation, high adipogenesis capacity, low extracellular matrix fibrosis, angiogenesis potential, adipocyte browning and low macrophages infiltration/activation (33). The obesity paradox is also attributable to increased cardiac lipid supply from adipose lipolysis in the fasting cycle due to systemic insulin resistance and adiposity (36). The specific molecular mechanism to explain obesity paradox in old age needs to be confirmed by basic research in the future.

In summary, obesity was associated with decreased AAC risk for adults aged 52 years or older in US. In the future, specific molecular mechanism and larger population-based studies stratified by age exploring the relationship between obesity and AAC may be warranted.

Limitations

Despite the strengths of this study, several limitations should also be considered. First, we examined a cross-sectional population sample in 2013–2014 from NHANES, which was the only investigation of the AAC that NHANES has done so far. Second, these results are based on U.S. adults with obesity, which may limit the generalizability to other populations. Finally, as with any observational study, we cannot exclude the possibility of residual or unmeasured confounding effects.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials. Further inquiries can be directed to the corresponding author.

Ethics statement

The survey protocol was approved by NCHS Ethics Review Board (https://www.cdc.gov/nchs/nhanes/irba98.htm), and all participants have written informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

TG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. BC: Conceptualization, Supervision, Visualization, Writing – review & editing. LH: Data curation, Resources, Visualization, Writing – original draft, Writing – review & editing. ZL: Data curation, Investigation, Methodology, Validation, Writing – review & editing. HZ: Formal analysis, Methodology, Writing – review & editing. SS: Data curation, Investigation, Methodology, Software, Writing – review & editing.

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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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Association of metabolic syndrome and sarcopenia with all-cause and cardiovascular mortality: a prospective cohort study based on the NHANES

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Background: Metabolic syndrome (MetS) and sarcopenia (SP) have emerged as significant public health concerns in contemporary societies, characterized by shared pathophysiological mechanisms and interrelatedness, leading to profound health implications. In this prospective cohort study conducted within a US population, we aimed to examine the influence of MetS and SP on all-cause and cardiovascular mortality.

Methods: This study analyzed data from the National Health and Nutrition Examination Survey (NHANES) III for the years 1999-2006 and 2011-2018, and death outcomes were ascertained by linkage to National Death Index (NDI) records through December 31, 2019. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for all-cause and cardiovascular mortality. In addition, subgroup and sensitivity analyses were conducted to test the robustness of the results.

Results: Over a median follow-up period of 13.3 years (95% CI: 12.8-13.8), 1714 deaths were observed. The groups characterized by MetS–/SP+, MetS+/SP–, and MetS+/SP+ exhibited higher all-cause mortality rates in comparison to the MetS-/SP- group, with the MetS+/SP+ group (HR 1.76, 95% CI: 1.37-2.25) displaying the highest all-cause mortality. Increased cardiovascular mortality was observed in the MetS+/SP– (HR 1.84, 95% CI: 1.24-2.72), and MetS+/SP+ groups (HR 2.39, 95% CI: 1.32-4.35) compared to the MetS–/SP– group, whereas it was not statistically significant in the MetS-/SP+ group. However, among males and individuals aged < 60, the presence of both MetS and SP (MetS+/SP+ group) was found to be significantly associated with a higher risk of all-cause and cardiovascular mortality.

Conclusion: The coexistence of MetS and SP increased the risk of all-cause and cardiovascular mortality, particularly in males and in nonelderly populations. Individuals with either MetS or SP may require more careful management to prevent the development of other diseases and thereby reduce mortality.

KEYWORDS

metabolic syndrome, sarcopenia, all-cause mortality, cardiovascular mortality, NHANES

1 Introduction

Metabolic syndrome (MetS) is a group of clinical syndromes characterized by the aggregation of multiple disease states such as abdominal obesity, hypertension, dyslipidemia, abnormal glucose metabolism, and hyperuricemia in an individual (1). According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of MetS has increased dramatically among U.S. adults, from 25.3% in 1988-1994 to 36.9% in 2015-2016 (2, 3). Most studies have shown that individuals with MetS have higher cardiovascular disease morbidity and mortality (4–6). Another study showed that MetS and its components were associated with all-cause, cardiovascular disease (CVD), and diabetes mortality (7).

Age-related reductions in skeletal muscle mass and strength, and diminished physical function are known as sarcopenia (SP) (8). In an aging society, the prevalence of SP is increasing globally, with an overall prevalence of 10-27% (9). Most studies have shown that individuals in SP are associated with a high risk of all-cause mortality (10–12).

Insulin resistance and chronic inflammation, as pathophysiological mechanisms common to both MetS and SP, interact to produce deleterious metabolic effects (13–17). MetS increases the risk of physical capacity and dysfunction (18–20) and is associated with lower muscle mass and strength (21). A meta-analysis demonstrated a positive association between SP and MetS (odds ratio, OR 2.01, 95% CI, 1.63-2.47) (22). MetS and SP are thought to be bi-directionally linked, increasing the risk of mutual morbidity (22, 23). Current studies on the comorbidity of MetS and SP have focused on the risk of cardiovascular disease, diabetes, and hyperlipidemia (24), and no studies comprehensively analyze the association of MetS and SP with mortality.

Abbreviations: MetS, Metabolic Syndrome; SP, Sarcopenia; NHANES, National Health and Nutrition Examination Survey; CVD, Cardiovascular disease; NDI, National Death Index; HRs, Hazard Ratios; CIs, Confidence Intervals; NCHS, National Center for Health Statistics; BP, blood pressure; FBG , fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; WC, waist circumference; EWC, Elevated waist circumference; EBP, Elevated blood pressure; RHDL-C, Reduced HDL-C; ETG, Elevated TGs; EGLU, Elevated fasting glucose; ASM, Appendicular skeletal muscle mass; DXA, Dual-energy X-ray; BMI, Body mass index; FNIH, Foundation for the National Institutes of Health; PIR, poverty-to-income ratio.

MetS and SP are highly prevalent worldwide and pose a significant public health burden. It may be valuable to assess the impact of their interaction on mortality in the general population. Therefore, this study investigates the association of MetS and SP with all-cause and cardiovascular mortality among U.S. adults using a sample that is nationally representative of the U.S. population.

2 Materials and methods

2.1 Study design and participants

Data for the study were obtained from the NHANES III, a research program conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention designed to assess the health and nutritional status of adults and children in the U.S. NHANES utilizes a complex, multistage, probability sampling approach to obtain data through questionnaires, interviews, mobile medical examinations, and laboratory tests (25). The NHANES data are free and available on the Web (26).

This study was conducted in accordance with the Declaration of Helsinki (27). Written informed consent was obtained from all study participants, and the program was approved by the Ethics Review Board of the National Center for Health Statistics (28).

This study analyzed data from 1999-2006 and 2011-2018 and included 80,630 participants. Participants who were aged < 18 years, pregnant females, had a history of cancer at the time of enrollment, missing data on metabolic syndrome-related components, including blood pressure (BP), fasting blood glucose (FBG), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and waist circumference (WC), missing data on the skeletal muscle mass of the extremities, and missing data on mortality were excluded, and 10,778 subjects were ultimately included in the study analysis. The flow chart of the study is shown in Figure 1.

2.2 Ascertainment of MetS and SP

MetS was defined according to the NCEP ATP III-2005 criteria (29). People with three or more of the following criteria were diagnosed with MetS: (1) elevated WC (EWC): WC ≥ 102 cm in men and ≥ 88 cm in women; (2) elevated BP (EBP): BP ≥ 130/

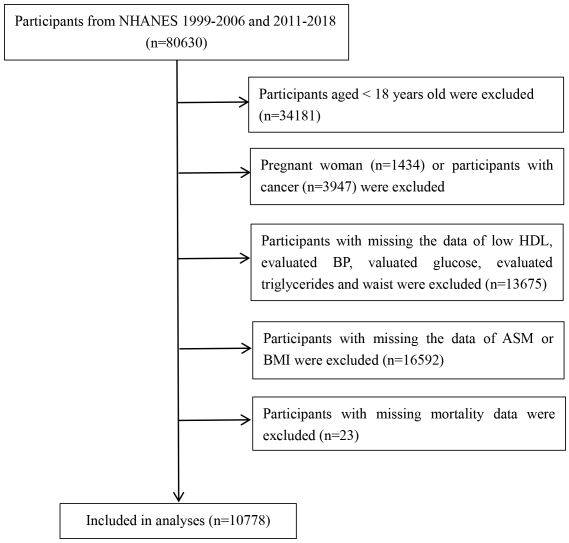

FIGURE 1
Study flowchart displaying the selection of patients according to exclusion criteria. BP, blood pressure; HDL, high-density lipoprotein cholesterol; ASM, appendicular skeletal muscle mass.

85 mm Hg or drug treatment of previously diagnosed hypertension; (3) reduced HDL-C (RHDL-C): < 40 mg/dL in men and < 50 mg/dL in women or specific treatment for reduced HDL-C; (4) elevated TG (ETG): TG level ≥ 150 mg/dL or drug treatment for elevated TG; and (5) elevated fasting glucose (EGLU): fasting glucose level of ≥100 mg/L or drug treatment for elevated glucose and previously diagnosed type 2 diabetes. The unit of HDL-C converted to mmol/L is equal to mg/dL*0.0259. The unit of TG converted to mmol/L is equal to mg/dL* 0.0113. The unit of FBG converted to mmol/L is equal to mg/dL*18.

Appendicular skeletal muscle mass (ASM), the sum of the lean mass of extremities, was assessed using dual-energy X-ray (DXA) (QDR Discovery; Hologic, Inc., Bedford, MA, USA). In this study, SP used ASM divided by body mass index (BMI) (ASM/BMI) with cutoff points of ≤ 0.789 in men and ≤ 0.512 in women according to the Foundation for the National Institutes of Health (FNIH) criteria, which widely used in recent research (30).

Based on these definitions, the participants were categorized into the following four groups according to the presence of MetS and SP: 1) without MetS or SP (MetS−/SP−), 2) with MetS but no SP (MetS+/SP−), 3) without MetS but with SP (MetS−/SP+), and 4) with both MetS and SP (MetS+/SP+).

2.3 Ascertainment of covariates

Study data also included sex, age, race and ethnicity, smoking status, drinking status, physical activity, marital status, education level, family poverty-to-income ratio (PIR), height, and weight. Participants' race and ethnicity were categorized into four groups: Mexican American, non-Hispanic White, non-Hispanic Black, or others (31). Never smokers were defined as those who smoked fewer than 100 cigarettes in their lifetime, those who smoked at least 100 cigarettes in their lifetime were categorized as current smokers, and those who smoked at least 100 cigarettes in their lifetime and quit were labeled ex-smokers (32). Alcohol consumption was determined by a cutoff of ≥ 12 drinks per year, with no alcohol consumption defined as drinking < 12 drinks per year (33). Ideal physical activity was defined as at least 150 minutes of moderate or 75 minutes of vigorous physical activity per week, according to US PA guidelines (34). Educational level was categorized as less than high school, high school or equivalent, college or above, and marital status was categorized as married, separated, including widowed and divorced groups, or never married (7). Family PIR levels were grouped into three categories: 0-1.0, 1.1-3.0, and > 3.0 (35). BMI was calculated as weight (kg) divided by height squared (m^2). Multiple interpolation was used for missing values of covariates.

2.4 Ascertainment of death

Mortality status was ascertained by probabilistic matching to the NDI through December 31, 2019, using a unique study identifier. Details of the matching method are available from the NCHS (36). Causes of death were classified according to the codes of ICD-10. Primary outcomes in this study were mortality from all causes, heart diseases (codes I00-I09, I11, I13, and I20-I51).

2.5 Statistical analysis

In accordance with the NHANES analysis guidelines, all analyses considered a complex survey design, including sample weights, clustering, and stratification. Missing values for covariates were supplemented using multiple interpolations. Continuous variables were expressed as weighted mean ± standard deviation

for weighted characterization, while categorical variables were expressed as frequencies with weighted percentages. Differences in covariates across the groups were performed using one-way ANOVA for continuous variables and the Rao-Scott chi-square test for categorical variables with adjusted weights. Survival curves associated with all-cause and cardiovascular mortality were plotted according to the presence of MetS and SP using the Kaplan-Meier method. Cox proportional hazards models were used to calculate hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for all-cause mortality and cardiovascular mortality, and *P* values for trends were calculated. Model 1 was unadjusted, Model 2 was adjusted for age, sex, and race/ethnicity, and Model 3 was adjusted for age, sex, race/ethnicity, education level, marital status, family PIR, smoking status, drinking status, and physical activity. We also performed stratified analyses by sex and age, obtaining *P* values for interactions. Cox regression analysis was performed in the SP population according to the number of abnormal metabolic components and the type of metabolic abnormality. To test the robustness of the findings, we performed three sensitivity analyses: first, we excluded participants with prior myocardial infarction or angina; second, we excluded participants with a prior history of stroke; and finally, we excluded participants who died within 2 years of the follow-up period.

All statistical analyses were performed using R (version 4.2.3; R Foundation for Statistical Computing) to account for the NHANES complex sample design, with 2-sided $P < 0.05$ considered statistically significant.

3 Results

3.1 Baseline characteristics

Table 1 summarizes the baseline characteristics of the four groups of subjects. Among the 10,778 subjects, 6,962 (64.6%) had neither MetS nor SP (MetS−/SP−), 486 (4.5%) had SP only (MetS−/SP+), 2693 (25.0%) had MetS only (MetS+/SP−), and 637 (5.9%) had both MetS and SP (MetS+/SP+). Subjects in the MetS+/SP+ group were significantly older than those in the other groups ($P < 0.001$). Subjects in the MetS+/SP+ group had higher all-cause mortality (25.2%) and cardiovascular mortality (7.2%). BMI, WC, TG, and FBG in the MetS+/SP+ group were also significantly higher than those in the other groups ($P < 0.001$). Differences between groups were significant except for the sex group.

3.2 Association of MetS and SP status with mortality

There were 1714 deaths during the follow-up period: 1149 (10.66%) from all-cause mortality and 313 (2.90%) from CVD.

TABLE 1 Baseline characteristics of the study subjects.

	Mets-/SP- (n=6962)	Mets-/SP+ (n=486)	Mets+/SP- (n=2693)	Mets+/SP+ (n=637)	*P* value
Age(years)	37.06 ± 13.21	45.74 ± 16.49	47.26 ± 12.99	52.95 ± 14.47	<0.001
Sex (%)					0.210
Male	3633(51.4)	266(55.6)	1295(50.2)	326(55.2)	
Female	3329(48.6)	220(44.4)	1398(49.8)	311(44.8)	
Race and ethnicity (%)					<0.001
Mexican American	1253(9.0)	199(19.8)	482(7.7)	297(21.6)	
Non-Hispanic White	1359(14.3)	110(21.6)	419(11.8)	90(15.7)	
Non-Hispanic Black	2669(64.5)	159(56.5)	1164(69.2)	217(59.7)	
Other races	1681(12.3)	18(2.1)	628(11.3)	33(3.0)	
Alcohol consumption (%)					0.005
Yes	3090(46.8)	201(42.5)	1123(42.2)	247(39.3)	
No	3872(53.2)	285(57.5)	1570(57.8)	390(60.7)	
Smoking status (%)					<0.001
Never smoker	4062(56.1)	298(61.2)	1359(49.3)	334(50.8)	
Ever smoker	1252(19.9)	111(20.2)	692(26.5)	192(28.0)	
Current smoker	1648(24.0)	77(18.7)	642(24.2)	111(21.2)	
Ideal physical activity (%)					0.006
Yes	3594(50.2)	228(50.4)	1221(45.5)	313(47.4)	

(Continued)

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TABLE 1 Continued

	Mets-/SP- (n=6962)	Mets-/SP+ (n=486)	Mets+/SP- (n=2693)	Mets+/SP+ (n=637)	*P* value
No	3368(49.8)	258(49.6)	1472(54.5)	324(52.6)	
Married status (%)					<0.001
married	3090(51.0)	262(55.9)	1478(59.1)	380(62.4)	
separated	873(12.1)	93(15.6)	583(19.3)	148(20.0)	
never married	2999(36.9)	131(28.5)	633(21.7)	109(17.6)	
Educational levels (%)					<0.001
less than high school	1556(15.3)	213(31.6)	739(18.0)	311(30.2)	
high school or equivalent	1545(22.0)	105(25.8)	651(27.4)	141(28.1)	
college or above	3861(62.7)	168(42.5)	1303(54.5)	185(41.7)	
Family poverty-to-income ratio level (%)					<0.001
0-1.0	1591(15.3)	132(21.4)	533(13.9)	180(21.2)	
1.1-3.0	2716(35.3)	223(42.0)	1149(37.8)	310(46.1)	
>3.0	2655(49.4)	131(36.6)	1011(48.3)	147(32.7)	
BMI(kg/m2)	26.16 ± 5.38	30.80 ± 6.31	32.38 ± 6.24	35.41 ± 7.22	<0.001
Waist(cm)	90.56 ± 13.50	101.54 ± 15.12	108.34 ± 14.02	114.09 ± 15.44	<0.001
TG(mmol/L)	1.13 ± 0.74	1.33 ± 0.66	2.25 ± 1.91	2.26 ± 1.95	<0.001
HDL(mmol/L)	1.45 ± 0.39	1.41 ± 0.37	1.16 ± 0.32	1.18 ± 0.34	<0.001
FBG(mmol/L)	5.28 ± 0.83	5.65 ± 1.66	6.51 ± 2.33	7.07 ± 2.74	<0.001
ABP(mmHg)	115.57 ± 13.54	122.16 ± 17.46	128.18 ± 16.83	132.97 ± 18.38	<0.001
DBP(mmHg)	69.07 ± 10.61	71.34 ± 11.57	75.69 ± 12.94	73.74 ± 14.07	<0.001
All-cause mortality (%)					<0.001
Yes	408(4.6)	106(16.8)	431(11.9)	204(25.2)	
No	6554(95.4)	380(83.2)	2262(88.1)	433(74.8)	
Cardiovascular mortality (%)					<0.001
Yes	93(0.9)	29(4.1)	135(3.3)	56(7.2)	
No	6869(99.1)	457(95.9)	2558(96.7)	581(92.8)	

Data are shown as the mean ± SD or frequency (percentage). SD, standard deviation; BMI, body mass index; TG, triglyceride; HDL, high-density lipoprotein cholesterol; FBG, fasting blood glucose; ABP, arterial blood pressure; DBP, diastolic blood pressure; MetS, metabolic syndrome; SP, sarcopenia.

Figure 2 depicts the survival curves of the four groups of subjects and shows significant differences in overall survival and cardiovascular survival among the groups during a median follow-up duration of 13.3 years (95% CI: 12.8-13.8) (three-group log-rank $P < 0.001$). The MetS−/SP− group had the best survival, whereas the MetS+/SP+ group had the worst survival among all the groups.

Table 2 shows the association of MetS and SP status with all-cause and cardiovascular mortality. After adjusting for sex, age, race and ethnicity, smoking status, drinking status, physical activity, marital status, education level, and PIR, compared to the MetS−/SP− group, the risk of all-cause mortality was increased in the MetS−/SP+ group (HR 1.52, 95% CI: 1.15-2.01, $P = 0.003$), the MetS+/SP− group (HR 1.32, 95% CI: 1.06-1.64, $P = 0.012$), and the MetS+/SP+ group (HR 1.76, 95% CI: 1.37-2.25, $P < 0.001$). There was an increased risk of cardiovascular death in the MetS+/SP− (HR 1.84, 95% CI: 1.24-2.72, $P = 0.002$) and MetS+/SP+ (HR 2.39, 95% CI: 1.32-4.35, $P = 0.004$) groups compared with the MetS−/SP− group, whereas there was no significant difference in the MetS−/SP+ group. The HRs for all-cause mortality gradually increased in the MetS−/SP−, MetS+/SP−, MetS−/SP+, and MetS+/SP+ groups (P for trend < 0.001). A similar trend was observed for cardiovascular mortality (P for trend < 0.001).

Table 3 presents the association of MetS and its components with all-cause and cardiovascular mortality in general and SP populations. After adjusting for covariates, when the number of metabolic abnormalities was ≥ 4, there was a significant positive association between the number of MetS components and all-cause and cardiovascular mortality. As the number of MetS components increased, the risk of all-cause and cardiovascular mortality

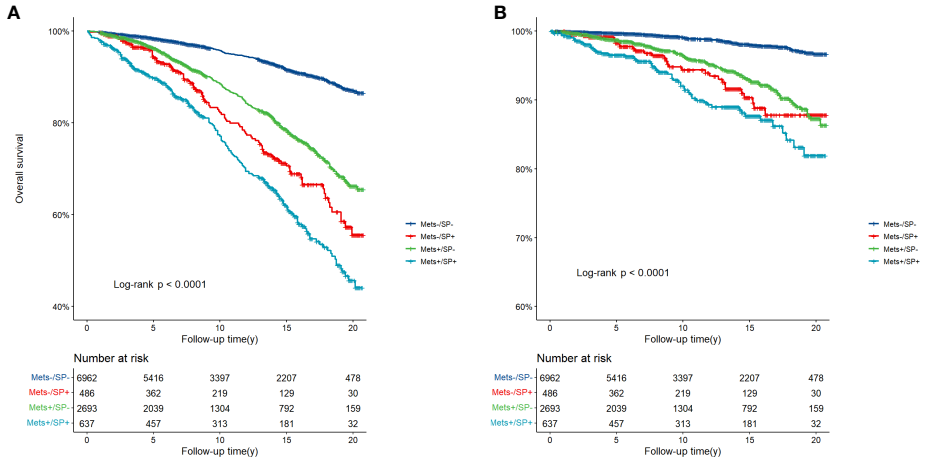

FIGURE 2
(A) Overall survival, and **(B)** CVD-related survival according to MetS and SP status. CVD, cardiovascular disease; MetS, metabolic syndrome; SP, sarcopenia.

increased. After adjusting for covariates, all five components of MetS were associated with an increased risk of all-cause and cardiovascular mortality. Only when the number of metabolic abnormalities was equal to 4 (HR 2.38, 95% CI: 1.51-4.92, P = 0.019) was associated with cardiovascular mortality in the SP population, and no other number of metabolic abnormalities was observed to be associated with all-cause and cardiovascular mortality (P > 0.05). Only ETG (HR 1.42, 95% CI: 1.00-2.00, P = 0.046) was associated with all-cause mortality, whereas the other metabolic abnormality components were not associated with all-cause and cardiovascular mortality.

3.3 Subgroup analysis

The results of subgroup analyses of MetS and SP status with all-cause and cardiovascular mortality by sex and age are shown in Table 4. Compared to the MetS−/SP− group, the MetS+/SP+ group had a higher risk of all-cause mortality (HR 2.23, 95% CI: 1.53-3.24, P < 0.001) and cardiovascular mortality (HR 3.29, 95% CI: 1.37-7.88, P = 0.008) among the males, while no similar situation was observed in the females. Individuals aged < 60 years with MetS and SP had a higher risk of all-cause mortality (HR 4.48, 95% CI: 2.64-7.63, P < 0.001) and cardiovascular mortality (HR 8.88, 95% CI:

TABLE 2 Risks of all-cause and cardiovascular mortality according to the presence of MetS or SP status.

	MetS-/SP-	MetS-/SP+	*P* value	MetS+/SP-	*P* value	MetS+/SP+	*P* value	*P* for trend
	HR	HR(95%CI)		HR(95%CI)		HR(95%CI)		
All-cause mortality								
Model 1	1 (ref)	4.41 (3.18,6.11)	<0.001	2.65 (2.19,6.11)	<0.001	6.27 (4.93,7.98)	<0.001	<0.001
Model 2	1 (ref)	1.57 (1.18,2.09)	0.002	1.33 (1.09,1.62)	0.006	1.89 (1.46,2.44)	<0.001	<0.001
Model 3	1 (ref)	1.52 (1.15,2.01)	0.003	1.32 (1.06,1.64)	0.012	1.76 (1.37,2.25)	<0.001	<0.001
Cardiovascular mortality								
Model 1	1 (ref)	5.64 (2.84,11.18)	<0.001	3.88 (2.65,5.66)	<0.001	9.59 (5.58,16.50)	<0.001	<0.001
Model 2	1 (ref)	1.60 (0.80,3.20)	0.188	1.82 (1.26,2.63)	0.002	2.469 (1.41,4.34)	0.002	<0.001
Model 3	1 (ref)	1.53 (0.79,2.96)	0.212	1.84 (1.24,2.72)	0.002	2.39 (1.32,4.35)	0.004	<0.001

Model 1: unadjusted.
Model 2: adjusted for age, sex, and race.
Model 3: adjusted for age, sex, race, physical activity, alcohol consumption, smoking status, educational levels, marital status, and family poverty-to-income ratio.
MetS, metabolic syndrome; SP, sarcopenia; HR, hazard ratio; ref, reference.

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TABLE 3 Associations of MetS and its components with all-cause and cardiovascular mortality in the general population and in the SP population.

	All-cause mortality	*P* value	Cardiovascular mortality	*P* value
	HR (95% CI)		HR (95% CI)	
In the general population				
Number of MetS				
< 3	1 (ref)		1 (ref)	
3	1.04(0.80,1.36)	0.761	1.22(0.81,1.84)	0.343
4	1.57(1.27,1.94)	<0.001	2.38(1.65,3.44)	<0.001
5	1.65(1.24,2.20)	<0.001	2.49(1.39,4.46)	0.002
***P* for trend**		<0.001		<0.001
Components of MetS				
EBP	1.30(1.09,1.56)	0.004	1.96(1.35,2.84)	<0.001
EGLU	1.27(1.09,1.47)	0.003	1.55(1.11,2.15)	0.009
ETG	1.27(1.10,1.47)	<0.001	1.38(1.05,1.81)	0.022
RHDL-C	1.35(1.12,1.61)	0.001	1.47(1.01,2.14)	0.043
EWC	1.35(1.10,1.67)	0.005	1.84(1.37,2.47)	<0.001
In the SP population				
Number of MetS				
< 3	1 (ref)		1 (ref)	
3	1.10(0.68,1.77)	0.706	1.22(0.47,3.16)	0.681
4	1.31(0.78,2.21)	0.311	2.38(1.15,4.92)	0.019
5	1.28(0.79,2.10)	0.318	1.03(0.42,2.53)	0.943
***P* for trend**		0.216		0.117
Components of MetS				
EBP	1.08(0.72,1.63)	0.71	1.79(0.77,4.16)	0.175
EGLU	1.09(0.74,1.59)	0.66	1.23(0.65,2.34)	0.539
ETG	1.42(1.00,2.00)	0.046	1.28(0.73,2.23)	0.388
RHDL-C	1.05(0.74,1.49)	0.798	1.23(0.64,2.37)	0.531
EWC	1.29(0.96,1.73)	0.088	1.64(0.75,3.58)	0.215

Model adjusted for age, sex, race, physical activity, alcohol consumption, smoking status, educational levels, marital status, and family poverty-to-income ratio. EBP, elevated blood pressure; EGLU, elevated fasting glucose; ETG, elevated triglycerides; RHDL-C, reduced high-density lipoprotein cholesterol; EWC, elevated waist circumference; ref, reference.

2.84-27.80, $P < 0.001$), whereas individuals aged ≥ 60 years with MetS and SP had higher hazard of all-cause mortality (HR 1.67, 95% CI: 1.32-2.10, $P < 0.001$), and cardiovascular mortality (HR 1.95, 95% CI: 1.07-3.53, $P = 0.028$).

3.4 Sensitivity analysis

Sensitivity analysis was performed by excluding the subjects with a previous myocardial infarction or angina (Supplementary Table 1). Compared to the MetS−/SP− group, the MetS+/SP+ group had an increased risk of all-cause mortality (HR 1.60, 95% CI: 1.21-2.10, $P < 0.001$) and cardiovascular mortality (HR 2.37, 95% CI: 1.17-4.80, $P = 0.016$). Subjects with SP only (MetS−/SP+ group) had only an increased risk of all-cause mortality (HR 1.57, 95% CI: 1.14-2.15, $P = 0.005$). Subjects with MetS only (MetS+/SP− group) had an increased risk of cardiovascular mortality (HR 1.72, 95% CI: 1.13-2.62, P = 0.012).

Sensitivity analysis was performed by excluding the subjects with a previous episode of stroke (Supplementary Table 2). All-cause mortality was significantly increased in the MetS−/SP+ (HR 1.55, 95% CI: 1.16-2.06, $P = 0.003$), MetS+/SP− (HR 1.31, 95% CI: 1.06-1.62, $P = 0.013$), and MetS+/SP+ (HR 1.70, 95% CI: 1.31-2.20, $P < 0.001$) groups compared with the MetS−/SP− group (P for trend < 0.001). Cardiovascular mortality was increased in the MetS+/SP− group (HR 1.79, 95% CI: 1.20-2.66, $P = 0.004$) and the MetS+/SP+ group (HR 2.38, 95% CI: 1.25-4.53, $P = 0.008$), but statistical significance was not reached in the MetS−/SP+ group.

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TABLE 4 Risks of all-cause and cardiovascular mortality according to the presence of MetS or sarcopenia status, stratified by sex and age.

	All-cause mortality			Cardiovascular mortality		
	HR (95%CI)	*P* value	*P* for interaction	HR (95%CI)	*P* value	*P* for interaction
Sex			0.001			0.806
Male[a]						
MetS-/SP-	1 (ref)			1 (ref)		
MetS-/SP+	1.72 (1.27,2.32)	<0.001		2.204 (0.91,4.95)	0.056	
MetS+/SP-	1.28 (0.97,1.68)	0.080		2.391 (1.42,4.01)	<0.001	
MetS+/SP+	2.23 (1.53,3.24)	<0.001		3.29 (1.37,7.88)	0.008	
Female[a]						
MetS-/SP-	1 (ref)			1 (ref)		
MetS-/SP+	1.31 (0.83,2.06)	0.251		0.92 (0.28,2.98)	0.882	
MetS+/SP-	1.36 (0.99,1.86)	0.053		1.28 (0.74,2.22)	0.373	
MetS+/SP+	1.26 (0.85,1.87)	0.261		1.56 (0.60,4.06)	0.367	
Age, years			<0.001			<0.001
<60 years[b]						
MetS-/SP-	1 (ref)			1 (ref)		
MetS-/SP+	2.04 (1.01,4.12)	0.047		2.97 (0.55,16.14)	0.208	
MetS+/SP-	2.00 (1.44,2.78)	<0.001		3.76 (1.85,7.69)	<0.001	
MetS+/SP+	4.48 (2.64,7.63)	<0.001		8.88 (2.84,27.80)	<0.001	
≥60 years[b]						
MetS-/SP-	1 (ref)			1 (ref)		
MetS-/SP+	1.90 (1.28,2.81)	0.001		1.85 (0.96,3.58)	0.068	
MetS+/SP-	1.33 (1.04,1.70)	0.024		1.47 (0.98,2.20)	0.064	
MetS+/SP+	1.67 (1.32,2.10)	<0.001		1.95 (1.07,3.53)	0.028	

Model[a]: adjusted for age, race, physical activity, alcohol consumption, smoking status, educational levels, marital status, and family poverty-to-income ratio.
Model[b]: adjusted for sex, race, physical activity, alcohol consumption, smoking status, educational levels, marital status, and family poverty-to-income ratio. MetS, metabolic syndrome; SP, sarcopenia; HR, hazard ratio; ref, reference.

Sensitivity analysis was performed by excluding the subjects who had died within two years of follow-up (Supplementary Table 3). Similarly, all-cause mortality was significantly increased in the MetS−/SP+ (HR 1.52, 95% CI: 1.09-2.11, P = 0.013), MetS +/SP− (HR 1.33, 95% CI: 1.07-1.67, $P = 0.011$), and MetS+/SP+ (HR 1.63, 95% CI: 1.26-2.11, $P < 0.001$) groups compared with the MetS −/SP− group (P for trend < 0.001). Cardiovascular mortality was significantly increased in the MetS+/SP− group (HR 1.87, 95% CI: 1.28-2.73, $P = 0.001$) and MetS+/SP+ group (HR 2.36, 95% CI: 1.30-4.31, $P = 0.005$).

4 Discussion

Our study retrospectively assessed the association of MetS and SP with all-cause and cardiovascular mortality mortality. In our study, the coexistence of MetS and SP was independently and positively associated with an elevated risk of all-cause and cardiovascular mortality after adjusting for potential confounders such as sociodemographic factors, lifestyle factors, and other factors. Mortality risks almost doubled in the MetS and SP coexistence group (HR 1.76 for all-cause

mortality, HR 2.39 for cardiovascular mortality), and such a trend was observed in males (HR 2.23 for all-cause mortality, HR 3.29 for cardiovascular mortality) and nonelderly individuals (HR 4.48 for all-cause mortality, HR 8.88 for cardiovascular mortality) more significantly. Our findings suggest that the coexistence of MetS and SP increases the risk of all-cause and cardiovascular mortality, especially in male and nonelderly populations.

In our study, 56.7% (637/1123) of patients with SP showed coexistence with MetS, and 19.1% (637/3330) of patients with MetS showed coexistence with SP. The reasons for this phenomenon may be related to some common pathogenesis between the two (13–17). Several features of MetS may damage muscle health, including insulin resistance and chronic systemic inflammation, which negatively affects muscle homeostasis, leading to reduced muscle mass and strength (14, 37–39), and oxidative stress leading to mitochondrial dysfunction and impaired muscle repair of damage (39, 40), which in turn leads to decreased muscle function (4). Skeletal muscle, as the largest organ in the body, plays a crucial role in maintaining glucose homeostasis and regulating carbohydrate metabolism (41). Low muscle mass may impair blood glucose uptake by altering myokine secretion, leading to a state of insulin resistance and increasing the degree of localized inflammation and metabolic disturbances, which may facilitate the development of MetS (42–44). MetS and SP may contribute to each other's development based on the mechanisms described above. As the incidence and prevalence of both MetS and SP are rapidly increasing in current society, the bidirectional relationship between these diseases may lead to amplified health risks in the population, and it is meaningful to study the mortality risk of MetS and SP comorbidity for an aging society.

Our study shows that all-cause and cardiovascular mortality was higher in the MetS and SP coexistence group than in the group with one disease alone, whereas there was no significant difference in the SP-only group compared with the standard control group, which is similar to the findings of Eyun Song et al. (4). The impact of MetS on cardiovascular mortality is higher than that of SP, which may be due to the common pathogenesis between MetS and CVD (4–6). MetS and SP may contribute to each other's disease progression through some mechanism, thus increasing the risk of death. However, the possible mechanisms leading to this situation need to be explored and verified by more basic and clinical studies.

Our study shows that the effect of the state of presence of MetS and SP on all-cause and cardiovascular mortality is not identical in different populations. In the male population, all-cause and cardiovascular mortality was significantly higher in the group in which MetS and SP coexisted and was higher than in the group in which MetS or SP alone was present. In contrast, we did not observe this trend in the female population. For the nonelderly population (< 60 years), this trend was also evident, however, in the elderly population (≥ 60 years), the group with the coexistence of MetS and SP had significantly higher cardiovascular mortality than the group with only one disease. Previous studies have shown that the adverse effects of MetS on muscle mass and strength are mainly seen in young males. However, females are mostly less susceptible to the adverse effects of MetS on muscle (42). This is similar to the results of the present study, where this trend of having a higher risk of death when MetS and SP coexisted was more pronounced in male and nonelderly populations. The mechanism responsible for this phenomenon may be related to the effects of adipokines on skeletal muscle (45), which are produced and released by adipose tissue, such as lipocalin, leptin, and proinflammatory cytokines (46). Skeletal muscle is a crucial target tissue affected by these molecules, and their circulation levels are influenced by age and sex (47). In young women, serum lipocalin and leptin do not appear to be significantly associated with skeletal muscle morphology and function (48). However, in males, skeletal muscle seems more vulnerable to the impact of adipokines. Another possible explanation could be sex hormones, with MetS being associated with reduced testosterone levels (49), and testosterone being positively correlated with muscle strength (50). Since testosterone levels decrease with age (51) and women have lower testosterone levels than men, young men with relatively high testosterone levels may be particularly vulnerable.

Our research has several advantages. First, we adopted a prospective cohort study of a large, nationally representative sample. For the study population, we had a relatively adequate follow-up period and a reliable assessment of the causes of death of the study population. Second, a nationally representative community sample, standardized data collection procedures, and complete follow-up of survival times conducted by the U.S. government more than validate our study. In addition, we performed a detailed analysis of the association of MetS and SP presence status with all-cause and cardiovascular mortality, adjusting for a large number of potential confounders. The analyses were stratified to explore the effects of sex and age on the experimental results, and three sensitivity analyses were conducted to investigate the stability of the results. However, this study has several limitations. First, the results of this study may be representative of U.S. residents only, and the definition and cutoff value of SP varied by race. Therefore, the results cannot be generalized to the general population of different races and need to be further validated in other races. Second, alcohol consumption, smoking, and ideal physical activity were self-reported, which may not be accurate. Third, residual bias could not be eliminated despite adjusting for confounding mortality-related variables.

5 Conclusions

In summary, for US adults, MetS or SP is associated with a high risk of all-cause and cardiovascular mortality, and this relationship is more pronounced in males or nonelderly adults. MetS and SP as comorbidities increased the risk of all-cause and cardiovascular death compared with the presence of each condition alone. Future research is needed to reveal the mechanisms underlying the association between MetS, SP, and mortality and finding simple and practical criteria for screening patients with MetS and SP for early intervention is important for improving the healthy life expectancy of the population, which should be of concern to health care professionals.

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 humans were approved by National Center for Health Statistics Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WH: Writing – review & editing, Writing – original draft, Software, Methodology, Data curation, Conceptualization. SD: Writing – review & editing, Writing – original draft, Software, Data curation. SL: Writing – review & editing, Methodology. QM: Writing – review & editing, Data curation. LC: Writing – review & editing, Data curation. LL: Writing – review & editing, Methodology. HW: Writing – review & editing, Supervision, Methodology. JS: Writing – review & editing, Supervision, Methodology.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1346669/full#supplementary-material

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Five percent weight loss is a significant 1-year predictor and an optimal 5-year cut-off for reducing the number of obesity-related cardiovascular disease risk components: the Japan Obesity and Metabolic Syndrome Study

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Objective: This study aimed to identify the amount of weight loss needed in patients with obesity to improve metabolic syndrome (MetS), a risk factor for cardiovascular disease (CVD), over a long period of time.

Methods: A total of 576 patients with obesity were enrolled in this study. Effects of continuous physician-supervised weight loss on the cumulative MetS components excluding abdominal circumference (defined as obesity-related CVD risk score) were investigated during a 5-year follow-up period. The extent of weight loss required to reduce the obesity-related CVD risk components was assessed using receiver operating characteristic (ROC) curve analyses.

Results: Of the 576 participants, 266 completed 5-year follow-up, with 39.1% and 24.1% of them achieving ≥5.0% and ≥7.5% weight loss at the 5-year follow-up, respectively. The area under the ROC curve for reducing the obesity-related CVD risk components was 0.719 [0.662–0.777] at 1 year and 0.694 [0.613–0.775] at 5 years. The optimal cut-off value for weight loss was 5.0% (0.66 sensitivity and

0.69 specificity) and the value with 0.80 specificity was 7.5% (0.45 sensitivity) at 5 years. Greater reductions in weight were associated with greater improvements in the obesity-related CVD risk score at all follow-up periods (*P*-trend <0.001). Obesity-related CVD risk score was significantly improved by 5.0–7.5% and ≥7.5% weight loss at 1 year ($P = 0.029$ and $P < 0.001$, respectively) and ≥7.5% weight loss at 5 years ($P = 0.034$).

Conclusions: A weight loss of ≥5.0% at 1 year and ≥7.5% at 5 years could reduce the number of obesity-related CVD risk components in patients with obesity.

KEYWORDS

obesity, weight loss, metabolic syndrome, cohort study, 5-year follow-up

1 Introduction

Obesity rates are rising globally (1), posing adverse health outcomes and contributing to developing metabolic syndrome (MetS) (2). It increases the risk of cardiovascular disease (CVD) (3). Therefore, there is a need to develop a weight management program that is effective for improving MetS and reducing the risk of CVD.

Contemporary guidelines state that a 5.0% or greater weight loss by dietary and exercise intervention is clinically important for individuals with overweight or obesity, based on epidemiological and interventional evidence (4–6). Additionally, it is also advised that individuals who are overweight or obese with MetS lose 5.0% of their body weight in order to manage this condition (7). Furthermore, a previous study reported that a 6-month lifestyle-induced weight loss program resulting in a >16% weight loss from baseline had a positive impact on MetS prevalence in Caucasian participants. This effect was observed over a 5-year follow-up period after the end of the program (8). In Japanese patients with obesity or MetS, a loss of ≥3.0% of baseline weight by a 6-month lifestyle modification program also improved obesity-related metabolic derangements at 6 months of follow-up after the end of the intervention (9). Moreover, our research group revealed that >5.0% weight loss from the baseline after 3 months of intervention beneficially influenced parameters of glycemic control, renal function, and arterial stiffness in patients with obesity in a National Hospital Organization cohort (10). These findings highlight the beneficial effects of weight loss on the management of MetS; however, the extent of weight loss from baseline to improve MetS over long periods has not been established in patients with obesity.

Because an increase in the number of MetS components elevates the risk of CVD incident (11), it is necessary to identify how much weight loss from baseline could reduce one or more MetS components in patients with obesity. Moreover, the extent of weight loss that exhibits long-term beneficial effects on the cumulative MetS components needs to be clarified, although the relationship between long-term weight loss and the cumulative number of MetS components has not been fully elucidated due to the challenging characteristics of maintaining weight loss (8, 12). To date, no prospective studies have addressed these issues in patients with obesity.

In the present study, to identify the extent of weight loss that beneficially impacts MetS in patients with obesity over long periods, we investigated the effects of a 5-year continuous physician-supervised intervention on the components of MetS excluding abdominal circumference (as obesity-related CVD risk) in outpatients with obesity in a multicenter cohort of the National Hospital Organization.

2 Materials and methods

2.1 Study design

A retrospective cohort study based on a prospective cohort study (Japan Obesity and Metabolic Syndrome Study [JOMS]) evaluated the effects of weight loss on the risk of CVD in patients with obesity in Japan.

2.2 Patients

The study population included patients with obesity aged between 20 and 79 years with a body mass index (BMI) of 25 or higher who visited the participating centers for their first or second visit between April 2005 and March 2007. The Japan Society for the Study of Obesity uses a BMI ≥25 for patients with obesity since this level is standardized to correspond to the international coordination of the World Health Organization (WHO) criteria for obesity, and evidence shows that obesity-related complications increase for a BMI ≥25 among the Japanese population (13, 14). In the present study, patients with obesity with BMI ≥25 with or without obesity-related health issues were included. The exclusion

criteria were those with severe hepatic dysfunction and severe renal dysfunction.

A total of 576 Japanese outpatients with obesity (250 men and 326 women, mean age: 51.6 years) were consecutively enrolled in a multi-center study (JOMS), which involved five National Hospital Organization hospitals (Kyoto, Tokyo, Nagoya and Kokura Medical Centers, and Mie Hospitals) and Oishi Clinic in Japan as part of a study conducted by the Policy Based Medical Service Network for Endocrine and Metabolic Diseases during the period from October 2005 to March 2007 (15, 16).

The patients received lifestyle guidance, mainly diet and exercise therapy, for weight loss, as recommended by the Japan Atherosclerosis Society's "Guidelines for the diagnosis and treatment of atherosclerotic cardiovascular disease" (17). The patients were instructed to consume dietary therapy consisting of 25 kcal/kg of ideal BW per day and walk at least 8000 steps per day. Since the ideal BMI for the Japanese population is considered to be 22 kg/m^2 (17), the ideal BW was defined as 22 × the square of the subject's height (ideal BMI [22 kg/m^2] × height [m]^2) in the present study. In addition, dietary and exercise guidance from a physician or nutritionist was provided at least once every three months. They are recommended to consume 60% of their total energy as carbohydrates, 20–25% as fat, and 15–20% as protein. When the patients with obesity had complications, such as type 2 diabetes, dyslipidemia, and/or hypertension, they received medications for each disease. However, they did not receive any medications for weight loss, including probiotics (18).

This study was approved by each institution's ethical committee, and written informed consent was obtained from all patients. This study was conducted following the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. The JOMS has been registered in the University Hospital Medical Information Network (UMIN) system (UMIN Study ID: 000000559), which is publicly available.

2.3 End-point definition: change in obesity-related CVD risk score

The primary endpoint was the change in obesity-related CVD risk scores between the baseline and follow-up periods. Obesity-related CVD risk score used as an endpoint in this study was the number of matches of four criteria: triglyceride (TG) level, high-density lipoprotein cholesterol (HDL-C) level, blood pressure, and fasting blood glucose level, to the exclusion of abdominal circumference from the NCEP-ATP III MetS risk score corresponding to Japanese standard cut-off values, referring to previous reports (19, 20). Cut-off values of these parameters for MetS were selected according to the guidelines of the Japan Society for the Study of Obesity (21): waist circumference ≥ 85 (men) and 90 (women) cm; fasting plasma glucose (FPG) ≥ 6.1 mmol/L; systolic blood pressure (SBP) ≥ 130 and/or diastolic blood pressure (DBP) ≥ 85 mmHg; TG ≥ 1.7 mmol/L; HDL-C < 1.0 mmol/L.

It has been reported that higher MetS risk scores, as defined by NCEP-ATP III, are associated with cumulative cardiovascular events (13, 22). However, since weight loss would reduce abdominal circumference evidently, the effects of weight loss on improving obesity-related CVD risk would be overestimated, if abdominal circumference were included in the risk score of the endpoint. Therefore, in this study, the obesity-related CVD risk score that excluded abdominal circumference from the MetS risk score was used as the endpoint.

At each follow-up period, the obesity-related CVD risk score increased by one when the patient's value exceeded the respective standard value or when a new drug treatment was initiated. In addition, the score decreases by one when a patient who was above the criteria or on medication for each disease was below the standard value, and the medication was terminated. The obesity-related CVD risk score is expressed as a score between 0 and 4, which is the number of matches of four criteria (TG level, HDL-C level, blood pressure, and FPG level), as described above. The endpoint, the amount of change, is expressed as a value between +4 and −4. The highest improvement is −4.

2.4 Data collection and laboratory assay methods

At 3, 12, and 60 months after weight reduction therapy, we measured MetS-related parameters (BMI, waist circumference, SBP, and DBP) and blood parameters (FPG, hemoglobin A1c [HbA1c], TG, total cholesterol, HDL-C, and low-density lipoprotein cholesterol [LDL-C]).

BMI was calculated as weight in kilograms divided by the square of height in meters as an index of obesity. SBP and DBP were measured twice by using an automatic electronic sphygmomanometer (BP-103iII; Nippon Colin, Komaki, Japan). Blood was collected from the antecubital vein in the morning after a 12-hour fasting period without taking medication to determine FPG, HbA1c, TG, total cholesterol, HDL-C, and LDL-C, according to standard procedures (15).

2.5 Statistical analysis

To detect a one-point obesity-related CVD risk score difference (SD = 2 points) between the weight loss and non-loss groups, 64 cases per group were needed at a 5.0% significance level and 80% power. To obtain 64 patients from each weight loss group, a total of 384 patients were required. Considering the variability in the number of participants and the occurrence of dropouts, a sample size of 580 cases was used.

The clinical characteristics of the patients at baseline were expressed as mean and standard deviation (SD), standard error (SE), or median and interquartile range. Categorical variables were expressed as headcounts and percentages.

For the time-series trend of weight loss, the weight change rate was divided into six groups, and the percentages were expressed as bar graphs for each follow-up period.

Receiver operating characteristic (ROC) analysis was used to determine the discriminative ability of the weight reduction rate to

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reduce at least one obesity-related CVD risk score and the cut-off value for the weight reduction rate. Discriminatory ability was evaluated by calculating the area under the curve (AUC). For each follow-up period, the optimal cut-off value was calculated using the Youden index method and a cut-off value that would ensure a specificity of 80% to more reliably reduce the obesity-related CVD risk score.

The association between the rate of weight change and the amount of change in the obesity-related CVD risk score and the mean difference in the obesity-related CVD risk score between the baseline and follow-up periods were shown in the six groups according to the rate of weight loss. One-way Analysis of Covariance (ANCOVA)-based trend tests and paired comparisons (within ±1% pairwise weight loss) with age and sex as covariates were performed.

In the sensitivity analysis, only 547 metabolically unhealthy patients with obesity, excluding 29 metabolically healthy individuals with obesity without diabetes, dyslipidemia, or hypertension, were analyzed in the same manner as the primary endpoint. The changes in MetS risk score (which had abdominal circumference in addition to four obesity-related CVD risk score components described above) were also analyzed in the total population (n = 576).

All statistical analyses were performed using SPSS Statistics ver. 24.0 (IBM Japan, Ltd., Tokyo, Japan) and $P < 0.05$ was defined as statistically significant.

3 Results

3.1 Baseline clinical characteristics

The baseline patient characteristics are summarized in Table 1. The mean age was 51.6 ± 14.0 years, and 326 (56.6%) patients were women. The mean BMI was 31.4 ± 5.9 kg/m^2 and 116 (20.1%) patients had a BMI ≥35. A total of 570 (99.0%) patients had at least one MetS component, and 441 (76.6%) had MetS. Approximately 40% of the participants were receiving medications for each MetS component (diabetes, 36.6%; dyslipidemia, 44.1%; hypertension, 45.3%). A total of 547 (95.0%) patients had at least one obesity-related CVD risk component.

Supplementary Figure 1 presents a flowchart of the study. Of the 576 participants, 168 dropped out at 12 months, and 142 dropped out at 60 months. A total of 266 (47.9%) patients were followed up until the end of the study. The reasons for patients' dropout included changes in the living environment (91 cases), transfer to other clinics due to successful weight loss (89 cases), retirement of the attending physician (65 cases), self-interruption for unknown reasons (33 cases), and the occurrence of death or cardiovascular events (31 cases).

3.2 Time series of weight loss

The time series of weight loss from the baseline are shown in Figure 1. In the 3rd month of the study, 43.1% of the patients achieved a weight loss of ≥3.0%, 28.6% achieved ≥5.0%, and 17.5%

TABLE 1 Baseline characteristics of patients with obesity.

	Total		
Sex (male/female) [n]	250	/	326
Age (years) [mean ± SD]	51.6	±	14.0
Body weight (kg)	82.3	±	19.6
BMI (kg/m^2)	31.4	±	5.9
≥ 35kg/m^2 (n, %)	119	,	20.7
Waist circumference (cm)	101.5	±	13.4
SBP (mmHg)	140.5	±	18.7
DBP (mmHg)	83.9	±	12.0
FPG (mmol/L)	7.0	±	2.8
HbA1c (%)	6.4	±	1.4
HbA1c (mmol/mol)	46.4	±	15.3
Total cholesterol (mmol/L)	5.4	±	1.4
TG (mmol/L)	1.6	[1.2, 2.4]	
HDL-C (mmol/L)	1.4	±	0.4
LDL-C (mmol/L)	3.3	±	0.8
Complications (n, %)			
Diabetes	256	,	44.4
Dyslipidemia	441	,	76.6
Hypertension	380	,	66.0
Medication (n, %)			
for diabetes	211	,	36.6
for dyslipidemia	254	,	44.1
for hypertension	261	,	45.3
MetS components (n, %)			
Waist circumference ≥ 85/90 cm	516	,	89.6
FPG ≥ 6.1 mmol/L	329	,	57.1
SBP ≥ 130 and/or DBP ≥ 85 mmHg	477	,	82.8
TG ≥ 1.7 mmol/L	376	,	65.3
HDL-C < 1.0 mmol/L	287	,	49.8
MetS risk score (n, %)			
0	6	,	1.0
1	38	,	6.6
2	91	,	15.8
3	144	,	25.0
4	145	,	25.2
5	152	,	26.4
Obesity-related CVD risk score (n, %)			
0	29	,	5.0
1	91	,	15.8

(Continued)

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TABLE 1 Continued

	Total		
2	145	,	25.2
3	152	,	26.4
4	159	,	27.6

Data are expressed as mean ± standard deviation (SD), median [interquartile range], or the number and percentage of patients. BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, Metabolic syndrome.

achieved ≥7.5%. The average weight loss was −3.3 ± 5.2%. At the 1-year follow-up, 48.0% of the patients had achieved a weight loss of ≥3.0%, 36.3% had achieved ≥5.0%, and 25.0% had achieved ≥7.5%. The average weight loss was −4.3 ± 7.4%. At 5 years of follow-up, 47.7% of the patients achieved a weight loss of ≥3.0%, 39.1% achieved ≥5.0%, and 24.1% achieved ≥7.5%. The average weight loss was −3.0 ± 8.8%.

3.3 Weight loss that is expected to reduce obesity-related CVD risk score by one or more

At 3 months, 1 year, and 5 years, 118 (20.5% [118/576]), 90 (22.1% [90/408]), and 47 (17.7% [47/266]) cases had reduced at least one obesity-related CVD risk component, respectively. Figure 2 shows the ROC curves for the percentage weight loss from baseline for the reduction of one or more obesity-related CVD risk components. The ROC–AUC of weight loss for a reduction in one or more obesity-related CVD risk components at 3 months was 0.620 [95% confidence interval: 0.564–0.677] (Figure 2). The ROC–AUC at 1 year was 0.719 [0.662, 0.777], and that at 5 years was 0.694 [0.613, 0.775] (Figures 2B, C). The optimal cut-off values for weight loss using the Youden Index were 2.7% at 3 months (sensitivity 0.60, specificity 0.59), 5.0% at 1 year (sensitivity 0.63, specificity 0.71), and 5.0% at 5 years (sensitivity 0.66, specificity 0.69). Furthermore, the weight loss cut-off values that could ensure a specificity of 0.80 or higher for a more reliable weight loss effect were 5.8% at 3 months (sensitivity 0.35, specificity 0.80), 7.5% at 1 year (sensitivity 0.43, specificity 0.80), and 7.5% at 5 years (sensitivity 0.45, specificity 0.80).

3.4 Change in obesity-related CVD risk score by weight loss

The relationship between weight loss and the change in the obesity-related CVD risk score is shown in Figure 3, which was the primary endpoint. During each follow-up period, the obesity-related CVD risk score decreased significantly in the higher weight loss group (linear trend test, $P < 0.001$). Compared to the group with a weight change of ±1% (reference group), significant improvement was observed in the group that achieved a weight loss of ≥7.5% at 3 months (mean difference of obesity-related CVD risk score: 0.03 [SE = 0.13] vs. −0.26 [0.16]; $P = 0.009$), 5.0–7.5% and ≥7.5% at 1 year (0.22 [0.18] vs. −0.22 [0.37], $P = 0.029$ in 5.0–7.5%; −0.49 [0.18], $P < 0.001$ in ≥7.5%), and ≥7.5% at 5 years (0.35 [0.47] vs. −0.46 [0.29]; $P = 0.034$).

The same sensitivity analysis was performed only for metabolically unhealthy patients with obesity at baseline (n = 519) (Supplementary Figure 2). At each follow-up period, the higher the weight loss, the more significantly the obesity-related CVD risk score was reduced (linear trend test, $P < 0.001$). Compared to the group with a weight change of ±1% (reference group), significant improvement was observed in the group that

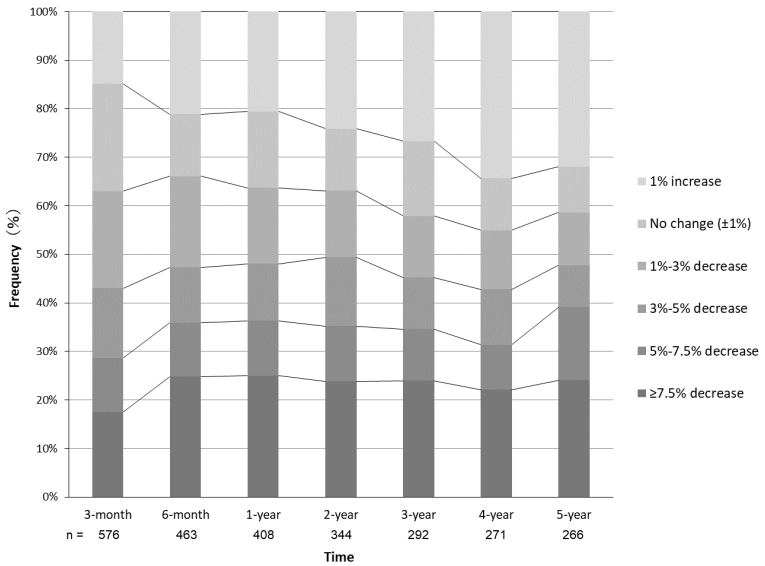

FIGURE 1
Time series of physician-supervised weight loss in patients with obesity. Frequencies of patients with the respective changes of weight from baseline are shown at each follow-up period.

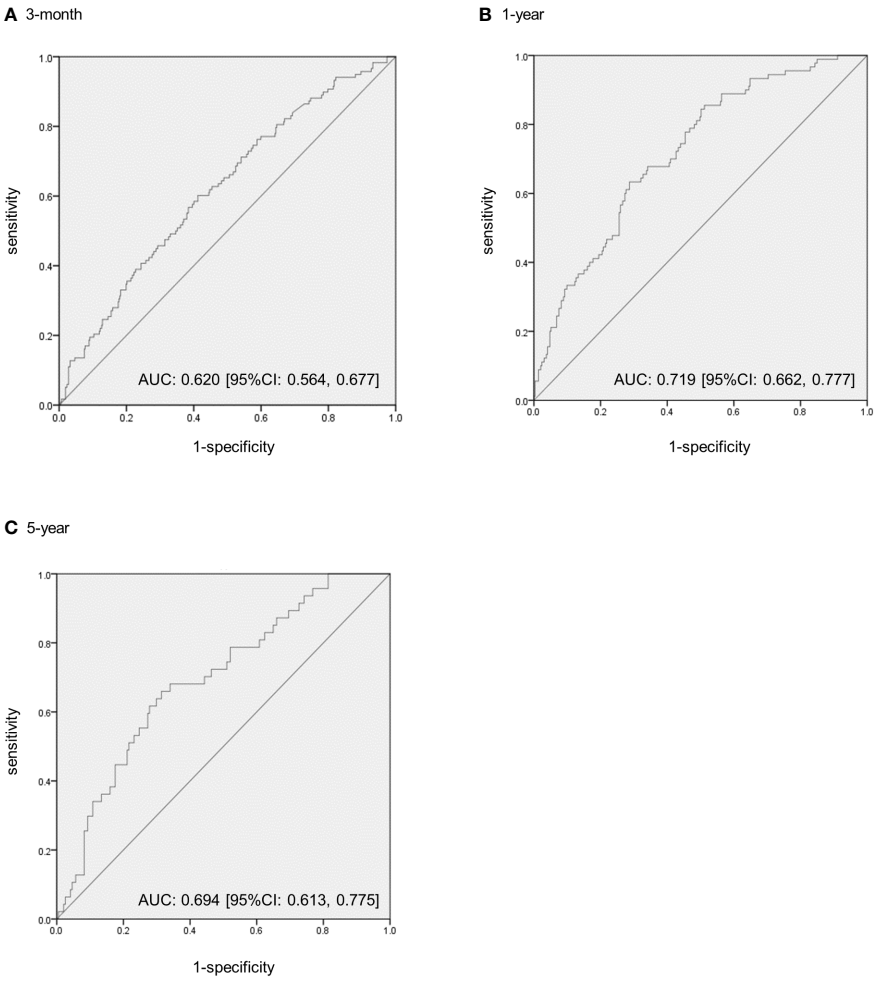

FIGURE 2
The receiver operating characteristic (ROC) curves to predict the extent of weight loss from baseline to reduce one or more obesity-related cardiovascular disease risk components in patients with obesity. **(A)** The ROC–area under the curve (AUC) at 3 months. **(B)** The ROC–AUC at 1 year. **(C)** The ROC–AUC at 5 years. CI, confidence intervals.

achieved a weight loss of ≥7.5% at 3 months (mean difference of obesity-related CVD risk score: 0.01 [0.13] vs. −0.27 [0.17]; P = 0.017), 5.0–7.5% and ≥7.5% at 1 year (0.20 [0.18] vs. −0.22 [0.37], P =0.039 in 5.0–7.5%; −0.51 [0.18], P < 0.001 in ≥7.5%), and ≥7.5% at 5 years (0.22 [0.47] vs. −0.41 [0.30]; P = 0.046). Similar results were obtained for the sensitivity analysis.

A further sensitivity analysis was performed using the MetS risk score, which included abdominal circumference as a component, as the endpoint (n = 576) (Supplementary Figure 3). At each follow-up period, the higher the weight loss, the more significantly the MetS risk score was reduced (linear trend test, P < 0.001). Compared to the group with a weight change of ±1% (reference group), significant improvement was observed in the group that achieved a weight loss of ≥7.5% at 3 months (mean difference of MetS risk score: 0.05 [0.14] vs. −0.53 [0.21]; P = 0.002), 5.0–7.5% and ≥7.5% at 1 year (0.29 [0.21] vs. −0.49 [0.37], P = 0.019 in 5.0–7.5%; −0.76 [0.20], P < 0.001 in ≥7.5%), and ≥7.5% at 5 years (0.35 [0.51] vs. −0.75 [0.34]; P = 0.022). Because of the inclusion of abdominal circumference as an endpoint, the score improvement due to weight loss was more pronounced than that of the obesity-related CVD risk score.

3.5 Obesity-related CVD risk components that improve with weight loss treatment

Of the 408 patients who completed the 1-year follow-up, 92 (22.5%) increased and 88 (21.6%) reduced one or more components of obesity-related CVD risk, respectively, and 228 (55.9%) had no change in the obesity-related CVD risk components.

Of the 141 patients who achieved at least 5.0% weight loss in 1 year, 57 (40.4%) had a reduction in one or more components of obesity-related CVD risk. According to the obesity-related CVD risk components, there were 24 (17.0%) patients with blood pressure improvement, 22 (15.6%) FPG improvement, 17 (12.1%) TG improvement, and 16 (11.0%) HDL-C improvement. Of the 96 patients who achieved at least 7.5% weight loss in 1 year, 41 (42.7%) showed a reduction in one or more components of obesity-related CVD risk. There were 17 (17.7%) cases of blood pressure improvement, 17 (17.7%) FPG improvement, 12 (12.5%) TG improvement, and 11 (11.5%) HDL-C improvement.

Of the 266 patients who completed the 5-year follow-up, 80 (30.1%) increased and 47 (17.7%) reduced at least one obesity-

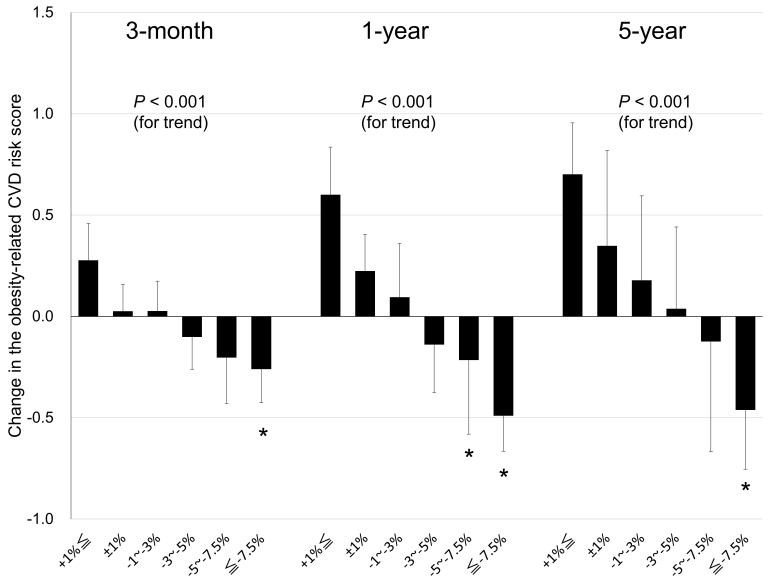

FIGURE 3
Relationship between weight loss and changes in obesity-related cardiovascular disease (CVD) risk score in patients with obesity at the 3-month, 1-year, and 5-year follow-up. Data are expressed as mean ± standard error. *$P < 0.05$ for the reference group (a weight change of ±1%) vs. the other group.

related CVD risk component, respectively, and 139 (52.3%) had no change in the obesity-related CVD risk components.

At 5 years of follow-up, of the 92 patients who achieved at least 5.0% weight loss, 31 (33.7%) had a reduction in one or more components of obesity-related CVD risk. There were 10 (10.9%) patients with blood pressure improvement, 11 (12.0%) FPG improvement, 14 (15.2%) TG improvement, and 13 (14.1%) HDL-C improvement. Of the 59 patients who achieved at least 7.5% weight loss in 5 years, 22 (37.3%) showed a reduction in one or more obesity-related CVD risk components. There were 6 (10.2%) patients with blood pressure improvement, 8 (13.6%) FPG improvement, 10 (16.9%) TG improvement, and 9 (15.3%) HDL-C improvement.

4 Discussion

The present study showed that the optimal cut-off value for weight loss was 5.0% to reduce one or more components of obesity-related CVD risk in patients with obesity for up to 5 years. Moreover, there was a need to achieve a weight loss of 7.5% from the baseline for these patients to reduce the number of obesity-related CVD risk components at 1 and 5 years, considering a cut-off value with a specificity of 0.80. These findings provide novel insights into the extent of weight loss in weight management programs aimed at improving the MetS components, particularly those excluding abdominal circumference, in patients with obesity.

We found the cut-off value for weight loss to be 5.0% with optimal sensitivity and specificity, and 7.5% with a specificity of 0.80, which is needed in patients with obesity to reduce the number of obesity-related CVD risk components for up to 5 years. Moreover, greater decreases in weight were significantly associated with greater improvements in the obesity-related CVD risk score in patients with obesity, irrespective of the concurrent presence or absence of MetS, at the 3-month, 1-year, and 5-year follow-ups. Conversely, only a loss of ≥7.5% weight from baseline among all the weight loss-stratified groups significantly reduced the obesity-related CVD risk score when compared with the reference group at all the follow-up periods in both patient groups. Accordingly, these findings highlight the possibility that weight loss of ≥7.5%, at least ≥5.0%, would be desirable for patients with obesity to improve obesity-related CVD risk components in the first 3 months to 5 years. In this context, a previous study reported that weight loss within the first two months predicted long-term weight loss for up to 8 years (23), further suggesting the significance of optimizing the outcome during early intervention periods to exhibit long-term beneficial effects (8). Moreover, obesity exacerbates MetS (24), thereby highlighting the need to achieve weight loss to counterbalance the detrimental effects of obesity. Thus, the effective extent of weight loss would be 7.5% or more to improve the obesity-related CVD risk components in patients with obesity based on the early improvement of the obesity-related CVD risk score, the cut-off value for weight loss, and the long-term beneficial effects on the obesity-related CVD risk score that were elucidated in this study.

Long-term maintenance of weight loss has been challenging because weight is typically lost rapidly by intervention but followed by progressive regain (8, 12); it is reported that ≥90% of individuals regained some of the weight after weight loss (25, 26). In the present study, outpatients with obesity continuously underwent physician-supervised intervention for up to 5 years, and 47.7%, 39.1%, and 24.1% of these patients achieved ≥3.0%, ≥5.0%, and ≥7.5% weight loss from baseline at the 5-year follow-up, respectively. Therefore, the results of this study revealed the effects of weight loss on the components of MetS in patients with obesity more appropriately than those of annual health checkups. In this context, the extent of weight loss for beneficial effects on MetS in patients with obesity

differs between the present study and previous studies (9). Reportedly, a loss of ≥3.0% of baseline weight by 6-month lifestyle modification program after health checkups improved obesity-related metabolic parameters and MetS components in Japanese patients with obesity or MetS at six months after the end of the intervention (9), thereby suggesting that weight loss of ≥3.0% would beneficially affect obesity-related metabolic derangements in these patients for up to 6 months (9). Conversely, in this study, a loss of 3.0–5.0% weight did not significantly improve MetS at all the follow-up periods; this might be due to the fact that the mean BMI differed between the present study (31.4 ± 5.9 kg/m^2) and the previous study (27.7 ± 2.5 kg/m^2). Another possibility is that outpatients with obesity had more serious psychological and social issues than individuals who attended health checkups, since obesity is related to these comorbidities (27). Nevertheless, based on the findings of this study that investigated the effects of 5-year continuous physician-supervised intervention, ≥7.5% would be the preferable extent of weight loss in light of long-term beneficial effects on components of MetS in Japanese patients with obesity.

Our findings further suggest the clinical significance of ≥5.0% weight loss to reduce the obesity-related CVD risk score in patients with obesity. Although a loss of ≥7.5% weight exhibited beneficial effects on obesity-related CVD risk score over a 5-year follow-up period, ≥7.5% weight loss might be a high-hurdle setting as realistic weight goals due to challenging characteristics of maintaining long-term weight loss (8, 28). Conversely, the optimal cut-off value for weight loss to reduce obesity-related CVD risk score components was 5.0% at 1 and 5 years, and a loss of ≥5.0% weight was a significant predictor of improving obesity-related CVD risk components at 1 year. Therefore, ≥5.0% weight loss might be effective as an initial goal in terms of patient adherence to weight loss; this could further help achieve early improvement of obesity-related CVD risk components.

Treatment responses are heterogeneous and can affect weight loss outcomes (8). However, this study shows that ≥5.0% and ≥7.5% weight loss reduced all types of MetS components, including blood pressure, FPG, TG, and HDL-C, in patients with obesity at the 1- and 5-year follow-up. MetS components were uniformly affected by weight loss, further suggesting the pleiotropic beneficial effects of weight loss on MetS components in patients with obesity. Although the detailed mechanisms remain unclear, a decrease in adipose tissue may be implicated in the weight loss-induced reduction of MetS components in these patients. The adipose tissue produces various adipokines that modulate metabolism, and the function and state of this tissue have been implicated in the pathogenesis of MetS (7, 8, 29). Therefore, the reduction in body fat mass by weight loss would result in an orchestrated improvement of MetS in patients with obesity, although the priority of the improvement may depend on the individual. Supporting these possibilities, our previous studies showed that weight loss improved adipokines such as adiponectin and leptin in patients with obesity (10, 15).

The present study used (i) MetS criteria defined by NCEP-ATPIII in 2001 (22) and (ii) cut-off values for MetS described in the guidelines of the Japan Society for the Study of Obesity in 2005 (21). However, a recent study reported that NCEP-ATPIII (waist circumference is not essential in this criteria) was better than the International Diabetes Federation criteria (waist circumference is essential in this criteria) at predicting the incidence of atherosclerotic cardiovascular diseases (30). Moreover, the cut-off values for MetS have not been changed in Japan since they were developed. Accordingly, the definition of and cut-off values for MetS in this study still remain useful as surrogate indexes of the risk of CVD, further suggesting that the findings of this study can be applied to individuals with MetS in recent years.

To prevent potential overestimation of the effects of weight loss on the improvement of obesity-related CVD risk components, abdominal circumference was excluded from the obesity-related CVD risk score in this study, because a decrease in abdominal circumference would be closely related to weight loss. Our results demonstrated the beneficial effects of weight loss on obesity-related CVD risk score, and those effects were more evident when the risk score included waist circumference. These findings corroborate the significance of weight loss in reducing the risk of obesity-related CVD in patients with obesity.

This study had some limitations. We investigated the effects of weight loss on MetS in patients with obesity without sex stratification. Sex differences may exist in the susceptibility to weight loss and subsequent effects on MetS status. The effects of potential confounding factors (e.g., smoking habits) were also not examined due to the limited sample size. Further interventional studies with larger sample sizes are required to address these issues. Another limitation is that our study included only Japanese patients; therefore, the results may not be generalizable to different races and/or ethnicities. Nevertheless, our findings will be helpful for extrapolating the target value of weight loss to improve MetS in other populations.

5 Conclusions

In conclusion, this study provides evidence of a novel target extent of weight loss for patients with obesity to improve the components of obesity-related CVD risk; a loss of ≥5.0% weight is a 1-year predictor of reducing the obesity-related CVD risk score and ≥7.5% weight loss would be effective for up to 5 years to improve obesity-related CVD risk components. These findings will help develop novel strategies for obesity management, focusing on the improvement of MetS, thereby contributing to reducing the risk of CVD in patients with 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 authors.

Ethics statement

The studies involving humans were approved by the Central Ethics Committee for Clinical Research at the National Hospital Organization headquarters. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HY: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. TJ: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. MT: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. SK: Writing – original draft, Writing – review & editing. KH: Writing – original draft, Writing – review & editing. IM: Writing – original draft, Writing – review & editing. MM: Writing – original draft, Writing – review & editing. KK: Writing – original draft, Writing – review & editing. MN: Writing – original draft, Writing – review & editing. NS-A: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision

MT is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1343153/full#supplementary-material

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The association between lymphocyte-to-monocyte ratio and all-cause mortality in obese hypertensive patients with diabetes and without diabetes: results from the cohort study of NHANES 2001–2018

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Objective: Obesity, hypertension and diabetes are high prevalent that are often associated with poor outcomes. They have become major global health concern. Little research has been done on the impact of lymphocyte-to-monocyte ratio (LMR) on outcomes in these patients. Thus, we aimed to explore the association between LMR and all-cause mortality in obese hypertensive patients with diabetes and without diabetes.

Methods: The researchers analyzed data from the National Health and Nutrition Examination Survey (2001-2018), which included 4,706 participants. Kaplan-Meier analysis was employed to compare survival rate between different groups. Multivariate Cox proportional hazards regression models with trend tests and restricted cubic splines (RCS) analysis and were used to investigate the relationship between the LMR and all-cause mortality. Subgroup analysis was performed to assess whether there was an interaction between the variables.

Results: The study included a total of 4706 participants with obese hypertension (48.78% male), of whom 960 cases (20.40%) died during follow-up (median follow-up of 90 months). Kaplan–Meier curves suggested a remarkable decrease in all-cause mortality with increasing LMR value in patients with diabetes and non-diabetes (P for log-rank test < 0.001). Moreover, multivariable Cox models demonstrated that the risk of mortality was considerably higher in the lowest quartile of the LMR and no linear trend was observed (P > 0.05). Furthermore, the RCS analysis indicated a non-linear decline in the risk of death as LMR values increased (P for nonlinearity < 0.001).

Conclusions: Increased LMR is independently related with reduced all-cause mortality in patients with obese hypertension, regardless of whether they have combined diabetes.

KEYWORDS

lymphocyte-to-monocyte ratio (LMR), all-cause mortality, obesity, hypertension, diabetes

Introduction

Metabolic syndrome is an increasingly common condition that includes obesity, dyslipidemia, insulin resistance and hypertension (1). The prevalence and incidence of obesity is on the rise and poses a significant population health burden worldwide (2). More than two thirds of deaths were linked to obesity (3).

Hypertension and diabetes mellitus (DM) are considered to be serious public health problems that have a significant negative impact on human life and increase health expenditure (4–6). Obesity, hypertension, and DM are major risk factors for cardiovascular disease and all-cause mortality (7–9). Therefore, it is important to identify relevant risk factor to avoid, delay or reduce deaths related to these diseases.

The ideal predictor should not only have good predictive value, be easy to identify during the diagnostic process, but also be low cost in clinical practice. The lymphocyte/monocyte ratio (LMR) is an easily measured parameter of systemic inflammatory burden and cellular immune response that has been studied as a factor associated with disease severity and prognosis in several clinical conditions (10, 11). Metabolic syndrome is a chronic, low-grade inflammatory condition (12). In patients with diabetes, intermediate products such as advanced glycosylation end products and immune complexes stimulate monocyte infiltration and aggravate cell damage, thus accelerating disease deterioration (13, 14). Monocytes are an important part of the innate immune system and play an active role in endogenous inflammation. It is able to migrate from the bloodstream to different tissues and differentiate into various types, including inflammatory dendritic cells, macrophages, and foam cells. This process triggers the secretion of pro-inflammatory cytokines, the production of matrix metalloproteinases and the formation of reactive oxidizing substances. Therefore, the accumulation of a large number of inflammatory cells with infiltrating ability promotes chronic inflammatory response in the body, leading to endothelial cell dysfunction, degradation and destruction of fibrin cytoskeleton, insulin resistance and so on. This eventually leads to metabolic disorders such as high blood pressure, diabetes and obesity. It had been found that the lymphocyte count was relatively low and the monocyte count was high in patients with cardiovascular disease, which had predictive and prognostic value in myocardial infarction (15, 16). Moreover, there are published studies that have found that reduced LMR is a risk factor for cardiovascular disease (17). In addition, the LMR was an independent predictor of re-hospitalization and long-term major cardiovascular and cerebrovascular adverse events in patients with myocardial infarction with elevated ST-segment after primary percutaneous coronary intervention (18). However, the association between LMR and the risk of all-cause death is unclear in patients of obese hypertension with diabetes or non-diabetes.

Therefore, we conducted this study to try to investigate the association between LMR and all-cause mortality in obese hypertensive patients.

Abbreviations: LMR, lymphocyte to monocyte ratio; WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SUA, serum uric acid; DM, diabetes mellitus; HF, heart failure; CAD, coronary artery disease; HTN, hypertension; hs-CRP, high-sensitivity C-reactive protein.

Methods

Study population

The National Health and Nutrition Examination Survey (NHANES) is a large cross-sectional research program that aims to assess the health and nutritional status of residents in the United States (USA). The program is performed by the Centers for Disease Control (CDC) and Prevention of the USA. The data of our study was obtained from the NHANES official website. We downloaded data from nine cycles of NHANES (2001-2018). In order to protect the rights of participants, NHANES has obtained the informed written consent of all participants. The exclusion criteria were as follows: (1) Patients without lymphocyte and monocyte data. (2) Incomplete information on waist circumference (WC), height, or weight. (3) Lacking of diabetes, fasting plasma glucose (FPG) or glycated hemoglobin (HbA1c) data. (4) Patients aged < 18. (5) Patients without follow-up data. The flowchart for patients screening was presented in Figure 1.

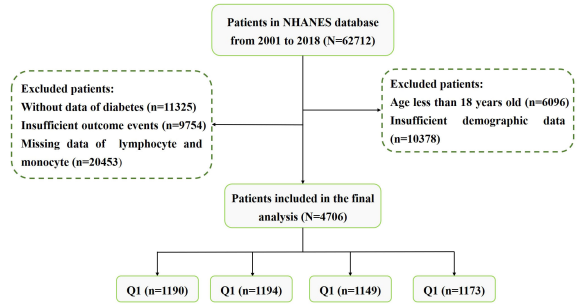

FIGURE 1
The screening flowchart of participants in our study.

Data collection and definitions

The following covariates are collected: (1) Demographics, including age, gender, race, smoking status (Current smokers: current smokers and have smoked at least 100 cigarettes; Former smoker: has smoked at least 100 cigarettes but does not currently smoke; Never smoked: less than 100 cigarettes), drinking, and education; (2) Laboratory indicators, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, estimated glomerular filtration rate (eGFR), total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), serum uric acid (SUA), FPG, HbA1c, platelet count, neutrophil count, lymphocyte count, monocyte count, and high-sensitivity C-reactive protein (hs-CRP); (3) Measurement indexes, including WC, height, weight, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP); (4) comorbidities, including heart failure, DM, stroke, coronary artery disease, and hypertension; (5) Endpoint, including follow-up survival status and duration.

Hypertension can be diagnosed if one of the following conditions was met: (1) SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, (2) taking antihypertensive medications. The diagnostic criteria for obesity were: (1) BMI ≥ 30 kg/m2, or (2) WC ≥ 85.0 cm for females and ≥ 90.0 cm for males. Obesity-hypertension referred to the presence of both hypertension and obesity. Diabetes was diagnosed if one of the following conditions was met: (1) FPG ≥ 7.0 mmol/L or 2-h post-meal blood glucose level of ≥ 11.1 mmol/L; (2) random blood glucose ≥ 11.1 mmol/L; (3) HbA1c ≥ 6.5%; (4) taking hypoglycemic drugs or using subcutaneous insulin injections; and (5) had been told by a doctor that he had diabetes. The LMR was calculated as lymphocyte count/monocyte count.

Outcomes

The main endpoint of this study was all-cause mortality during follow-up.

Statistical analysis

We divided the subjects into four groups (Q1-Q4) based on the quartile of the LMR. Continuous variables were expressed in terms of mean and standard deviation, while categorical variables were presented in terms of frequency and percentage. Baseline characteristics were compared between different groups using univariate ANOVA for continuous variables and Pearson Chi-square test, corrected Chi-square test or Fisher exact test for categorical variables. All-cause mortality was calculated for each LMR quartile array throughout the follow-up period. Kaplan-Meier survival analysis was performed to assess the incidence rate of all-cause death between groups. Log-rank tests were used to evaluate the differences we observed. To evaluate the independent predictive value of the LMR, we developed three multivariate Cox proportional risk models to control for confounding factors. Crude Model was unadjusted, Adjust I Model was adjusted for age, gender, and race, and Adjust II Model was adjusted for gender, age, race, smoking, education, WC, BMI, SBP, DBP, AST, AST, serum creatinine, eGFR, FPG, HbA1c, TC, TG, LDL-C, SUA, hs-CRP, heart failure, stroke and coronary artery disease. The restricted cubic splines (RCS) analysis was employed to further investigate the dose-effect relationship with the LMR and the risk of all-cause mortality in patients of obese hypertension. The receiver operator characteristic curve (ROC) analysis was used to assess the accuracy of the LMR in predicting survival outcomes. A two-tailed $p < 0.05$ indicated statistical significance.

All analyses were conducted using SPSS statistical software (version 26.0) and R software (version 4.3.2). Moreover, GraphPad Prism software (version 8.0) was employed to make graphs.

Results

Baseline characteristics

We eventually included 4706 subjects with obese hypertension by inclusion and exclusion criteria. The baseline characteristics of the study subjects were shown in Table 1, stratified by the LMR quartile. The average age of the participants was 59.71 years old and 48.78% were male. Average LMR in the enrolled patients was 3.89 ± 1.97. According to the quartiles of the LMR, the laboratory characteristics at baseline were shown in Table 2. Participants with a higher LMR were more likely to be younger, female, former smoker, non-Hispanic Black and lower education, compared with participants in the first quartile. Moreover, significant differences in laboratory indicators were observed between the groups, with participants in the highest quartile showing significantly higher levels of TC, TG, LDL-C, HbA1c and platelet, lower levels serum creatinine, eGFR, SUA, neutrophil and hs-CRP compared with those in the first quartile. In terms of comorbidities, participants in the higher quartile had lower prevalence rates of diabetes, heart failure, coronary artery disease and stroke compared with those in the first quartile. In addition, all-cause mortality decreased gradually (32.61% vs 21.44% vs 14.19% vs 13.04%, $P < 0.001$) with increasing LMR.

Correlation between the LMR and all –cause mortality

There were 960 incident cases of all-cause mortality during follow-up (median follow-up of 90 months). The Kaplan-Meier

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TABLE 1 Baseline characteristics according to the LMR quartiles.

Variable	Q1 (n = 1190)	Q2 (n = 1194)	Q3 (n = 1149)	Q4 (n = 1173)	*P* value
Age (years)	65.26 ± 14.06	60.89 ± 14.42	57.84 ± 14.47	54.74 ± 14.59	< 0.001
Male, n (%)	755 (63.44)	629 (52.68)	519 (45.17)	392 (33.42)	< 0.001
Race, n (%)					< 0.001
Mexican American	98 (8.23)	149 (12.48)	180 (15.67)	190 (16.20)	
Other Hispanic	71 (5.96)	85 (7.12)	100 (8.70)	98 (8.35)	
Non-Hispanic White	726 (61.01)	604 (50.59)	487 (42.38)	351 (29.92)	
Non-Hispanic Black	212 (17.82)	267 (22.36)	292 (25.41)	416 (35.46)	
Other Race	83 (6.97)	89 (7.45)	90 (7.83)	118 (10.06)	
Smoking, n (%)					< 0.001
Never smoker	215 (18.07)	228 (19.10)	255 (22.19)	271 (23.10)	
Former smoker	654 (54.96)	589 (49.33)	520 (45.25)	492 (41.94)	
Current smoker	321 (26.97)	377 (31.57)	374 (32.55)	410 (34.95)	
Drinking, n (%)	295 (24.79)	264 (22.11)	255 (22.19)	265 (22.59)	0.775
Education, n (%)					0.002
Less than high school	267 (22.44)	329 (27.47)	326 (28.37)	354 (30.18)	
High school or equivalent	307 (25.80)	289 (24.20)	286 (24.89)	263 (22.42)	
College or above	616 (51.76)	576 (48.24)	537 (46.73)	556 (47.40)	
Anthropometric indicators					
WC (cm)	107.74 ± 14.61	107.42 ± 14.05	106.98 ± 13.80	107.56 ± 14.11	0.618
BMI (kg/m^2)	31.07 ± 7.06	31.55 ± 6.53	32.05 ± 6.65	32.86 ± 7.32	< 0.001
SBP (mmHg)	134.28 ± 21.11	134.87 ± 22.03	132.96 ± 18.97	133.39 ± 19.47	0.108
DBP (mmHg)	68.21 ± 16.04	71.03 ± 15.42	72.42 ± 14.07	72.77 ± 14.79	< 0.001
Comorbidities					
DM, n (%)	346 (29.08)	307 (25.71)	276 (24.02)	324 (27.62)	0.033
HF, n (%)	156 (13.11)	93 (7.79)	42 (3.66)	58 (4.94)	< 0.001
CAD, n (%)	168 (14.12)	135 (11.31)	69 (6.00)	53 (4.52)	< 0.001
Stroke, n (%)	117 (9.83)	84 (7.04)	62 (5.40)	74 (6.31)	< 0.001
Outcomes					
All-cause mortality, n (%)	388 (32.61)	256 (21.44)	163 (14.19)	153 (13.04)	< 0.001

WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; HF, heart failure; CAD, coronary artery disease

survival analysis curves showed the prevalence of all-cause mortality in several groups that have been divided based on the LMR quartiles in Figure 2. Participants with a higher LMR demonstrated a significantly higher survival rate compared to those with a lower LMR in DM (*P* for log-rank test < 0.001) (Figure 2A). Similarly, there was significant difference observed in patients with non-DM (*P* for log-rank test < 0.001) (Figure 2B).

Further, Cox analysis revealed a significant relationship between the LMR and all-cause mortality in the crude model [HR (95% CI): 0.78 (0.72-0.86), P < 0.001] and the adjusted models [Adjusted I: HR (95% CI): 0.89 (0.82-0.98), P = 0.006; Adjusted II: HR (95% CI): 0.88 (0.80-0.98), P = 0.017] in patients with DM when the LMR was considered a continuous variable. However, there was a significant association between LMR and all-cause mortality only in the crude model [HR (95% CI): 0.73 (0.68-0.77), P < 0.001] in patients without DM (Table 3). When LMR was treated as a categorical variable, it was observed that, compared with patients in the Q1 group, patients in the highest LMR group (Q4) with DM suggested a significantly decreased risk of all-cause mortality in three established Cox models, as showed by the following findings: crude model [HR (95% CI): 0.46 (0.26-0.49), P < 0.001], Adjust I model [HR (95% CI): 0.61 (0.43-0.85), P = 0.004], and Adjust II model [HR (95% CI): 0.59 (0.39-0.86), P = 0.007]. However, there was

TABLE 2 Baseline levels of laboratory indicators according to the LMR quartiles.

Laboratory parameters	Q1 (n = 1190)	Q2 (n = 1194)	Q3 (n = 1149)	Q4 (n = 1173)	*P* value
ALT (U/L)	24.95 ± 18.55	24.89 ± 16.43	25.42 ± 14.15	24.74 ± 14.13	0.764
AST (U/L)	26.51 ± 16.81	25.74 ± 16.22	25.10 ± 11.08	24.57 ± 11.73	0.063
Scr (mg/dL)	1.14 ± 1.02	1.01 ± 0.55	0.93 ± 0.55	0.88 ± 0.35	< 0.001
eGFR (ml/min/1.73m^2)	72.11 ± 23.76	78.02 ± 22.84	83.28 ± 21.57	86.07 ± 21.51	< 0.001
TC (mmol/L)	4.74 ± 1.13	4.95 ± 1.10	5.03 ± 1.05	5.03 ± 1.12	< 0.001
TG (mmol/L)	1.52 ± 1.00	1.64 ± 1.30	1.68 ± 1.31	1.69 ± 1.28	0.002
LDL-C (mmol/L)	2.71 ± 0.96	2.87 ± 0.92	2.94 ± 0.88	3.06 ± 0.95	< 0.001
HDL-C (mmol/L)	1.34 ± 0.44	1.33 ± 0.40	1.33 ± 0.40	1.34 ± 0.36	0.964
FPG (mmol/L)	6.62 ± 2.61	6.26 ± 2.18	6.58 ± 2.75	6.51 ± 2.97	0.315
HbA1c (%)	6.05 ± 1.11	6.03 ± 1.22	6.10 ± 1.35	6.21 ± 1.42	< 0.001
SUA (mg/dl)	6.24 ± 1.55	5.89 ± 1.54	5.83 ± 1.45	5.73 ± 1.41	< 0.001
PLT (1000 cells/uL)	230.79 ± 70.89	238.63 ± 65.01	246.85 ± 69.11	255.19 ± 74.66	< 0.001
Neu (1000 cells/uL)	4.75 ± 1.96	4.31 ± 1.61	4.01 ± 1.52	3.75 ± 1.48	< 0.001
Lym (1000 cells/uL)	1.48 ± 0.47	1.87 ± 0.45	2.18 ± 0.35	2.72 ± 0.63	< 0.001
Mono (1000 cells/uL)	0.70 ± 0.25	0.58 ± 0.14	0.53 ± 0.31	0.43 ± 0.18	< 0.001
LMR	2.14 ± 0.46	3.19 ± 0.25	4.09 ± 0.28	6.16 ± 0.54	< 0.001
hs-CRP (mg/L)	6.72 ± 1.92	5.70 ± 1.02	4.75 ± 1.41	4.28 ± 1.44	0.007

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SUA, serum uric acid; PLT, platelet; Neu, neutrophile; Lym, lymphocyte; Mono, monocyte; LMR, lymphocyte to monocyte ratio; hs-CRP, high-sensitivity C-reactive protein

non-trend decreasing risk of mortality with elevated the LMR, as shown by the results of the trend test (P for trend > 0.05) (Table 3). Similar results were observed in patients without DM [crude model: HR (95% CI): 0.31 (0.24-0.39), P < 0.001; Adjust I model: HR (95% CI): 0.74 (0.57-0.96), P = 0.021; Adjust II model: HR (95% CI): 0.71 (0.54-0.93), P = 0.014; P for trend > 0.05] (Table 3).

The detection of nonlinear relationship

Considering that multivariate Cox proportional hazard analysis suggested a non-linear relationship between the baseline LMR and all-cause mortality, we used RCS analysis to further explore this association in patients with obesity-related hypertension (Figure 3). We studied the population of diabetes and non-diabetes separately. The RCS analysis revealed a non-linear association between LMR and all-cause mortality in both diabetic (P for non-linearity < 0.001, Figure 3A) and non-diabetic patients (P for non-linearity < 0.001, Figure 3B).

Subgroup analysis

To evaluate the specific effect of the LMR on the outcomes, stratification was performed according to age, gender, DM, heart

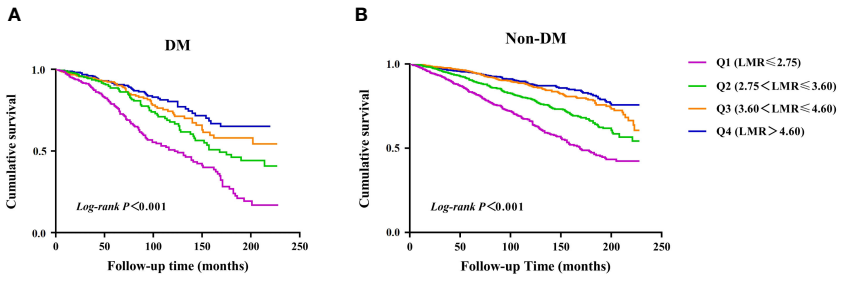

FIGURE 2
Kaplan–Meier survival analysis curves for all-cause mortality. **(A)** diabetes, **(B)** non- diabetes.

TABLE 3 Association between quartiles of LMR with risk of all-cause mortality.

LMR	Crude		Adjust I		Adjust II	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
DM						
Per 1 Unit increase	0.78 (0.72-0.86)	< 0.001	0.89 (0.82-0.98)	0.006	0.88 (0.80-0.98)	0.017
Quartiles						
Q1	Ref		Ref		Ref	
Q2	0.53 (0.40-0.71)	< 0.001	0.69 (0.51-0.94)	0.018	0.64 (0.46-0.92)	0.014
Q3	0.41 (0.30-0.56)	< 0.001	0.60 (0.43-0.84)	0.003	0.65 (0.44-0.92)	0.017
Q4	0.46 (0.26-0.49)	< 0.001	0.61 (0.43-0.85)	0.004	0.59 (0.39-0.86)	0.007
P for trend		0.428		0.621		0.414
Non-DM						
Per 1 Unit increase	0.73 (0.68-0.77)	< 0.001	0.94 (0.88-1.00)	0.060	0.95 (0.89-1.01)	0.090
Quartiles						
Q1	Ref		Ref		Ref	
Q2	0.58 (0.48-0.69)	< 0.001	0.80 (0.65-0.97)	0.022	0.81 (0.65-0.98)	0.038
Q3	0.34 (0.27-0.42)	< 0.001	0.58 (0.46-0.73)	< 0.001	0.63 (0.48-0.80)	< 0.001
Q4	0.31 (0.24-0.39)	< 0.001	0.74 (0.57-0.96)	0.021	0.71 (0.54-0.93)	0.014
P for trend		0.053		0.313		0.086

CI, confidence interval; HR, hazard ratio; LMR, Lymphocyte to monocyte ratio; DM, diabetes mellitus.
Crude, Unadjusted model.
Adjust I: adjusted for gender, age, race.
Adjust II: adjusted for gender, age, race, smoking, education, WC, BMI, SBP, DBP, AST, AST, serum creatinine, eGFR, FPG, HbA1c, TC, TG, LDL-C, SUA, neutrophil count, platelet count, hs-CRP, heart failure, stroke and coronary artery disease.

failure and coronary artery disease in Figure 4. Although female was a protective factor for all-cause mortality, there was no interaction between the gender [female: HR (95% CI): 0.850 (0.782-0.931), $P < 0.001$; P for interaction > 0.05). Similarly, there was no significant interaction in diabetes subgroups and other subgroups (P for interaction > 0.05).

ROC curve analysis of LMR

The ROC curve for the LMR in predicting all-cause mortality was depicted in Figure 5. The ROC curve revealed a moderate ability of LMR to predict mortality in obesity-related hypertension with DM [AUC=0.618, 95% CI (0.582-0.655), $P < 0.001$, Figure 5A]

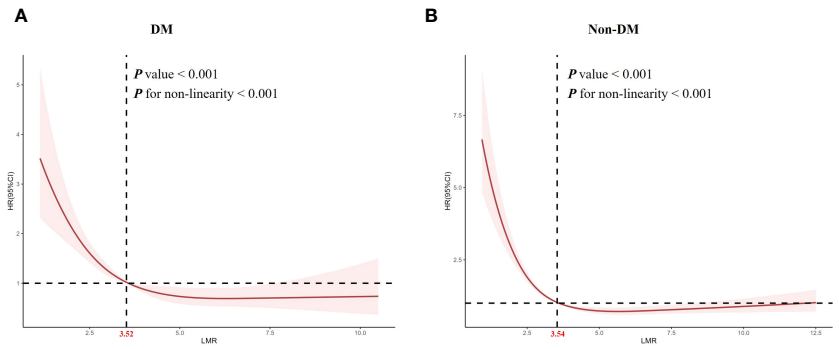

FIGURE 3
Restricted cubic spline analysis of LMR with all-cause mortality. **(A)** diabetes, **(B)** non- diabetes.

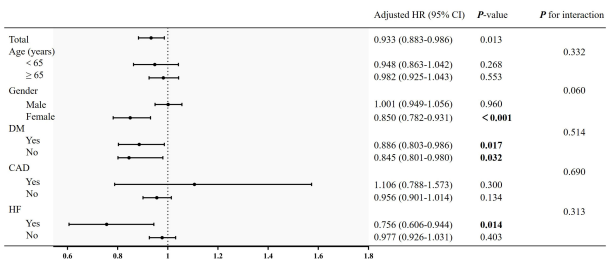

FIGURE 4
Subgroup analysis of the association between LMR and all-cause mortality. Adjusted for age, gender, race, smoking, education, WC, BMI, SBP, DBP, AST, AST, serum creatinine, eGFR, FPG, HbA1c, TC, TG, LDL-C, SUA, neutrophil count, platelet count, hs-CRP, heart failure, stroke and coronary artery disease.

and without DM [AUC=0.643, 95% CI (0.625-0.674), $P < 0.001$, Figure 5B]. The cut-off values were 3.06 and 3.25, respectively. The sensitivity was 0.686 and 0.643, while the specificity was 0.522 and 0.595, respectively.

Discussion

The study was conducted to explore the association between the LMR and survival outcomes in patients with obese hypertension. In our study, among the 4706 participants from nine NHANES cycles (2001-2018), a decreased LMR was strongly related to all-cause mortality and was an independent risk factor for reduced survival. Moreover, there was a non-linear relationship between LMR and all-cause mortality in both diabetic and non-diabetic patients.

Since LMR consists of lymphocyte and monocyte counts, it has the advantage of being relatively inexpensive and can be obtained routinely. A low lymphocyte count indicates a persistent, relatively deficient immune state, and a high monocyte count indicates a non-specific or systemic inflammatory state (19–22). As a composite parameter reflecting two opposing immune and inflammatory pathways, LMR is more predictive than lymphocyte or monocyte alone. Inflammation plays an important role in the pathophysiology of many metabolic diseases (23). Moreover, previous studies demonstrated that activation of the immune system and chronic inflammation were involved in the occurrence and development of these diseases (24). LMR has been reported to be associated not only with an increased risk of death from multiple malignant diseases, but also with a poor prognosis for coronary artery disease (25–27).. In our study, compared with participants of the higher LMR, the lower LMR had higher levels of neutrophil and hs-CRP and a higher prevalence of metabolic disorders such as diabetes, heart failure and coronary artery disease. This suggested that lower LMR may be associated with higher levels of inflammation and adverse outcomes.

Our findings of association between the LMR and all-cause mortality in the obese hypertension patients were somewhat consistent with recent studies (28–31). Previous study has demonstrated that the lower LMR was associated with cardiovascular mortality and all-cause mortality in adult asthma patients (28). In another study, the researchers found that patients with pulmonary embolism had a significantly increased risk of 30-day all-cause mortality with the reduction of LMR (29). Furthermore, poor overall survival was strongly associated with low LMR in patients with thyroid cancer (30). A study on the prognosis of patients with heart failure also showed that a lower LMR significantly increased the risk of all-cause death within 6 months (31). Notably, they did not further explore the specific correlation between LMR and mortality, whereas our study demonstrated that a non-linear relationship between the LMR and all-cause mortality. The possible mechanism of the above findings is: proinflammatory cytokines activate lymphocytes and monocytes (32). This activated cell is a potential source of pro-inflammatory cytokines, leading to further activation of these cells, which contributes to systemic inflammation in obese hypertensive patients. High levels of proinflammatory cytokines may cause some adverse effects in patients, including myocardial remodeling and promoting arrhythmia (33). Ultimately, there was an increased risk of adverse outcome events.

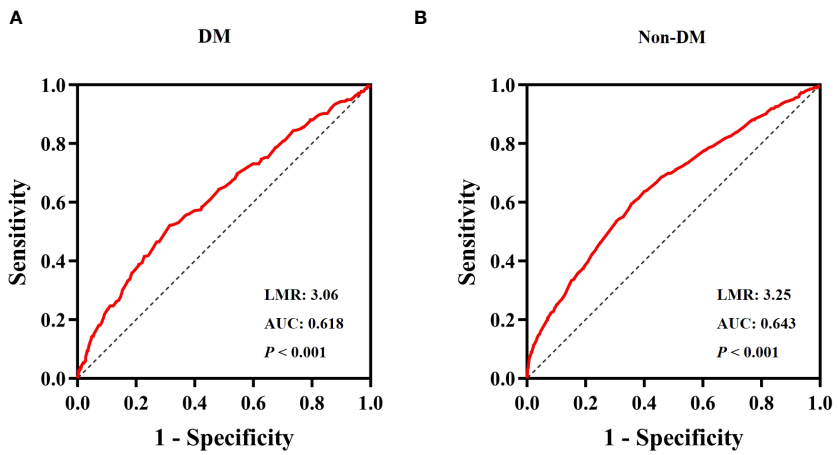

FIGURE 5
ROC Curve analysis for LMR predicted all-cause mortality. **(A)** diabetes, **(B)** non- diabetes.

To our knowledge, this was the first study that explored the prognostic effect of LMR on patients with obese hypertension. However, there are some limitations in this study. Firstly, this was a single-center retrospective study, so potential bias could be present. Moreover, the sample size was not particularly large, and the incidence of death was relatively low. Future large-sample and prospective studies are warranted to strengthen our findings. Finally, there were no other indicators of inflammation levels or immune status except hs-CRP. Thus, we cannot reveal the exact pathophysiological mechanisms underlying LMR. Therefore, basic experiments or animal experiments are needed to further explore the specific mechanism.

Conclusions

We found that LMR is a valuable tool for predicting the risk of all-cause mortality in patients with obese hypertension combined with diabetes or without diabetes, and that the relationship between LMR and mortality is non-linear. Thus, LMR may be helpful in predicting risk and assessing prognosis in these patients. In addition, more research is needed to explore whether intervening with LMR can contribute to improve clinical outcomes for these patients.

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

LW: Writing – original draft, Writing – review & editing. JG: Investigation, Writing – original draft. BL: Writing – original draft. YF: Writing – original draft. ZY: Writing – original draft. SG: Writing – original draft. ZS: Writing – original draft. ZZ: Writing – original draft. JH: Writing – original draft. CW: Writing – original draft. WM: Writing – review & editing. FW: Writing – review & editing.

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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.

Publisher's note

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Positive association between blood ethylene oxide levels and metabolic syndrome: NHANES 2013-2020

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Purpose: The exposure of Ethylene oxide (EO) is linked to systemic inflammatory response and various cardiovascular risk factors. Hemoglobin's binding to ethylene oxide (HbEO) was used to measure serum EO level. This research aims to explore the association between metabolic syndrome (MetS) and HbEO, and between HbEO and components of metabolic syndrome.

Method: This research included 1842 participants from 2013 to 2020 in National Health and Nutrition Examination Survey (NHANES) database. Weighted logistic regression models were used to analyze the relationship between HbEO and metabolic syndrome risk, using odds ratio (OR) and 95% confidence interval (CI). The restricted cubic spline plot explores whether there is a dose-response relationship between HbEO and MetS risk. Subgroup analysis was performed to analyze study heterogeneity.

Results: Significant differences were found in gender, educational level, marital status, diabetes status and hypertension among different groups ($P < 0.001$, $P = 0.007$, $P = 0.003$, $P < 0.001$, $P < 0.001$, respectively). The serum HbEO level exhibited positive correlation with metabolic syndrome risk in Q2 level (OR=1.64, 1.04~2.48), Q3 level (OR=1.99, 1.29~3.08), and Q4 level (OR=2.89, 1.92~4.34). The dose-response association suggested a possible linear association between serum HbEO and metabolic syndrome risk (*P*-overall=0.0359, *P*-non-linear=0.179). L-shaped association was found between HbEO and the risk of MetS in female population, obese population and mid-age and elder population (*P*-overall<0.001, *P*-non-linear=0.0024; *P*-overall=0.0107, *P*-non-linear=0.0055 *P*-overall<0.001 *P*-non-linear=0.0157).

Conclusion: This study indicates a linear correlation between MetS and HbEO, with MetS risk escalating as HbEO levels increase. The prevalence of MetS varies depending on BMI, age and gender, and these factors can also influence MetS prevalence when exposed to EO.

KEYWORDS

metabolic syndrome, ethylene oxide, inflammation, epidemiology, NHANES

1 Introduction

Metabolic syndrome (MetS) is defined as a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia (1). MetS is a critical health issue that elevates the likelihood of individuals developing heart disease, diabetes, stroke, and conditions linked to the buildup of fatty deposits in the walls of arteries, known as atherosclerosis (2–4). The prevalence of MetS has been studied in various countries. In the US, Zimmet et al. (5) found that it increased from 32.5% in 2011 to 36.9% in 2016, while Hirode et al. reported a prevalence of 34.7%. In European countries, the prevalence varied from 12% to 26% (6). In China, the prevalence increased from 8% in 1992 to 10.6% in 2002 in urban areas and from 4.9% in 1992 to 5.3% in 2002 in rural areas. The prevalence of MetS in China was estimated to have increased to 15.5% in 2017 (7). Currently, there is no global data available on MetS. However, its prevalence is approximately three times higher than that of diabetes, therefore, the global prevalence of MetS is estimated to be a quarter, and for adults over 40 years old, the prevalence is around 40% (8, 9). Furthermore, the prevalence of MetS is correlated with the prevalence of obesity. As obesity becomes increasingly common, MetS has emerged as a significant public health concern (6, 8).

Ethylene oxide (EO) is present throughout in the environment, deriving from sterilized medical equipment, fumigated food, cosmetics, and inhalation of contaminated air, tobacco smoke and car exhaust fumes (10, 11). EO is a direct-acting alkylating agent, and acute exposure to EO can cause nausea, bronchitis, and pulmonary edema; Chronic long-term exposure increases the risk of neurological disorders and cancer (12, 13). EO can induce dose-related increases in hemoglobin adduct frequencies, genetic mutations, and genetic translocations in exposed rodent germ cells (14, 15). Cytogenetic studies *in vitro* and *in vivo* have confirmed the genotoxicity and mutagenicity of EO. Studies have also provided substantial evidence of carcinogenicity to rodents (16). Exposure to EO is linked to systemic inflammatory response (17, 18) and various cardiovascular risk factors such as smokers, serum lipid levels and diabetes (3, 16, 19–21). With the widespread industrialization and extensive use of chemical substances, there is an increasing interest in understanding the relationship between environmental factors such as EO and kinds of MetS. Xu Zhu et al. (22) found hemoglobin's binding to ethylene oxide (HbEO) was positively associate with total cholesterol (TC), total triglycerides, low-density lipoprotein and inflammatory biomarkers but negatively associated with high-density lipoprotein. Jingyu Guo et al. (3) found that higher HbEO levels were significantly associated with an increased prevalence of diabetes mellitus. The group led by Ningtao Wu (23) discovered that HbEO levels are strongly and non-linearly correlated with diastolic blood pressure (DBP). Iokfai Cheang et al. (24) reported that elevated quartiles of HbEO were inversely associated with BMI, WC and obesity following full adjustment.

Since the diseases associated with MetS are the leading causes of morbidity and mortality, identifying the underlying cause of MetS has been the focus of many studies (25). However, a comprehensive understanding of the exact relationship between the MetS and HbEO remains lacking. As EO was proved to be a risk factors for MetS components, it is important to figure out if EO is also a risk factor for MetS. Therefore, this study examines the potential connection between EO exposure and MetS by analyzing data extracted from National Health and Nutrition Examination Survey (NHANES), to unveil plausible pathogenic mechanisms. The insights gained from this research can contribute to a better comprehension of the intricate relationship between chemical substances in modern life and chronic diseases.

2 Patients and methods

2.1 Study population

National Health and Nutrition Examination Survey (NHANES) is an ongoing, nationally representative series of surveys conducted every two years to monitor the health and nutritional status of non-institutionalized citizens in the United States (26). The study cohort was confined to the survey period from 2013 to March 2020, as EO measurements were unavailable before this timeframe (27, 28). In NHANES 2013-2020, a total of 33657 participants completed both interviews and medical examinations. We selected adults aged 18 to 65 years for the study. According to the NCEP ATP III-2005 criteria, the components defining metabolic syndrome primarily consist of plasma glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), and waist circumference. Therefore, participants with missing data on the components defining MetS will be excluded. Participants with missing demographic information such as marital status, severe drinking habits, family income-poverty ratio (PIR), educational level, and smoking status were also excluded. Ultimately, our study included 1842 participants (Figure 1).

2.2 Assessment of ethylene oxide and metabolic syndrome

The modified Edman reaction measures HbEO in human whole blood or red blood cells. This method is applied to N-terminal hemoglobin adducts and has been optimized to enhance product yield, sensitivity, and automation (29). Thus, NHANES staff utilize this method to detect HbEO.

MetS was characterized based on the NCEP ATP III-2005 criteria (30, 31), which entail the presence of three or more of the following conditions: 1) increased waist circumference (EWC), defined as waist circumference ≥102 cm in men and ≥88 cm in women; 2) high blood pressure, indicated by blood pressure levels ≥130/85 mm Hg or the use of medication for previously diagnosed hypertension; 3) reduced levels of HDL-C, with values below <40 mg/dL in men and <50 mg/dL in women, or the use of specific treatment for low HDL-C; 4) elevated triglycerides (TGs), defined as TG levels ≥150 mg/dL or the use of medication for high TG levels; and 5) increased fasting glucose, represented by fasting glucose levels ≥100 mg/L or the use of medication for high glucose levels and a previous diagnosis of type 2 diabetes.

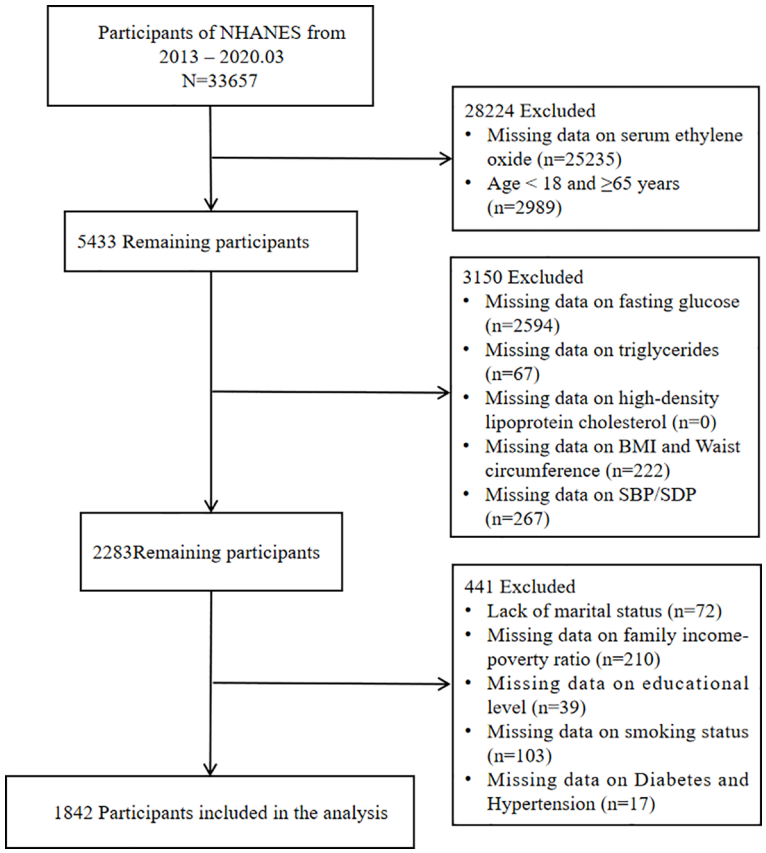

FIGURE 1
Flow chart of the patients included in the study.

2.3 Assessment of covariates

Based on previous research, smoking, and drinking status was categorized into three groups: "never," "former," and "current" (32, 33). Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported physician diagnosis, or current use of antihypertensive medication (34). Information regarding marital status, educational attainment, and ethnicity was extracted from the fundamental demographic data in the NHANES database. Diabetes was delineated by criteria such as glycated hemoglobin (HbA1c) levels equal to or exceeding 6.5%, fasting blood glucose levels greater than or equal to 7 mmol/L, self-reported diabetes, or the present use of antidiabetic medication (35). These subgroups comprise individuals categorized as either normal weight/overweight (BMI < 30 kg/m^2) or obese (BMI ≥ 30 kg/m^2) (36). PIR was used to assess household income levels and classified into three groups (<1.3, 1.3 - 3.5, > 3.5) (37). The following data were collected to diagnose MetS: triglycerides, glucose, and HDL-C.

2.4 Statistical analysis

To better ascertain the relationship between HbEO levels and MetS, we categorized HbEO levels into four groups using quartiles (Q1<22.62, Q2: 22.62-33.515, Q3: 33.515-148, Q4 >148 pmol/g Hb) (28, 38, 39). Statistical analyses were conducted following the guidelines of NHANES, considering the complex sampling design of the survey to address the bias associated with sample selection, oversampling, and nonresponse (22). Therefore, weights were calculated using the WTSAF2YR weight calculation method for the biochemical markers.

When describing the baseline characteristics of the study population, the data are presented as weighted means ± standard deviation (SD) for continuous measurements, and as unweighted counts along with weighted percentages for categorical measurements. Due to the severe skewness in the distributions of triglycerides and plasma glucose, these variables are presented with the median [interquartile range (IQR)]. The Wilcoxon rank-sum test (ranksum test) was employed to compare independent samples of these variables. Statistical significance was assessed using Student's *t* test for continuous variables and chi-square tests for categorical variables. Weighted multivariable logistic regression models was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs). The multivariable weighted model was adjusted for age, sex, BMI (non-obese or obese), race, marital status, smoking status, alcohol drinking status, PIR, diabetes, and hypertension. The relationship between HbEO and MetS was also modeled using restricted cubic splines (RCS) with three knots positioned at the 1st, 50th, and 90th percentiles. To assess the

robustness of the study, we conducted three sensitivity analyses. Firstly, the International Diabetes Federation-2009 criteria was adopted to redefine the metabolic syndrome (40, 41). Then, we performed the primary analysis on the participants redefined according to these criteria to assess the reliability and robustness of our results. Secondly, due to the skewed distribution of HbEO data, we logarithmically transformed serum ethylene oxide levels (27), and included the transformed log (HbEO) as a continuous variable in two models (38, 39). The study outcomes were defined as MetS according to ATP criteria. Lastly, dietary intake is a significant factor influencing metabolism, and in the United States, dietary quality is determined by the Healthy Eating Index-2015 (HEI-2015) (42). HEI-2015 is used to assess dietary quality based on a population-based scoring algorithm. Evaluation of HEI-2015 comprises 13 dietary components, including Dairy, total protein foods, and seafood and plant proteins, which encompass alternative dairy and protein products (43, 44). We included participants' total HEI-2015 scores as covariates in the final model to evaluate whether diet quality affects model contributions. It is important to emphasize the use of weighting variable WTDRD1 based on the NHANES analysis guidelines using dietary recall data (excluding missing dietary data n=731, resulting in a final sample size of n=1111) for the third analysis. The visualization of the 13 components was conducted through radar plots (Supplementary Figure 1).

To explore potential sources of variability in the relationship between HbEO and the studied outcomes, we extended our investigation through subgroup analyses based on sex, age, non-obese or obese status, hypertension, and diabetes. The selection of specific variables for subgroup analyses was based on their clinical relevance to liver diseases and their potential influence on the relationship between HbEO and the studied outcomes. Including these variables in our analysis allowed us to assess the presence of effect modifications (interactions). This was further examined by incorporating a product term of each stratifying variable and HbEO into the primary model, followed by a Wald test. The entire statistical analysis was conducted using the statistical computing and graphics software R (version 4.1.3) and STATA (version 17.0), with statistical significance set at $P < 0.05$.

3 Results

3.1 Demographic characteristics of participants

The study involved 1842 participants with an average age of 44 (Table 1), comprising 900 male participants and 942 female participants. MetS components include reduced high-density lipoprotein cholesterol, elevated triglycerides, elevated plasma glucose, elevated waist circumference, elevated systolic blood pressure and diastolic blood pressure. The study population was subsequently categorized into two groups: one without metabolic syndrome and another with metabolic syndrome. There were significant differences in MetS components between males and females ($P < 0.001$). Significant differences were also found in educational level, marital status, and diabetes status among different groups ($P = 0.007$, $P = 0.003$, $P < 0.001$, respectively). Furthermore, individuals with MetS were significantly more prevalent in the hypertension group compared to those without ($P < 0.001$).

3.2 Multivariate weighted logistic analysis between HbEO and MetS

In the multivariate weighted logistic analysis, the investigation focused on assessing the correlation between HbEO levels and the risk of MetS and the correlation between HbEO and the risk associated with individual MetS components. (Table 2) The serum HbEO level exhibited a positive correlation with metabolic syndrome risk in Q2 level (OR=1.64, 95% CI: 1.04~2.48), Q3 level (OR=1.99, 95% CI: 1.29~3.08), and Q4 level (OR=2.89, 95% CI: 1.92~4.34) in model 1, with a significant *p*-value for trend (*P*=0.01), indicating that with the level of HbEO increased, the MetS risk increased. Regarding elevated waist circumference, a significantly positive association was found in the Q4 level (OR=2.28, 95% CI: 1.04~5.01) with a significant *p*-value for trend (*P*=0.05) in model 1. As for elevated blood pressure, a significantly positive association was found in Q4 level in model 1 (OR=1.64, 95% CI: 1.07~2.52). Regarding reduced high-density lipoprotein cholesterol, a significantly positive association was found in Q2 and Q4 in model 1 with a significant *p*-value for trend (*P*=0.002) and in Q4 in model 2 (OR=3.03, 95% CI: 1.60~5.75) with a significant *p*-value for trend (*P*=0.04). As for elevated total triglycerides, a significantly positive association was found in Q3 and Q4 in model 1 (OR=1.81, 95% CI: 1.15~2.84; OR=2.78, 95% CI: 1.66~4.65, respectively) with a significant *p*-value for trend (*P*=0.04) and in Q3 and Q4 in model 2 (OR=1.72, 95% CI: 1.05~2.81; OR=2.28, 95% CI: 1.19~4.37, respectively). Regarding diabetes, a significant negatively association was found in Q4 in model 1 (OR=0.62, 95%CI: 0.39~0.99) and in Q3 and Q4 in model 2 (OR=0.57, 95%CI: 0.33~0.98; OR=0.40, 95%CI: 0.19~0.84).

3.3 Dose-response analysis between HbEO and MetS

The dose-response association between HbEO level and MetS risk indicated that increasing levels of serum HbEO were associated with a higher risk of MetS (Figure 2). However, the *p*-value for non-linearity was more significant than 0.05, suggesting a possible linear association between serum HbEO and MetS risk (*P*-overall=0.0359, *P*-non-linear=0.179). For the female population, there was a non-linear and L-shape association between HbEO level and MetS risk (*P*-overall<0.001, *P*-non-linear=0.0024) (refer to Supplementary Figure 2). Regarding the population without obesity, a significantly non-linear and inverted U-shape association was found between HbEO and MetS risk (*P*-overall=0.0107, *P*-non-linear=0.0055) (refer to Supplementary Figure 3). For the population aged 50 and older, a significantly non-linear and inverted U-shape association was found between HbEO and MetS

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TABLE 1 Characteristics of participants with available data in the NHANES 2013–2020.

Characteristics	Metabolic Syndrome		
	No (N=1234)	Yes (N=608)	*P values
Age, Mean (SD), years	40.48 (13.13)	47.52 (11.27)	<0.001
Sex, male, n %	630 (51.5)	270 (50.3)	0.739
HDL-C, Mean (SD), mg/dl	57.84 (15.65)	44.16 (10.23)	<0.001
Triglycerides, Median (IQR), mg/dL	76 (54-105)	147 (101-219)	<0.001
Plasma Glucose, Median (IQR), mg/dL	97 (92-103)	108 (102-123)	<0.001
Waist circumference, Mean (SD), cm	88.85 (9.67)	112.40 (12.14)	<0.001
SBP, Mean (SD), mmHg	117.36 (14.77)	125.31 (15.36)	<0.001
SDP, Mean (SD), mmHg	70.21 (10.60)	75.50 (10.87)	<0.001
BMI, category, n %			<0.001
Non-obese	917 (74.3)	188 (27.0)	
Obese	317 (25.7)	420 (73.0)	
Race, n %			0.218
Mexican American	167 (9.3)	106 (10.9)	
Non-Hispanic Black	266 (11.9)	136 (11.1)	
Non-Hispanic White	440 (62.3)	230 (64.6)	
Other Race	361 (16.5)	136 (13.4)	
Educational level, n %			0.007
High School or below	211 (12.8)	150 (17.1)	
High School Grad/GED or Equivalent	288 (22.9)	148 (29.0)	
College graduate or above	348 (33.1)	110 (21.7)	
Some College or AA degree	387 (31.2)	200 (33.2)	
Maital status, n %			0.003
Married/Living with Partner	735 (62.2)	373 (67.0)	
Widowed/Divorced/ Separated	182 (14.8)	142 (19.5)	
Never married	317 (23.0)	93 (13.5)	
Drinking status, n %			0.177
Former	81 (6.6)	62 (8.7)	
Now	913 (79.0)	422 (73.8)	
Never	240 (14.4)	124 (17.5)	
Smoking status, n %			0.347
Former	222 (21.3)	111 (21.6)	
Never	660 (53.3)	296 (48.5)	
Now	352 (25.4)	201 (29.9)	
Diabetes status, n %			<0.001
No	1027 (85.4)	264 (46.0)	
Pre-diabetes	66 (3.3)	227 (34.0)	
Diabetes mellitus	141 (11.3)	117 (20.0)	
Hypertension, yes, n %	1495 (18.6)	1868 (59.5)	<0.001
PIR, n %			0.201
<1.3	775 (24.4)	712 (23.4)	
1.3-3.5	1440 (31.3)	1161 (37.2)	
≥3.5	1632 (44.3)	1098 (39.4)	

BMI, body mass index; PIR, family income-poverty ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; IQR, interquartile range.
Metabolic Syndrome defined as ATP-III.
*For continuous variables, P-values were calculated using weighted Student's t test, and for categorical variables, P-values were computed using weighted chi-square tests.

risk (*P*-overall<0.001, *P*-non-linear=0.0157) (refer to Supplementary Figure 4).

3.4 Sensitive analysis

In sensitivity analysis (Supplementary Table 1) that used the IDF definition for MetS, the serum HbEO levels were positively associated with MetS risk in Q3 and Q4 levels (OR=1.71, 95% CI: 1.13~2.58; OR=2.60, 95% CI: 1.69~3.99, respectively) in model 1 with a significant *p*-value for trend (*P*=0.02). In model 2, serum HbEO levels were positively associated with MetS risk in Q4 level (OR=2.65, 95% CI: 1.35~5.19), with a non-significant *p*-value for trend (*P*=0.14). The analysis elucidated a positive correlation between logarithmic-transformed HbEO [Log (HbEO)] levels and the susceptibility to MetS (refer to Supplementary Table 2). In Model 1, the odds ratio (OR) denoting the association between Log (HbEO) levels and MetS risk was determined to be 1.31 (95% CI: 1.12~1.53), while in Model 2, it was 1.26 (95% CI: 1.03~1.55). The positive association persisted after adjusting for the Healthy Eating Index-2015 score within the model (refer to Supplementary Table 3). In Model 1, a discernible elevation in the risk of MetS was observed concomitant with EO levels. For instance, relative to the reference group, the OR for MetS was 2.29 (95% CI: 1.25~4.20) in the Q2 level of EO levels, 1.96 (95% CI: 1.23~3.41) in the Q3 level, and 2.77 (95% CI: 1.65~4.66) in Q4 level. Similarly, in Model 2, the risk of MetS exhibited a progressive augmentation with elevated EO levels (OR=2.17, 95% CI: 1.05~4.49) in Q2 level; OR=2.09, 95% CI: 1.13~3.87) in Q3 level; OR=2.23, 95% CI: 1.10~4.53) in Q4 level. These findings underscore a consistent and statistically significant positive association between EO exposure and the predisposition to MetS, even after adjustment for plausible confounding variables such as the Healthy Eating Index-2015 score.

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TABLE 2 Multivariate weighted logistics model analysis reveals the association between HbEO levels and the risk of Metabolic Syndrome as well as its components.

Characteristics	MetS		EWC		Hypertension		RHDL-C		ETGs		Diabetes	
EO Group	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Q1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Q2	**1.64 (1.04,2.58)**	1.50 (0.86,2.61)	2.04 (0.91,4.59)	1.86 (0.83,4.18)	0.47 (0.53,1.43)	0.76 (0.45,1.27)	**1.70 (1.00,2.87)**	1.52 (0.90,2.55)	1.40 (0.88,2.23)	1.27 (0.79,2.03)	0.86 (0.51,1.46)	0.88 (0.52,1.51)
Q3	**1.99 (1.29,3.08)**	**1.91 (1.13,3.22)**	1.46 (0.73,2.95)	1.17 (0.55,2.51)	1.39 (0.89,2.17)	1.15 (0.72,1.84)	1.31 (0.84,2.04)	1.24 (0.75,2.06)	**1.81 (1.15,2.84)**	**1.72 (1.05,2.81)**	0.67 (0.41,1.08)	**0.57 (0.33,0.98)**
Q4	**2.89 (1.92,4.34)**	**2.98 (1.54,5.77)**	**2.28 (1.04,5.01)**	0.91 (0.23,3.71)	**1.64 (1.07,2.52)**	0.90 (0.43,1.87)	**3.84 (2.69,5.47)**	**3.03 (1.60,5.75)**	**2.78 (1.66,4.65)**	**2.28 (1.19,4.37)**	**0.62 (0.39,0.99)**	**0.40 (0.19,0.84)**
P for trend	**0.01**	0.13	**0.05**	0.15	0.91	0.23	**0.002**	**0.04**	**0.04**	0.33	0.47	0.62

CI, confidence interval; OR, odds ratio; EO, ethylene oxide; MetS, metabolic syndrome; EWC, elevated waist circumference; RHDL-C, reduced high-density lipoprotein cholesterol; ETGs, elevated total triglycerides.
Model 1: adjusted for age, sex, race, BMI;
Model 2: adjusted for variables in Model 2 plus marital status, educational level, drinking status, smoking status, hypertension, diabetes, PIR.
Quartiles for ethylene oxide (<22.62, 22.62-33.515, 33.515-148, >148) pmol/g Hb.
The bold values represent that the p-value associated with the respective Odds Ratio (OR) is less than 0.05.

3.5 Subgroup analysis

Subgroup analysis was conducted to investigate potential sex, age, and BMI interactions with the relationship between serum HbEO and the risk of MetS (Figure 3). Notably, the subgroup analysis of age showed a significant difference between age groups (*P* for interaction=0.028), suggesting an interaction between serum HbEO and MetS about age. The serum HbEO level in males in Q3 and Q4 was significantly associated with an increased risk of MetS (OR=3.02, 95%CI: 1.38~6.58; OR=2.78, 95%CI: 1.07~7.23, respectively). This relationship was also observed in females in Q4 (OR=4.02, 95%CI: 1.15~14). There was a significant association between an increased risk of MetS and serum HbEO level in individuals aged 50 and over in Q3 and Q4 (OR=2.58, 95%CI: 1.25~5.33; OR=5.83, 95%CI: 2.19~15.48, respectively). Furthermore, the level of serum HbEO in individuals without obesity in Q3 and Q4 was also significantly associated with an increased risk of MetS (OR=2.88, 95%CI: 1.34~6.17; OR=4.94, 95%CI: 1.85~13.2, respectively). Subgroup analysis for hypertension and diabetes suggested hypertension and diabetes had no impact on the prevalence of MetS (*P*=0.411, *P*=0.993, respectively) (Supplementary Figure 5).

4 Discussion

This study demonstrated that HbEO is a risk factor for MetS and its components including elevated waist circumference, reduced high-density lipoprotein cholesterol and elevated total triglycerides. This finding remained consistent across subgroup analyses and sensitivity analyses. Grouped RCS curves revealed a notable increase in the risk of metabolic syndrome among women, non-obese individuals, and those aged over 50 years when exposed to EO.

Recent data suggest that MetS is the majority of the population's attributable risk of premature death from cardiovascular disease (45). Although MetS appears more common in genetically predisposed people, acquired underlying risk factors—overweight or obesity and elevated waist circumference, insulin resistance, dyslipidemia, glucose intolerance, hypertension, physical inactivity, and atherosclerotic diet—often cause clinical manifestations (46). Environmental contamination also contribute to MetS development (25, 47). EO, as the reactive epoxide, mainly comes from the sterilization of chemical plants, commercial sterilization operations, and medical facilities (48, 49). Exposure to EO may lead to a range of adverse health effects, including angina, heart attack, total cardiovascular disease, dyslipidemia, and its genotoxicity and mutagenic abilities have been widely reported in several experimental studies (21, 22, 24, 27, 49, 50). The research of Zhu, Huang and Cheang suggests that the relationship between EO and lipid abnormalities, chronic obstructive pulmonary disease, and asthma is mediated by the inflammatory response caused by EO (22, 27, 28). Studies have found that exposure to EO can cause inflammation in rodent organs and promote the occurrence of pulmonary fibrosis in rodents (51, 52). Long-term chronic exposure to EO leads to a decrease in glutathione reductase activity and an increase in hepatic lipid peroxide associated with oxidative stress *in vivo*, which is thought to be an essential pathogenic mechanism involved in lipid metabolism (53–56). In the

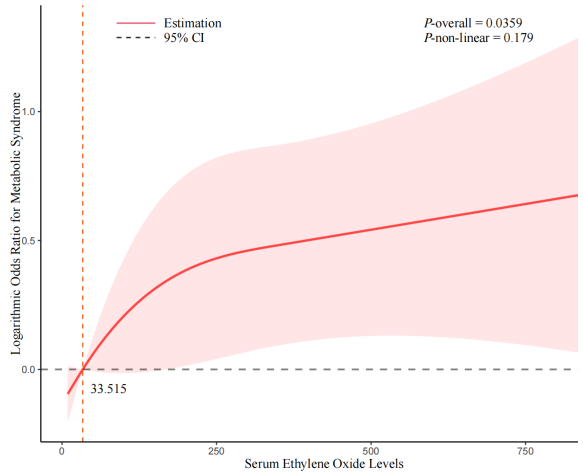

FIGURE 2
Non-linear association between serum ethylene oxide and the risk of Metabolic Syndrome. Cubic spline models adjusted for age (years), sex, BMI (<30 or ≥ 30kg/m2), race/ethnicity (Mexican American, Non-Hispanic Black, Non-Hispanic White, Other Race), educational level (9-11th grade or below, high school grad/GED or equivalent, college graduate or above, some college or AA degree), marital status (married/living with partner, widowed/divorced/separated, never married), smoking status (former, now, or never), drinking status (former, now, or never), PIR, diabetes (no, pre-diabetes, or diabetes mellitus), hypertension (yes or no). Knots = 3. Abbreviations: BMI, body mass index; CI, confidence interval.

pathogenesis of MetS, inflammation related to obesity and overweight plays a significant role, contributing substantially to associated pathological outcomes (57). There is reason to believe that the mechanism of the increased risk of MetS due to elevated HbEO levels may be the pro-inflammatory effects of EO.

Notably, subgroup analysis found no sex disparity in MetS prevalence, which is in line with the findings of previous researches (58, 59). However, the L-shaped relationship between EO levels and the risk of MetS in the female group was also found in grouped RCS analysis, which is in line with what Assmann (60) discovered. Therefore, there is a certain contradiction in our results. With aging, there is a decline in sex hormones, leading to hormonal imbalance, resulting in an increase in testosterone levels and a decrease in estrogen levels in females (61). Estrogen acts at the cellular and organ levels mediated by α and β estrogen receptors, regulating feeding behavior, glucose utilization, insulin production, and visceral fat deposition (62). In the majority of women, post-menopause is not only characterized by redistribution of body weight but also by weight gain. Obesity and weight gain largely contribute to the increased prevalence of MetS after menopause (63). Central obesity also causes endocrine disruption through various mechanisms, including increased sensitivity of the hypothalamic-pituitary axis, increased cortisol, decreased gender-specific steroids, and increased adrenal androgens in women (61). However, the complex interplay among various biological and sex hormone-related factors in the underlying pathophysiology of MetS suggests that hormones do not solely drive gender-related disparities (64). While notable gender differences do exist, with females appearing to have a higher risk of MetS and males exhibiting a higher cardiovascular risk, these differences are not solely attributable to hormonal influences. In addition to hormones and genetic factors, factors such as binge eating, reduced physical activity, cultural expectations, educational attainment, and socioeconomic status contribute to gender and geographical disparities (65). In summary, future research should delve into the contribution of HbEO to MetS in different gender contexts.

MetS is typically closely associated with obesity, which not only constitutes a component of MetS but also serves as an independent risk factor contributing to its development. However, the grouped RCS curve reveals that the risk of MetS shows a rapid increase followed by a gradual decrease with increasing levels of EO in the non-obese group, a pattern not observed in the obese group. Studies exploring the relationship between obesity and HbEO have indicated a negative correlation (24). Therefore, the effect of obesity on HbEO may counterbalance the effect of EO on metabolic syndrome, offering a partial explanation for this phenomenon. On the other hand, obesity plays a significant role in exerting adverse effects on major cardiovascular risk factors (including hypertension, dyslipidemia, and diabetes), being a principal component of metabolic syndrome, and may act as an independent risk factor for atherosclerosis and cardiovascular events (66). However, some reports indicate that overweight and obese patients with coronary heart disease have lower overall mortality and cardiovascular mortality risks compared to those with underweight and normal weight (67). This is the obesity paradox, and HbEO is likely to participate in this mechanism by affecting the body's inflammatory response (66). However, more and deeper mechanisms need to be explored, and more robust evidence can be provided. Furthermore, any acute disruption of a physiological regulatory system tends to elicit a response aimed at restoring balance. When being stimuli, changes in one system and homeostasis affect another system (57). Therefore, when HbEO levels are low, the immune system may be the first to respond, releasing inflammatory factors. When the concentration of HbEO reaches a certain threshold, other systems in the body also react to HbEO or when the concentration of HbEO reaches a threshold, the immune system also happens to reach homeostatic equilibrium. This is evidenced by the fact that as HbEO concentrations continue to rise, the risk of metabolic syndrome begins to decrease. This suggests that non-obese individuals may be more susceptible to the effects of epoxyethane exposure, thereby bearing a higher risk.

The average age of individuals diagnosed with MetS was observed to be higher than that of those without MetS, suggesting an age-related impact on the susceptibility to MetS in relation to EO exposure. This finding aligns with the outcomes of several previous investigations (68–71). With advancing age, the incidence of central obesity, hypertension, diabetes, dyslipidemia, and hormonal imbalances such as declining sex hormone levels may collectively contribute to the escalation of MetS prevalence (72). Notably, among individuals aged over 50, a distinctive L-shaped association between EO levels and MetS risk was discerned, a pattern not evident among those under 30 or between the ages of 30 and 50. Considering the age-related decline in physical performance and the accumulation of HbEO in the body alongside diminished HbEO metabolism, a convergence of factors partially elucidates the heightened vulnerability to MetS among middle-aged and elderly individuals exposed to EO.

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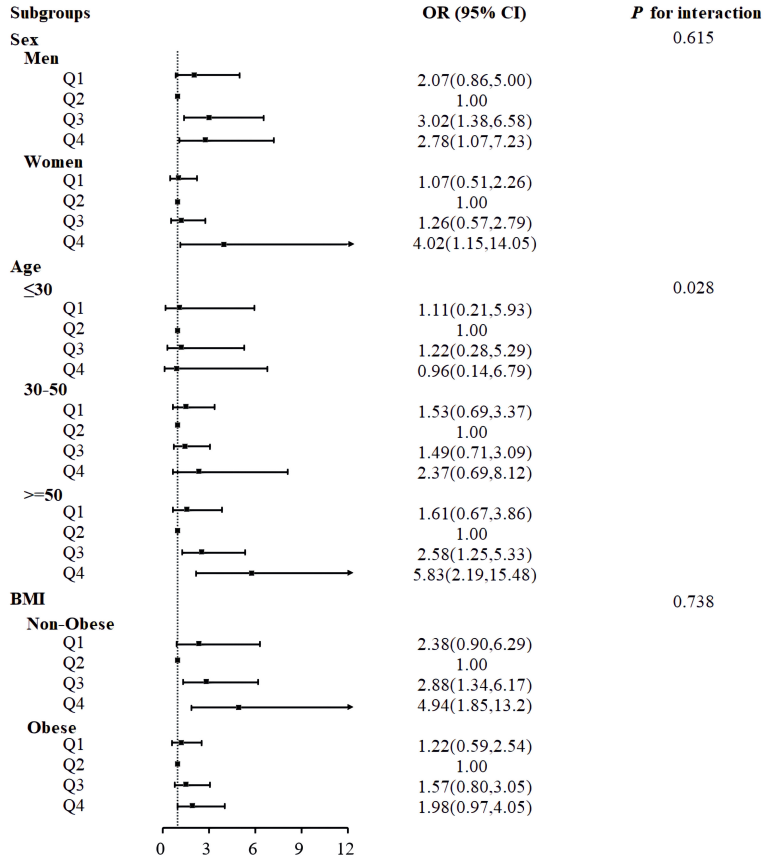

FIGURE 3
Associations between serum ethylene oxide and metabolic syndrome in subgroups. Models were adjusted for age (years), sex, BMI (<30 or ≥ 30kg/m^2), race/ethnicity (Mexican American, Non-Hispanic Black, Non-Hispanic White, Other Race), educational level (9-11th grade or below, high school grad/GED or equivalent, college graduate or above, some college or AA degree), marital status (married/living with partner, widowed/divorced/separated, never married), smoking status (former, now, or never), drinking status (former, now, or never), PIR, diabetes (no, pre-diabetes, or diabetes mellitus), hypertension (yes or no).

This research investigates the relationship between exposure to EO and the risk of MetS, and between exposure to HbEO and the risk of the components of Mets, adding new evidence to the exploration of the pathogenesis of MetS, enriches the etiology of MetS, and provides a new direction for the treatment of it. Secondly, the data used to analyze was from a nationally representative series of surveys, so it was advantageous to generalize the findings gained from this study. At the same time, the limitations also should be mentioned. Firstly, this is a retrospective study, so that the causal relationship cannot be detected. Secondly, the questionnaire contains recall questions, which would cause bias. Finally, the mechanism underlying how EO exposure increases the risk of MetS has not been extensively explored in the current article. Therefore, additional studies are warranted to elucidate this mechanism and provide robust evidence. By conducting more relevant studies, we can strengthen the evidence base and gain deeper insights into the relationship between EO exposure and MetS risk.

5 Conclusion

This study demonstrates that HbEO is a risk factor for MetS and its components. As the levels of HbEO increase, the risk of developing MetS continues to rise. The risk of MetS associated with exposure to HbEO varies depending on gender, age, and BMI.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/index.htm.

Ethics statement

The studies involving humans were approved by National Center for Health Statistics Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CZ: Writing – original draft, Writing – review & editing. LJ: Data curation, Writing – review & editing, Investigation. SW: Writing –

review & editing, Data curation, Methodology. RZ: Data curation, Writing – review & editing. YY: Data curation, Writing – review & editing. LY: Conceptualization, Supervision, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1365658/full#supplementary-material

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Corrigendum: Positive association between blood ethylene oxide levels and metabolic syndrome: NHANES 2013-2020

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In the published article, there was an error in the second affiliation. Instead of "Department of General Surgery, Affiliated Hospital of Southwest Jiaotong University, College of Medicine, Southwest Jiaotong University, Chengdu, Sichuan, China", it should be "Department of General Surgery, The Third People's Hospital of Chengdu, Affiliated Hospital of Southwest Jiaotong University, College of Medicine, Southwest Jiaotong University, Chengdu, Sichuan, China".

In the published article, there was an error in Yanjun Liu's affiliation. Yanjun Liu was not affiliated with "College of Medicine, Southwest Jiaotong University, Chengdu, Sichuan, China" and this has been removed from his affiliations.

The authors apologize for these errors and state that they do not change the scientific conclusions of the article in any way. The original article has been updated.

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Association between a metabolic score for insulin resistance and hypertension: results from National Health and Nutrition Examination Survey 2007–2016 analyses

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Background: The Metabolic Score for Insulin Resistance (METS-IR) offers a promising and reliable non-insulin-based approach to assess insulin resistance and evaluate cardiometabolic risk. However, evidence for the association between METS-IR and hypertension was still limited.

Methods: Participants from the National Health and Nutrition Examination Survey (NHANES) database from 2007-2016 were selected for weighted multivariable regression analyses, subgroup analyses and restricted cubic spline (RCS) modeling to assess the association between the METS-IR and hypertension, as well as systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Results: This study enrolled 7,721 adults aged ≥20 years, 2,926 (34.03%) of whom was diagnosed as hypertension. After adjusting for all potential covariates, an increased METS-IR (log_2 conversion, denoted as log_2METS-IR) was independently associated with a higher prevalence of hypertension (odd ratio [OR] 3.99, 95% confidence interval [CI] 3.19~5.01). The OR for hypertension in subjects with the highest quartile of METS-IR was 3.89-fold (OR 3.89, 95% CI 3.06~4.94) higher than that in those with the lowest quartile of METS-IR. This positive correlation became more significant as METS-IR increased (p for trend < 0.001). Log_2METS-IR was significantly correlated with increase in SBP (β 6.75, 95% CI 5.65~7.85) and DBP (β 5.59, 95% CI 4.75~6.43) in a fully adjusted model. Consistent results were obtained in subgroup analyses. Hypertension, SBP and DBP all exhibited a non-linear increase with the rise in METS-IR. The minimal threshold for the beneficial association of METS-IR with hypertension, SBP and DBP were all identified to be 46.88.

Conclusion: The findings of this study revealed a significant positive association between METS-IR and hypertension among US adults, suggesting METS-IR as a potential tool for assessing hypertension risk.

KEYWORDS

metabolic score for insulin resistance (METS-IR), insulin resistance, metabolic syndrome, hypertension, NHANES

Introduction

Hypertension is a major risk factor for CVD, particularly ischemic heart disease and stroke. It has become a leading cause of global mortality and disability-adjusted life years (1–3). In 2010, about 31.1% of the global adult population (1.39 billion) had hypertension, comprising nearly 10% of worldwide healthcare spending (4). However, hypertension is not accompanied by obvious relevant symptoms, and patients can have hypertension without knowing it (5). Indeed, hypertension frequently coexists with a broader spectrum of anthropometric and metabolic abnormalities, encompassing abdominal (visceral) obesity, characteristic dyslipidemia (low high-density lipoprotein cholesterol and elevated triglyceride levels), glucose intolerance, insulin resistance, and hyperuricemia (6). Therefore, early identification and prevention of hypertension, along with comprehending its association with metabolic components is an essential issue.

Insulin resistance (IR) is closely linked to the substantial development and progression of diabetes (7–9). At present, the high insulin normoglycemic clamp (HEC) stands as the gold standard for assessing insulin sensitivity in peripheral tissues (10). Nonetheless, this invasive approach is intricate, time-consuming, and technically demanding, leading to the common preference for simpler indicators to assess insulin resistance. Traditional tools such as the homeostatic model assessment for IR (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI), which use fasting insulin levels to measure insulin resistance, face practical limitations and variability (11). In addition to other insulin resistance assessment tools that do not require fasting insulin levels, including the product of glucose and triglycerides (TyG index), the product of glucose, triglycerides, and body mass index (TyG-BMI index), and the ratio of triglycerides divided by high density lipoprotein-cholesterol (TG/HDL-C ratio) (12–14), METS-IR emerges as an innovative tool for estimating insulin resistance. It employs readily available primary care parameters: fasting blood glucose (FBG), triglycerides (TG), high density lipoprotein-cholesterol (HDL-C), and body mass index (BMI). This approach eliminates the need for costly and variable fasting insulin tests. As a simple, indirect method, METS-IR identifies insulin resistance and corresponds with the underlying pathophysiological factors of metabolic syndrome, including obesity, dyslipidemia, hyperglycemia and intra-abdominal fat accumulation. Consequently, METS-IR also emerges as a promising metric for evaluating cardiometabolic risk (10, 15–17).

However, there are only few studies on the association between the METS-IR index and hypertension, with studies limited only to China, Mexico and Japan (15, 16, 18–22). The association between METS-IR and hypertension in the US population remains unclear. In this cross-sectional study, we aimed to explore the association between METS-IR and hypertension using data from the National Health and Nutrition Examination Survey (NHANES).

Methods

Study design and participants

Data were downloaded from the NHANES, a nationally representative cross-sectional survey designed and conducted by the National Center for Health Statistics (NCHS). The survey samples the US population using a stratified, multistage probability approach and offers health and nutrition statistics on the non-institutionalized civilian population in the United States. The NCHS Research Ethics Review Board authorized the survey, verifying that all participants provided informed consent. Detailed statistics are accessible at https://www.cdc.gov/nchs/nhanes/.

To evaluate the participants' nutritional and physical health, standardized in-home interviews, physical examinations, and laboratory tests were carried out at mobile examination centers. 50,588 participants were involved in five NHANES cycles from 2007-2016. We excluded 21,387 participants under the age of 20 years, 17,065 with missing complete data about METS-IR and hypertension, 173 with pregnancy and breastfeeding, 4,242 with missing data of covariates. Eventually, 7,721 representative participants were enrolled in the study (Figure 1).

Exposure variable

The arithmetic formula of METS-IR was (Ln[(2×FBG(mg/dL)) +TG(mg/dL)]×BMI(kg/m^2))/[Ln(HDL-C(mg/dL))] (23). After an 8.5-hour overnight fast, morning blood samples were collected to measure fasting glucose and total triglyceride levels. Enzymatic

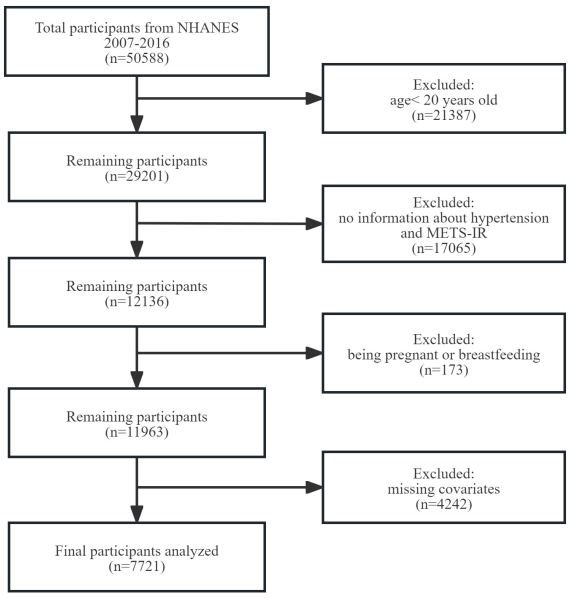

FIGURE 1
Flowchart of participant selection. NHANES, National Health and Nutrition Examination Survey. METS-IR, metabolic score for insulin resistance.

assays were utilized, and automated biochemical analyzers were employed to determine both triglyceride and fasting blood glucose concentrations. Serum triglyceride levels were assessed using Roche Modular P and Roche Cobas 6000 chemistry analyzers. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2).

Outcome variable

Hypertension was defined using these criteria: (1) average SBP ≥140 mmHg, (2) average DBP ≥90 mmHg, (3) self-reported hypertension, or (4) the use of prescribed antihypertensive medications. These criteria adhere to the guidelines established by the International Society of Hypertension, with a threshold of 140/90 mmHg (24).

Covariates

This study incorporated several covariates potentially affecting the association between METS-IR and hypertension. Demographic variables encompassed gender (male/female), age (years), race, educational attainment, family income, smoking and drinking habits, and physical activity levels. Biochemical parameters included uric acid (UA), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C). Health risk factors comprised diabetes and cardiovascular disease (CVD). Racial/ethnic backgrounds were categorized into four groups: non-Hispanic white, non-Hispanic black, Mexican American, and other races. Educational attainment was stratified into three levels: less than 9 years, 9 to 12 years, and over 12 years of education. Family income was classified based on the poverty income ratio (PIR), as defined in a US government report. The categories for family income were defined as follows: low (PIR≤ 1.3), medium (PIR > 1.3 to ≤ 3.5), and high (PIR > 3.5). Smoking status was determined according to the criteria used in prior research, requiring a history of having smoked at least 100 cigarettes during one's lifetime. Drinking status was assessed based on the consumption of a minimum of 12 alcoholic beverages within a year (25). Physical activity was quantified using Physical Activity Level (PAL) scores, which assess the intensity and frequency of various activities, including vigorous (2 points) or moderate (1 point) work-related activity, vigorous (2 points) or moderate (1 point) leisure-time physical activity, and walking or bicycling for transportation (1 point). PAL scores ranged from 0 (minimum) to 5 (maximum) (26). Based on these scores, we categorized physical activity as mild (PAL score 0-1), moderate (PAL score 2-3), or vigorous (PAL score 4-5). In our study, individuals were classified as diabetic based on any of the following: a self-reported diagnosis of diabetes from a doctor or health professional; self-reported use of insulin or diabetic pills; a fasting glucose concentration of ≥7.0 mmol/L; a 2-hour oral glucose tolerance test result of ≥11.1 mmol/L; or a glycohemoglobin HbA1c level of ≥6.5% (27). Cardiovascular disease (CVD) cases were identified through self-reported physician diagnoses, including congestive heart failure, coronary heart disease, angina, heart attack, or stroke (28, 29).

Statistical analysis

For our statistical analyses, we followed the NHANES analytical guidelines, which are detailed at https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx. Our approach accounted for the survey's complex sampling design, incorporating the Fasting Subsample 2 Year Mec Weight (WTSAF2YR×1/5). Baseline characteristics were stratified by quartiles of METS-IR. Continuous variables were presented as means ± standard error (SE), while categorical variables were expressed as percentages. To evaluate differences across the quartiles of METS-IR, we employed either the chi-squared test with Rao & Scott's second-order correction or the Wilcoxon rank-sum test, both adapted for the analysis of complex survey samples. METS-IR was $\log_2$-transformed prior to regression analysis due to its right-skewed distribution. Weighted logistic regression was employed to evaluate the associations between METS-IR and hypertension, estimating the OR and 95% CI for each one-unit increase in $\log_2$METS-IR as well as for each METS-IR quartile. Additionally, weighted linear regression was used to assess the relationships between $\log_2$METS-IR and both SBP and DBP, estimating the regression coefficient (β) and its corresponding 95% CI. Five adjustment models were applied in the present study, with adjustment for potential confounders ascertained. Model 1 made no adjustments for covariates. Model 2 included adjustments for sex, age, race, education level, and family

income. Model 3 incorporated additional adjustments for smoking status, drinking status, and physical activity. Model 4 extended the adjustments to include UA, TC, and LDL-C. Model 5 further expanded the adjustments to encompass diabetes and CVD.

We further explored potential modifications in the relationship between log_2METS-IR and hypertension as well as SBP and DBP, considering variables such as sex, age (<65 vs. ≥65 years), race, education level (<9 years, 9~12 years, and ≥12 years), family income (low vs. medium or high), smoking status (No vs. Yes), drinking status (No vs. Yes), physical activity (mild vs. moderate or vigorous), diabetes (No vs. Yes), and CVD (No vs. Yes). We assessed subgroup heterogeneity using weighted multivariate logistic regression and examined interactions between subgroups and METS-IR through likelihood ratio testing.

Additionally, we employed RCS regression to evaluate non-linearity relationship between METS-IR and hypertension as well as SBP and DBP, following adjustment for variables in Model 5.

Since the sample size was determined based on available data, no prior statistical power calculation was conducted. We conducted our analyses using R software (version 4.3.3; R Foundation for Statistical Computing; http://www.Rproject.org), the R survey package (version 4.2.1), and Free Statistics software (version 1.9.2; Beijing Free Clinical Medical Technology Co., Ltd.). A two-sided p-value < 0.05 was considered statistically significant in all analyses. Data analysis was conducted from October 2023 to March 2024.

Results

Baseline characteristics of participants

In this study, out of a total of 50,588 patients, we included 7,721 adults aged 20 and above, representing a weighted population of 156,951,593 individuals. The cohort's mean age, adjusted for the sample design, was 46.27 years (SE = 0.31), and it comprised 3,845 women, accounting for 49.65% of the weighted sample. Among these individuals, 2,926 (34.03%) were identified as having hypertension. The mean SBP and DBP were 120.37 (SE = 0.26) and 69.32 (SE = 0.26), respectively. METS-IR were significantly associated with all examined characteristics (all p<0.05). Table 1 displays the baseline characteristics according to the METS-IR quartiles in a weighted analysis, whereas Supplementary Table 1 presents the baseline characteristics by METS-IR quartiles in an unweighted analysis. To further validate the results, multiple imputations were conducted, with the distribution of baseline characteristics illustrated in Supplementary Table 2.

TABLE 1 Characteristics of the study population according to the quartiles of METS-IR, weighted[a].

Characteristic	Overall N = 7721	Quartile 1 N = 1930	Quartile 2 N = 1930	Quartile 3 N = 1930	Quartile 4 N = 1931	*p* value
Sex, n (%)						<0.001
Male	3,876 (50.35)	753 (36.46)	1,009 (51.85)	1,095 (58.19)	1,019 (55.74)	
Female	3,845 (49.65)	1,177 (63.54)	921 (48.15)	835 (41.81)	912 (44.26)	
Age, Mean (SE)	46.27 (0.31)	44.19 (0.67)	47.68 (0.48)	47.46 (0.43)	45.87 (0.48)	<0.001
Race, n (%)						<0.001
Non-Hispanic White	3,649 (70.34)	955 (71.61)	926 (71.04)	856 (69.20)	912 (69.41)	
Non-Hispanic Black	1,354 (9.89)	319 (9.37)	343 (10.01)	343 (9.67)	349 (10.52)	
Mexican American	1,134 (7.82)	172 (4.83)	250 (6.70)	353 (9.79)	359 (10.17)	
Other races	1,584 (11.95)	484 (14.19)	411 (12.25)	378 (11.34)	311 (9.90)	
Education level (year), n (%)						<0.001
< 9	643 (4.50)	104 (2.63)	159 (4.65)	208 (5.80)	172 (5.04)	
9~12	2,800 (32.40)	605 (27.75)	687 (31.57)	745 (35.63)	763 (34.97)	
≥12	4,278 (63.10)	1,221 (69.62)	1,084 (63.78)	977 (58.57)	996 (59.99)	
Family income, n (%)						<0.001
Low	2,404 (21.35)	557 (20.72)	556 (18.81)	599 (21.68)	692 (24.24)	
Medium	2,836 (35.22)	669 (31.33)	716 (35.69)	746 (37.35)	705 (36.74)	
High	2,481 (43.43)	704 (47.95)	658 (45.50)	585 (40.97)	534 (39.01)	

(Continued)

TABLE 1 Continued

Characteristic	Overall N = 7721	Quartile 1 N = 1930	Quartile 2 N = 1930	Quartile 3 N = 1930	Quartile 4 N = 1931	*p* value
Smoking status, n (%)						0.027
No	4,256 (55.06)	1,140 (58.32)	1,053 (53.59)	1,042 (54.46)	1,021 (53.70)	
Yes	3,465 (44.94)	790 (41.68)	877 (46.41)	888 (45.54)	910 (46.30)	
Drinking status, n (%)						0.042
No	1,977 (20.96)	484 (19.73)	467 (19.30)	502 (21.57)	524 (23.31)	
Yes	5,744 (79.04)	1,446 (80.27)	1,463 (80.70)	1,428 (78.43)	1,407 (76.69)	
Physical activity, n (%)						<0.001
Mild	3,735 (43.65)	847 (38.04)	894 (41.02)	955 (45.87)	1,039 (50.00)	
Moderate	3,257 (45.78)	875 (50.22)	846 (47.36)	790 (43.20)	746 (42.07)	
Vigorous	729 (10.57)	208 (11.74)	190 (11.62)	185 (10.93)	146 (7.93)	
UA, umol/L, Mean (SE)	325.81 (1.27)	284.79 (2.38)	314.05 (2.30)	340.72 (1.89)	366.03 (2.25)	<0.001
TC, mmol/L, Mean (SE)	5.02 (0.02)	4.96 (0.03)	5.02 (0.03)	5.12 (0.03)	4.99 (0.03)	0.001
LDL-C, mmol/L, Mean (SE)	3.01 (0.01)	2.78 (0.03)	3.04 (0.02)	3.18 (0.03)	3.06 (0.03)	<0.001
Diabetes, n (%)						<0.001
No	6,957 (92.65)	1,851 (97.20)	1,791 (94.60)	1,717 (92.41)	1,598 (86.16)	
Yes	764 (7.35)	79 (2.80)	139 (5.40)	213 (7.59)	333 (13.84)	
CVD, n (%)						0.010
No	7,062 (93.02)	1,798 (94.19)	1,772 (93.28)	1,764 (93.72)	1,728 (90.87)	
Yes	659 (6.98)	132 (5.81)	158 (6.72)	166 (6.28)	203 (9.13)	
SBP, mmHg, Mean (SE)	120.37 (0.26)	116.01 (0.46)	120.18 (0.41)	121.70 (0.40)	123.81 (0.46)	<0.001
DBP, mmHg, Mean (SE)	69.32 (0.26)	66.83 (0.34)	68.29 (0.39)	70.29 (0.38)	72.01 (0.35)	<0.001
Hypertension, n (%)						<0.001
No	4,795 (65.97)	1,457 (79.97)	1,256 (68.03)	1,100 (61.49)	982 (53.61)	
Yes	2,926 (34.03)	473 (20.03)	674 (31.97)	830 (38.51)	949 (46.39)	
METS-IR, Mean (SE)	48.70 (0.26)	33.67 (0.10)	42.89 (0.06)	51.34 (0.07)	67.71 (0.35)	<0.001

[a]All means and SEs for continuous variables and percentages for categorical variables were weighted. SE, standard error; UA, uric acid; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; CVD, cardiovascular disease; SBP, systolic pressure; DBP, diastolic pressure; METS-IR, the Metabolic Score for Insulin Resistance.

Associations of METS-IR with hypertension and SBP/DBP

Table 2 displays the associations between the METS-IR and hypertension. Across all five adjusting models, METS-IR was positively associated with hypertension. The ORs for log_2METS-IR, analyzed as a continuous variable, were consistently significant: OR 3.27 (95% CI 2.71~3.95, p <0.001) in Model 1; OR 4.46 (95% CI 3.65~5.45, p < 0.001) in Model 2; OR 4.46 (95% CI 3.64~5.47, p < 0.001) in Model 3; OR 4.08 (95% CI 3.26~5.10, p < 0.001) in Model 4; and OR 3.99 (95% CI 3.19~5.01, p < 0.001) in Model 5. We converted METS-IR from a continuous to a categorical variable (quartiles) for sensitivity analysis. In the fully adjusted Model 5, the adjusted ORs for hypertension in quartiles 2, 3, and 4 were 1.91 (95% CI 1.54~2.37), 2.7 (95% CI 2.15~3.40), and 3.89 (95% CI 3.06~4.94), respectively, using quartile 1 as the reference. This pattern of significant positive association persisted across all models (p < 0.001), underscoring a robust link between METS-IR levels and hypertension risk. Additionally, there was a significant increasing trend in hypertension risk across METS-IR quartiles (p for trend < 0.001, displayed in Table 2). Sensitivity analysis using multiple imputation of missing datasets corroborated these findings (see Supplementary Table 3).

Across all regression models (Table 3), a significant positive association was observed between log_2 METS-IR and both SBP and DBP. Specifically, in full adjusted model 5, the adjusted β for SBP was 6.75 (95% CI 5.65~7.85, P < 0.001) and the adjusted β for DBP was 5.59 (95% CI 4.75~6.43, p <0.001), indicating that each unit of increased log_2 METS-IR was associated with 6.75 mmHg increased of SBP and 5.59 mmHg increased of DBP, respectively. This observation also persisted in other models (model 1, model 2, model 3 and model 4). Sensitivity analysis employing multiple

TABLE 2 Association between METS-IR and hypertension.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Log_2METS-IR	3.27 (2.71~3.95)	<0.001	4.46 (3.65~5.45)	<0.001	4.46 (3.64~5.47)	<0.001	4.08 (3.26~5.10)	<0.001	3.99 (3.19~5.01)	<0.001
METS-IR, Quartile										
Quartile 1	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Quartile 2	1.88 (1.57~2.25)	<0.001	1.78 (1.45~2.19)	<0.001	1.78 (1.45~2.18)	<0.001	1.9 (1.53~2.37)	<0.001	1.91 (1.54~2.37)	<0.001
Quartile 3	2.5 (2.06~ 3.03	<0.001	2.64 (2.14~3.26)	<0.001	2.63 (2.13~3.24)	<0.001	2.68 (2.12~ 3.38)	<0.001	2.7 (2.15~3.40)	<0.001
Quartile 4	3.45 (2.84~4.21)	<0.001	4.43 (3.57~5.49)	<0.001	4.39 (3.53~ 5.45)	<0.001	3.97 (3.13~5.02)	<0.001	3.89 (3.06~4.94)	<0.001
Trend.test		<0.001		<0.001		<0.001		<0.001		<0.001

METS-IR, the Metabolic Score for Insulin Resistance; OR, odds ratio; CI, confidence interval; UA, uric acid; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; CVD, cardiovascular disease.
Model 1: No covariates were adjusted.
Model 2: Adjusted by sex, age, race, education level and family income.
Model 3: Adjusted by sex, age, race, education level, family income, smoking status, drinking status and physical activity.
Model 4: Adjusted by sex, age, race, education level, family income, smoking status, drinking status, physical activity, UA, TC and LDL-C.
Model 5: Adjusted by sex, age, race, education level, family income, smoking status, drinking status, physical activity, UA, TC, LDL-C, diabetes and CVD.

TABLE 3 Association between METS-IR and SBP/ DBP.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
SBP	7.92 (6.80~ 9.03)	<0.001	6.48 (5.54~7.42)	<0.001	6.55 (5.57~7.53)	<0.001	6.98 (5.88~8.08)	<0.001	6.75 (5.65~7.85)	<0.001
DBP	5.14 (4.40~5.87)	<0.001	4.95 (4.26~5.63)	<0.001	4.97 (4.29~5.65)	<0.001	5.51 (4.68~6.34)	<0.001	5.59 (4.75~6.43)	<0.001

METS-IR, the Metabolic Score for Insulin Resistance; CI, confidence interval; SBP, systolic pressure; DBP, diastolic pressure; UA, uric acid; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; CVD, cardiovascular disease.
Model 1: No covariates were adjusted.
Model 2: Adjusted by sex, age, race, education level and family income.
Model 3: Adjusted by sex, age, race, education level, family income, smoking status, drinking status and physical activity.
Model 4: Adjusted by sex, age, race, education level, family income, smoking status, drinking status, physical activity, UA, TC and LDL-C.
Model 5: Adjusted by sex, age, race, education level, family income, smoking status, drinking status, physical activity, UA, TC, LDL-C, diabetes and CVD.

imputation of missing datasets yielded consistent results (Supplementary Table 4), corroborating the observed associations.

Subgroup analyses revealed a consistent positive association between log_2 METS-IR and hypertension across various subgroups. However, significant interaction effects were observed in family income and smoking status subgroups, indicating differential associations in these groups (*p* for interaction <0.05), as shown in Figure 2A. Regarding SBP, a significant positive association with log_2METS-IR was detected in all subgroups with interaction effects observed in age, education level, family income, smoking status and physical activity subgroups (P for interaction <0.05), as depicted in Figure 2B. For DBP, a consistent positive association with log_2METS-IR was observed across all groups, with interaction effects identified specifically within the age subgroups (P for interaction <0.05), illustrated in Figure 2C.

Using RCS regression and adjusting for all covariates, we observed a significant positive non-linear relationship between METS-IR and hypertension risk, as well as SBP and DBP (all *p* for non-linearity < 0.001) (Figures 3A-C). The minimal thresholds for the beneficial association of METS-IR with hypertension (estimate OR =1), SBP (estimate β =0) and DBP (estimate β =0) were all 46.88.

Discussion

In this population-based, cross-sectional study, we explored the association between METS-IR, an new tool for estimating insulin resistance, and hypertension. After adjusting for potential confounders, our results showed that METS-IR, either as a

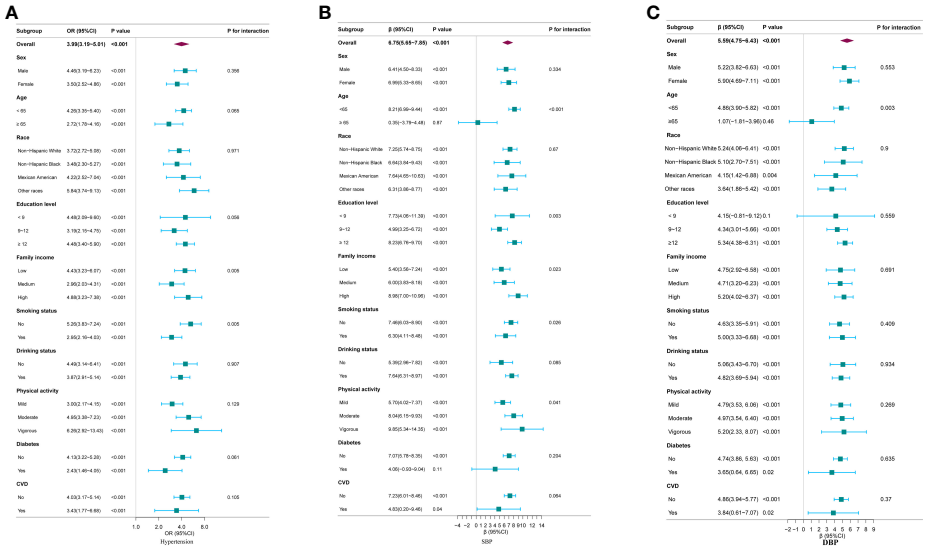

FIGURE 2
Subgroup analysis for the association between log_2METS-IR and hypertension, as well as SBP and DBP. **(A)** Hypertension; **(B)** SBP; **(C)** DBP. Except for the stratification component itself,each stratification factor was adjusted for all other variables (sex, age, race, education level, family income, smoking status, drinking status, physical activity, UA, TC, LDL-C, diabetes and CVD).

continuous or a categorical variable, was significantly associated with hypertension among US adults. This positive association also extended to the level of SBP and DBP. The subgroup analyses yielded similar results. Through RCS regression analysis, we observed a non-linear dose-response relationship between METS-IR and hypertension risk. The minimal thresholds for the beneficial association of METS-IR with hypertension, SBP and DBP were all 46.88. Our results indicate that METS-IR, readily assessable in primary care settings, could be an effective early marker for hypertension, contributing to primary prevention strategies.

Many studies have found that hypertension and insulin resistance were closely related and mutually causal. The well-established bidirectional link between hypertension and insulin resistance is substantiated by Wang et al.'s meta-analysis. This study found that elevated fasting insulin levels or insulin resistance, quantified using HOMA-IR, correlate with an increased risk of hypertension in the general population. Notably, individuals with the highest fasting insulin and HOMA-IR levels showed a 54% and 43% increased risk, respectively, of developing hypertension (30). Lin et al.'s study demonstrated that individuals with hypertension experienced a more significant increase in HOMA-IR over five years (ΔHOMA2-IR/5 yr) compared to non-hypertensive individuals (adjusted $p = 0.044$). Furthermore, those with treated hypertension were at the highest risk of developing diabetes, as evidenced by a hazard ratio (HR) of 2.98 ($p < 0.001$), and exhibited the greatest change in ΔHOMA2-IR/5 yr relative to those with normal blood pressure (31). Although some studies have identified a relationship between insulin resistance or hyperinsulinemia and hypertension, others, such as Ferrannini et al., have reported more ambiguous associations (32). Specifically, their study involving 2,241 normotensive, nondiabetic individuals showed that a substantial increase in plasma insulin

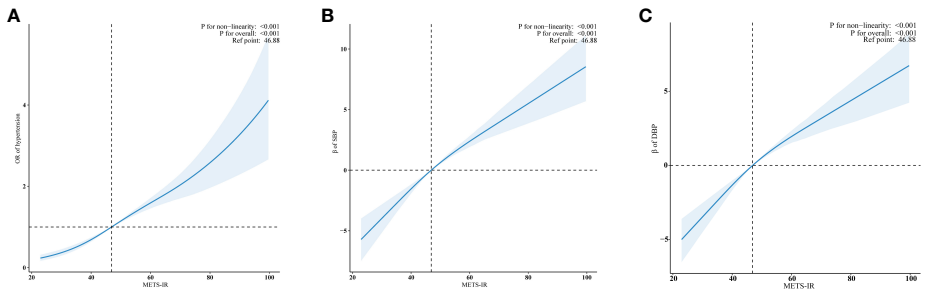

FIGURE 3
Examination of the dose-response relationship between log_2METS-IR and hypertension, as well as SBP and DBP by RCS model. **(A)** Hypertension; **(B)** SBP; **(C)** DBP. The RCS model adjusted for sex, age, race, education level, family income, smoking status, drinking status, physical activity, UA, TC, LDL-C, diabetes and CVD. Only 99% of the data is shown.

concentration (200 μU/mL) was associated with only a minimal rise in blood pressure (BP) of 1 mm Hg. Moreover, other researchers have observed similar plasma insulin levels in normotensive, nondiabetic individuals and those with hypertension, hinting at a possible inverse relationship between insulin and BP (33). Furthermore, in various types of secondary hypertension not linked to obesity, such as renovascular or mineralocorticoid-induced hypertension, there is no evidence to suggest the presence of insulin resistance (34). These findings indicate that hyperinsulinemia or insulin resistance alone cannot fully account for a direct relationship with hypertension.

However, the metabolic outcomes of insulin resistance, including obesity, hyperglycemia, and dyslipidemia, may exacerbate hypertension (33). A novel measure for evaluating insulin resistance, named METS-IR, has been developed. This metric is calculated from fasting levels of glucose, triglycerides, HDL-C, and BMI. Crucially, METS-IR integrates aspects of obesity and metabolic syndrome and avoids dependence on fasting insulin levels (10). Several studies have investigated the relationship between METS-IR and hypertension. Han et al.'s research in normoglycemic individuals from Gifu, Japan, identified a significant link between high METS-IR and both pre-hypertension (adjusted OR = 1.95, 95% CI: 1.61–2.36) and hypertension (adjusted OR = 2.12, 95% CI: 1.44–3.11), persisting even after adjusting for confounders in multivariable logistic regression. Furthermore, when considering METS-IR as a continuous variable, each unit increase was associated with a 7% rise in pre-hypertension (adjusted OR = 1.07, 95% CI: 1.06–1.08) and a 13% increase in hypertension (adjusted OR = 1.13, 95% CI: 1.10–1.16). Stratified analyses showed a positive correlation between METS-IR and both pre-hypertension and hypertension across diverse normoglycemic subgroups (22). However, as the study data were sourced from Japanese subjects, the applicability of the findings to other ethnic groups remains uncertain. Additionally, this research, being a secondary analysis of pre-existing data, lacks clarity on the specific procedures used during medical consultations, such as the methodology for measuring blood pressure. Xu et al. explored the association between the METS-IR and hypertension in the non-overweight Chinese population. They observed a significant increase in the risk of developing hypertension in the third quartile group (HR 1.58, 95% CI 1.12–2.22), with an even higher risk in the fourth quartile group (HR 1.96, 95% CI 1.40–2.76), compared to the lowest quartile of METS-IR. The study identified a linear dose-response relationship between METS-IR and hypertension risk (HR 1.08, 95% CI 1.04–1.12) (35). The study failed to address key lifestyle influences like physical activity, alcohol consumption, and smoking, which are significant for blood pressure. Additionally, its findings, based primarily on Chinese participants, may not extend to other ethnic groups. Li et al. discovered that METS-IR served as a potent predictor of CVD and its subtypes among patients with hypertension and obstructive sleep apnea, thereby aiding in the identification of high-risk individuals and offering personalized CVD prevention strategies (15). In another study conducted by the same researchers, it was suggested that there exists an association between METS-IR and the risk of both overall stroke and ischemic stroke specifically among patients with hypertension (16). These two studies primarily concentrated on assessing the cardiovascular and cerebrovascular risks associated with METS-IR among patients with hypertension.

Our study, however, focused on exploring the association between METS-IR and hypertension among adults aged 20 years and older in the US, utilizing data from NHANES. We excluded BMI and waist circumference to avoid co-linearity with METS-IR, while included diabetes and CVD due to their known associations with hypertension. In our fully adjusted model, accounting for diabetes and CVD, we still found a robust association between METS-IR and hypertension risk, as well as SBP and DBP, even though prior research had already established the connections between METS-IR and both diabetes and CVD. Notably, our study reveals a dose-response relationship between METS-IR and hypertension, marking a significant finding in understanding hypertension's metabolic drivers. We have established specific METS-IR thresholds at 46.88, linked to hypertension, SBP, and DBP, offering clinicians and researchers precise, actionable criteria for early detection and intervention. This development enhances hypertension risk stratification, incorporating METS-IR into assessments for a more refined prediction of hypertension risk. Such integration paves the way for personalized and more effective prevention strategies. Beyond its immediate findings, our study paves the way for future research into the mechanisms by which METS-IR influences hypertension. It opens up new avenues for exploring potential interventions that could mitigate this risk, thereby contributing to the broader goal of reducing the global burden of hypertension.

Pathophysiological evidence supports a link between METSIR and hypertension. Metabolic outcomes of insulin resistance may lead to hypertension through various mechanisms, including adipokines from fat tissue, altered gut microbiota, sympathetic nervous system (SNS) activation, imbalance in antinatriuretic and natriuretic hormones, and dysfunction in vascular and renal systems (36–39). Both animal and human studies suggest that hypertension in metabolic syndrome arises from factors that increase renal sodium reabsorption, leading to extracellular fluid volume expansion. Notably, three mechanisms are critical in this process: kidney compression by surrounding fat, renin-angiotensin-aldosterone system activation, and heightened SNS activity. Chronic obesity exacerbates hypertension and causes cardiovascular and renal damage, especially in conjunction with metabolic issues like hyperglycemia and hyperlipidemia (40, 41). Further investigation is needed to elucidate the exact underlying mechanisms and enhance our understanding of the pathophysiology of hypertension.

Several advantages can be attributed to our study. A representative sample of the US population is collected in the NHANES from 2007- 2016 based on a well-designed study protocol with extensive quality assurance and quality control. As a second step, we controlled for confounding covariates to ensure that our results are reliable and applicable to a broad range of individuals. We acknowledge, however, that the study has certain limitations. First, as a result of the cross-sectional nature of the study, we could not determine the temporal association between METS-IR and hypertension. Recognizing this limitation, we suggest that future research on the relationship between METS-IR and hypertension

should include longitudinal designs. Such studies would enable researchers to track changes over time, providing clearer insights into whether elevated METS-IR levels precede the development of hypertension, thereby offering stronger evidence of a potential causal relationship. Second, because of a lack of data covariates, a large number of participants were excluded, which might cause bias. To mitigate this, we utilized multiple imputation (MI) techniques to address the gaps in our data, followed by a thorough re-analysis of the imputed dataset. Our sensitivity analysis shows that our primary conclusions remain stable, even when considering the potential impact of missing data, thus bolstering our confidence in the robustness of our findings. Third, the study did not eliminate bias from additional potential confounders, like dietary patterns, genetic predispositions, and psychosocial stressors, that were not adjusted for. Last, we recognize that relying on diagnoses derived from databases, instead of direct clinical measurements or diagnoses from medical institutions, introduces potential biases into our study. This limitation stems from the inherent nature of cross-sectional studies, which often depend on previously collected data and may lack the specificity and accuracy of clinical diagnoses. These limitations highlight the importance of conducting future longitudinal studies to investigate these aspects further.

Conclusion

The findings of this cross-sectional study suggest that a higher METS-IR was independently associated with a higher prevalence of hypertension and a higher SBP and DBP. These findings indicate that METS-IR could potentially act as an effective tool for assessing hypertension risk and formulating targeted intervention strategies based on METS-IR levels. However, further longitudinal studies are necessary to validate these findings. Additional research is also needed to uncover the mechanisms through which METS-IR influences hypertension and to identify potential targets for therapy.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.cdc.gov/nchs/nhanes/.

Ethics statement

The studies involving humans were approved by The NCHS Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

JZ: Writing – review & editing, Writing – original draft. TZ: Writing – review & editing, Writing – original draft. YY: Writing – review & editing, Writing – original draft. JW: Writing – review & editing, Writing – original draft. DZ: Writing – review & editing. YH: Writing – review & editing. YT: Writing – review & editing. XF: Writing – review & editing. XW: Writing – review & editing, Writing – original draft. YF: Writing – review & editing, Writing – original draft.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1369600/full#supplementary-material

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Surrogate indices of insulin resistance using the Matsuda index as reference in adult men—a computational approach

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Background: Overweight and obesity, high blood pressure, hyperglycemia, hyperlipidemia, and insulin resistance (IR) are strongly associated with non-communicable diseases (NCDs), including type 2 diabetes, cardiovascular disease, stroke, and cancer. Different surrogate indices of IR are derived and validated with the euglycemic–hyperinsulinemic clamp (EHC) test. Thus, using a computational approach to predict IR with Matsuda index as reference, this study aimed to determine the optimal cutoff value and diagnosis accuracy for surrogate indices in non-diabetic young adult men.

Methods: A cross-sectional descriptive study was carried out with 93 young men (ages 18–31). Serum levels of glucose and insulin were analyzed in the fasting state and during an oral glucose tolerance test (OGTT). Additionally, clinical, biochemical, hormonal, and anthropometric characteristics and body composition (DEXA) were determined. The computational approach to evaluate the IR diagnostic accuracy and cutoff value using difference parameters was examined, as well as other statistical tools to make the output robust.

Results: The highest sensitivity and specificity at the optimal cutoff value, respectively, were established for the Homeostasis model assessment of

insulin resistance index (HOMA-IR) (0.91; 0.98; 3.40), the Quantitative insulin sensitivity check index (QUICKI) (0.98; 0.96; 0.33), the triglyceride-glucose (TyG)-waist circumference index (TyG-WC) (1.00; 1.00; 427.77), the TyG-body mass index (TyG-BMI) (1.00; 1.00; 132.44), TyG-waist-to-height ratio (TyG-WHtR) (0.98; 1.00; 2.48), waist-to-height ratio (WHtR) (1.00; 1.00; 0.53), waist circumference (WC) (1.00; 1.00; 92.63), body mass index (BMI) (1.00; 1.00; 28.69), total body fat percentage (TFM) (%) (1.00; 1.00; 31.07), android fat (AF) (%) (1.00; 0.98; 40.33), lipid accumulation product (LAP) (0.84; 1.00; 45.49), leptin (0.91; 1.00; 16.08), leptin/adiponectin ratio (LAR) (0.84; 1.00; 1.17), and fasting insulin (0.91; 0.98; 16.01).

Conclusions: The computational approach was used to determine the diagnosis accuracy and the optimal cutoff value for IR to be used in preventive healthcare.

KEYWORDS

surrogate indices, insulin resistance, young adult men, computational approach, Matsuda index

Introduction

The world population with obesity [body mass index (BMI) ≥ 30 kg/m^2] in the year 2020 was 988 million individuals (14%), and by 2035, it is projected to reach 1.914 billion people (24%) (1). Moreover, according to the statistics of the International Diabetes Federation (IDF), approximately 537 million adults between the ages of 20 and 79 worldwide have diabetes, and it is expected to reach 643 million by the year 2030 (2). Additionally, obesity is associated with chronic and low-grade inflammation due to the abnormal or excessive fat secretions of adipokines that might lead to decreases in insulin sensitivity in target tissues, such as adipose tissue, skeletal muscle, and liver (3, 4). The insulin resistance (IR) or impaired insulin sensitivity is considered to be one of the major invisible changes, between 10 and 15 years, before the diagnosis and progression of different non-communicable diseases (NCDs), including type 2 diabetes (T2DM), nonalcoholic fatty liver disease (NAFLD), heart disease, and stroke (3–5).

On the other hand, progression to hyperglycemia and T2DM may be caused by impaired insulin secretion due to beta cell dysfunction or insulin insensitivity of target tissues (6, 7). In patients with diabetes mellitus, chronic hyperglycemia and IR are risk factors for the pathogenesis of atherosclerosis and long-term cardiovascular complications and, therefore, the main cause of disability and death. It is important to highlight that the diagnosis of IR and T2DM is based on determinations of fasting glucose and glycated hemoglobin (HbA1c) levels and 2-h post-load plasma glucose (2h-PG) measurements after an oral glucose tolerance test (OGTT), methodology that in many circumstances cannot detect this pathology in the early stages, as described elsewhere (8). On the other hand, the Matsuda index, the Homeostasis model assessment of insulin resistance index (HOMA-IR), and the Quantitative insulin sensitivity check index (QUICKI) are the most common surrogate indices with the highest accuracy for evaluating insulin sensitivity/resistance and showed a strong significant correlation with the clamp-derived insulin sensitivity [euglycemic–hyperinsulinemic clamp (EHC)] test (6, 9). Additionally, previously studies have demonstrated that the Matsuda index determined after an OGTT, which combines both hepatic and peripheral tissue insulin sensitivity analysis, has greater diagnostic ability than the HOMA-IR index, which is based on fasting analysis samples and is associated primarily with hepatic IR (9, 10). Moreover, fasting glucose, 1h-PG, and 2h-PG have been studied to predict IR and their relation with several parameters used in diagnosing IR in diverse NCDs (8, 11). In this way, there is an urgent need to establish the most predictive IR index with excellent sensitivity, specificity, and optimal cut-off value for health impact assessment in chronic NCDs.

On the other hand, several surrogate indices have been proposed in population studies that are based on anthropometric, biochemical, and hormonal determinations to assess insulin sensitivity/resistance using reliable, accessible, and less expensive methods. However, owing to the high cutoff value variability observed, additional studies are required to validate the reliable cutoff values of these indices for detecting IR (12, 13). Additionally, previous studies have shown that the use of fasting and 2h-PG levels has relatively low accuracy for early prediction of impaired glucose tolerance and T2DM, cardiovascular disease (CVD), and mortality rate (14). In this way, several surrogate indices that evaluate IR have been validated, including Matsuda, HOMA-IR, QUICKI, triglyceride-glucose (TyG) index, triglycerides-to-HDL-C ratio (TG/HDL-c), BMI (kg/m^2), visceral adiposity index (VAI), TyG-waist circumference (TyG-WC), TyG-body mass index (TyG-BMI), TyG-waist-to-height ratio (TyG-WHtR), lipid accumulation

product (LAP), leptin/adiponectin ratio (LAR), total body fat percentage (TFM %), android fat (AF %), waist circumference (WC), and waist-to-height ratio (WHtR) (12–23).

Obesity-associated IR as a risk factor that may increase the progression to prediabetes, T2DM, and CVD as the leading cause of global death, and prompt implementation of accurately surrogate indices might be used as predictive tools for population-based screening programs for recommendations of preventive action to address and mitigate NCDs and to reduce the period of undiagnosed diabetes and complications at the time of diagnosis, several years before the onset of symptoms. The EHC technique is the gold standard method for the detection of IR with limited clinical applicability; however, different surrogate indices of IR have been proposed, and some of these values remain dubious due to the lack of standard, desirable, and local cutoff value guidelines for early detection to improve the diagnosis and treatment of disorders associated with hyperglycemia and IR (9, 24).

Thus, the aims of this study are to propose a computational approach to accurately determine the optimal cutoff values and the ability to predict IR using the Matsuda index as reference for surrogate indices of insulin sensitivity/resistance in non-diabetic young adult men, and to use this approach quickly, easily, and at a low cost for IR screening and preventive medicine.

Materials and methods

Ethical considerations

This protocol was approved by the Ethics Committee of the School of Medicine—Universidad Nacional de Colombia (protocols B.FM.1.002-CE-0194-22 and B.FM.1.002-CE-081-22) and conducted in accordance with the Helsinki Declaration. All individuals were informed about the aim of this research study and gave their written consent prior to enrollment in the protocol study. The inclusion criteria were as follows: lean (BMI between 18.0 and 24.9 kg/m^2) and obese (BMI ≥ 30 kg/m^2) young adult men (18–31 years of age). Participants with preexisting metabolic diseases, T2DM, liver disease, and renal and cardiovascular dysfunction who were taking thyroid medications and current therapy that could alter metabolism were excluded.

Study design and participants

The methodology of the current study has been described in detail elsewhere (25). Briefly, an exploratory cross-sectional study with case and control selection of the individuals (obese and healthy men) was conducted with 93 young adult men (ages 18–30). Weight, height, WC, systolic blood pressure (SBP, mmHg), and diastolic blood pressure (DBP, mmHg) were determined by trained personnel. Body composition, including TFM (%), gynoid fat (GF, %), and central fat mass (AF, %), was obtained by dual energy x-ray absorptiometry (DXA) (Lunar Prodigy Primo - GE Healthcare). BMI was determined as weight (kg) divided by height (m) squared (kg/m^2).

Analytical assessment

All subjects underwent a 75-g OGTT after an overnight fast of 8–10 h. Blood samples were drawn in a dry tube from an antecubital vein between 7:00 and 8:00 a.m. during fasting before glucose ingestion (0 h) and 30, 60, and 120 min after a 75-g oral glucose load. Samples were centrifuged (4,000*g*) and serum was transferred into plastic tubes and stored at −80°C until analysis. At each point, glucose and insulin were determined; meanwhile, lipid profile and leptin and adiponectin levels were analyzed in fasting state, as described elsewhere (25). Leptin and adiponectin levels were determined by ELISA, as described previously (25).

Calculation of indices

The Matsuda index, HOMA-IR, QUICKI, TyG index, TG/HDL-c, VAI, TyG-WC, BMI (kg/m^2), TyG-BMI, WHtR, TyG-WHtR, LAP, and LAR were calculated as described elsewhere (12, 22, 26–33). Formulas for surrogate indices are described in the Supplementary Materials.

Statistical analysis

The average ± standard deviation (SD) for each variable was presented in a tabular array. Initially, a descriptive analysis was performed separating groups into IR and non-IR levels, with the Matsuda index as reference. IR was defined according to the cutoff value of the Matsuda index as described elsewhere (13, 15). The optimal starting cutoff value for Matsuda was generated from the arithmetic average of the maximum of the IR level with the minimum of the non-IR level (in this case, the optimal starting value was 4.03).

For the bivariate analysis, a scatter diagram was made to detect the monotonic or linear pattern of the relationship of the variables and to describe the windows of separation or overlap of importance to define the starting point of the algorithm or initial conditions. Thus, bivariate analyses for the Matsuda index and glucose, insulin levels, hormonal levels, anthropometric measures, and different surrogate indices were also performed. Furthermore, the violin plots showing the interquartile range distribution of IR and non-IR individuals based on the optimal cutoff value and diagnosis performance (sensitivity and specificity) were obtained using the iterative computational approach process for the different variables. The R code for both the computational proposal and the final statistical analysis appears on the GitHub described in the Supplementary Materials.

Computational approach description

The computational approach for diagnosis accuracy and determination of the optimal cutoff values for prediction of insulin sensitivity/resistance is described in the Supplementary Materials. The key steps involved in the algorithm approach are listed below; however, in the Supplementary Materials, the code is

developed and commented on so that any user can understand each step until the output is generated:

1. Standardize by *Z*-score (SD) all quantitative variables: This was done because of the large differences in the variances of each variable (34).

2. Generation of the midpoints of the window of separation (Matsuda) and overlap or separation for the second variable in the bivariate scatter plot: Since Matsuda was an index that clearly separated the groups related to IR perfectly, the separation window was called the situation that occurred with this index, where the window corresponded to the maximum in the IR group and the minimum in the non-IR group. The overlap window occurs when the maximum of the IR group falls above the minimum of the non-IR group; in this case, the midpoint of these extremes was also constructed but the window was called an overlap window.

3. A matrix of spatial weights. This was done to give a spatial connotation to the observations, looking for those closest to the separation or overlapping windows to have the highest weight, since, at the intersection of these two regions, there is an area with the highest possibility of misclassifying an observation. The staging in this case was min–max [0,1] (unity-based normalization) so that the weights would fall in this range. In addition, once standardized, the weights matrix was standardized by rows so that the sum of each row would yield a total weight equal to unity (35, 36).

4. Spearman's correlation coefficient (r). The scatter diagram between the Matsuda index and any other with which it was contrasted evidenced a monotonic relationship that is not necessarily linear. In this sense, this correlation coefficient was used as a weighting in the components of the objective function, because from a spatial context, the coordinate in the abscissa or the ordinate may have different importance, so the quadratic spearman correlation coefficient acts as a weighting, since the higher the value of this measure, the greater the weight given to this coordinate.

5. Generation of the new coordinates of the initial cutoff point. With the weights and midpoints of separation or overlap windows, the vector of coordinates is generated in "x" (for Matsuda) and coordinates are generated in "y" (for the index with which the bivariate dispersion diagram is made). The new coordinates are given by the vectors:

$$x_o = r^2 W X_z + (1 - r^2) X_z$$

$$y_o = r^2 W X_z + (1 - r^2) Y_z$$

where W represents the weight matrix, r represents the Spearman correlation coefficient, X_z and Y_z are the original standardized variables corresponding respectively to the Matsuda index and the other variable with which the scatter diagram is made.

6. Then, the distance (d) between the average of the coordinates of x_o and y_o is calculated with the midpoint of the separation window (Matsuda) and the midpoint of the separation window or overlap of the variable with which bivariate dispersion is generated. The expression for this distance is given by:

$$d = \sqrt{(\overline{x_o} - x_w)^2 + (\overline{y_o} - y_w)^2}$$

where x_w and y_w represent the midpoints of the separation window and the overlap or separation window (if applicable), respectively. As the construction of the weight matrix W was initially defined as the inverse of the distances between all points standardized in min–max mode, in the literature, the possibility of raising the weight matrix to a power p appears (in this case in values from 0.50 to 2.50 in step of 0.01) so that it can be verified if with these new matrices of iterative weights a distance less than that established with $p = 1$ can be obtained (the usual case and the one represented in the equations described above).

7. To give greater robustness to the algorithm, an iteration block is proposed where it is removed (with replacement) one by one from the observations. This process is repeated n times, where n is the number of rows in the data matrix.

The pseudocode for this iterative procedure could be:

Pseudocode:

```
for j in range(start = 1, end = 93, step = 1):

datos = datos(without j row)

W = "preprocessing"

for p in range(start = 0.5, end = 2.5, step = 0.01)

x, y = cutoff by p

end for

xm, ym = cutoff with minimum distance

return Youden index

end for

cutoff selected = maximum Youden index
```

8. For the minimum distance of the first iterative process and the maximum Youden of the second process after the calculations of the confusion matrix, with sensitivity and specificity with the cutoff point obtained from the minimum distance, the optimal cutoff point is obtained since the Jackknife process (first order) could have adjusted the data coordinate vectors of the two variables that make up the scatter plot.

9. Finally, for each variable contrasted with Matsuda, the cutoff points as well as the sensitivity and specificity values are recorded.

Results

The characteristics of the study participants are described in Table 1. Considering the cutoff values for the Matsuda index, the

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TABLE 1 Characteristics of non-insulin and insulin-resistant (IR) individuals.

Variable	Non-insulin-resistant individuals* (*n* = 48)	Insulin-resistant (IR) individuals* (*n* = 45)
Age (years), mean (range)	23 (18–30)	24 (18–31)
Body mass index (BMI) (kg/m^2)	21.6 ± 1.9 (17.6–25.8)	36.3 ± 4.8 (30.5–48.3)
Height (cm)	172.5 ± 5.8 (161–184)	173.8 ± 6.8 (155–192)
Waist circumference (WC) (cm)	76.2 ± 5.2 (67–87)	108.7 ± 8.1 (96–128)
Hip circumference (HC) (cm)	93.0 ± 5.8 (78.2–104.1)	119.6 ± 10.1 (100.0–146.0)
Waist-to-height ratio (WHtR)	0.4 ± 0.0 (0.4–0.5)	0.6 ± 0.1 (0.5–0.8)
Total fat mass (TFM %)	19.0 ± 5.8 (7.1–30.1)	42.5 ± 4.8 (32.7–53.8)
Android fat (AF%)	25.2 ± 8.3 (10.5–44.1)	53.5 ± 4.3 (43.5–62.4)
Gynoid fat (GF %)	25.0 ± 5.5 (11.9–34.8)	45.0 ± 5.1 (35.3–55.8)
[AF (%)/GF (%)] ratio	1.0 ± 0.2 (0.6–1.3)	1.2 ± 0.1 (1.1–1.4)
Systolic blood pressure (SBP) (mmHg)	111.0 ± 12.4 (90.0–148.0)	129.0 ± 12.5 (110.0–152.0)
Diastolic blood pressure (DBP) (mmHg)	70.3 ± 8.8 (50.0–90.0)	84.0 ± 10.6 (60.0–102.0)
Mean blood pressure (MBP) (mmHg)	83.9 ± 8.6 (67.0–108.0)	98.9 ± 10.4 (80.0–119.0)
Fasting glucose (mg/dL)	82.7 ± 7.3 (69–98)	89.5 ± 11.3 (74–122)
Glucose (mg/dL) 30′ OGTT	109.4 ± 19.4 (71.0–156.0)	135.5 ± 24.2 (95.0–201.0)
Glucose (mg/dL) 60′ OGTT	81.8 ± 16.0 (53–115)	116.1 ± 31.3 (56–201)
Glucose (mg/dL) 120′ OGTT	74.0 ± 12.0 (53–101)	91.2 ± 24.8 (50–149)
Fasting insulin (μIU/mL)	6.4 ± 2.9 (2.5–17.3)	27.4 ± 10.9 (12.5–58.1)
Insulin 30′ OGTT (μIU/mL)	63.5 ± 37.6 (2.5–192.5)	233.3 ± 107.8 (46.3–497.5)
Insulin 60′ OGTT (μIU/mL)	39.5 ± 20.5 (9.5–92.0)	170.4 ± 91.4 (35.3–406.5)
Insulin 120′ OGTT (μIU/mL)	23.7 ± 12.0 (4.8–62.5)	99.8 ± 81.3 (10.7–377.9)
Triglycerides (mg/dL)	90.1 ± 30.7 (47.0–174.0)	177.1 ± 79.4 (55.0–398.0)
Total cholesterol (mg/dL)	161.0 ± 33.0 (93.0–254.0)	186.1 ± 26.8 (127.0–245.0)
HDL- cholesterol (mg/dL)	48.4 ± 7.2 (34.0–65.0)	42.4 ± 9.6 (31.0–76.0)
Leptin (ng/mL)	7.6 ± 0.7 (6.5–10.1)	27.2 ± 13.1 (14.4–78.4)
Adiponectin (μg/mL)	15.3 ± 1.8 (11.5–19.1)	13.3 ± 1.9 (8.9–17.6)
LAR (ng/μg)	0.5 ± 0.7 (0.4–0.7)	2.0 ± 0.9 (1.0–5.6)
Matsuda	8.3 ± 3.2 (4.3–16.6)	1.8 ± 0.8 (0.6–3.7)
HOMA-IR	1.3 ± 0.6 (0.5–3.4)	6.1 ± 2.8 (2.3–13.9)
QUICKI	0.4 ± 0.0 (0.3–0.4)	0.3 ± 0.0 (0.2–0.3)
TyG	4.4 ± 0.2 (4.1–4.9)	4.8 ± 0.3 (4.2–5.3)
TG/HDL-c	1.9 ± 0.7 (1.0–4.1)	4.2 ± 1.9 (0.7–10.3)
TyG-WC	339.6 ± 30.5 (274.5–403.7)	518.1 ± 49.1 (433.5–632.1)
TyG-WHtR	1.8 ± 0.2 (1.6–2.4)	3.0 ± 0.3 (2.4–3.7)
TyG-BMI	95.8 ± 10.8 (71.6–121.9)	171.8 ± 23.5 (141.2–238.9)
LAP	12.4 ± 8.0 (1.4–31.4)	86.5 ± 42.5 (23.6–201.9)
VAI	2.3 ± 0.9 (0.9–5.2)	5.3 ± 2.6 (0.9–12.8)

*Insulin sensitivity/resistance was determined using the Matsuda index cutoff value (4.03) as reference. Homeostatic model assessment index (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), triglyceride-glucose (TyG) index, triglycerides-to-HDL-c ratio (TG/HDL-C), visceral adiposity index (VAI), TyG-waist circumference (TyG-WC), TyG-body mass index (TyG-BMI), TyG-waist-to-height ratio (TyG-WHtR), lipid accumulation product (LAP), leptin/adiponectin ratio (LAR), total fat mass (TFM %), android fat (AF %), body mass index (BMI) (kg/m^2), waist circumference (WC), and waist-to-height ratio (WHtR). Data are mean ± SD and range in parentheses.

individuals were initially classified into insulin resistant (IR) and non-IR, as described elsewhere (13, 15). Then, the optimal cutoff value for the Matsuda index (4.03) was obtained employing progressive iterative approximation using the computational approach until it reaches the cutoff value threshold (Figure 1).

It is important to highlight that QUICKI, BMI (kg/m^2), total body fat (TBF %), AF (%), WC (cm), TyG-WHtR, WHtR, leptin levels, and LAR have been described as predictors of insulin sensitivity/resistance in young male adults, yielding similar results to those described in Table 1 in the individuals grouped into IR and non-IR in this study, findings that confirm the high diagnosis accuracy classification using the Matsuda index cutoff value as reference (4.03) when the computational approach is applied for IR discrimination (Table 1) (21, 22, 37–44). Additionally,

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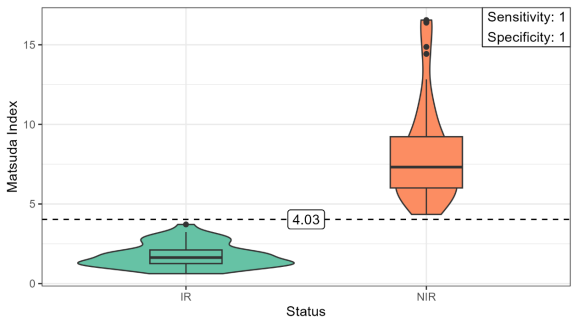

FIGURE 1
The figure shows the violin plot of the distribution of IR and non-IR individuals in relation to the cutoff value (4.03) and the diagnosis performance (sensitivity and specificity) for the prediction of IR determined using the algorithmic approach for the Matsuda index. Low values of the Matsuda index are associated with the risk of IR. The violin plots show the interquartile range distribution of IR and non-IR individuals.

anthropometric measurement, clinical features, leptin, lipid profile, glucose, and insulin levels during fasting at each point of the OGTT and surrogate indices of muscle and hepatic insulin sensitivity are described in IR and non-IR young individuals as described in Table 1.

Furthermore, this study determines the bivariate distribution of IR and non-IR individuals using the cutoff value of Matsuda index as reference obtained by the computational approach (independent variable), who represent the most accurately diagnostic performance surrogate index for predicting IR compared with the EHC technique, the gold standard method for the detection of IR (Table 2, Figure 2, and Supplementary Figure 1) (9).

Furthermore, the cutoff value used to discriminate IR, defined with the Matsuda index (4.03), and the diagnosis performance using the computational approach described above for the determination of IR in young men for surrogate indices, anthropometric measurement, leptin, serum glucose, and insulin levels are described in Table 2 (dependent variable). Therefore, individuals with Matsuda index values below the cutoff of 4.03 were defined as insulin resistant (Figure 2).

On the other hand, the scatter plots in Figure 2 and Supplementary Figure 1 show the bivariate distribution segregated by the status of groups of IR and non-IR individuals using the cutoff value of Matsuda index as reference (midpoint of the separation window) (*X*-axis) in relation to the different cutoff values of IR/insulin sensitivity for surrogate IR indices, lipid indices, anthropometric measurement, leptin and serum insulin, and glucose level values (*Y*-axis) (left column of Figure 2). As it can be observed in Figure 2, low values of the Matsuda index are independently associated with the risks of IR (<4.03) (Tables 1 and 2, Figure 2, and Supplementary Figure 1). Additionally, the violin plots show the distribution of groups of IR and non-IR individuals in relation to the different cutoff values and the diagnosis performance (sensitivity and specificity) for the prediction of IR for surrogate indices, anthropometric measurement, leptin and serum glucose, and insulin levels (Table 2, Figure 2, and Supplementary Figure 1) (right column of Figure 2). Therefore,

TABLE 2 Diagnosis performance determined by computational approach using the Matsuda index as reference for predicting insulin resistance (IR) in young men of surrogate indices, lipid indices, anthropometric measurement, serum glucose, and insulin levels.

Index	Cutoff value*	Sensitivity	Specificity
Matsuda	4.03	1.00	1.00
Body mass index (BMI) (kg/m^2)	28.69	1.00	1.00
Waist circumference (WC) (cm)	92.63	1.00	1.00
WHtR	0.53	1.00	1.00
Total fat mass (TFM %)	31.07	1.00	1.00
Android fat (AF %)	40.33	1.00	0.98
HOMA-IR	3.34	0.91	0.98
Leptin (ng/mL)	16.08	0.91	1.00
LAR (ng/μg)	1.17	0.84	1.00
QUICKI	0.33	0.98	0.96
TyG	4.60	0.73	0.77
TG/HDL-c	2.93	0.69	0.92
TyG-WC	427.77	1.00	1.00
TyG-WHtR	2.48	0.98	1.00
TyG-BMI	132.44	1.00	1.00
LAP	45.49	0.84	1.00
VAI	3.64	0.69	0.92
Fasting glucose (mg/dL)	85.92	0.6	0.65
Glucose (mg/dL) 60′ OGTT	98.02	0.69	0.81
Glucose (mg/dL) 120′ OGTT	82.10	0.51	0.77
Fasting Insulin (μIU/mL)	16.02	0.91	0.98

Diagnosis performance determined by computational approach was assessed using the Matsuda index as reference (cutoff value 4.03*). Homeostatic model assessment index (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), triglyceride-glucose (TyG) index, triglycerides-to-HDL-C ratio (TG/HDL-c), visceral adiposity index (VAI), TyG-waist circumference (TyG-WC), TyG-body mass index (TyG-BMI), TyG-waist-to-height ratio (TyG-WHtR), lipid accumulation product (LAP), leptin/adiponectin ratio (LAR), body mass index (BMI kg/m^2), total fat mass (TFM %), android fat (AF %), waist circumference (WC), and waist-to-height ratio (WHtR).

the computational approach determined the best diagnostic performance (sensitivity and specificity) and cutoff values to discriminate IR for BMI (1.00; 1.00; 28.69), WC (1.00; 1.00; 92.63), WHtR (1.00; 1.00; 0.53), TyG-WC (1.00; 1.00; 427.77), TyG-BMI (1.00; 1.00; 132.44), TyG-WHtR (0.98; 1.00; 2.48), TFM (%) (1.00; 1.00; 31.07), AF (%) (1.00; 0.98; 40.33), LAP (0.84; 1.00; 45.49), HOMA-IR (0.91; 0.98; 3.40), QUICKI (0.98; 0.96; 0.33), LAP (0.84; 1.00; 45.49), LAR (0.84; 1.00; 1.17), leptin (0.91; 1.00; 16.08), and fasting insulin (0.91; 0.98; 16.01) (Table 2 and right column of Figure 2). Additionally, TyG (0.73; 0.77; 4.60), TG/HDL-c (0.69; 0.92; 2.93), VAI (0.69; 0.92; 3.64), fasting glucose (mg/dL) (0.60; 0.65; 85.92), glucose (mg/dL) 60′ OGTT (0.69; 0.81; 98.02), and

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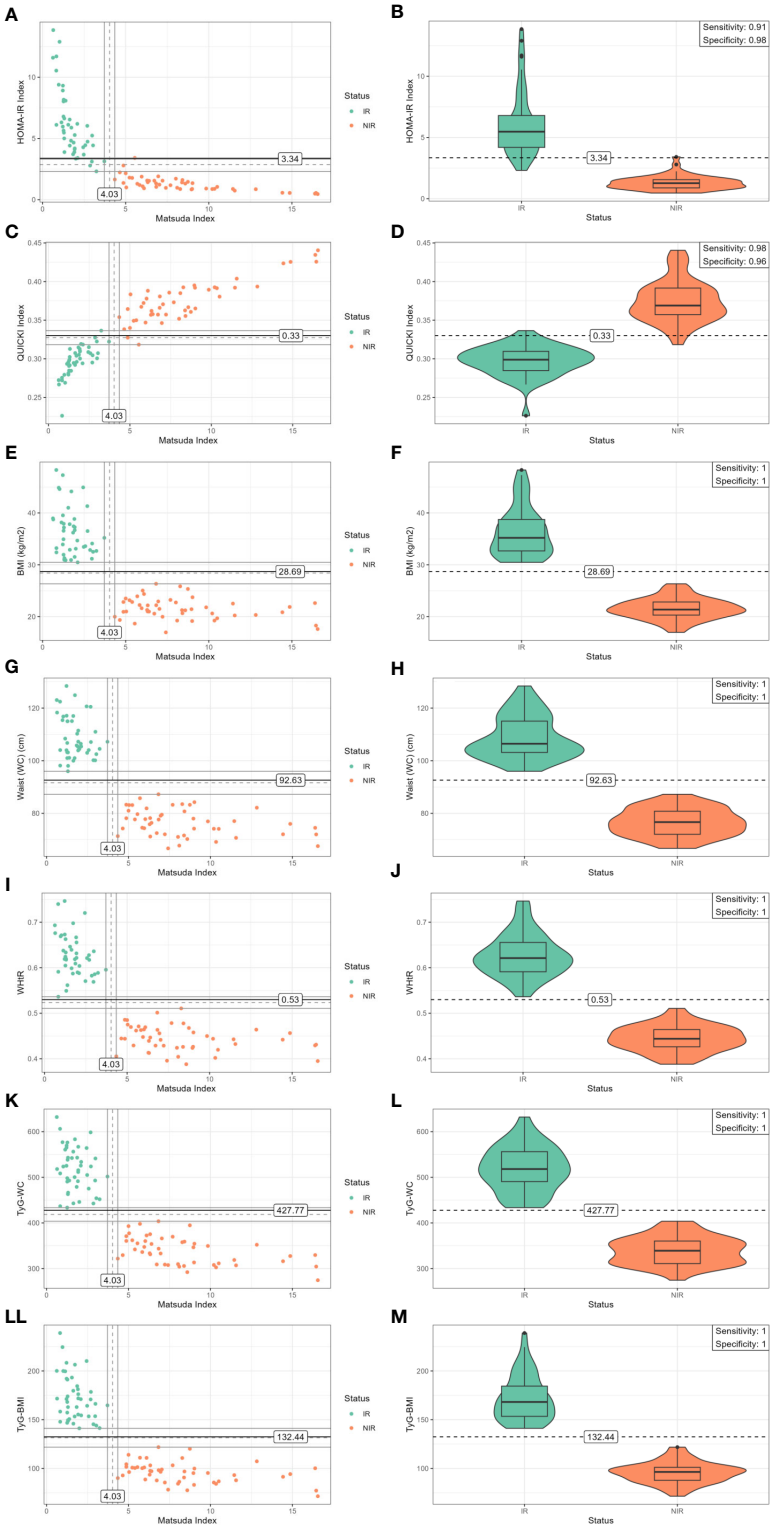

FIGURE 2 (Continued)

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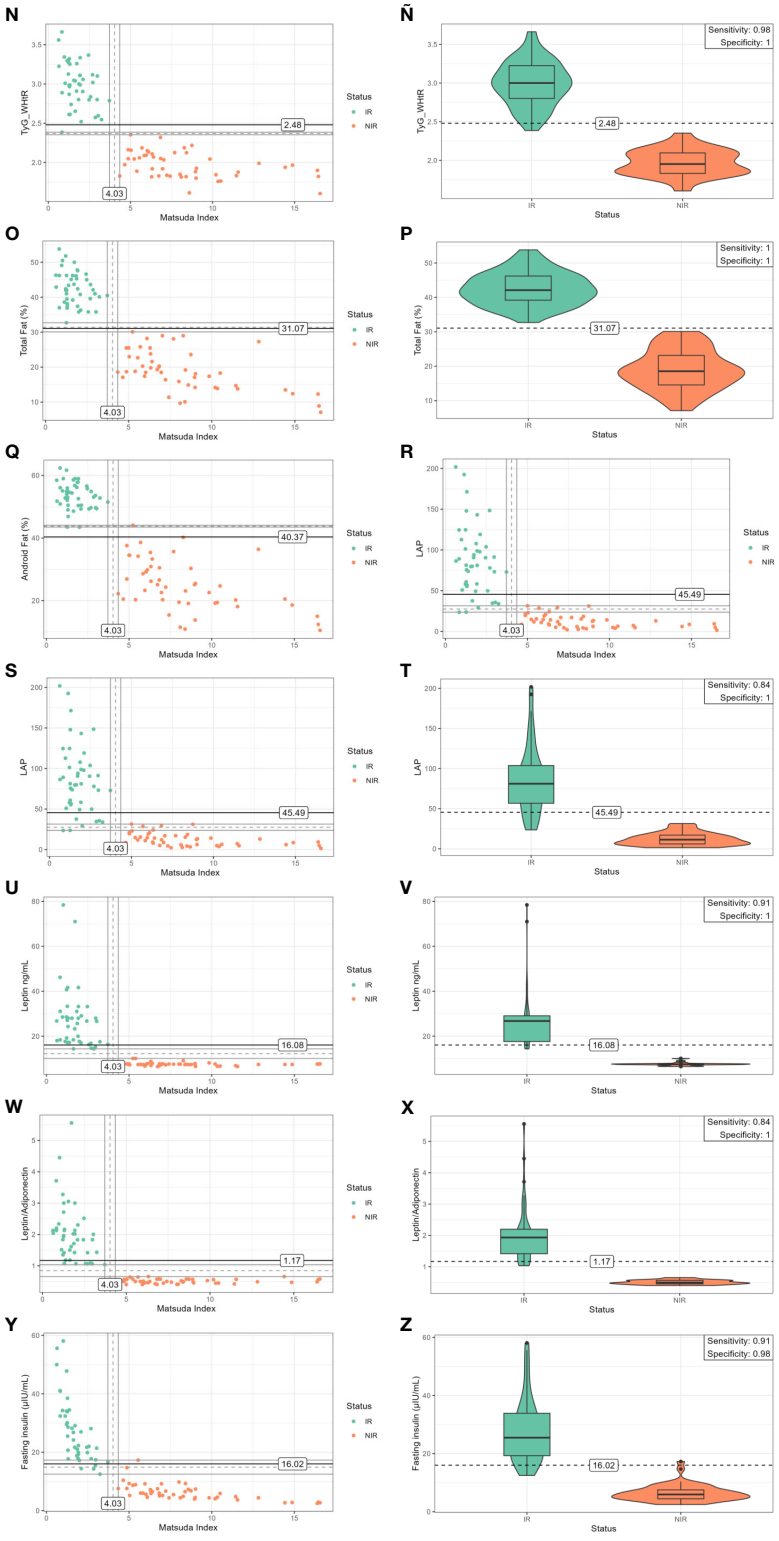

FIGURE 2
The figures in the left column **(A, C, E, G, I, K, LL, N, O, Q, S, U, W, Y)** show the scatter plot depicting the bivariate distribution segregated by the status of IR and non-IR individuals (each dot represents an individual), using the cut-off value of the Matsuda index as reference (4.03) (*X*-axis) and its interaction with surrogate indices, anthropometrics measurements, glucose, and insulin levels (*Y*-axis). Matsuda index values below the cut-off of 4.03 are independently associated with IR. The right column shows the violin plots of the distribution of IR and non-IR individuals in relation to the different cut-off values and the diagnosis performance **(B, D, F, H, J, L, M, Ñ, P, R, T, V, X, Z)** (sensitivity and specificity) using the algorithmic approach for prediction of insulin resistance of the surrogate indices. The violin plots show the interquartile range distribution of IR and non-IR individuals. Homeostatic model assessment index (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), triglyceride-glucose (TyG) index, triglycerides-to-HDL-C ratio (TG/HDL-c), visceral adiposity index (VAI), TyG-waist circumference (TyG-WC), TyG-body mass index (TyG-BMI), lipid

glucose (mg/dL) 120′ OGTT (0.51; 0.77; 82.10) showed modest diagnostic accuracy derived from the computational approach (Table 2, right column of Figure 2 and Supplementary Figure 1).

The Spearman correlation matrix of all pairs of variables included in the model was created and the correlation value was presented in the cells (Figure 3). Additionally, the vector of Matsuda's correlations with different indices or variables was extracted from the correlation matrix and ordered by magnitude, since Matsuda was considered the gold standard among these indices and colors represent the magnitude of the Spearman correlation (Figure 4).

Finally, given the exploratory character of the present study based on a mathematical model, there was no pre-specified inferential hypothesis. The nature of the study is multivariate for a binary classifier. Rajput et al. have recommended an effect size of 0.5 or higher to evaluate a decided sample size in machine learning applications; by having 20 correlations with Matsuda, a convenient threshold can be set that at least 95% of the correlations are greater than 0.5, and in our case, 19 of the 20 correlations were greater than 0.5 (45). The stability of the algorithm at such high correlations gave us the guarantee of its good performance for all pairs of variables involving Matsuda.

Discussion

In the present study, using a computational approach, we determined the diagnosis accuracy and the cutoff values for the determination of IR with the Matsuda index as reference for surrogate indices of muscle and hepatic insulin sensitivity/resistance, lipid indices, anthropometric measures, hormonal levels, serum glucose, and insulin levels in non-diabetic young adult men. This approach can be used quickly, easily, and at a low cost in routine IR screening for preventive health services.

In this regard, BMI, TyG-WC, TyG-BMI, WHtR, WC, TyG-WHtR, TFM (%), AF (%), LAP, Leptin, LAR, HOMA-IR, QUICKI, and fasting insulin levels showed high diagnostic accuracy for the prediction of IR using the computational approach. Moreover, it is important to highlight that some cutoff values determined in this study using the computational approach are similar to those described in previous research, between TyG-WC, TyG-BMI, TyG-WHtR, WHtR, WC, BMI, HOMA-IR, leptin, LAR, and QUICKI indices and insulin levels, variables that are highly correlated with IR and T2DM (13, 30–32, 40, 46–52). In contrast, consistent with previous studies, TyG, TG/HDL-c, VAI, fasting glucose (mg/dL), glucose (mg/dL) 60′ OGTT, and glucose (mg/dL) 120′ OGTT displayed moderate diagnostic accuracy for detecting IR, as described elsewhere (14, 29–33, 47, 51, 53). It must be noted that the cutoff value for the TyG index obtained in the present study (4.60) has the same value as described for the first time by the authors who proposed this index (29, 30). Moreover, the cutoff value for the TG/HDL-c index (2.93) obtained in the present study resembles the value described by Wakabayashi et al. (33). It is worth noting that different studies have demonstrated that TyG and TG/HDL-c indices are significantly associated with the risk of T2DM, stroke, and cardiovascular mortality (54, 55).

Researchers have found that visceral obesity accompanied by hypertrophy and hyperplasia of adipose tissue is characterized by low-grade chronic inflammation, IR, and different metabolic alterations (56, 57). Different studies have shown marked differences and guidelines for unification criteria in relation to the cutoff values and diagnosis performance for surrogate indices and variables that allow to predict IR, particularly those related to anthropometric measurement, and hormonal and biochemical parameters according to age, race, and ethnicity (20, 52, 58–61). Thus, although WC is gender and race/ethnicity specific, its use as a surrogate index for the determination of IR in population studies is

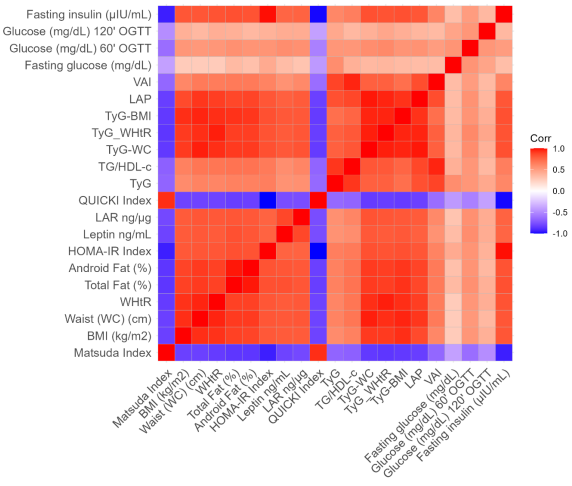

FIGURE 3
The Spearman correlation matrix of all pairs of variables included in the algorithm approach model was created and the correlation value was presented in the cells. The colors represent the magnitude of the Spearman correlation. Homeostatic model assessment index (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), triglyceride-glucose (TyG) index, triglycerides-to-HDL-C ratio (TG/HDL-c), visceral adiposity index (VAI), TyG-waist circumference (TyG-WC), TyG-body mass index (TyG-BMI), lipid accumulation product (LAP), body mass index (BMI kg/m^2), total fat mass (TFM %), android fat (AF %), waist circumference (WC), and waist-to-height ratio (WHtR).

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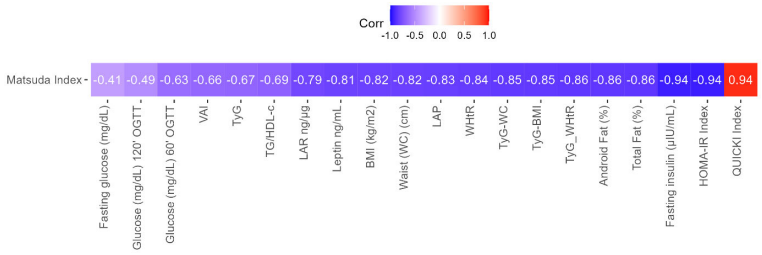

FIGURE 4
Vector of Matsuda's correlations with different indices or variables. The vector was extracted from the correlation matrix and ordered by magnitude, since Matsuda was considered the gold standard among these indices. The colors represent the magnitude of the Spearman correlation. Homeostatic model assessment index (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), triglyceride-glucose (TyG) index, triglycerides-to-HDL-C ratio (TG/HDL-c), visceral adiposity index (VAI), TyG-waist circumference (TyG-WC), TyG-body mass index (TyG-BMI), lipid accumulation product (LAP), body mass index (BMI kg/m^2), total fat mass (TFM %), android fat (AF %), waist circumference (WC), and waist-to-height ratio (WHtR).

limited because it may lead to the underestimation or overestimation of IR prediction; therefore, this index should be adjusted to height for a robust and universal use as a surrogate index for predicting IR (20, 40, 62). Similarly, it is important to highlight that BMI is age, gender, and race/ethnicity specific to predict IR, and countless cutoff values have been described in different population studies; therefore, this index should be carefully applied in personalized medicine rather than in population studies for predicting IR (44, 63, 64). Additionally, Teresa Vanessa Fiorentino et al. have demonstrated that the LAP index showed higher diagnostic accuracy compared with TyG, TG/HDL-C ratio, and VAI indices in detecting IR and CVDs (65). In addition, Nayeon Ahn et al. have demonstrated that VAI, LAP, and TyG showed high discrimination performance in the diagnosis of individuals with prediabetes and T2DM (32, 66).

In contrast, in the present study, the WHtR cutoff value determined via a computational approach is highly consistent with data from previous research findings according to age and race/ethnicity (40, 67–71). Moreover, it has been demonstrated in different studies that the surrogate indices TyG-WC, TyG-WHtR, and TyG-BMI presented high diagnostic accuracy for predicting IR, presented highly conserved cutoff values across different human populations studies, and can be easily calculated from routine laboratory tests, as described elsewhere (12, 29, 30). Furthermore, it is important to highlight that different studies have shown that TyG-WC, TyG-WHtR, and TyG-BMI indices are strong predictors of IR, T2DM, and metabolic diseases such as hepatic steatosis (72, 73).

On the other hand, different studies have shown a stronger relationship between TFM (%) and AF (%) with IR (74, 75). Furthermore, abdominal-android and visceral fat accumulation is strongly associated with the risk of CVD, T2DM, stroke, and several negative health outcomes (76, 77). Therefore, in this study, using the computational approach, and having the Matsuda index as reference, the cutoff values for IR prediction were determined for TFM (%) and AF (%). However, high variation between body fat distribution and IR has been demonstrated across gender and ethnic/racial population studies (75, 76). Additionally, different studies have demonstrated that obese individuals often present with hyperleptinemia, chronic low-grade systemic inflammation, and IR (78). It has been reported that LAR is associated with IR and metabolic syndrome (49). In this regard, in the present study, the LAR index was determined by computational approximation using the Matsuda index as reference, with similar findings to those described elsewhere (79).

Moreover, in the present study, the diagnosis accuracy performance and the cutoff values for the prediction of IR for HOMA-IR and QUICKI indices were determined via a computational approach. The results showed a high-accuracy performance to determine IR for both indices; however, the HOMA-IR index presents multiple cutoff values across racial/ethnic groups of population studies (80, 81). In contrast, the QUICKI index cutoff value is highly conserved in different gender and racial/ethnic population studies (0.33) despite fasting glucose and insulin levels being common variables used to determine both indices (52, 82).

Previous reports have demonstrated that the QUICKI index is one of the simplest and best evaluated and validated surrogate indices with higher predictive power and accuracy for determining insulin sensitivity/resistance and the development of diabetes (24, 83). In addition to the QUICKI index, TyG-WC, TyG-WHtR, and TyG-BMI indices present high predictive accuracy and are cost-effective to use quickly and easily for the early detection of IR screening, monitoring, and evaluating therapeutic interventions and preventive medicine in the general population.

It is important to highlight that worldwide population migrations have been increasing significantly for different reasons, such as political, demographic, economic, and social causes, and usually happen within a country, across borders, and across continents (84). Migration studies have demonstrated that the highest international migration rates occur in Oceania (22%), North America (16%), and Europe (12%); low migration rates occur in Asia (1.8%), Africa (1.9%), and Latin America and the Caribbean (2.3%) (84). In this way, migration from low- and middle-income countries to high-income countries exposes migrant populations to epigenetic modification that might lead to the development of deleterious effects on the health of individuals mostly through NCDs such as obesity, diabetes, hypertension,

stroke, infectious disease, cancers, and mental disorders (85). Furthermore, it has been generally demonstrated that the most commonly used IR indices might vary with age, gender, and ethnicity, and thus, healthcare services have to take into consideration that these indices must be implemented for precise patient monitoring to detect and diagnose medical conditions in real time (59, 86). Thus, the analysis of cutoff values and diagnosis performance for different surrogate indices through a computational approach and using the Matsuda index as reference could contribute in the future to implement health policies and preventive care strategies for the rapid, massive, and low-cost identification of patients with IR in order to reduce the high costs of chronic and NCDs.

The main strength of our study is having used for the first time the Matsuda index as reference for detecting the cutoff values and diagnosis performance to determine the risk of IR of different surrogates' indices using an accurate, robust, and flexible computational approach. In addition, it is worth highlighting that the Matsuda index is a whole-body insulin sensitivity surrogate index with high diagnostic performance, when compared with the gold standard method for assessing insulin sensitivity in humans, the EHC technique. Additionally, in the present study, the cutoff values determined for the different surrogate indices, which showed the highest diagnosis performance using a computational approach, are in agreement with human population studies designed with a large number of individuals and taking into consideration the ethnicity/race, age, and gender, as described above. Furthermore, the validity of the current methodology and results is strongly supported by anthropometric parameters such as total fat, visceral fat, WC and BMI, serum insulin, leptin, and adiponectin levels, and by clinical variables that have been used previously to determine IR and are in accordance with the different cutoff points established for the different indices in the current study.

On the other hand, this study has some limitations, including the exploratory cross-sectional design with case and control selection of the individuals (obese and healthy men), and the development of the algorithm only in adult volunteer men selected. Other studies should be developed in the future taking into account demographic variables such as age, gender, ethnicity, and all the spectrum of IR. With a larger sample size and consecutive recruitments, we will expect to overcome those limitations in order to know the real diagnosis performance of surrogate indices of IR. Finally, the present study aims to contribute to the prevention of NCDs such as IR/insulin sensitivity in any context, quickly and at a low cost, taking into account that through the algorithmic approach, the cutoff points and diagnostic performance must be established for the different indices of IR and according to ethnicity/race, age, and gender.

Conclusions

In this study, a computational approach was used to determine the diagnosis accuracy and the cutoff values for different surrogate indices to determine IR using the Matsuda index as reference. Some of these indices are easy to implement in daily clinical practice, showing high diagnostic accuracy, with similar cutoff values for the prediction of IR to those indices described in previous research. Therefore, TyG-WC, TyG-BMI, WHtR, TyG-WHtR, and QUICKI must be studied and adjusted for age, gender, and race/ethnicity for estimating insulin sensitivity/resistance using a computational approach.

Data availability statement

Data generated during the study was included in this article. Also, the data of the current study are available from the corresponding author upon request.

Ethics statement

This protocol was approved by the Ethics Committee of the School of Medicine – Universidad Nacional de Colombia (protocols B.FM.1.002- CE-0194-22 and B.FM.1.002- CE-081-22). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

VM-S: Conceptualization, Writing – review & editing. AL-F: Conceptualization, Formal analysis, Writing – review & editing. CE-P: Conceptualization, Formal analysis, Writing – review & editing. ÁB-C: Data curation, Writing – review & editing. MG: Methodology, Writing – review & editing. GO-R: Conceptualization, Writing – review & editing. RF-V: Writing – original draft. JP-F: Conceptualization, Formal analysis, Writing – review & editing. LM-A: Conceptualization, Formal analysis, Writing – review & editing. JR-R: Data curation, Writing – review & editing. MM-P: Conceptualization, Formal analysis, Writing – review & editing. SC-C: Writing – original draft. EL: Data curation, Formal analysis, Validation, Writing – original draft. CR-M: Data curation, Formal analysis, Validation, Writing – review & editing. AD-C: Data curation, Formal analysis, Methodology, Writing – review & editing. AR-P: Writing – original draft. JC: Writing – original draft.

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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/fendo.2024.1343641/full#supplementary-material

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Associations between estimated glucose disposal rate and arterial stiffness and mortality among US adults with non-alcoholic fatty liver disease

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Background: The estimated glucose disposal rate (eGDR), an effective indicator of insulin resistance, has been related to acute coronary syndrome, ischemic stroke and heart failure. This study aims to explore the relationship between eGDR and arterial stiffness, all-cause mortality and cardiovascular mortality in patients with non-alcoholic fatty liver disease (NAFLD).

Methods: Participants with NAFLD were chosen from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2018. The main outcomes are arterial stiffness (represented by estimated pulse wave velocity, ePWV), all-cause and cardiovascular mortality. Multiple cox regression models, restricted cubic spline, sensitivity analysis and subgroup analysis were carried out to investigate the correlation between the insulin resistance indicators and mortality and arterial stiffness. Furthermore, receiver operating characteristic curves were used to compare the predictive value of the eGDR with the triglyceride-glucose (TyG) index and the homeostasis model assessment of insulin resistance (HOMA-IR) for all-cause and cardiovascular mortality.

Results: In this study, a total of 4,861 participants were included for analysis. After adjusting confounding factors in the multivariate weighted cox regression model, the eGDR was inversely associated with the all-cause mortality (Q4 vs. Q1, HR =0.65 (0.48-0.89, P=0.01) and cardiovascular mortality (Q4 vs. Q1, HR =0.35 (0.19-0.65, P<0.001). Compared with TyG index and HOMA-IR, the eGDR shows excellent predictive value in all-cause mortality (0.588 vs. 0.550 vs. 0.513, $P < 0.001$) and cardiovascular mortality (0.625 vs. 0.553 vs. 0.537, $P < 0.001$). In addition, we found a significant negative correlation between eGDR and arterial

stiffness (β=-0.13(-0.14–0.11, P< 0.001). However, TyG index and HOMA-IR showed no significant correlation to arterial stiffness.

Conclusions: Low eGDR (an indicator of insulin resistance) levels are related to an increased risk of arterial stiffness and mortality in NAFLD patients in the United States.

KEYWORDS

insulin resistance, non-alcoholic fatty liver disease, estimated glucose disposal rate, arterial stiffness, mortality, NHANES

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease characterized by abnormal accumulation of fat in the liver. Furthermore, NAFLD does not involve viruses, alcohol, or autoimmune factors. NAFLD (1), accounting for approximately one-third of the population globally, has brought substantial economic and medical burden (2). Moreover, the burden of fatty liver disease is rapidly growing in every region of the world over the past years (3). What is particularly concerning is the rising incidence of NAFLD among younger age groups (4). Approximately 20% of patients with NAFLD will progress to metabolic dysfunction-associated steatohepatitis which can increase the risk of developing liver cirrhosis in the future (5). Additionally, cardiovascular disease (CVD) is the main cause of death in individuals with NAFLD, further highlighting its significant impact on individuals and societies (6). The incidence of cardiovascular adverse events is higher in NAFLD patients, including stroke and myocardial infarction (7, 8). In spite of effective efforts in NAFLD prevention and treatment, managing NAFLD remains challenging. Consequently, evaluating the prognosis of NAFLD patients holds immense importance in the field of public health.

Insulin resistance (IR) is a pathological state in which the body's sensitivity to insulin decreases (9). IR plays an important role in NAFLD and cardiovascular disease. Some studies have shown that IR promotes the generation of liver fat, which is closely related to the onset and progression of NAFLD (10). In addition, IR is involved in the development of atherosclerosis, hypertension, heart failure and other cardiovascular diseases (11). Although the gold standard for assessing IR is the euglycemic hyperinsulinemic clamp, the clinical utility is limited due to the invasive and costly nature (12). At present, the widespread utilization of the homeostasis model assessment of insulin resistance (HOMA-IR) has been observed. However, it has certain limitations for patients receiving insulin therapy. Therefore, the estimated glucose disposal rate (eGDR) (13)and the triglyceride-glucose (TyG) index (14) have been developed for clinical application.

The eGDR was initially created as a validated measure to assess IR in individuals with type 1 diabetes (T1D) according to hypertension, waist circumference (WC) and glycated hemoglobin A (HbA1c) (15). In comparison to the euglycemic hyperinsulinemic clamp, this technique offers increased accuracy and is suitable for large-scale clinical research (16). Some studies have found that low eGDR is associated with the increased risk of prevalence and poor prognosis in various diseases, such as fatty liver disease, acute coronary syndrome, heart failure and stroke (17–20).

The association between eGDR and NAFLD outcomes is still not well understood, despite its close relationship with many diseases. This study aims to explore the relationship between eGDR and arterial stiffness (represented by estimated pulse wave velocity, ePWV), all-cause mortality and cardiovascular mortality in patients with NAFLD.

Materials and methods

Data source and study participates

We carried out our study by utilizing data from the National Health and Nutrition Examination Survey (NHANES) database available at www.cdc.gov/nchs/nhanes.com. The purpose was to evaluate the health conditions of individuals aged 20 and older in the United States. The data sets were gathered from various states and counties across the nation. These samples were obtained from all NHANES participants from 1999 to 2018 (n = 101306), we excluded participants whom younger than 20 years (n =46235), those missing data for GGT, waist circumference, fasting insulin or fasting glucose (n = 32486), Participants with tested positive or missing data for HBV/HCV infection(n = 632) and heavy alcohol use(n = 6879), participants without NAFLD (n = 9771), those without HbA1c(n = 5), blood pressure data (n = 229), pregnant participants (n = 59) and participants missing data on follow-up information (n = 6) and other covariates data (n = 153). The analysis sample comprised 4861 participants in total. The screening process details were illustrated in Figure 1.

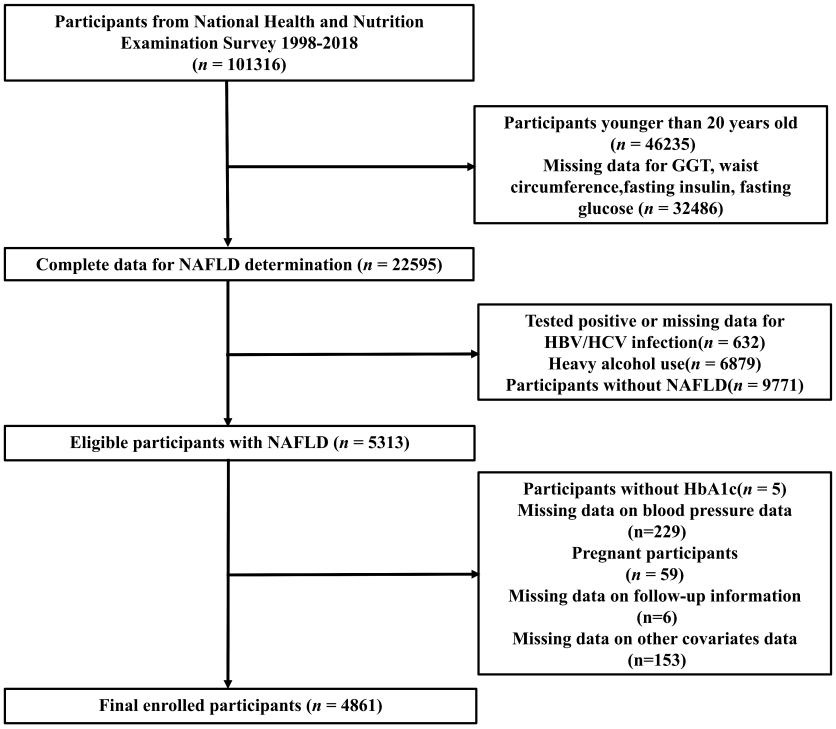

FIGURE 1
The flow chart of participant selection.

Diagnosis of NAFLD

The diagnosis of NAFLD usually involves detecting liver fat through imaging examinations such as abdominal ultrasound and magnetic resonance imaging. Additionally, we need to exclude other clear factors of liver injury. If necessary, further liver biopsy is also required. These methods require high operational requirements and are costly. Moreover, steatosis can only be detected when the steatosis rate of liver cells exceeds 20%-30%, it has not been widely applied. Therefore, a score for assessing fatty liver disease in the United States population was developed by CE Ruhl (21). Therefore, we used us-FLI≥30 as a criterion for diagnosing NAFLD.

Calculation of IR indicators and ePWV

The eGDR (mg/kg/min) was created as a measure of IR and calculated by using the following formula: eGDR = 21.158 − (0.09∗WC) − (3.407∗HT)− (0.551∗HbA1c) [WC = waist circumference (cm), HT = hypertension (yes = 1/no = 0) and HbA1c = HbA1c (%)] (15). In 2008, TyG index was introduced as a reliable and specific predictor of IR. It has been shown to have a good correlation with the hypoglycemic-hyperinsulinemic clamp test and HOMA-IR. The TyG index was calculated as Ln [fasting triglycerides (mg/dL) × Fasting glucose (mg/dL)/2] (22). HOMA-IR is an indicator used to evaluate an individual's IR level but it is expensive. The HOMA-IR was calculated as fasting insulin (μU/mL) × fasting plasma glucose (mg/dL)/405 (23). We used ePWV to evaluate arterial stiffness. According to the equation, ePWV was calculated from age and mean blood pressure (MBP): $9.587 - 0.402 \times age + 4.560 \times 10^{-3} \times age^2 - 2.621 \times 10^{-5} \times age^2 \times MBP + 3.176 \times 10^{-3} \times age \times MBP - 1.832 \times 10^{-2} \times MBP$. MBP was calculated as diastolic blood pressure+0.4 × (systolic blood pressure − diastolic blood pressure) (24).

Covariates

In this study, we selected covariates related to NAFLD based on previous research. Demographic information was obtained from the NHANES database, which contained data on age (in years), sex (categorized as male or female), racial/ethnic background (including white, black, Mexican and others), educational attainment (categorized as less than high school, high school, and post-high school education). This information was obtained from the NHANES demographic questionnaire. Body mass index (BMI) was calculated by dividing weight [kg] by the square of height [m^2]. We obtained smoking status (yes/no) from the questionnaire. Coronary heart disease (CHD) and congestive heart failure (CHF) were diagnosed based on medical history. In addition, we collected glycated hemoglobin (HbA1c) (%), total cholesterol (TC) (mmol/L), triglycerides (TG) from laboratory examination data. We calculated the estimated glomerular filtration rate (eGFR) based on the creatinine data of participants provided by NHANES using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method (25). Hypertension was diagnosed based on guidelines provided by the Joint National Committee on Prevention,

Detection, Evaluation, and Treatment of High Blood Pressure. We applied hypertension assessment criteria: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg and the patients using anti-hypertensive medications for the period of being investigated (26). We applied diabetes evaluation criteria: doctor diagnosis as diabetes, HbA1c ≥ 6.5%, fasting glucose ≥ 7.0mmol/L, random blood glucose ≥ 11.1mmol/L, 2h OGTT blood glucose ≥ 11.1mmol/L, or being treated with diabetes drugs and insulin (27).

Mortality

To assess the mortality, we paired the National Death Index data with the mortality information for the period ending on December 31, 2019 (https://www.cdc.gov/nchs/data-linkage/mortality.htm). Outcomes were be defined as all-cause and cardiovascular mortality. Causes of death were defined according to the codes of ICD-10. Cardiovascular mortality was defined using ICD-10 codes 100-109,111,113,120-151 (28).

Statistical analysis

Firstly, we divided the data into four groups according to the quartile of eGDR. Continuous variables were presented as means (95% confidence intervals (CI)) and proportions with their respective 95% CI were employed for categorical variables. In order to ascertain variations between the four groups, the variance analysis or Kruskal–Wallis test were conducted for continuous variables, while chi-square tests were utilized for categorical variables. Statistical significance was considered at P values < 0.05. We excluded other missing variables after obtaining the main data for the study. Due to the small number of missing variables, we excluded them to ensure the objectivity and accuracy of the results. Finally, the analysis sample comprised 4861 participants in total. When conducting various statistical analyses, we adjusted for demographic variables, hematological indicators and medication information which may have an impact on the prognosis of NAFLD patients (29). Next, we conducted weighted linear regression analyses in order to examine the correlation between eGDR and ePWV. Restricted cubic splines are an important tool in statistics used for smooth fitting and modeling of data, as well as analyzing complex relationships between continuous variables. To examine the correlation between eGDR and ePWV, we employed a restricted cubic spline method. In the multivariate cox regression model, other confounding factors are adjusted so that the real effect can be displayed. Therefore, weighted cox regression analyses were used to investigate the relationship between eGDR and all-cause mortality and cardiovascular mortality. We constructed two models: Model I and Model II. Model I was adjusted for age, sex, race. Model II was adjusted for age, sex, race/ethnicity, education levels, smoking, BMI, TC, TG, eGFR, DM, CHD, CHF, hyperlipidemia, anti-diabetic drugs and anti-hyperlipidemic drugs. Results were presented as hazard ratios (HRs) with 95% CIs. Restricted cubic spline method was used for the correlation between eGDR and mortality. To further ensure the robustness and credibility of the results, sensitivity analysis and subgroup analysis have been adopted in many studies (30). Furthermore, different researchers have utilized different approaches for analysis, such as weighted and unweighted methods. NHANES uses complex sampling techniques to enhance the accuracy and relevance of results. However, discrepancies may arise between weighted and unweighted analyses. Therefore, we conducted a sensitivity analysis using unweighted regression to verify our findings. Receiver operating characteristic (ROC) curve chart is a graph used to evaluate the performance of diagnostic systems and find the optimal threshold. Consequently, we used ROC curves to compare the predictive value of the eGDR with the triglyceride-glucose (TyG) index and the homeostasis model assessment of insulin resistance (HOMA-IR) for all-cause and cardiovascular mortality. Finally, we aim to further clarify the relationship between eGDR and NAFLD in different subgroups.

Results

The baseline characteristics of participants

A total of 4.861 participants with NAFLD were involved in the study. As showed in Table 1, we divided the data into four groups according to the quartile of eGDR. The baseline characteristics of all participants, including age, sex, race, education levels, smoking, BMI, waist circumference, HbA1c, TG, TC, HOMA_IR, TyG, ePWV, eGFR, DM, CHD, CHF, hyperlipidemia, anti-diabetic drugs, anti-hyperlipidemic drugs, all-cause mortality and cardiovascular mortality are presented in Table 1. Table 1 shows significant differences in clinical characteristics between the four groups. Compared with the lower eGDR group, patients with higher eGDR were younger, higher levels of education, fewer white people. The high eGDR group has fewer smokers, a lower proportion of hyperlipidemia, CHD, CHF and lower use of hypoglycemic and lipid-lowering drugs. Participants with higher eGDR had lower BMI, WC, ePWV, TyG index, HOMA-IR, HbA1c, higher TC and eGFR ($P < 0.001$). Additionally, both all-cause mortality and cardiovascular mortality significantly decrease as eGDR increases.

Relationship between eGDR and arterial stiffness

In the unadjusted linear regression analysis, we observed a negative correlation between eGDR and ePWV (β=-0.24(-0.26–0.21, P< 0.001). In Model II, eGDR was significantly negatively correlated with ePWV (β=-0.13(-0.14–0.11, P< 0.001). However, TyG index and HOMA-IR showed no significant correlation to arterial stiffness (Table 2). Restricted cubic spline indicated a non-linear inverse relationship between eGDR and ePWV (P for nonlinear < 0.05). As eGDR increases, ePWV decreases more significantly (Figure 2).

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TABLE 1 Clinical characteristics of study population grouped by eGDR quartiles.

Variables	Overall	eGDR-Q1	eGDR-Q2	eGDR-Q3	eGDR-Q4	*P* value
Age, %	54.69 (54.10,55.28)	57.17 (56.22,58.12)	59.66 (58.73,60.58)	54.81 (53.60,56.02)	47.50 (46.38,48.63)	<0.001***
Gender, %						0.29
Female	43.01 (39.83,46.20)	42.29 (38.48,46.09)	45.51 (41.77,49.25)	43.98 (39.66,48.30)	40.39 (36.83,43.94)	
Male	56.99 (52.93,61.04)	57.71 (53.91,61.52)	54.49 (50.75,58.23)	56.02 (51.70,60.34)	59.61 (56.06,63.17)	
Race/ethnicity, %						<0.001***
White	72.93 (66.69,79.18)	74.37 (70.99,77.75)	77.16 (74.06,80.25)	73.89 (70.80,76.98)	66.64 (62.87,70.41)	
Black	5.94 (5.20, 6.69)	10.17 (8.10,12.23)	6.30 (4.95, 7.66)	4.95 (3.89, 6.01)	2.57 (1.84, 3.30)	
Mexican	9.93 (8.46,11.39)	5.67 (4.30, 7.04)	6.89 (5.17, 8.60)	9.11 (7.25,10.97)	17.63 (14.81,20.46)	
Others	11.19 (9.83,12.55)	9.79 (7.43,12.15)	9.65 (7.72,11.58)	12.05 (10.19,13.91)	13.16 (10.48,15.84)	
Education levels, %						0.04*
Less than high school	21.63 (19.57,23.69)	20.19 (17.25,23.14)	22.37 (19.29,25.44)	21.01 (18.04,23.98)	22.88 (19.70,26.05)	
High school or equivalent	24.57 (22.01,27.13)	26.32 (22.96,29.68)	27.13 (23.82,30.45)	24.89 (21.41,28.37)	20.16 (17.11,23.22)	
College or above	53.81 (49.87,57.74)	53.49 (49.18,57.79)	50.50 (46.65,54.35)	54.11 (49.96,58.25)	56.96 (53.03,60.89)	
BMI, kg/m2	33.88 (33.58,34.18)	39.76 (39.23,40.30)	33.11 (32.73,33.50)	32.66 (32.20,33.12)	30.22 (29.88,30.55)	<0.001***
waist circumference, cm	113.03 (112.36,113.70)	127.40 (126.35,128.45)	111.91 (111.14,112.69)	110.42 (109.30,111.55)	103.02 (102.27,103.77)	<0.001***
HbA1c, %	6.05 (6.00,6.10)	6.86 (6.73,6.99)	5.99 (5.93,6.05)	5.83 (5.76,5.91)	5.54 (5.50,5.58)	<0.001***
TG, mmol/L	2.03 (1.96,2.10)	2.07 (1.96,2.18)	1.99 (1.89,2.09)	2.01 (1.88,2.15)	2.05 (1.90,2.21)	0.78
TC, mmol/L	5.08 (5.03,5.13)	4.86 (4.78,4.94)	5.04 (4.95,5.12)	5.13 (5.05,5.22)	5.26 (5.15,5.36)	<0.001***
HOMA_IR	7.40 (7.07,7.73)	10.80 (9.88,11.71)	6.86 (6.30, 7.43)	6.63 (6.18, 7.07)	5.43 (5.07, 5.80)	<0.001***
TyG	7.50 (7.47,7.52)	7.68 (7.62,7.74)	7.48 (7.44,7.53)	7.44 (7.39,7.49)	7.38 (7.34,7.43)	<0.001***
ePWV	9.00 (8.92,9.07)	9.35 (9.24,9.47)	9.74 (9.60,9.88)	9.03 (8.87,9.18)	7.93 (7.81,8.05)	<0.001***
eGFR, mL/min/1.73 m^2	87.32 (86.50,88.15)	84.80 (83.17,86.42)	81.86 (80.41,83.31)	87.99 (86.49,89.50)	94.27 (92.86,95.68)	<0.001***
Smoking, %						0.005**
No	54.35 (50.77,57.94)	52.14 (48.18,56.10)	50.36 (46.61,54.11)	55.56 (51.59,59.52)	59.09 (55.51,62.67)	
Yes	45.65 (41.77,49.52)	47.86 (43.90,51.82)	49.64 (45.89,53.39)	44.44 (40.48,48.41)	40.91 (37.33,44.49)	
DM, %						<0.001***
No	67.43 (62.71,72.15)	40.52 (36.57,44.47)	66.25 (62.97,69.53)	75.02 (71.80,78.24)	86.69 (84.33,89.05)	
Yes	32.57 (30.15,34.99)	59.48 (55.53,63.43)	33.75 (30.47,37.03)	24.98 (21.76,28.20)	13.31 (10.95,15.67)	
CHD, %						<0.001***
No	92.39 (86.76,98.02)	88.56 (85.75,91.38)	91.37 (89.42,93.31)	92.58 (90.52,94.64)	96.79 (95.48,98.11)	
Yes	7.61 (6.42, 8.80)	11.44 (8.62,14.25)	8.63 (6.69,10.58)	7.42 (5.36, 9.48)	3.21 (1.89, 4.52)	
Hyperlipidemia, %						0.10
No	10.95 (9.59,12.32)	10.14 (7.97,12.31)	8.91 (6.72,11.11)	11.87 (9.21,14.53)	12.79 (10.39,15.18)	
Yes	89.05 (83.37,94.72)	89.86 (87.69,92.03)	91.09 (88.89,93.28)	88.13 (85.47,90.79)	87.21 (84.82,89.61)	
CHF, %						<0.001***
No	94.99 (89.17,100.81)	90.62 (88.60,92.64)	94.50 (92.96,96.04)	96.31 (95.02,97.60)	98.32 (97.49,99.14)	
Yes	5.01 (4.19, 5.84)	9.38 (7.36,11.40)	5.50 (3.96, 7.04)	3.69 (2.40, 4.98)	1.68 (0.86, 2.51)	

(Continued)

TABLE 1 Continued

Variables	Overall	eGDR-Q1	eGDR-Q2	eGDR-Q3	eGDR-Q4	*P* value
Anti-diabetic drugs, %						<0.001***
No	80.54 (75.24,85.84)	59.88 (55.93,63.83)	80.75 (78.11,83.39)	87.34 (84.95,89.73)	93.33 (91.42,95.24)	
Yes	19.46 (17.67,21.25)	40.12 (36.17,44.07)	19.25 (16.61,21.89)	12.66 (10.27,15.05)	6.67 (4.76, 8.58)	
Anti-hyperlipidemic drugs, %						<0.001***
No	68.11 (63.62,72.59)	56.97 (53.42,60.52)	59.31 (55.82,62.79)	71.82 (68.08,75.55)	83.45 (80.34,86.56)	
Yes	31.89 (29.22,34.56)	43.03 (39.48,46.58)	40.69 (37.21,44.18)	28.18 (24.45,31.92)	16.55 (13.44,19.66)	
All-cause mortality, %						<0.001***
No	83.15 (77.82,88.48)	79.23 (76.19,82.27)	80.07 (77.31,82.83)	81.68 (79.04,84.32)	91.21 (89.32,93.09)	
Yes	16.85 (15.15,18.55)	20.77 (17.73,23.81)	19.93 (17.17,22.69)	18.32 (15.68,20.96)	8.79 (6.91,10.68)	
Cardiovascular mortality, %						<0.001***
No	95.40 (89.44,101.37)	93.44 (91.63,95.26)	93.95 (92.33,95.58)	95.43 (94.03,96.83)	98.61 (97.91,99.31)	
Yes	4.60 (3.86, 5.33)	6.56 (4.74,8.37)	6.05 (4.42,7.67)	4.57 (3.17,5.97)	1.39 (0.69,2.09)	

Continuous data were presented as the mean and 95% confidence interval, category data were presented as the proportion and 95% confidence interval. eGDR, estimated glucose disposal rate; BMI, body mass index; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; TyG, triglyceride and glucose index; ePWV, estimated pulse wave velocity; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CHD, coronary heart disease; CHF, congestive heart failure; ***P value<0.001, **P value<0.01, *P value<0.05.

Kaplan–Meier survival analysis curves for mortality based on eGDR

1051 all-cause deaths and 283 CVD deaths were showed during the follow-up period. The mortality rate of eGDR group was shown in the Figure 3. We observed significant differences in mortality between different eGDR groups (all-cause mortality: P <0.001; cardiovascular mortality: P <0.001). The all-cause mortality and cardiovascular mortality rates were significantly decreased in the higher eGDR group.

Relationship between eGDR and mortality

We also used cox regression model to evaluate the association between eGDR and mortality. Represented as a continuous variable, we observed a negative correlation between eGDR and all-cause mortality with a hazard ratio (HR) of 0.93 (95%CI: 0.89-0.98) and cardiovascular mortality with a hazard ratio (HR) of 0.84 (95%CI: 0.77-0.92). Compared with participants having lowest eGDR, those having highest eGDR had a reduction of 35% (adjusted HR, 0.65; 95% CI, 0.48-0.89) in the risk for all-cause mortality and 65% (adjusted HR, 0.35; 95% CI, 0.19-0.65) in the risk for cardiovascular mortality in Model II (Table 3).

A restricted cubic spline was used to examine the association between eGDR and mortality. The findings indicated a linear inverse relationship between eGDR and mortality (all-cause mortality: P for non-linear=0.34; cardiovascular mortality: P for non-linear=0.69) (Figure 4). As eGDR rose, there was a substantial decrease in the risk of mortality (Figure 4).

Sensitivity analysis

Similarly, sensitivity analysis adopting unweighted logistic analysis reveals that the lower risk of mortality was showed in the

TABLE 2 Beta between ePWV by eGDR in the NHANES 1999-2018.

	Non-adjusted model		Model I		Model II	
	Beta [95% CI]	*P* value	Beta [95% CI]	*P* value	Beta [95% CI]	*P* value
eGDR	-0.24 (-0.26, -0.21)	<0.001**	-0.08 (-0.10, -0.07)	<0.001**	-0.13 (-0.14, -0.11)	<0.001***
TyG	0.19 (0.10,0.28)	<0.001**	0.08 (0.02, 0.14)	0.01*	0.11 (-0.03, 0.25)	0.14
HOMA-IR	0.01 (0.00,0.01)	0.16	0 (0.00, 0.00)	0.82	0 (-0.01, 0.00)	0.30

Data are presented as Beta (95% CI). Model I adjusted for age, sex, and race/ethnicity. Model II adjusted for age, sex, race/ethnicity, education levels, smoking, BMI, TC, TG, eGFR, DM, CHD, CHF, Hyperlipidemia, anti-diabetic drugs and anti-hyperlipidemic drugs. eGDR, estimated glucose disposal rate; BMI, body mass index; TC, total cholesterol; TG, triglycerides; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; TyG, triglyceride and glucose index; ePWV, estimated pulse wave velocity; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CHD, coronary heart disease; CHF, congestive heart failure; ***P value<0.001, **P value<0.01, *P value<0.05.

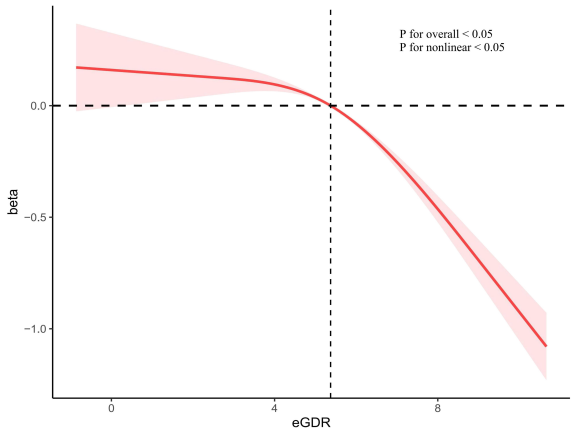

FIGURE 2
The correlation of eGDR with ePWV in a restricted cubic spline model. Adjusted for age, sex, race/ethnicity, education levels, smoking, BMI, TC, TG, eGFR, DM, CHD, CHF, Hyperlipidemia, anti-diabetic drugs and anti-hyperlipidemic drugs. eGDR, estimated glucose disposal rate; BMI, body mass index; TC, total cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CHD, coronary heart disease; CHF, congestive heart failure.

highest eGDR (all-cause mortality: HR = 0.61, 95%CI: 0.48-0.77; cardiovascular mortality: HR = 0.34, 95%CI: 0.20-0.57) in Model II (Table 4). These results suggest a consistent inverse relationship between eGDR and mortality.

ROC curve analysis of eGDR, TyG index and HOMA–IR

The ROC curves of eGDR, TyG index, and HOMA-IR predicting mortality in NAFLD patients are shown in Table 5 and Figure 5. Compared with TyG index and HOMA-IR, the eGDR shows excellent predictive value in all-cause mortality (0.588 vs. 0.550 vs. 0.513, $P < 0.001$) and cardiovascular mortality (0.625 vs. 0.553 vs. 0.537, $P < 0.001$). In predicting all-cause mortality, its AUC was 0.588 (0.574,0.602) and the optimal cut-off value was 5.95. The sensitivity was 73.64 and the specificity was 53.15. In predicting cardiovascular mortality, its AUC was 0.625 (0.611,0.639) and the optimal cut-off value was 5.70. The sensitivity was 77.00 and the specificity was 54.50.

Subgroups analysis

We conducted subgroup analysis to examine the possible link between eGDR and mortality among diverse subgroups categorized by age, sex, race, BMI, smoking, CHD and hyperlipidemia (Supplementary Tables S1, S2). For all-cause mortality, eGDR may have interactive effects in different BMI populations (Figure 6). The influence of eGDR on cardiovascular mortality did not vary among the subgroups (Figure 7).

Discussion

Previous studies have found that low eGDR is associated with the increased risk of prevalence and poor prognosis in various diseases. Specifically, our findings demonstrate that the eGDR was inversely associated with the all-cause mortality and cardiovascular mortality after accounting for confounding factors in the adult population of the United States. It performs better than the TyG index and HOMA-IR in predicting these outcomes. The relationship between eGDR and all-cause as well as cardiovascular mortality follows a linear pattern, as depicted by the fitted smoothing curves. Interestingly, the effect of eGDR on cardiovascular mortality does not differ significantly among

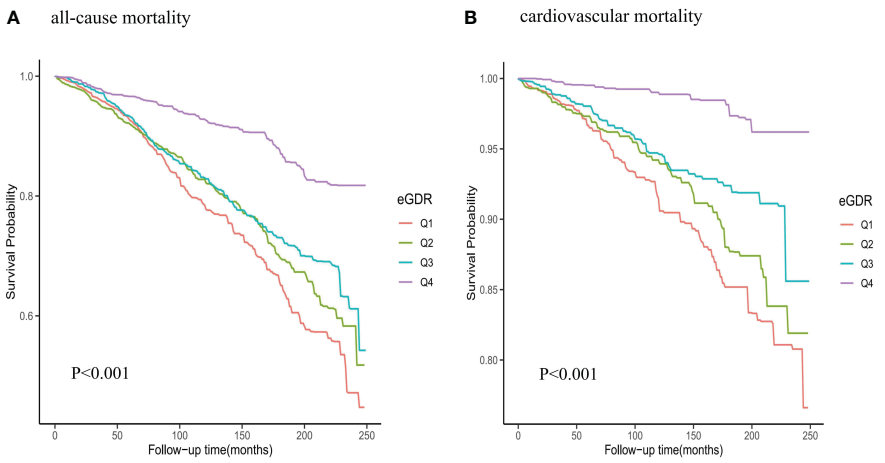

FIGURE 3
Kaplan-Meier survival analysis curves for all-cause and cardiovascular mortality among eGDR groups. **(A)** all-cause mortality; **(B)** cardiovascular mortality.

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TABLE 3 Weighted cox regression analysis on the association between eGDR and mortality.

	Non-adjusted model		Model I		Model II	
	HR [95% CI]	*P* value	HR [95% CI]	*P* value	HR [95% CI]	*P* value
All-cause mortality						
Continuous eGDR	0.86 (0.83,0.89)	<0.001***	0.91 (0.88, 0.95)	<0.001***	0.93 (0.89,0.98)	0.01*
eGDR-Q1	Reference	–	Reference	–	Reference	–
eGDR-Q2	0.84 (0.68,1.04)	0.11	0.77 (0.62, 0.96)	0.02*	0.82 (0.64,1.06)	0.13
eGDR-Q3	0.76 (0.60,0.95)	0.02*	0.89 (0.71, 1.12)	0.33	0.89 (0.63,0.98)	0.36
eGDR-Q4	0.33 (0.25,0.42)	<0.001***	0.55 (0.42, 0.72)	<0.001***	0.65 (0.48,0.89)	0.01*
Cardiovascular mortality						
Continuous eGDR	0.78 (0.73,0.83)	<0.001***	0.81 (0.75, 0.88)	<0.001***	0.84 (0.77, 0.92)	<0.001**
eGDR-Q1	Reference	–	Reference	–	Reference	–
eGDR-Q2	0.79 (0.54,1.16)	0.23	0.74 (0.50, 1.10)	0.14	0.82 (0.53, 1.28)	0.39
eGDR-Q3	0.58 (0.37,0.92)	0.02*	0.72 (0.46, 1.11)	0.14	0.94 (0.55, 1.59)	0.81
eGDR-Q4	0.15 (0.09,0.26)	<0.001***	0.26 (0.16, 0.45)	<0.001***	0.35 (0.19, 0.65)	<0.001***

Data are presented as HR (95% CI). Model I adjusted for age, sex, and race/ethnicity. Model II adjusted for age, sex, race/ethnicity, education levels, smoking, BMI, TC, TG, eGFR, DM, CHD, CHF, Hyperlipidemia, anti-diabetic drugs and anti-hyperlipidemic drugs. eGDR, estimated glucose disposal rate; BMI, body mass index; TC, total cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CHD, coronary heart disease; CHF, congestive heart failure; ***P value<0.001, **P value<0.01, *P value<0.05.

different subgroups. For all-cause mortality, eGDR may have interactive effects in different BMI populations. In addition, we found a significant negative correlation between eGDR and arterial stiffness. However, TyG index and HOMA-IR showed no significant correlation to arterial stiffness.

Previous studies have shown that IR is common in diabetes patients, and severe IR is positively related to poor prognosis (31). Many studies have shown that IR also plays an important role in other diseases, including hypertension, NAFLD, CHF, etc (32–34). We also found that IR plays an important role in NAFLD. Additionally, research suggests that an intricate interplay between metabolic elements, adipose tissue breakdown and IR leads to a harmful progression that could connect fatty liver disease with severe cardiovascular disease. The difference from previous studies is that the severity of IR can also predict poor prognosis in NAFLD. Furthermore, individuals diagnosed with fatty liver disease face an increased likelihood of atherosclerosis, adverse cardiovascular events and higher mortality (35). Previous studies have shown that NAFLD is linked to increased levels of IR, a significant pathophysiological factor that plays a role in the onset and advancement of the disease (36). In addition, the elastic fibers in the inner layer of the artery undergo degeneration and the intima becomes hard, which can lead to an increase in arterial hardness (37). Arterial stiffness is considered an independent risk predictor of

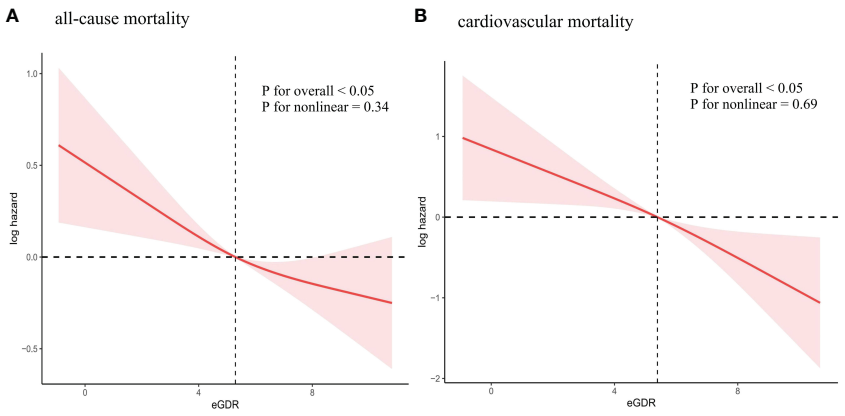

FIGURE 4
Association between eGDR and all-cause and cardiovascular mortality. **(A)** all-cause mortality; **(B)** cardiovascular mortality. Adjusted for age, sex, race/ethnicity, education levels, smoking, BMI, TC, TG, eGFR, DM, CHD, CHF, Hyperlipidemia, anti-diabetic drugs and anti-hyperlipidemic drugs. eGDR, estimated glucose disposal rate; BMI, body mass index; TC, total cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CHD, coronary heart disease; CHF, congestive heart failure.

TABLE 4 Unweighted cox regression analysis on the association between eGDR and mortality in sensitive analysis.

	Non-adjusted model		Model I		Model II	
	HR [95% CI]	*P* value	HR [95% CI]	*P* value	HR [95% CI]	*P* value
All-cause mortality						
Continuous eGDR	0.86(0.84,0.88)	<0.001***	0.92(0.90, 0.95)	<0.001***	0.92(0.89,0.96)	<0.001***
eGDR-Q1	Reference	–	Reference	–	Reference	–
eGDR-Q2	0.83(0.71,0.97)	0.02*	0.75(0.64, 0.88)	0.003**	0.74(0.63,0.88)	<0.001***
eGDR-Q3	0.75(0.63,0.87)	<0.001***	0.87(0.74, 1.03)	0.10	0.87(0.72,1.05)	0.14
eGDR-Q4	0.34(0.28,0.41)	<0.001***	0.58(0.47, 0.71)	<0.001***	0.61(0.48,0.77)	<0.001***
Cardiovascular mortality						
Continuous eGDR	0.79(0.75,0.83)	<0.001***	0.84(0.79, 0.89)	<0.001***	0.85(0.79, 0.91)	<0.001**
eGDR-Q1	Reference	–	Reference	–	Reference	–
eGDR-Q2	0.79(0.59,1.05)	0.11	0.73(0.55, 0.97)	0.03*	0.74(0.55, 1.01)	0.06
eGDR-Q3	0.60(0.44,0.81)	<0.001***	0.74(0.54, 1.01)	0.06	0.79(0.55, 1.14)	0.21
eGDR-Q4	0.16(0.10,0.25)	<0.001***	0.30(0.19, 0.48)	<0.001***	0.34(0.20, 0.57)	<0.001***

Data are presented as HR (95% CI). Model I adjusted for age, sex, and race/ethnicity. Model II adjusted for age, sex, race/ethnicity, education levels, smoking, BMI, TC, TG, eGFR, DM, CHD, CHF, Hyperlipidemia, anti-diabetic drugs and anti-hyperlipidemic drugs. eGDR, estimated glucose disposal rate; BMI, body mass index; TC, total cholesterol; TG, triglycerides; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; CHD, coronary heart disease; CHF, congestive heart failure; ***P value<0.001, **P value<0.01, *P value<0.05.

cardiovascular events (38). IR can damage the endothelium of blood vessels and lead to inflammatory reactions, which may easily lead to arterial stiffness and arteriosclerosis (39). A Meta-analysis of 37,780 Individuals showed that IR is closely related to arterial stiffness (40). Another study suggests that the TyG index is closely related to arterial stiffness in uncontrolled hypertensive patients in American adults (41). In addition, we found that low eGDR levels are related to an increased risk of arterial stiffness in NAFLD patients in our study. This indicates that IR also plays an important role in arteriosclerosis in NAFLD.

IR is related to various factors such as inflammation, oxidative stress, microRNA expression, abnormal insulin metabolism signaling pathways and mitochondrial dysfunction in the body (42). IR is also an important characteristic of NAFLD. Therefore, the evaluation of IR indicators is closely associated with the prognosis of NAFLD patients. Inflammation and oxidative stress are closely related to IR. Recently, many studies found that high levels of inflammation and oxidative stress both lead to high mortality rates in patients with fatty liver disease (43, 44). Furthermore, the eGDR and TyG index have been proven to be a simple indicator for evaluating IR. Based on these findings, our results indicate that low eGDR levels are related to an increased risk of all-cause mortality and cardiovascular mortality in NAFLD patients in the United States. And the predictive ability of eGDR on outcomes is superior to TyG index and HOMA-IR.

TABLE 5 ROC curves analysis on the association between IR indicators and mortality.

IR indicators	Best thresholds	Sensitivity	Specificity	AUC (95% CI)	*P* for difference
All-cause mortality					
eGDR	5.95	73.64	53.15	0.588(0.574,0.602)	Reference
TyG	7.70	41.3	67.9	0.550(0.536,0.564)	0.002**
HOMA-IR	11.33	17.8	89.1	0.513(0.498,0.527)	<0.001***
Cardiovascular mortality					
eGDR	5.70	77.00	54.50	0.625(0.611,0.639)	Reference
TyG	7.51	55.80	54.60	0.553(0.538,0.567)	<0.001***
HOMA-IR	5.64	52.30	55.60	0.537(0.523,0.551)	<0.001***

ROC, receiver operating characteristic; IR, insulin resistance; eGDR, estimated glucose disposal rate; TyG, triglyceride-glucose index; HOMA-IR, homeostasis model assessment of insulin resistance; ***P value<0.001, **P value<0.01, *P value<0.05.

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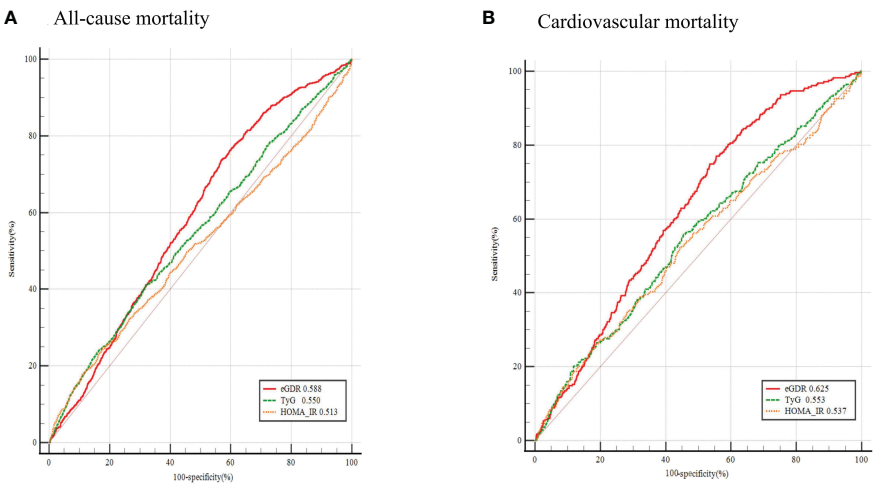

FIGURE 5
ROC Curve analysis for eGDR, TyG index and HOMA-IR Predicted all-cause and cardiovascular mortality. **(A)** All-cause mortality; **(B)** Cardiovascular mortality. ROC receiver operating characteristic; eGDR, estimated glucose disposal rate; TyG index triglyceride glucose index; HOMA-IR homeostasis model assessment of insulin resistance.

In addition, the NHANES data is designed through complex, multi-stage probability sampling to ensure the robustness of the results. In subgroup analysis, eGDR has a certain predictive effect on all-cause mortality in different BMI populations especially in overweight populations. It may be due to the increased risk of IR in overweight or obese populations. The effect of eGDR on cardiovascular mortality does not differ significantly among different subgroups. These are points worth paying attention to in our study.

This research demonstrates, for the first time, the relationship between eGDR and arterial stiffness and mortality. These findings can provide important reference value for the prognosis of patients with NAFLD in the adult population of the United States. This study utilized a large sample of national databases and had a long

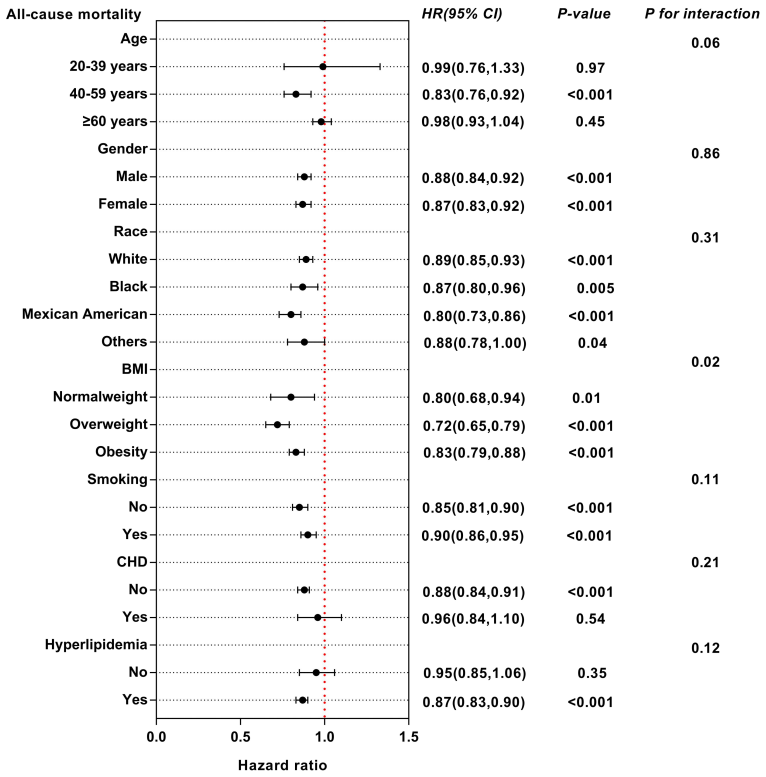

FIGURE 6
Subgroup analysis of multi-variable adjusted association of eGDR with all-cause mortality.

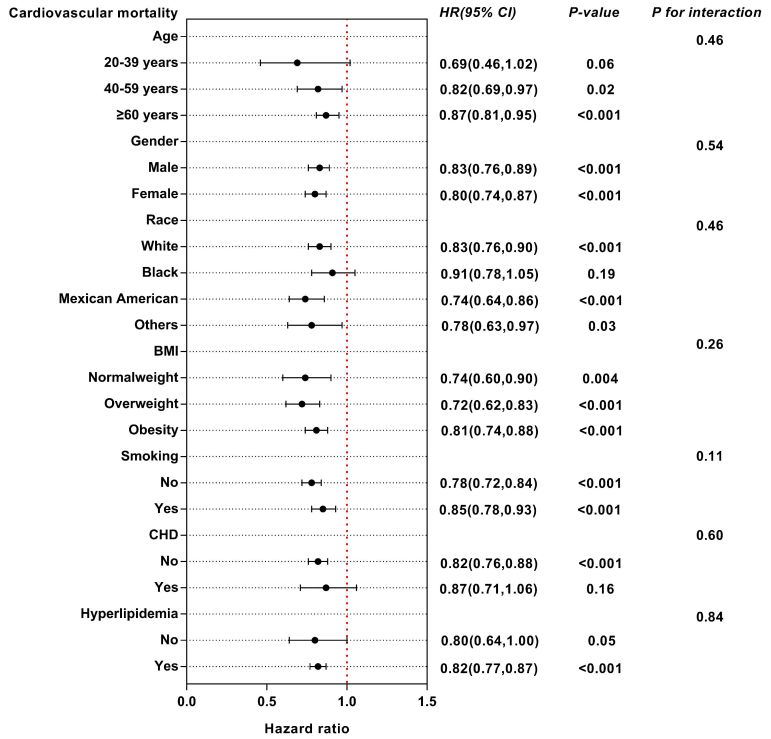

FIGURE 7
Subgroup analysis of multi-variable adjusted association of eGDR with cardiovascular mortality.

follow-up time, which enhances the credibility of the research findings. However, there are some limitations in our study. Firstly, this study did not monitor the dynamic changes of eGDR, which may provide greater reference value. Second, the findings of the NHANES study are primarily applicable to the American population because of the variations in disease characteristics across different racial groups. Finally, the diagnosis of NAFLD mainly relies on us-FLI, which may lead to selection bias. Therefore, future research needs to consider these limitations.

Conclusion

Low eGDR (an indicator of insulin resistance) levels are related to an increased risk of arterial stiffness and mortality in NAFLD patients in the United States. However, further prospective studies are still needed to reveal their relationship.

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

JS: Writing – original draft. RM: Writing – review & editing. LY: Writing – review & editing.

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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

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The association of body mass index variability with cardiovascular disease and mortality: a mediation analysis of pooled cohorts

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Aim: We aimed to investigate the effect of BMI variability on CVD and mortality and to explore the mediation effects of the main cardiovascular risk factors contributing to this association.

Method: Participants aged 40-65 years were pooled from three cohort studies (ARIC [Atherosclerosis Risk in Communities], MESA [Multi-ethnic Study of Atherosclerosis], and TLGS [Tehran Lipid and Glucose Study]. We employed root mean squared error of the fractional mixed model to calculate BMI variability in the measurement period. In the event assessment period, the hazard ratios for CVD and mortality were estimated using Cox proportional hazard regression models. In the next step, the mediation and interaction effects of fasting plasma glucose, total cholesterol, and systolic blood pressure were determined.

Results: A total of 19073 participants were included in this pooled analysis. During a median of 20.7 years of follow-up, 3900 (20.44%) CVD and 6480 (33.97%) all-cause mortality events were recorded. After adjusting for potential confounders, BMI variability was linked to the 1.3 (1.2-1.4) and 1.7 (1.6-1.8) increased risk of CVD and mortality, respectively. Fasting plasma glucose mediated approximately 24% and 8% of the effect of BMI variability on CVD and mortality, respectively. However, systolic blood pressure and total cholesterol did not have mediation effects in this association.

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Conclusion: High BMI variability is independently associated with the development of CVD and mortality. This association is partly mediated through fasting plasma glucose. Modern cardiometabolic therapies that lower fasting glucose may reduce the risk of future CVD and mortality in individuals with high BMI variability.

KEYWORDS

cardiovascular disease, mortality, body mass index, weight variability, mediation analysis

Introduction

Obesity is a well-known risk factor for cardiovascular disease (CVD) and mortality (1, 2). Overweight and obese individuals with additional cardiovascular risk factors are recommended to lose weight through lifestyle modifications (3). However, weight loss maintenance is challenging and is followed by weight regain in the long term (4). In a systematic review of observational studies, 42% of the general population reported personal weight control attempts (5). Adherence to a weight loss strategy plan, metabolic adaptation, energy homeostasis, and pregnancy are the factors that may lead to recurrent cycles of weight loss and regain and, thus, unsuccessful attempts at sustained weight loss (6).

The obesity paradox refers to the seemingly counterintuitive notion that body mass index (BMI) is not a consistent cardiovascular risk factor in overweight and obese individuals (7, 8), and questions the cardiovascular health benefits of weight loss in the long term (9–11). Body weight variability has been examined as an additional risk factor to explain the controversial findings on the effect of weight loss on CVD and mortality (12, 13). Although several studies suggested that weight variability independently increases the risk of CVD and mortality (12), some studies found no association or decreased risk for future CVD (14–16). In addition, the relationship between weight variability and CVD is inconsistent among different subpopulations (17, 18). The mechanisms through which weight variability increases the risk of CVD and mortality are not understood, and a few studies have explored the correlation of weight variability with cardiovascular risk factors (19, 20).

To address the gap in the literature, the current study investigated the association of BMI variability with CVD incidence and all-cause mortality in a large pooled sample and in different subpopulations. We also delved deeper into the underlying mechanisms driving the link between BMI variability and CVD and mortality by performing mediation analyses. This would help to determine the specific cardiovascular risk factors that act as intermediaries in this relationship, shedding new light on the potentially complex relationship between BMI variability and CVD and mortality.

Methods

Study population

The current study was based on data from three large population-based cohort studies designed to investigate the risk factors for non-communicable diseases: Atherosclerosis Risk in Communities (ARIC), Multi-Ethnic Study of Atherosclerosis (MESA), and Tehran Lipid and Glucose Study (TLGS). The Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), managed by the National Heart, Lung, and Blood Institute (NHLBI), granted access to the public-use datasets for the ARIC and MESA studies by coordinating their storage and distribution. Previous publications have provided detailed and comprehensive descriptions of the cohorts' design, protocols, and participant characteristics (21–23).

ARIC

The ARIC study is a prospective multi-center cohort of 15,972 adults aged 45-64 in 1987-1989, randomly selected and recruited from four clinical sites in the United States (Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN). The study participants were enrolled in seven study examination visits with three-year intervals (visit 1: 1987-1989, visit 2: 1990–1992, visit 3: 1993–1995, visit 4: 1996–1998, visit 5: 2011–2013, visit 6: 2016–2017, and visit 7: 2018–2019) and followed annually through telephone interviews to obtain most recent health-related information.

MESA

In 2000-2002, the MESA study recruited a population-based sample of 6,814 individuals between 45 and 84 years old from six field centers across the United States (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and Saint Paul, MN). The subsequent follow-up examination visits were performed during 2002-2004 (visit 2), 2004-2005 (visit 3), 2005-2007 (visit 4), and 2010-2012 (visit 5) and 2016-2018 (visit 6). The participants were contacted at 9-12 months intervals for updates on medical conditions.

TLGS

The TLGS is an ongoing population-based cohort study initiated during 1999-2001 by recruiting 18,555 members aged≥3 years in Tehran, Iran. The examination visits were held in approximate three-year intervals (visit 2: 2002-2005, visit 3: 2005-2008, visit 4: 2009-2011, visit 5: 2011-2014, visit 6: 2015-2018). Participants were followed annually for any medical event by telephone calls.

Study timeline

The timeline for the current study was divided into two distinct periods: a measurement period, beginning at baseline and continuing until the end of the fourth examination visit, and an event assessment period, which started from the fourth examination until the end of the study (Figure 1). We included a total of 32628 participants aged 40 to 65 years old at baseline from the ARIC (n=14996), MESA (n=4084), and TLGS (n=13548) cohorts. Participants with CVD (n=430), cancer (n=526), estimated glomerular filtration rate (eGFR)<30 mL/min/1.73m^2 (n=32), and missing covariates at baseline (n=2293) were excluded. Participants with CVD and mortality events in the measurement period (n=362) and with less than three BMI records during the measurement period (n=9912) were also excluded.

Definition of variables

BMI was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Diabetes was defined as fasting plasma glucose (FPG) 126 mg/dl or the use of glucose-lowering medication. Hypertension was determined by systolic blood pressure (SBP)≥140mmHg, diastolic blood pressure≥90mmHg, or the use of antihypertensive medications. The education level categories were: 1) primary school (less than 6 years of education), 2) high school (6-12 years of education), and 3) higher education degree (12 years or more of education). Two categories were used to classify smoking status: current and non-smokers (former and never smokers). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 formula.

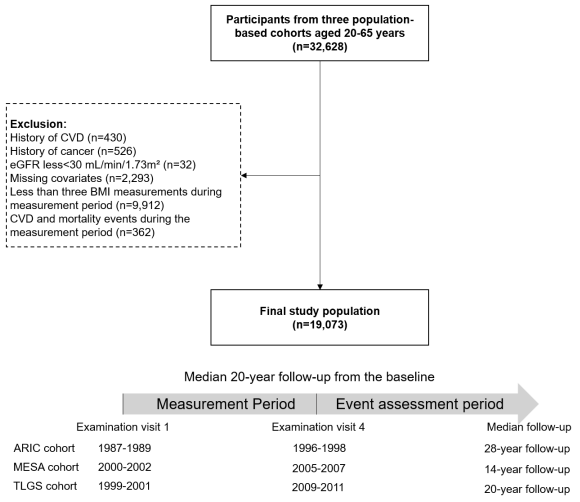

FIGURE 1
Flowchart of the study participants and timeline of the pooled study cohort. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; BMI, body mass index; ARIC, Atherosclerosis Risk in Communities; MESA, Multi-Ethnic Study of Atherosclerosis; TLGS, Tehran Lipid and Glucose Study.

Definition of outcomes

Our primary outcomes were incident CVD and all-cause mortality. Incident CVD was defined as a composite of fatal and non-fatal coronary heart disease (CHD) and stroke; incident CHD was defined as myocardial infarction, angina if followed by revascularization or medical treatment, coronary procedures, and death due to CHD. The outcome review committees in each study adjudicated the classification and incidence date of events to examine hospitalization and mortality based on previously published study protocols (21–23).

Statistical analysis

The baseline characteristics of the study population were reported as mean values with standard deviation (SD) for continuous variables and as percentages for categorical variables. The data were compared using appropriate statistical tests, the Chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.

Our investigation in this study was based on the variability of BMI values instead of weight, as weight changes can be affected by variations in height. In the current study, we ran mixed effect regression models using fractional polynomials to obtain the BMI trend of each individual in the measurement period and calculated BMI variability using the root mean squared error (RMSE) (1). In this method, BMI variability is not sensitive to the mean values and number of measurements. Moreover, it captures large weight variations and not the non-linearity in the natural trend of BMI (18, 24).

Estimation of BMI trend in longitudinal age

Briefly, we used mixed-effect regression models to investigate the BMI trend of each individual in longitudinal age since mixed-effect regression models account for the correlations that arise from the multiple BMI measurements taken from one person. This model estimates both the population-level effect (fixed effect; with age as the covariate) and the individual-level effect (random effect). By including the random effect, we also captured the variability of BMI change between individuals. We used fractional polynomials to obtain the best-fit mixed-effect regression model since the fractional polynomials is a flexible approach that allows the power of the polynomial terms to be any real number and fit curves that are not possible with traditional polynomials.

To estimate BMI trends, we fitted smooth trends using fractional polynomial mixed models (with random intercept) that accounted for the longitudinal age at each measurement. We derived the trend parameters for longitudinal age and intercept using random effects (Equation 1).

$$BMI_{i,j} = (\beta_0 + b_{0i}) + \beta_1 age_{ij} + \beta_2 age_{ij}^{\ 2} + \beta_3 age_{ij}^{\ 3} + \varepsilon_{ij} \quad (1)$$

In the equation, $BMI_{i,j}$ is the BMI of the participant "i" at the examination visit "j". β_0 represents the intercept and b_{0i} represents the random intercept for each individual i with the assumption of normal distribution. This random intercept term accounts for individual variation that cannot be explained by the other variables in the model. The population parameters, $\beta_1 - \beta_3$, represent the estimated changes in BMI values over longitudinal age. The optimal model for the BMI trend of individuals was selected based on the fractional model. Equation (2) represents the final optimal model for predicting BMI values:

$$\widehat{BMI}_{i,j} = (\hat{\beta}_0 + \hat{b}_{0i}) + \hat{\beta}_1 age + \hat{\beta}_2 age^2 + \hat{\beta}_3 age^3 \quad (2)$$

BMI variability calculation

After obtaining the BMI trend for each individual (the final model), we calculated the intraindividual BMI variability using the root mean squared error (RMSE) formula (Equation 3) i.e., the average of the square root of the difference between the actual and fitted BMI (obtained from the final model) values at each time point.

$$RMSE_i = \sqrt{\frac{\sum_{j=1}^{k} (BMI_{i,j} - \widehat{BMI}_{i,j})^2}{N}} \quad (3)$$

$BMI_{i,j}$ = Actual (observed) longitudinal BMI.

$\widehat{BMI}_{i,j}$ = Estimated (fitted) longitudinal BMI.

i represents each individual in the dataset.

k represents the number of BMI records for an individual.

j represents the records of BMI measurement for each individual.

N represents the number of measurements for an individual.

Survival analysis

To assess the relationship between BMI variability (expressed as BMI-RMSE) and the risk of study outcomes, multivariate-adjusted Cox proportional hazards regression models were utilized. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated using the lowest tertile of BMI variability as the reference group. Model 1 was adjusted for age at baseline and sex. Model 2 was adjusted for age, sex, education level, premature CVD family history, and smoking status. Model 3 was adjusted for model 2 and baseline BMI, fasting plasma glucose, systolic blood pressure, and total cholesterol.

Mediation analysis

We investigated the role of metabolic indices of FPG, total cholesterol (TC), and SBP, using their mean values in the measurement period, in explaining the effect of BMI variability on CVD incidence and all-cause mortality. To conduct mediation analysis, we performed preliminary analysis to evaluate the association of BMI variability with the potential mediators and the association of the potential mediators with the outcomes. We then conducted the mediation analysis using a four-way decomposition (25). In this method, the total effect of the exposure on the outcome can be divided into four components. The effect was attributed to both mediation and interaction, interaction only, mediation only, and neither mediation nor interaction. The lowest BMI variability tertile was considered the reference group, and the direct and indirect effect of BMI variability on CVD and mortality was calculated accordingly. The analysis was conducted using R-3.0.3 (R Foundation for Statistical Computing) and Med4way package in STATA 14.0 (StataCorp, College Station, TX, USA) (25).

Results

Table 1 presents the baseline characteristics of the study participants according to the BMI variability tertiles. This pooled cohort comprised 19073 participants (51.89% women) with a mean age of 53 ± 6 years at baseline. The value of BMI variability ranged from 0.02-0.63 Kg/m^2 in the first, 0.63-1.07 Kg/m^2 in the second, and 1.07-9.32 Kg/m^2 in the third tertiles. Toward the highest tertile, the mean values of baseline BMI, SBP, FPG, TG, TC, and BMI change increased while the mean age decreased. The highest BMI variability tertile had a higher prevalence of women, individuals with obesity, and lower education levels, while the lowest BMI variability tertile showed a higher prevalence of current smokers.

During a median of 20.7 years of follow-up, 3900 (20.45%) incident CVD events and 6480 (33.97%) deaths were recorded. Table 2 displays the association of BMI variability with CVD events and mortality. After adjusting for age, sex, education, smoking status, and family history of CVD, the highest BMI variability tertile had increased risk for future CVD (HR:1.3; 95% CI:1.2 - 1.4) and mortality (HR: 1.7, 95% CI:1.6 - 1.8). In the fully adjusted model, the participants in the highest tertile had persistently greater risk of CVD (HR: 1.3, 95% CI: 1.2 - 1.4) and mortality (HR: 1.6, 95% CI: 1.5-1.7). In the continuous approach, for each 1-SD increment in BMI variability, the HRs for CVD incidence and mortality were 1.3 (95%CI: 1.2 - 1.4) and 1.7 (95%CI: 1.6 - 1.8), respectively. The subgroup analyses exhibited no difference in the association of BMI variability with CVD and mortality between the sexes and subpopulations based on obesity, diabetes, hypertension, and smoking status (Supplementary Tables 1, 2).

In the preliminary analysis, we test the mediation to see how the relationships works between the variables. So, we investigated the association between BMI variability (independent variable) and mediators (FPG, TC, and SBP), as well as the association between these mediators and CVD and mortality (dependent variable). Using the linear mixed model, the estimated beta coefficients for BMI variability as exposure and FPG, TC, and SBP as outcomes

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TABLE 1 Baseline characteristics of participants of the pooled cohort.

Characteristic	BMI variability RMSE Tertiles				P-value
	Total	Tertile 1 (.0258, 0.638)	Tertile 2 (0.638, 1.076)	Tertile 3 (1.076, 9.32)	
Number of participants	19,073	6,359	6,362	6,352	
Age (years)	53 ± 6	53 ± 6	53 ± 6	53 ± 6	<0.001
Female	9897 (51.9)	3083 (48.5)	3229 (50.7)	3585 (56.4)	<0.001
Premature CVD Family history	1580 (8.3)	531 (8.3)	561 (8.82)	488 (7.7)	
Education level					<0.001
Illiterate/primary	5199 (27.3)	1516 (23.9)	1762 (27.7)	1921 (30.3)	
High school	8095 (42.5)	2661 (41.9)	2756 (43.4)	2678 (42.2)	
Higher education	5753 (30.2)	2173 (34.2)	1837 (28.9)	1743 (27.5)	
Current smoker					<0.001
Yes	1828 (12.5)	631 (13.3)	645 (13.4)	552 (11.0)	
No	12745 (87.5)	4120 (86.7)	4153 (86.6)	4472 (89.0)	
BMI (Kg/m^2)	27.8 ± 5.2	26.30 ± 3.4	27.2 ± 4.7	30.1 ± 6.2	<0.001
BMI categories					<0.001
BMI<30 Kg/m^2	13624 (71.4)	5424 (85.3)	4744 (74.8)	3456 (54.4)	
BMI≥30 Kg/m^2	5449 (28.6)	935 (14.7)	1618 (25.4)	2896 (45.6)	
SBP (mm Hg)	120.7 ± 18.2	119.5 ± 17.6	120.6 ± 18.24	122.0 ± 18.7	<0.001
DBP (mm Hg)	72.4 ± 10.1	72.9 ± 10.0	72.1 ± 10.17	72.0 ± 10.2	<0.001
FPG (mg/dl)	103.9 ± 34.8	99.8 ± 26.4	102.7 ± 30.84	109.4 ± 43.97	<0.001
TG (mg/dl)	141.9 ± 99.8	137.2 ± 87.6	140.8 ± 95.3	147.9 ± 114.51	<0.001
TC (mg/dl)	212.3 ± 42.0	210.1 ± 40.1	212.7 ± 41.2	214.0 ± 44.6	<0.001

The categorical and continuous variables were reported as count (percentage) and mean ± SD, respectively.
BMI, body mass index; RMSE, root mean squared error; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol.

were 14.1 (95% CI: 12.8-15.4), 0.6 (95% CI: -0.6-1.9), and 3.3 (95% CI: 2.7-3.9) per 1 SD increase in BMI variability, respectively (Table 3). The highest BMI variability tertile was significantly associated with mean FPG and SBP with beta coefficients of 12.2 (95%CI: 11.1-13.2) and 3.1 (95%CI: 2.5-3.6), respectively. However, BMI variability was not associated with higher values of TC in the quantile approach (P value=0.2). We also performed independent risk calculations to evaluate the association of mean FPG, TC, and SBP (from first to fourth visits during the measurement period) with CVD and mortality outcomes (Table 4). After adjusting for potential confounders, the risk of future CVD increased for each unit increase in the mean of FPG (HR: 1.2; 95%CI: 1.1-1.3), TC (HR: 1.1; 95%CI: 1.0-1.2), and SBP (HR: 1.2; 95%CI: 1.1-1.3). The HRs for the association between the mean of FPG, TC, and SBP measurements and mortality were 1.2 (95%CI: 1.1-1.3), 1.0 (95%CI: 0.99-1.1), and 1.2 (95%CI: 1.1-1.2), respectively.

The relationship between BMI variability and CVD and mortality was determined considering the mediating effects of the mean values of FPG, TC, and SBP using the four-way effect decomposition (Table 5, Figure 2). After considering both the mediations and interactions, BMI variability was associated significantly with CVD (HR: 1.10, 95% CI: 1.05-1.14) and mortality (HR: 1.28, 95% CI: 1.24-1.33). For the outcome of mortality, when investigating FPG as a mediator, BMI variability was responsible for 92%, and FPG accounted for 8% of the total effect (P value<0.001), while TC and SBP were not significant mediators in the relationship (P value=0.5). The HR of the direct effect of the BMI variability on CVD was 1.08 (95% CI: 1.03-1.12), explaining 75.7% of the overall effect. The indirect effect of BMI variability via FPG as the only significant mediator was 1.02 (95% CI: 1.02-1.03) indicating 24.3% of the relationship between BMI variability and future CVD.

Discussion

This pooled analysis of cohort studies investigated the association between BMI variability and CVD and mortality over

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TABLE 2 Association of BMI variability (BMI-RMSE) with all-cause mortality and CVD event.

	Events	IR (95% CI) *	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
All-Cause Mortality					
BMI-RMSE (per 1 SD)	6480	15.6 (15.2-16.0)	**1.7 (1.6 - 1.8)**	**1.7 (1.6 - 1.8)**	**1.7 (1.6 - 1.8)**
BMI-RMSE Tertiles					
Tertile 1	1816	12.9 (12.4 - 13.6)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Tertile 2	2105	15.2 (14.6 - 15.9)	**1.2 (1.1 - 1.3)**	**1.2 (1.1 - 1.3)**	**1.2 (1.1 - 1.3)**
Tertile 3	2559	18.6 (17.9 - 19.4)	**1.7 (1.6 - 1.8)**	**1.7 (1.6 - 1.8)**	**1.6 (1.5 - 1.7)**
CVD Event					
BMI-RMSE (per 1 SD)	3900	10.2 (9.9 -10.6)	1.4 (1.3-1.5)	1.4 (1.3- 1.5)	1.3 (1.2-1.4)
BMI-RMSE Tertiles					
Tertile 1	1222	9.5 (9.0 - 10.0)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Tertile 2	1265	10.0 (9.4 - 10.5)	**1.1 (1.0 - 1.2)**	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.2)
Tertile 3	1413	11.3 (10.7 - 11.9)	**1.4 (1.2 - 1.5)**	**1.3 (1.2 - 1.4)**	**1.3 (1.2-1.4)**

Model 1: age, sex.
Model 2: age, sex, education, smoking status, and family history of cardiovascular disease.
Model 3: age, sex, education, smoking status, family history of cardiovascular disease, baseline body mass index, fasting plasma glucose, total cholesterol, and systolic blood pressure.
BMI, body mass index; RMSE, root mean squared error; CVD, cardiovascular disease.
Bolded values were statistically significant (P < .05). * IR Incidence rate per 1,000 person-years.

two decades. After adjusting for potential confounders, highest compared to the lowest BMI variability tertile was associated with a 30% and 60% increased risk of CVD and mortality, respectively. There was no significant difference in this association based on sex, obesity, smoking status, presence of diabetes, or hypertension. Subsequently, the mediating and interaction effects of the three important cardiometabolic factors, including FPG, SBP, and TC, were explored. We estimated that FPG mediated 24% of the excess risk for CVD and 8% of the excess risk for mortality. On the other hand, SBP and TC were not significant mediators in the association of BMI variability with CVD and mortality.

There is an ongoing controversy surrounding the impact of weight variability on CVD and mortality, especially among different subgroups. Several studies have suggested a link between weight fluctuation and a higher likelihood of future CVD and mortality (17), while others have not found any association (26, 27). Additionally, contrary findings have also emerged, suggesting that weight fluctuation could provide protection against CVD (14, 18). The underlying pathophysiology in the relationship between weight variability and CVD and mortality is not yet understood. Weight variability may be an indicator of underlying metabolic dysfunction (e.g., insulin resistance and inflammation) (28–30). It is also suggested that high variations in weight may lead to loss of muscle mass and an increase in fat mass (31, 32), increasing the risk of chronic diseases such as CVD.

Our findings suggested that high BMI variability was associated with an increased risk of future CVD and mortality, and this association was not significantly different among subpopulations

TABLE 3 Association between BMI Variability (BMI-RMSE) and time-serial measures of cardiometabolic risk factors using linear mixed model.

	Fasting plasma glucose		Total cholesterol		Systolic blood pressure	
	β (95% CI)	P value	β (95% CI)	P-value	β (95% CI)	P-value
BMI-RMSE (per 1 SD)	14.1 (12.8-15.4)	<0.001	0.6 (-0.6 - 1.9)	0.33	3.3 (2.7 - 3.9)	0.001
BMI-RMSE Tertiles						
Tertile 1	Reference		Reference		Reference	
Tertile 2	3.7 (2.7 - 4.8)	<0.001	1.1 (-0.03 - 2.2)	0.06	1.1 (0.5 - 1.7)	<0.001
Tertile 3	12.2 (11.1 - 13.2)	<0.001	0.7 (-0.4 - 1.9)	0.2	3.1 (2.5 - 3.6)	<0.001

Adjusted for age, sex, education, smoking status, family history of cardiovascular disease.
BMI, body mass index; RMSE, root mean squared error.

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TABLE 4 Associations between the mean values of cardiovascular risk factors during the measurement period and CVD event and all-cause mortality.

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
All-Cause Mortality			
Mean fasting plasma glucose	**1.3 (1.2 - 1.4)**	**1.3 (1.2 - 1.4)**	**1.2 (1.2 - 1.3)**
Mean systolic blood pressure	**1.2 (1.1 - 1.3)**	**1.2 (1.1 - 1.2)**	**1.2 (1.1 - 1.2)**
Mean total cholesterol	1.0 (0.99 - 1.1)	1.0 (0.99 - 1.1)	1.0 (0.99 - 1.1)
CVD Event			
Mean fasting plasma glucose	**1.3 (1.2 - 1.4)**	**1.3 (1.2 - 1.4)**	**1.2 (1.1 - 1.3)**
Mean systolic blood pressure	**1.3 (1.2 - 1.4)**	**1.3 (1.2 - 1.4)**	**1.2 (1.1 - 1.3)**
Mean total cholesterol	**1.1 (1.0 - 1.2)**	**1.1 (1.0 - 1.2)**	**1.1 (1.0 - 1.2)**

Model 1: age, sex.
Model 2: age, sex, education, smoking status, and family history of cardiovascular disease.
Model 3: age, sex, education, smoking status, family history of cardiovascular disease, baseline body mass index, fasting plasma glucose, total cholesterol, and systolic blood pressure.
CVD, cardiovascular disease.
Bolded values were statistically significant ($P < .05$).

(Supplementary Tables 1, 2), which is consistent with the latest report by Zou et al. (17). However, it is noteworthy that high BMI fluctuation did not significantly increase the risk of future CVD in obese participants, while it increased the risk of all-cause mortality. BMI variability was associated with CVD and mortality in participants with and without diabetes.

In the current study, we determined the direct effect of BMI variability on CVD and mortality and quantified how much of the effect is mediated through FPG, SBP, and TC. Using a linear mixed model, after adjusting for confounders, we found a significant relationship between BMI variability and the time-serial values of FPG, TC, and SBP. Recent animal studies support our findings by demonstrating the adverse impact of weight cycling on glucose, insulin, and inflammatory markers' levels (29, 33, 34). Weight variability is suggested to contribute to adipocyte enlargement and an increase in lipogenic enzymes, myristic acid, palmitic acid, palmitoleic acid, and stearic acid, resulting in glucose metabolism impairment (35, 36). Previous studies have found an independent association between high weight variability and incident diabetes (37–39), although only a few prospective studies have examined the correlation of BMI variability with the slope and alterations in cardiovascular risk factors using multiple linear regression (19, 20, 40). These studies suggested that BMI variability was associated with HbA1C levels but not SBP or TC. Notably, the impact of BMI variability on FPG was not explored. The discrepancy in the results regarding the association of BMI variability with TC and SBP may stem from differences in BMI variability calculation methods, study populations, analytical approaches, and follow-up duration. Our study, in contrast to previous ones, consisted of a large sample size.

The results of the mediation analysis revealed that 24% of the excess risk of BMI variability for CVD and 8% for mortality was mediated by FPG, while TC and SBP did not demonstrate significant mediation effects. A pooled cohort analysis conducted by the global burden of diseases reported that more than 44% of the excess risk of high baseline BMI (being overweight or obese) was mediated through FPG, TC, and SBP (41). Our study is the first to analyze the mediation effect of these risk factors in the association of BMI variability and adverse health outcomes. The non-significant mediation effect of TC and SBP in our study may be due to their weaker association with BMI variability compared to FPG (Table 3). These findings provide new insight into understanding the complex relationship between BMI variability, major cardiovascular risk factors, and CVD and mortality.

In the current study, for the first time, the direct and indirect effect of BMI variability on CVD and mortality was investigated in a pooled cohort analysis of three large longitudinal population-based studies with long follow-ups. Many studies resort to simple statistical methods to measure BMI variability, overlooking the non-linear nature of BMI trend and mistakenly perceiving it as fluctuation (24). To address this, we employed the RMSE within a random coefficient model to differentiate between true non-linear changes in BMI and BMI fluctuation. There are also some limitations in this study. Our study included the BMI measurements taken in the clinic and the BMI measurements were not self-reported although it is noteworthy that the measurements in the clinic are done with unified standard protocols. We did not assess whether the participants had intentions of losing or gaining weight. However, the primary goal was that unintentional weight loss may have been an indicator of underlying diseases. Also, our findings solely pertained to BMI variability and lacked information regarding alterations in fat mass, muscle mass, and change in body composition. Future research should prioritize lifelong maintenance of body weight and reduction of sporadic weight fluctuations, especially in the context of primary cardiac prevention. This approach can help in sustaining healthy weight levels and minimizing associated health risks.

In conclusion, BMI variability is an independent predictor for incident CVD and mortality and there is no significant difference in this association across subpopulations. FPG mediates 24% and 8% of excess risk of BMI variability for the development of CVD and mortality, respectively; however, SBP and TC are not significant mediators in this association. These findings present new potential implications for preventing CVD and mortality in individuals with high BMI variability. Modern cardiometabolic interventions focusing on glycemic monitoring and management might help reduce the risk of future CVD and mortality during frequent weight loss attempts.

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TABLE 5 Mediation analysis of the association of BMI variability (RMSE) with CVD event and all-cause mortality.

	BMI variability mediation with	HR (95% CI)	P-value	Mediation (%)
All-Cause Mortality	**Mean fasting plasma glucose**			
	Total Effect	1.28 (1.24 - 1.33)	<0.001	100%
	Direct Effect	1.26 (1.22 - 1.31)	<0.001	92%
	Indirect Effect	1.02 (1.00-1.03)	<0.001	8%
	Mean total cholesterol			
	Total Effect	1.27 (1.23-1.31)	<0.001	100%
	Direct Effect	1.26 (1.23-1.31)	<0.001	99.8%
	Indirect Effect	1.00 (1.00-1.00)	0.5	0.2%
	Mean systolic blood pressure			
	Total Effect	1.27 (1.23-1.31)	<0.001	100%
	Direct Effect	1.27 (1.23-1.31)	<0.001	99.6%
	Indirect Effect	1.00 (1.00-1.00)	0.5	0.4%
CVD Event	**Mean fasting plasma glucose**			
	Total Effect	1.10 (1.05-1.14)	<0.001	100%
	Direct Effect	1.08 (1.03-1.12)	<0.001	75.7%
	Indirect Effect	1.02 (1.02-1.03)	<0.001	24.3%
	Mean total cholesterol			
	Total Effect	1.10 (1.05-1.14)	<0.001	100%
	Direct Effect	1.09 (1.06-1.15)	<0.001	97.1%
	Indirect Effect	1.01(1.00-1.00)	0.2	2.9%
	Mean systolic blood pressure			
	Total Effect	1.10 (1.06-1.14)	<0.001	100%
	Direct Effect	1.10 (1.06-1.15)	<0.001	99.9%
	Indirect Effect	1.00(1.00-1.00)	0.8	0.1%

Adjusted for age, sex, education, smoking status, family history of cardiovascular disease.
CVD, cardiovascular disease.

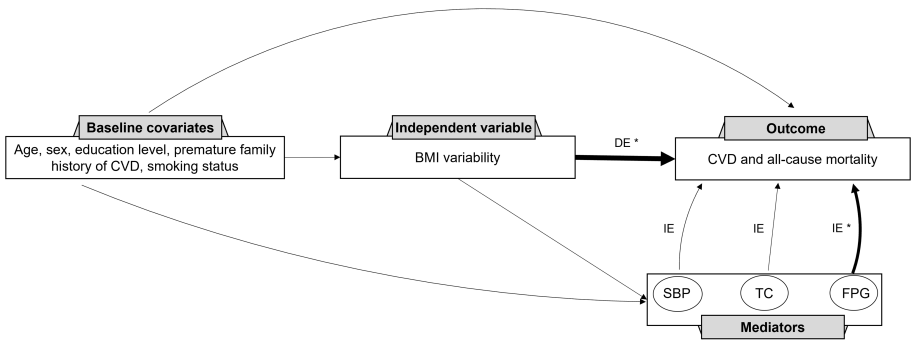

FIGURE 2
Direct Acyclic Graph (DAG) for the contribution of systolic blood pressure, total cholesterol, and fasting plasma glucose to the association between BMI variability and CVD and mortality. CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; TC, total cholesterol; FPG, fasting plasma glucose; DE, direct effect; IE, indirect effect. * Significant association to the outcome.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Datasets generated during and/or analyzed during the current study are not publicly available due to institutional policies but are available from the corresponding author on reasonable request. Requests to access these datasets should be directed to amouzegar@endocrine.ac.ir.

Ethics statement

The studies involving humans were approved by the National Research Council of the Islamic Republic of Iran (IR.SBMU.ENDOCRINE.REC.1402.060), the Human Research Review Committee of the Endocrine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. MH: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. SM: Data curation, Formal Analysis, Methodology, Visualization, Writing – original draft. DK: Methodology, Writing – review & editing. FA: Supervision, Writing – review & editing. MB: Supervision, Writing – review & editing. AA: Project administration, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1345781/full#supplementary-material

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Epigenetics of hypertension as a risk factor for the development of coronary artery disease in type 2 diabetes mellitus

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Hypertension, a multifaceted cardiovascular disorder influenced by genetic, epigenetic, and environmental factors, poses a significant risk for the development of coronary artery disease (CAD) in individuals with type 2 diabetes mellitus (T2DM). Epigenetic alterations, particularly in histone modifications, DNA methylation, and microRNAs, play a pivotal role in unraveling the complex molecular underpinnings of blood pressure regulation. This review emphasizes the crucial interplay between epigenetic attributes and hypertension, shedding light on the prominence of DNA methylation, both globally and at the gene-specific level, in essential hypertension. Additionally, histone modifications, including acetylation and methylation, emerge as essential epigenetic markers linked to hypertension. Furthermore, microRNAs exert regulatory influence on blood pressure homeostasis, targeting key genes within the aldosterone and renin-angiotensin pathways. Understanding the intricate crosstalk between genetics and epigenetics in hypertension is particularly pertinent in the context of its interaction with T2DM, where hypertension serves as a notable risk factor for the development of CAD. These findings not only contribute to the comprehensive elucidation of essential hypertension but also offer promising avenues for innovative strategies in the prevention and treatment of cardiovascular complications, especially in the context of T2DM.

KEYWORDS

coronary artery disease, hypertension, type 2 diabetes mellitus, epigenetics, genetic variation, DNA methylation, histone, modification

1 Introduction

Essential hypertension (EH) is a prevalent condition, affecting around 95% of adults diagnosed with high blood pressure. EH constitutes a substantial public health concern with considerable economic implications, accounting for an annual healthcare expenditure of approximately $50 billion in the United States alone (1–3). In 2013, EH was responsible for more than 350,000 deaths in the United States, making it a leading cause of mortality (2, 3). However, despite significant investments in healthcare, the precise etiology of EH remains elusive, impeding progress in treatment development. EH arises from a complex interplay of environmental factors, genetics, and epigenetics, which collectively influence biological pathways and contribute to the pathogenesis of hypertension. Notably, EH represents a major risk factor for renal injuries, cardiovascular pathologies, and cognitive dysfunction (4, 5).

While earlier perspectives diminished the role of genetics in hypertension, recent research has underscored the substantial impact of genetic and epigenetic determinants on blood pressure regulation and related conditions. Genome-wide association studies (GWAS) have identified common genetic variants associated with EH. However, owing to its polygenic nature, targeted, single-gene therapies for EH remain unavailable (6, 7).

Epigenetics, which explores the dynamic interplay between genetic factors and the environment, emerges as a critical player in the regulation of blood pressure. Epigenetic changes can be influenced by environmental stimuli such as nutrition, aging, and pharmaceuticals, and importantly, these changes possess the potential for reversibility (8, 9). This characteristic sets the stage for a spectrum of treatment possibilities distinct from those for genetic disorders. Epigenetics has garnered global attention, as evidenced by initiatives like the International Human Epigenome Consortium and the Human Epigenome Project (8, 10).

This comprehensive perspective aims to contribute to the understanding of the intricate interplay between genetics, epigenetics, and hypertension, with a specific focus on the chromosomal locus 9p21.3, in the context of CAD development in individuals with T2DM. The review focuses on the interaction between epigenetics and hypertension, specifically examining the role of DNA methylation, base methylation, gene methylation, and histone modification in hypertension pathogenesis. Additionally, the review discusses the therapeutic potential of miRNAs in hypertension and their role as diagnostic biomarkers. It also classifies epigenome modifications in hypertension based on pathophysiology and explores the epigenetic interplay between hypertension and CAD in T2DM. The review further investigates the environmental influences on epigenetics and hypertension, the relationship between pre-eclampsia, epigenetics, and hypertension, and provides insights into future directions in this field. This review focuses on discussing the role of microRNAs (miRNAs) and histone modifications in hypertension, excluding studies on long non-coding RNAs (LncRNAs).

2 Exploring the genetic significance of chromosomal locus 9p21.3 in hypertension, CAD, and T2DM

In this context, our manuscript proposes important additions, emphasizing the interaction of epigenetics and hypertension as a critical factor in the development of coronary artery disease (CAD) in type 2 diabetes mellitus (T2DM) (11). Specifically, we focus on the chromosomal locus 9p21.3, a genomic risk zone for cardiovascular diseases, which includes two distinct risk haplotypes for ischemic heart disease (IHD) and T2DM (12). These haplotypes, characterized by adjacent blocks of 50–100 single nucleotide polymorphisms (SNPs) separated by a recombination peak, exhibit linkage disequilibrium ensuring non-random joint inheritance for each disease (13). The potential overlap of T2DM SNPs in the CAD block makes the 9p21.3 locus a promising candidate for shared genetic risk for both CAD and T2DM (14). This condition sets the stage for the mechanical linkage of the 9p21.3 chromosomal locus to CAD and T2DM via ANRIL, the product of the cyclin-dependent kinase inhibitor gene (CDK2A/B) (15).

Moreover, the wide prevalence of risk haplotypes for hypertension, IHD, and T2DM (up to 50% of representatives of many populations) with a strong additive effect leads to at least 15% of cases of IHD and T2DM, making the chromosomal locus 9p21.3 the largest known genomic source of morbidity (16). The identification of a potential transcriptional regulatory mechanism in this locus, induced by the long non-coding mRNA ANRIL, suggests a common genetic signature for hypertension, CAD, and T2DM, alongside common environmental risks and clinical associations (17).

Additionally, the direct vascular and immunomodulatory functions of ANRIL, accelerating several signaling pathways (TNF-α-NF-kB-ANRIL and YY1-IL6/8), contribute to systemic inflammation, indirectly influencing the development of cardiometabolic diseases (18). This indicates a potential common genetic signature of hypertension, IHD, and T2DM at the level of the chromosomal locus 9p21.3 (16).

Furthermore, SNPs included in risk haplotypes for hypertension, coronary heart disease, and T2DM may be associated with differential expression of ANRIL splice variants (19). Determining their significance for the population at the level of significance for other populations could confirm the hypothesis of their association with differential expression of ANRIL splice variants for testing in subsequent studies (*in vivo* and *in vitro*) (20).

The locus 9p21.3, associated with risk haplotypes for hypertension, ischemic heart disease (IHD), and T2DM, represents a significant genetic source of morbidity, with potential implications for shared genetic risk factors and common environmental influences. Further research into the transcriptional regulatory mechanisms of this locus, particularly the role of the long non-coding mRNA ANRIL, may elucidate novel therapeutic targets and diagnostic biomarkers for cardiometabolic diseases.

3 Interaction between epigenetics and hypertension

Epigenetics refers to heritable changes in gene expression that occur without alterations in the DNA sequence. These changes are mediated by various mechanisms, including DNA methylation, histone modifications, and non-coding RNAs. Epigenetic modifications play a crucial role in regulating gene expression and have been implicated in the pathogenesis of various diseases, including hypertension (Figure 1).

DNA methylation is a well-established epigenetic mechanism in mammals (21), involving the covalent attachment of a methyl group to the 5' position of a cytosine (C) within DNA (22). Genomic DNA frequently comprises short sequences of guanine (G) and cytosine dinucleotides linked by phosphodiester bonds, forming what are known as 'CpG islands' (23). Hypermethylation of CpG sites, typically occurring at cytosine bases, results in gene silencing. These epigenetic marks also play a pivotal role in determining active and inactive genomic regions by modulating the interplay between transcription factors and DNA (24). However, it is important to acknowledge that multiple cell types may exhibit similar levels of methylation, giving rise to diverse phenotypic expressions. Research has demonstrated a close association between the onset and severity of hypertension and DNA methylation levels, highlighting the imperative need for further exploration in this domain (23).

It is noteworthy that patho-clinical investigations related to EH and organ damage are often constrained by the limited availability of relevant animal samples. As a consequence, peripheral blood commonly serves as the preferred material for extensive human cohort studies. Nevertheless, the progression of the disease and its severity can influence the bio-metabolic processes governing DNA methylation, resulting in altered methylation patterns across different sample types (25). Some studies, such as the work by Kato et al., propose that blood and various tissues manifest analogous methylation patterns, suggesting that DNA methylation markers identified in blood mononuclear cells can serve as proxies for methylation profiles in other tissues (26). Conversely, investigations in rodents indicate that certain tissues may display distinct methylation patterns in response to specific pharmacological exposures. Hence, relying solely on the evaluation of blood mononuclear cells as epigenetic indicators may not consistently suffice for the assessment of diverse bodily samples (26).

3.1 Methylation of DNA

DNA methylation is a fundamental epigenetic mechanism that plays a crucial role in regulating gene expression. It involves the addition of a methyl group to the cytosine residue of a CpG dinucleotide, resulting in the formation of 5-methylcytosine. DNA methylation is essential for normal development and cellular differentiation, and aberrant DNA methylation patterns have been implicated in various diseases, including EH.

DNA methylation can be categorized into two primary types: gene-specific and global, depending on whether it pertains to the methylation status of a specific gene region or encompasses the overall level of 5-methylcytosine (5mC) across the entire genome (27). The methylation of DNA serves a dual purpose: it contributes to the preservation of genome integrity and exerts regulatory control over gene expression at the mRNA level (28). A multitude of studies have underscored the impact of DNA methylation on diverse pathophysiological processes, including EH, prompting extensive investigations into its role in hypertension and related cardiovascular disorders (29, 30). For a comprehensive overview of reported epigenetic modifications, such as DNA methylation, during the course of EH, please refer to Table 1.

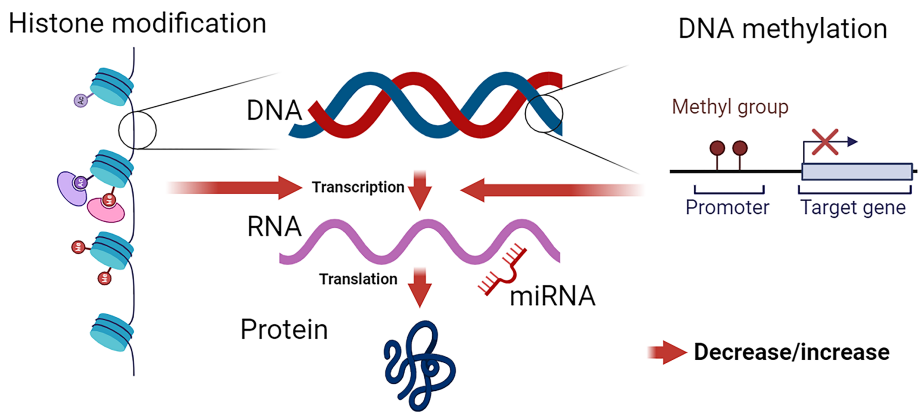

FIGURE 1
Epigenetic Modifications: Influence on Chromatin Structure and Gene Expression. DNA, wrapped around nucleosomes, comprises four pairs of histone proteins. Histones are susceptible to various epigenetic modifications, including acetylation, methylation, phosphorylation, sumoylation, and biotinylation. These modifications alter chromatin formation, leading to either an open (active) or closed (inactive) state, thereby modulating transcriptional activity. DNA methylation directly impacts DNA structure, influencing gene transcription. The effect of DNA methylation depends on the specific methylated site. miRNAs primarily target the 3' UTR of mRNA (though 5' targeting is possible), leading to the negative regulation of protein production by mRNA degradation or post-transcriptional regulation of mRNA stability.

TABLE 1 Review of epigenetic characteristics related to DNA methylation and hydroxyl-methylation in hypertension.

Epigenetic occurrence	Target gene	Severity	Study case	Effect	Reference
Methylation of DNA	5mC	High	Human placenta	Pre-eclampsia	(31)
DNA hydroxyl-methylation	5mC	High	Rat heart	Cardiac hypertrophy	(32)
Gene-specific DNA methylation					
HSD11B2	5mC	High	Human PBMCs	Renal sodium reabsorption	(33)
	5mC	Low	Rat adrenal gland	RAAS activation	(34)
NKCC1	5mC	Low	SHR hearts and aorta	Ionic transport	(35)
ACE	5mC	High	Human, PBMCs Rat liver and lungs *In vitro* HepG2, HT29, HMEC-1, SUT	RAAS activation	(36)
Atgr1a	5mC	Low	SHR endothelial cells	RAAS activation	(37)
PANX1	5mC	High	Heart and kidney in rat	Vitamin D3 deficiency	(38)

In EH, studies have shown alterations in both global DNA methylation levels and gene-specific DNA methylation patterns (39). Global DNA methylation refers to the overall level of methylation across the entire genome (40). Changes in global DNA methylation levels have been observed in hypertension, with some studies reporting global hypomethylation (41), while others have reported hypermethylation (42). These changes in global DNA methylation may contribute to the dysregulation of genes involved in blood pressure regulation and vascular function.

Gene-specific DNA methylation refers to the methylation status of specific genes or genomic regions (43). In EH, aberrant DNA methylation of genes related to the renin-angiotensin system (RAS), endothelial function, and vascular smooth muscle contraction has been reported (44). For example, hypermethylation of the angiotensinogen (AGT) gene promoter has been associated with increased blood pressure levels in EH patients (45).

3.2 Base methylation

About 3–4% of all cytosines in the genome, known as 5mC, are distributed throughout the DNA structure (Figure 2). Research efforts have revealed a connection between different pathological conditions and specific mRNA expression patterns, as well as gene-specific 5mC levels (46, 47). Furthermore, approximately 30 single nucleotide polymorphism (SNP) variants associated with hypertension have been identified via GWAS that are correlated with methylation markers, affirming the involvement of DNA methylation in EH (48). In parallel with 5mC, there exists a derivative known as 5-hydroxymethylcytosine (5hmC), which assumes a pivotal role in the demethylation process and is present in genomic DNA. Analogous to 5mC, 5hmC is pervasive throughout the mammalian genome, exhibiting distinct profiles across various tissues (49). A substantial body of research supports the role of 5hmC in gene regulation (50, 51). Additionally, a study in rats has provided initial evidence of a substantial correlation between hypertension and 5hmC levels (52). Nevertheless, current data linking EH to DNA hydroxymethylation remains limited, necessitating further research to elucidate the function of 5hmC in human EH.

The meticulous mapping of 5mC, which delineates DNA methylation patterns, offers a valuable blueprint for comprehending DNA functionality and stability. Previous investigations on DNA methylation have established a connection between 5mC levels and EH (53). Some studies have reported lower levels of 5mC in the DNA of whole blood in hypertensive patients, implying an inverse relationship between DNA methylation levels and the severity of EH (54). Conversely, pre-eclampsia, a form of hypertension occurring during pregnancy, has been positively associated with DNA hypermethylation (55). These findings strongly underscore the potential impact of DNA methylation on the development of EH. Studies in young males have indicated that DNA methylation may play a significant role in the development of EH, with its effects influenced by age (56). Furthermore, a recent animal study has demonstrated that cardiac hypertrophy, considered a relative index of EH following pressure overload, can be markedly ameliorated through the inhibition of DNA methylation, thereby emphasizing the role of DNA methylation in EH-associated cardiovascular damage in rat (32).

In summary, DNA methylation, particularly 5mC, is crucial in the development of EH. It is linked to various pathologies, mRNA expression patterns, and gene-specific 5mC levels. GWAS have associated hypertension-related SNP variants with methylation markers, supporting the role of DNA methylation in EH. Another important modification, 5hmC, is also implicated in EH and gene regulation, but further research is needed. Mapping 5mC patterns helps understand DNA functionality and stability, providing insights into potential EH treatments.

3.3 Gene methylation

Recent studies have primarily focused on investigating methylation patterns within specific gene regions, with gene-specific epigenetic modifications predominantly occurring within genomic regions called CpG islands, often situated in gene promoter

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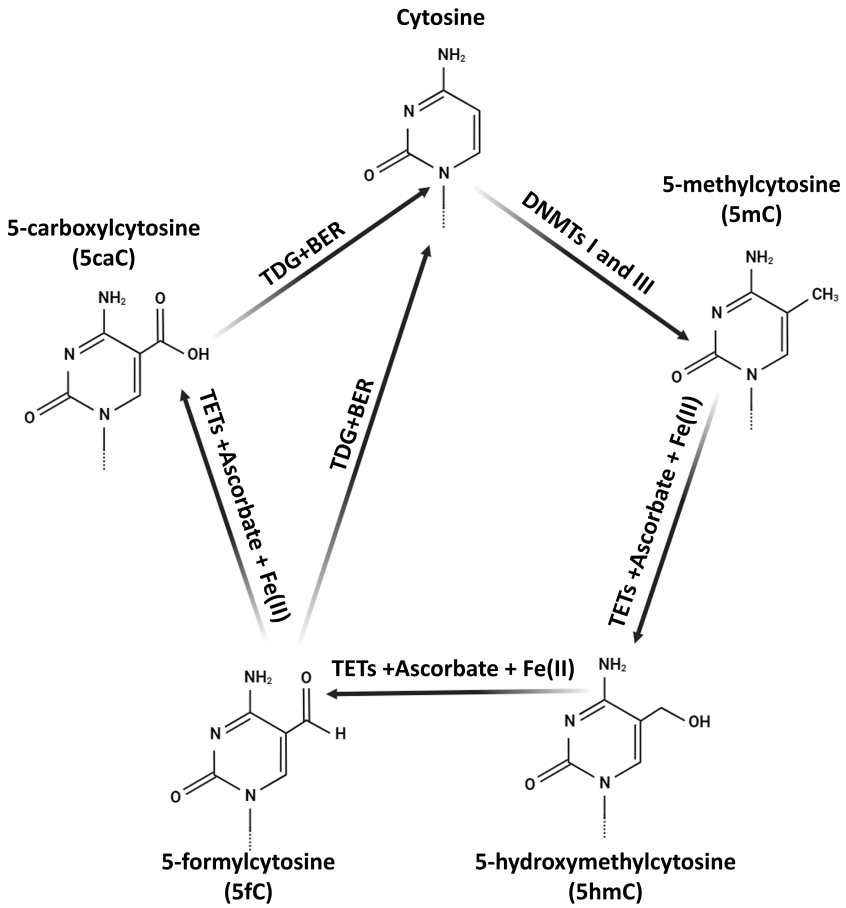

FIGURE 2
The biochemical pathways of 5-hydroxymethylcytosine (5hmC) in mammalian DNA. The synthesis of 5hmC is initiated by the TET protein-mediated oxidation (hydroxylation) of 5-methylcytosine (5mC). TET proteins along with co-factors Fe(II) and ascorbate generate 5hmC. Subsequent TET-driven oxidation of 5hmC consistently results in the formation of 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC). These oxidized forms are then replaced with cytosine (C) through thymine-DNA glycosylase (TDG)-mediated base excision repair (BER). Additionally, DNA methyltransferases I and III (DNMTs I and III) facilitate the transfer of a methyl group to cytosine, producing 5mC.

regions (57). These CpG islands are found at the promoters of approximately 40% of genes, while other genomic regions also contain CpG sites Remarkably, in typical somatic cells, nearly 90% of CpG islands may undergo methylation, but those within promoter regions are relatively spared from such modifications (58, 59). Hypermethylation of CpG islands, particularly in promoter regions, plays a pivotal role in repressing gene transcription, as evidenced by numerous human and animal studies that consistently demonstrate an inverse relationship between 5mC levels and gene expression (60). It is important to note, however, that this correlation is not universally consistent and remains a subject of ongoing debate. Earlier research indicated a positive association between elevated levels of 5hmC and increased gene expression, suggesting that lower levels of 5mC result in gene silencing, while elevated levels of 5hmC are linked to gene activation (52, 61).

Furthermore, methylation of DNA at specific gene loci can influence the interplay between gene transcription factors and other epigenetic factors, such as histone modifications, leading to diverse expression patterns of the affected genes (62). Numerous genes documented in the literature have highlighted the role of epigenetic alterations in modulating biological and molecular processes relevant to EH. For example, the stimulation of sympathetic activity and the activation of the RAS, leading to altered sodium reabsorption in the kidney, are significant contributors to EH (63). Several RAAS genes are frequently studied in the context of EH. Additionally, the entire RAAS components can be found in the brain and may exhibit dysfunctional activity in various pathological conditions, including EH. In this context, the HSD11B2 gene, responsible for cortisol regulation, may experience suppression due to promoter hypermethylation, resulting in abnormal cortisol levels and the onset of EH (64). Studies in hypertensive rat models have further indicated a direct association between hypertension and hypermethylation of HSD11B2 (65). Moreover, in newborns, hypermethylation of the HSD11B2 gene, coupled with reduced HSD11B2 mRNA levels, suggests a potential mechanism for EH through abnormal renal sodium reabsorption (66–68).

Research has also demonstrated that DNA methylation in promoters can be modulated to enable the expression of genes such as Cytochrome P450 Family 11 Subfamily B Member 2 (CYP11B2), which plays a significant role in blood pressure regulation (69). In spontaneous hypertensive rats, hypomethylation in the gene promoter of the cotransporter, Na+/K+/2Cl (NKCC),

leads to an increase in NKCC levels, correlated with postnatal hypertension. These findings collectively illustrate that dynamic changes in DNA methylation can influence gene expression, thereby impacting blood pressure regulation (70).

The RAAS pathway occupies a central role in EH, with genetic variants and altered epigenetic regulation of key genes in this pathway known to exert regulatory control over EH (71). Additionally, other genes associated with EH exhibit differential DNA methylation patterns associated with EH risk in a sex-, age-, and therapy-specific manner (Table 2).

In summary, gene-specific DNA methylation and its impact on various biological and molecular pathways could play a pivotal role in EH. As a result, epigenetic markers hold the potential to estimate EH levels, associated risks, and enhance our understanding of its pathogenesis.

3.4 Histone modification

Nucleosomes are the basic units of chromatin, consisting of DNA wrapped around histone proteins. Histones are a family of proteins that play a crucial role in DNA packaging and gene regulation. Histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitination, alter the structure of chromatin and regulate gene expression. These modifications can affect the accessibility of DNA to transcription factors and RNA polymerase, thereby influencing gene transcription.

Post-translational modifications occurring at the N-terminal histone tails of genomic DNA, such as acetylation, methylation, ubiquitination, and phosphorylation, represent integral epigenetic regulators associated with hypertension (23, 76). These histone modifications exert a profound influence on chromatin dynamics, often with discernible consequences. For example, histone acetylation primarily facilitates gene transcription, while histone deacetylation leads to gene silencing. However, such interactions are not universally reliable and can be context-dependent. Methylation of lysine at position 79 (H3K79) represses gene transcription, whereas methylation of histone arginine promotes it. Additionally, hypermethylation of lysine 9 (K9) results in gene suppression, whereas its hypomethylation allows gene transcription (77, 78). In these modifications, the interplay between epigenetic elements and histone tails controls DNA accessibility across the histones, thereby modulating the transcription of relevant genes. Moreover, these dynamics create an interactive environment for chromatin-modifying enzymes, enabling the specific regulation of gene expression (79).

Earlier studies have suggested that epigenetic elements can be passed down across generations (80). Recent research has even offered paternal epigenetic alterations in histones as potential indicators of offspring fertility, thereby proposing a suitable model for understanding how paternal epigenetic patterns can impact the health and development of offspring (81).

The latest investigations in hypertensive animal models, particularly rats, have indicated associations between histone modifications and the upregulation of ACE1 (82). A significant overexpression of ACE1 has also been reported in hypertensive offspring from lipopolysaccharide-treated rats, linked to histone H3 acetylation (H3Ac) within the ACE1 gene promoter region (83). Similarly, some studies have reported that hypertensive rats exhibited reduced levels of a specific gene (HSD11B2), attributed to the downregulation of H3K36 trimethylation, underscoring the role of histone modification in the regulation of chromatin structure in EH (83).

Studies conducted with human umbilical vein endothelial cells (HUVECs) have shown that hyperacetylation of H4K12 and H3K9, as well as di- and trimethylation of H3K4 at the promoter of the iNOS gene, contributes to an increase in blood pressure by modulating iNOS gene expression (84–86). These findings reveal that changes in iNOS mRNA gene expression due to histone acetylation can play a fundamental role in EH.

In this context, Cho et al. have demonstrated a correlation between hypomethylation and histone H3 in NKCC1 mRNA and protein levels following angiotensin II-triggered upregulation, indicating that epigenetic modifications can modulate the transcription of NKCC1 and related renal sodium reabsorption to influence blood pressure (87). Trouble-makers of telomeric silencing (TOT) have been linked to hypertension (88, 89). Specifically, TOT1a interaction with leukemia chromosome 9 (AF9) leads to H3K79 hypermethylation, suppressing the renal epithelial sodium channel (ENaC-α) and maintaining lower or normal blood pressure. However, aldosterone-mediated disruption of TOT1a-AF9 interaction results in H3K79 hypomethylation, leading to the activation of ENaC-α and ultimately, the development of severe hypertension (90).

Furthermore, Mehrotra et al. have reported that EH-mediated end-organ injuries, such as cardiac hypertrophy in rats subjected

TABLE 2 Epigenetic regulation of genes associated with essential hypertension (EH) in human (54, 72–75).

Gene	DNA methylation levels	Gene expression	EH risk
RAAS pathway genes	Altered	Upregulated	High
Estrogen receptor-α	Altered	Upregulated	High
PANX1	Altered	Upregulated	High
SULF1	Altered	Upregulated	High
NET	Altered	Upregulated	High
TIMP3	Altered	Upregulated	High
SERPINA3	Altered	Upregulated	High
CUL7	Altered	Upregulated	High
ADD1	Altered	Upregulated	High
Mfn2	Altered	Upregulated	High
IL-6	Altered	Upregulated	High
TLRs	Altered	Upregulated	High
IFN-γ	Altered	Upregulated	High
GCK	Altered	Upregulated	High

to a hypertensive condition and salt stimulation, result from higher levels of H3K4me3 and AcH4, alongside reduced levels of H3K9me3 and H3K27me3 in the overexpressed atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) promoters (91).

Moreover, the central nervous system plays a crucial role in regulating histone modifications that affect arterial blood pressure. For example, the induction of melatonin neurons via H3 acetylation leads to increased hypertension in the medulla of the ventrolateral region through an upsurge in brainstem outflow, contributing to EH (92). Sympathetic nervous system-renal interactions direct hypertension in the presence of high salt levels. The activation of the sympathetic nervous system-renal axis can stimulate sodium retention, leading to both low and high levels of sodium reabsorption and increased systemic renin release, along with decreased kidney blood flow (93, 94). Additionally, the downregulation of the gene with-no-lysine kinase-4 (WNK4) is associated with salt-sensitive hypertension in rodents (95), and this downregulation is linked to histone modifications (96–98). Mu et al. have indicated that salt-induced acetylation of H3 and H4 results in WNK4 suppression, while concurrent overexpression of NCC leads to salt retention and subsequent hypertension (99). High-salt diets can also induce hypertension, which is related to lysine-specific demethylase-1 (LSD1) deficiency and the consequent hypermethylation of H3K9 (99).

Post-translational modifications occurring on DNA, particularly at the N-terminal histone tail sites, encompass processes such as ubiquitination, acetylation, methylation, and phosphorylation. These modifications play a pivotal role as epigenetic regulators associated with hypertension (88, 100). Each specific histone modification exerts a unique influence on chromatin structure, often yielding similar outcomes. For instance, histone acetylation predominantly facilitates gene transcription, while histone deacetylation tends to favor gene silencing. However, it is essential to acknowledge that this correlation is not universally consistent and remains a subject of ongoing debate. H3K79 acts as a repressor of gene transcription, whereas methylation of histone arginine can increase transcription. Furthermore, hypermethylation of histone K9 results in gene suppression, while its hypomethylation triggers gene transcription (82, 101). These modifications involve a tight interplay between epigenetic factors and histone tails, influencing the extent to which DNA is coiled around histones and, in turn, controlling the transcription of related genes. These dynamics also create sites of interaction for chromatin-altering enzymes, enabling the activation of gene expression (102). Additionally, past studies suggest the possibility of epigenetic markers being inherited across generations (103). A recent investigation even proposes a paternal mode of histone inheritance based on epigenetics, capable of impacting the fertility and health of future offspring (81).

In conclusion, histone acetylation and methylation can regulate chromatin and, subsequently, gene expression (Table 3). However, despite the evolving techniques and tools, the clinical application of histone epigenetics in prognostic and diagnostic approaches for EH remains challenging due to the complex nature of histone modifications.

TABLE 3 Summary of histone modifications and their role in essential hypertension (EH) (23, 76–78).

Histone modification	Role in EH
Histone acetylation	Promotes gene transcription by loosening chromatin structure
Histone methylation	Can activate or repress gene expression depending on the specific lysine residue and methylation state
Histone ubiquitination	Plays a role in DNA damage repair and gene expression regulation
Histone phosphorylation	Regulates chromatin condensation and gene expression

4 Role of miRNAs and epigenetics in hypertension pathogenesis: a brief overview

The miRNAs are small, non-coding RNA molecules that play a crucial role in post-transcriptional regulation of gene expression. They are typically about 21–23 nucleotides in length and function by binding to the 3' untranslated region (UTR) of target messenger RNA (mRNA), leading to mRNA degradation or inhibition of translation. This process allows miRNAs to fine-tune the expression of target genes, impacting various cellular processes such as proliferation, differentiation, and apoptosis. In the context of EH, miRNAs have been implicated in the regulation of genes involved in blood pressure control and vascular function.

Transitioning to the realm of major blood pressure-regulating pathways, the RAAS stands as a well-established pathway, wherein angiotensin II governs fluid balance and blood pressure by stimulating aldosterone production. Research indicates that miR-21, a microRNA regulated by the RAAS-modulated AGT gene, may trigger aldosterone production in human adrenocortical cells under *in vitro* conditions, hinting at the potential role of miR-21 in human hypertension (104). Indeed, evidence points to a close connection between miR-21 and organ damage associated with hypertension (105). Moreover, miR-27a and miR-27b have been linked to the downregulation of ACE1 gene expression, while reduced levels of miR-330 can upregulate angiotensin II type-2 (AT2) receptor gene translation, thereby affecting the RAAS pathway in the fetal brain under malnourished conditions (106) (Table 4).

Experimental research conducted *in vitro* using HUVECs has illuminated that hyperacetylation of H4K12 and H3K9, alongside methylation (di- and tri-) of H3K4 within the eNOS gene promoter, triggers an increase in eNOS gene expression, which plays a pivotal role in blood pressure regulation (85, 111). This suggests that alterations in eNOS mRNA levels in response to histone acetylation may play a pivotal role in the context of EH.

In summary, the intricate web of genetic and metabolic signaling involved in EH implies the engagement of numerous miRNAs in the modulation of key genes. Consequently, based on our recent insights, miRNAs emerge as promising new biomarkers for unraveling the pathogenesis of EH, potentially leading to future clinical applications.

TABLE 4 Role of miRNAs in essential hypertension (EH): Target genes and effects.

miRNA	Effect on EH
miR-21	Stimulates aldosterone production, potentially contributing to hypertension (104)
miR-27a; miR-27b; miR-330	Downregulates ACE1 gene expression, affecting the RAAS pathway (106)
miR-5589; miR-539; miR-4436b-3p; miR-4500; miR-130b-5p; miR-4458; miR-4424; miR-497–3p; miR-4452; miR-374b-5p; miR-5584–3p	Associated with hypertension, potential diagnostic biomarker (107–110)

In a specific study, Cytoscape software was employed to construct 36 pairs of co-expression networks involving miRNAs and mRNAs, comprising 22 miRNAs and 25 mRNAs. Among these, 3 mRNAs (ARID3A, KIAA0513, and LRPAP1) exhibited connections with 3 distinct miRNAs, while 4 mRNAs (ADARB1, RASGRP1, ARF3, and FUCA2) showed associations with two miRNAs each. The remaining 18 mRNAs were linked to one miRNA each. Notably, this analysis revealed that LRPAP1, ARID3A, and KIAA0513 may have the potential to influence hypertension. A specific relationship was observed between has-miRNA-5589 and three target mRNAs. Additionally, miRNAs such as hsa-miR-539, hsa-miR4436b-3p, hsa-miR-4500, hsa-miR-130b-5p, hsa-miR-4458, hsa-miR-4424, hsa-miR-497–3p, hsa-miR-4452, hsa-miR374b-5p, and hsa-miR-5584–3p exhibited connections with 2 target mRNAs each, while the remainder showed connections with 1 target mRNA. This suggests that hsa-miRNA-5589–5p may play a particularly significant role in the onset of hypertension. In conclusion, these results indicate that mRNAs KIAA0513, LRPAP1, ARID3A, and hsa-miRNA-5589–5p can be considered as diagnostic biomarkers for patients with hypertension. Furthermore, the combination of hsa-miRNA-5589–5p and LRPAP1 may have diagnostic utility for hypertension. To explore the potential upstream regulation of these three key genes, the modulatory interaction between transcription factors and LRPAP1, ARID3A, and KIAA0513 was investigated (107–110). Among the 123 mRNAs associated with hypertension, only the CEBPA transcription factor gene was identified. Subsequent exploration of the public chromatin immunoprecipitation sequencing (ChIP-seq) Cistrome database (http://cistrome.org/db/#/) revealed the presence of CEBPA binding peaks upstream of both LRPAP1 and ARID3A. These findings further support the notion that CEBPA may play a role in regulating LRPAP1 and ARID3A in individuals with hypertension (112).

In summary, hypertension, a prevalent cause of cardiovascular disease worldwide, affects millions of people globally. Detecting hypertension in its early stages is crucial for effective blood pressure management. Moreover, miRNA and mRNA expression profiles were investigated for correlation between miRNA-mRNA networks and the development of hypertension. Firstly, Weighted Gene Co-expression Network Analysis (WGCNA) was employed to identify 123 mRNAs relevant to hypertension. Subsequently, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed on these selected mRNAs. The results indicated that these mRNAs were enriched in terms related to interleukin 4 (IL4) regulation, signaling adaptor activity, and pathways such as tuberculosis, platelet activation, and the pentose phosphate pathway. Previous studies have linked tuberculosis infection to hypertension, suggesting a connection between these pathways and hypertension. Platelet activation is also related to hypertension, and the pentose phosphate pathway has relevance owing to its function in managing reactive oxygen species (ROS), which can contribute to oxidative stress-related hypertension. These findings support the involvement of the screened mRNAs in hypertension.

Subsequently, 35 Differentially Expressed miRNAs (DEMs) were identified between hypertension patients and healthy individuals, and 25 target mRNAs for these DEMs were identified, forming a miRNA-mRNA co-expression network. Among these mRNAs, ARID3A, LRPAP1, and KIAA0513, along with hsa-miRNA-5589–5p, demonstrated associations with hypertension. These could hold promise as suitable biomarkers for patients with hypertension. KIAA0513 has been linked to neuroplasticity, which can contribute to hypertension. ARID3A, a member of the ARID family, is applied as a bimolecular target for drugs in order to treat diseases, particularly hypertension. LRPAP1, involved in the suitable localization and folding of LDL receptor-related protein (LRP1), has known associations with hypertension and angiogenesis, a potential avenue for hypertension treatment. Additionally, public data revealed that CEBPA binding peaks were present upstream of LRPAP1 and ARID3A, strengthening the possibility of CEBPA's regulatory role in hypertension (113). The miRNA-mRNA network constructed in our study may serve as a valuable diagnostic biomarker for hypertension patients. While miRNA-mRNA networks have previously been utilized to detect markers for various diseases, including hypertension, the regulatory networks involving LRPAP1, KIAA0513, and ARID3A have been less explored. Therefore, the findings of mentioned study provide further evidence of the potential diagnostic utility of these mRNAs and miRNAs in hypertension.

5 Therapeutic potential of miRNAs in hypertension

Currently, available therapies for pulmonary arterial hypertension (PAH) primarily focus on managing its symptoms rather than addressing its root causes, leading to less-than-optimal treatment outcomes and high mortality and morbidity rates associated with PAH. Thus, gaining a comprehensive understanding of the epigenetic mechanisms underlying PAH is imperative for the development of more effective treatments. Recent evidence has increasingly emphasized the significant role of miRNAs and long non-coding RNAs (lncRNAs) in the pathogenesis of PAH. Further research is essential to unlock the potential for innovative therapeutic approaches.

One study explored a treatment approach involving the administration of synthetic miR-204 to rats induced with PAH

through monocrotaline (MCT). The intra-tracheal nebulization of synthetic miR-204 led to a reduction in pulmonary arterial blood pressure, decreased thickness of pulmonary arterial walls, and a decline in ventricular wall thickness. Importantly, this treatment resulted in a significant reduction in the activation of the STAT3–NFAT signaling pathway, leading to reduced proliferation and increased susceptibility to apoptosis in pulmonary arterial smooth muscle cells (PASMCs). Additionally, the downregulation of miR-204 in the buffy coat suggests its potential utility as a diagnostic marker for PAH (114).

Intriguing research investigated the impact of exosomes on animals (mice) with hypoxia-induced PAH and human pulmonary artery endothelial cells (hPAECs). Exosomes play a pivotal role in facilitating intercellular communication through paracrine signaling. In this study, researchers isolated exosomes from mesenchymal stromal cells (MSCs) derived from Wharton's jelly in human umbilical cords and mouse bone marrow. These exosomes, termed MSC-derived exosomes (MSDEXs), were employed for treatment. MSDEX treatment increased the concentration of miR-204, a molecule typically decreased in PAH patient cells. Furthermore, this treatment inhibited the STAT3 signaling pathway, known to induce the miR-17/92 cluster while suppressing mRNA expression of miR-204 (115). This innovative therapeutic strategy enabled the modulation of various molecular pathways related to PAH, particularly those associated with miRNA dysfunction.

In another study, researchers transfected cells with miR-124 molecules, resulting in a reduction of lactic acid and glycolysis concentration, restoring them to normal levels. This transfection also normalized the rate of cell proliferation (116).

Chen et al. focused on modulating miR-29 levels in PASMCs obtained from transgenic mice with hereditary PAH (HPAH) resulting from a BMPR2 mutation (117). Over a two-week course, these mice received injections of anti-miR-29 (amiR-29). This therapeutic approach notably reduced pulmonary vascular resistance (PVR) and systolic pressure. It also reversed the enhanced muscularization observed in HPAH-affected mice. Furthermore, amiR-29 administration had beneficial effects on the molecular characteristics of the PASMCs, reducing insulin resistance and improving mitochondrial morphology, which is often compromised in HPAH (117).

Potus et al. restored normal angiogenesis in examined cells by increasing the concentration of miR-126 (118). In a 2015 study, they successfully corrected impaired angiogenesis in endothelial cells from skeletal muscles and increased microcirculation density through transfection with a miR-126 mimic. Additionally, in a 2015 study, scientists restored vascular density in cardiomyocytes obtained from PAH patients through miR-126 administration. Intravenous injection of the miR-126 mimic demonstrated advantages for rats with MCT-induced PAH, leading to improvements in ventricular performance and cardiac outcomes on echocardiography in the rodents after two weeks of such treatment (118).

Overall, these findings demonstrate the therapeutic potential of miRNAs and other epigenetic modifications in the treatment of hypertension. Further research is needed to fully elucidate the mechanisms involved and to develop effective therapeutic strategies for hypertension and related conditions.

6 miRNAs as diagnostic biomarkers in hypertension

Circulating miRNAs have garnered significant attention not only for their regulatory functions but also due to their accessibility and remarkable stability. As a result, these circulating miRNAs have emerged as promising diagnostic biomarkers for various pathological conditions, including cardiovascular diseases (119).

In a study conducted by Matshazi et al., an increased expression of miR-182–5p and miR-126–3p was notably observed in individuals with hypertension, whether screen-detected or previously diagnosed, in comparison to normotensive individuals. Nevertheless, significant differences in the mRNA levels of miR-30a-5p, miR-30e-3p, and miR-1299 were not detected between normotensive individuals and those with detected hypertension. Multivariable logistic regressions did not reveal an association between hypertension and the expression of miR-30e-3p and miR-1299. However, they did establish a connection between the expression of miR-126–3p, miR-182–5p, and miR-30a-5p with both screen-detected and previously known hypertension, especially in the latter group. This study, conducted within an African population, is significant as it represents the first instance of identifying differential expression of miRNAs in whole blood based on blood pressure status. These miRNAs may serve as a potential panel of diagnostic biomarkers for hypertension. Moreover, the research reaffirmed prior findings concerning miR-126 and the miR-30 family, highlighting their potential involvement in hypertension development. Further exploration of these non-coding RNAs may open new avenues for prognosis and therapy in the context of cardiovascular diseases (120).

In another study, Yang et al. evaluated miR-505 as a prospective diagnostic biomarker for hypertension. Their findings provided evidence of miR-505's prognostic relevance in hypertension-related inflammation. Clinical data indicated a positive correlation between plasma levels of miR-505, systolic blood pressure, and CRP. CRP serves as an inflammatory marker linked to target organ damage in hypertensive patients, such as vascular alterations and cardiovascular events. The positive association of plasma miR-505 with CRP aligns with clinical outcomes suggesting miR-505's pro-inflammatory role, further substantiating its link to systemic inflammation in hypertension (119).

Furthermore, a study led by Charkiewicz and colleagues examined 88 men with hypertension, assessing various miRNAs in their serum levels. Elevated levels of miR-145–5p, miR-1–3p, and miR-423–5p pointed to the potential involvement of these specific miRNAs in hypertension. It is important to note that limited studies have explored this area, making comparisons with existing literature somewhat challenging. MiR-145–5p and miR-1–3p are believed to safeguard vascular smooth muscle cells by regulating processes related to proliferation and migration. Interestingly,

circulating miR-423–5p levels were found to be reduced shortly after a severe myocardial infarction, followed by an increase after five months in the same group of patients, highlighting the dynamic nature of miRNA levels. Discrepancies in miRNA levels among various research centers may stem from differences in study methods, patient selection, age, sex, or ethnicity (121). Liang et al. assessed 1,141 miRNAs in two subgroups of genotype-positive hypertension patients and identified 20 miRNAs with potential significance in patients with hypertension (122).

7 Epigenome modifications in hypertension: a classification based on pathophysiology

7.1 Salt-sensitive and salt-resistant hypertension

Salt-sensitive hypertension is characterized by an exaggerated blood pressure response to changes in salt intake, while salt-resistant hypertension is less affected by salt intake (123). Recent studies have suggested that epigenetic modifications, particularly DNA methylation, may play a role in the development of salt-sensitive hypertension by regulating genes involved in sodium handling and blood pressure regulation (23). Understanding the epigenetic basis of salt-sensitive and salt-resistant hypertension could lead to the development of targeted therapies that modulate these epigenetic mechanisms to treat or prevent hypertension based on individual salt sensitivity (124).

7.2 RAS-dependent hypertension

The RAS plays a crucial role in blood pressure regulation, and epigenetic modifications have been implicated in its dysregulation in hypertension (125). DNA methylation and histone modifications have been shown to regulate the expression of genes in the RAS, such as AGT and ACE, influencing blood pressure control (126). Targeting epigenetic modifications in the RAS could be a promising approach for the treatment of RAS-dependent hypertension (127). Drugs that modulate DNA methylation or histone acetylation patterns could potentially restore RAS balance and reduce blood pressure (128).

7.3 Vascular function-dependent hypertension

Epigenetic modifications have also been implicated in the regulation of vascular function in hypertension (82). Changes in DNA methylation and histone modifications can alter the expression of genes involved in vascular smooth muscle contraction, endothelial function, and vascular remodeling, contributing to hypertension development (129). Future research should focus on elucidating the specific epigenetic changes associated with vascular function-dependent hypertension and developing targeted therapies to restore vascular function and reduce blood pressure.

8 Epigenetic interplay between hypertension and coronary artery disease in T2DM

8.1 Epigenetic links between hypertension and CAD

8.1.1 Shared pathways

Recent studies have highlighted the role of epigenetic modifications, such as DNA methylation and histone modifications, in the regulation of endothelial function in both hypertension and CAD (130). Aberrant DNA methylation patterns in genes related to endothelial function, such as eNOS and ET-1, have been associated with endothelial dysfunction, a common feature of both conditions (131). Epigenetic changes, particularly histone modifications and non-coding RNAs, have been implicated in the regulation of inflammatory pathways in hypertension and CAD (130). For example, miRNAs have been shown to modulate the expression of inflammatory genes, such as IL-6 and TNF-alpha, contributing to inflammation in both conditions (132). Epigenetic modifications, including DNA methylation and histone acetylation, have been linked to oxidative stress, a key mechanism underlying endothelial dysfunction and vascular damage in hypertension and CAD (133). These epigenetic changes can alter the expression of genes involved in antioxidant defense mechanisms, exacerbating oxidative stress in both conditions (134).

8.1.2 Epigenetic biomarkers

Recent studies have identified specific DNA methylation changes associated with both hypertension and CAD, suggesting that DNA methylation patterns may serve as potential biomarkers for cardiovascular risk assessment in individuals with T2DM (135). For example, hypermethylation of the ACE gene has been linked to increased risk of hypertension and CAD (136). Histone modifications, such as acetylation and methylation, have also been proposed as potential biomarkers for cardiovascular risk in individuals with T2DM (137). Altered histone acetylation patterns in genes related to inflammation and oxidative stress have been associated with increased risk of hypertension and CAD (138).

8.2 Epigenetic factors in the development of CAD in T2DM

8.2.1 Synergistic effects

Recent evidence suggests that the combination of hypertension, epigenetic modifications, and T2DM can lead to a greater risk of developing CAD than each factor alone (139). The synergistic effects of these factors may involve complex interactions between genetic and environmental factors, leading to dysregulation of pathways related to endothelial function, inflammation, and

oxidative stress (140). Epigenetic modifications associated with hypertension and T2DM, such as DNA methylation and histone modifications, may interact synergistically to alter gene expression patterns related to CAD development (141). For example, hypermethylation of genes involved in lipid metabolism and endothelial function may exacerbate atherosclerosis in individuals with both conditions (142).

8.2.2 Clinical implications

Recognizing the synergistic effects of hypertension, epigenetic modifications, and T2DM on CAD development is crucial for effective risk assessment and management strategies (143). Clinicians should consider these factors when evaluating cardiovascular risk in patients with T2DM. Understanding the epigenetic basis of hypertension as a risk factor for CAD in T2DM opens up new avenues for therapeutic interventions. Targeting specific epigenetic pathways implicated in CAD pathogenesis may offer novel therapeutic strategies to reduce cardiovascular risk in this population. For example, drugs that modulate DNA methylation or histone acetylation patterns could potentially be used to prevent or treat CAD in individuals with T2DM and hypertension (144).

8.3 Future directions

Future studies should aim to elucidate the specific epigenetic changes that contribute to the development of CAD in individuals with hypertension and T2DM. By identifying these changes, researchers can gain insights into the underlying mechanisms of CAD in this population and identify potential therapeutic targets. Additionally, these studies should focus on identifying epigenetic biomarkers that can be used for risk stratification in individuals with hypertension and T2DM. These biomarkers could help clinicians identify patients at higher risk of developing CAD and tailor treatment strategies accordingly.

Understanding the epigenetic basis of hypertension and CAD in individuals with T2DM may pave the way for precision medicine approaches. These approaches could target specific epigenetic pathways to reduce cardiovascular risk in this population. For example, drugs that modulate DNA methylation or histone modifications could be developed to target these pathways. Future studies should focus on validating epigenetic biomarkers that have been identified as potential targets for precision medicine approaches. Validation studies will be crucial in determining the effectiveness of these biomarkers in predicting CAD risk and guiding treatment decisions.

The concept of personalized medicine, which considers individual genetic and epigenetic profiles, holds promise for the development of targeted therapies for CAD in patients with T2DM and hypertension. Future research should focus on identifying specific epigenetic signatures associated with CAD in this population and developing personalized treatment approaches based on these signatures. However, the implementation of personalized medicine approaches in clinical practice may present challenges, including the need for robust validation studies, development of cost-effective testing methods, and integration of genetic and epigenetic data into clinical decision-making.

9 Environmental influences on epigenetics and hypertension

9.1 Diet influences on epigenetics and hypertension

Diets rich in nutrients such as folate, vitamin B12, and other methyl donors can influence DNA methylation patterns, potentially affecting genes involved in blood pressure regulation (145). Conversely, diets high in salt or fat may lead to epigenetic changes that contribute to hypertension (146). Studies have shown that dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in fruits, vegetables, and low-fat dairy products, can lead to changes in DNA methylation associated with lower blood pressure (147).

9.2 Pollution influences on epigenetics and hypertension

Exposure to environmental pollutants, such as particulate matter, polycyclic aromatic hydrocarbons (PAHs), and heavy metals, can alter DNA methylation patterns and gene expression, potentially contributing to the development of hypertension (148). Epidemiological studies have linked exposure to air pollution with changes in DNA methylation of genes related to inflammation and oxidative stress, which are implicated in hypertension (149).

9.3 Ethnicity and geography influences on epigenetics and hypertension

Ethnicity and geographic location can impact epigenetic patterns through differences in lifestyle, diet, cultural practices, and environmental exposures, all of which may contribute to variations in hypertension prevalence among different populations (23). Studies have shown ethnic differences in DNA methylation patterns associated with hypertension-related genes, suggesting that genetic and environmental factors unique to certain populations may play a role in hypertension disparities (150).

10 Relationship between pre-eclampsia, epigenetics, and hypertension

Pre-eclampsia is a hypertensive disorder that occurs during pregnancy and is characterized by high blood pressure and proteinuria (151). It shares some pathophysiological features with EH, suggesting a potential common etiology involving genetic and epigenetic factors (152). Epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNA expression, play a crucial role in the pathogenesis of pre-eclampsia (153). These epigenetic changes can alter the

expression of genes involved in vascular function, inflammation, and placental development, contributing to the development of hypertension in pre-eclamptic women (154). Current research in this field has focused on elucidating the specific epigenetic changes associated with pre-eclampsia and their role in the pathogenesis of the disorder (155). Studies have identified differential DNA methylation patterns in placental tissue and maternal blood of women with pre-eclampsia compared to healthy pregnant women, suggesting that these epigenetic changes may contribute to the development of the disorder (156). Recent research has also provided insights into the pathogenesis of pre-eclampsia, highlighting the role of aberrant placentation, oxidative stress, and immune dysregulation (157). These processes are influenced by epigenetic mechanisms, further implicating epigenetic factors in the development of hypertension in pre-eclampsia. Further research is needed to unravel the complex interplay between genetic and epigenetic factors in pre-eclampsia and hypertension. Longitudinal studies that follow women with pre-eclampsia beyond pregnancy may provide valuable insights into the long-term effects of epigenetic changes on hypertension risk later in life.

11 Conclusion

The amalgamation of evidence gleaned from diverse databases provides crucial insights into EH, a multifaceted condition intricately regulated by multiple genes. These genes undergo intricate control through diverse epigenetic mechanisms, including histone modifications, DNA methylation, and miRNAs. A noteworthy proportion of EH-associated genes harbor CpG sites susceptible to DNA methylation and are subject to the regulatory influence of various miRNAs, thereby being responsive to a spectrum of epigenetic determinants. The synergistic interplay of these epigenetic modifications holds immense potential for advancing the diagnostic and therapeutic paradigms of EH.

Advanced technologies such as Genome-Wide Association Studies (GWAS) and Epigenome-Wide Association Studies (EWAS) empower the exploration of epigenetic and genetic variations across different forms of hypertension. Through these methodologies, novel loci influencing blood pressure regulation have been unveiled, with ongoing research poised to uncover further insights. The expansive realm of epigenetics continuously uncovers additional hereditary variations intertwined with hypertension.

In a concerted effort to unravel the intricate crossroads of genetic and epigenetic regulatory elements, researchers aspire to deepen their comprehension of hypertension's pathogenesis, paving the way for personalized therapeutic interventions. High-throughput techniques, including whole-genome and exome sequencing, offer a holistic perspective for the simultaneous exploration of multiple risk variants.

Understanding the role of environmental influences on epigenetics is essential for elucidating the mechanisms underlying hypertension. By considering the impact of diet, pollution, and ethnicity on epigenetic modifications, we can gain a more comprehensive understanding of the multifactorial nature of hypertension and develop more targeted strategies for its prevention and management.

In conclusion, a comprehensive understanding of hypertension's risk factors, incorporating both epigenetic and genetic markers, forms an imperative foundation for tailoring personalized therapeutic strategies. This integrated approach holds promise for advancing precision medicine in the management of EH and related cardiovascular complications.

Author contributions

RZ: Conceptualization, Funding acquisition, Project administration, Writing – review & editing. TV: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. NM: Data curation, Methodology, Resources, Writing – review & editing. RA: Methodology, Validation, Writing – review & editing. AK: Data curation, Methodology, Resources, Writing – review & editing. AT: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Writing – original draft.

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Conflict of interest

The author AT was employed by the company PerciaVista R&D Co.

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Publisher's note

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Triglyceride-glucose index as a potential predictor of major adverse cardiovascular and cerebrovascular events in patients with coronary heart disease complicated with depression

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Background: Triglyceride-glucose (TyG) index is a surrogate marker of insulin resistance and metabolic abnormalities, which is closely related to the prognosis of a variety of diseases. Patients with both CHD and depression have a higher risk of major adverse cardiovascular and cerebrovascular events (MACCE) and worse outcome. TyG index may be able to predict the adverse prognosis of this special population.

Methods: The retrospective cohort study involved 596 patients with both CHD and depression between June 2013 and December 2023. The primary outcome endpoint was the occurrence of MACCE, including all-cause death, stroke, MI and emergent coronary revascularization. The receiver operating characteristic (ROC) curve, Cox regression analysis, Kaplan-Meier survival analysis, and restricted cubic spline (RCS) analysis were used to assess the correlation between TyG index and MACCE risk of in patients with CHD complicated with depression.

Results: With a median follow-up of 31 (15–62) months, MACCE occurred in 281 (47.15%) patients. The area under the ROC curve of TyG index predicting the risk of MACCE was 0.765(0.726–0.804) (P<0.01). Patients in the high TyG index group(69.73%) had a significantly higher risk of developing MACCE than those in the low TyG index group(23.63%) (P<0.01). The multifactorial RCS model showed a nonlinear correlation (nonlinear P<0.01, overall P<0.01), with a critical value of 8.80 for the TyG index to predict the occurrence of MACCE. The TyG index was able to further improve the predictive accuracy of MACCE.

Conclusions: TyG index is a potential predictor of the risk of MACCE in patients with CHD complicated with depression.

KEYWORDS

triglyceride-glucose index, predictor, MACCE, coronary heart disease, depression

Background

The latest epidemiological report by the World Health Organization shows that cardiovascular disease (CVD) is the primary cause of death globally, contributing to approximately 32% of global mortality (1). Ischemic heart disease contributes to a large proportion of these deaths, accounting for approximately 16% of global deaths (2). Depression is a disorder characterized by depressed mood (e.g., sadness, irritability, emptiness, or loss of pleasure), frequently accompanied by additional cognitive, behavioral, or neurovegetative symptoms that have a notable impact on patient's functioning (3). Depression is prevalent among patients with CVD (4, 5), with approximately 20–30% of patients with coronary heart disease (CHD) experiencing depression (6, 7). Studies have demonstrated that, in patients with CHD, depression not only significantly affects patient's quality of life (5) but also increases the risk of all-cause death, cardiac-related death, and new cardiac events by 2.3-fold, 2.7-fold, and 1.6-fold, respectively (4, 8, 9).

Encouragingly, 86% of cardiovascular (CV) deaths can be prevented by addressing behavioral risk factors (10). Therefore, there is an urgent need to identify patients at high risk for CHD comorbid with depression by exploring new predictors, allowing for the implementation of early interventions to reduce the incidence of adverse CV events. In recent years, several studies have demonstrated that insulin resistance (IR) not only has a significant impact on the development of metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM), but is also closely related to the onset of CVD and atherosclerotic disease (11–13). In addition, IR can also adversely affect the prognosis of patients with psychiatric disorders, such as anxiety and depression, by affecting neuronal and synaptic activity and exacerbating neuroinflammation (14–16). Therefore, IR may be a key factor affecting the prognosis of patients with CHD complicated with depression.

The triglyceride-glucose (TyG) index is a representative marker of IR and is calculated as follows: ln[fasting blood glucose × fasting triglyceride/2]. Despite its lower accuracy for assessing IR compared with that of the gold standard high insulin normoglycemic clamp, it is still widely used because of its simplicity, reliability, and ready applicability (17, 18).

Previous studies have demonstrated that the TyG index score is not only significantly associated with T2DM, MetS, and atherosclerosis but also served as an independent risk factor for the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE) in CHD, regardless of the patient having T2DM (19, 20). TyG levels are closely related to the occurrence and progression of depression (21, 22). Therefore, TyG may be an important prognostic indicator in patients with CHD complicated with depression.

However, no studies have evaluated the prognostic significance of the TyG index score in patients with CHD complicated with depression. Therefore, this study aimed to explore the predictive value of the TyG index score for MACCE in patients with both CHD and depression.

Methods

Study participants

This single-center, retrospective, cohort study involved 596 patients with comorbid CHD and depression who sought treatment at the Dongfang Hospital of Beijing University of Chinese Medicine from June 2013 to December 2023. The following criteria were used for inclusion: (1) individuals aged 18 years or older; (2) Patients with a diagnosis of CHD; (3) Patients meeting the diagnosis of major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). CHD was defined based on meeting at least one of the criteria (23): (1) Percutaneous coronary angiography or computed tomographic angiography revealed ≥ 50% stenosis in at least one coronary artery trunk or primary branch; (2) Presence of typical symptoms of exertional angina, accompanied by a positive stress test (electrocardiogram stress test, stress echocardiography, or nuclide myocardial stress imaging); (3) A documented history of myocardial infarction (MI); (4) Previous diagnosis of unstable. angina pectoris, characterized by typical ischemic chest pain, electrocardiogram changes, and elevated markers of muscle damage, or dynamic ST segment changes during ischemic episodes, or confirmation of severe lesions through coronary angiography leading to symptomatic manifestations. The definition of depression refers to the DSM-5 diagnostic criteria for major depressive disorder (24). The exclusion criteria included: (1) Incomplete data about fasting blood glucose (FBG) or triglyceride (TG); (2) New York Heart Association(NYHA) classification IV heart failure; (3) Type1 diabetes mellitus;(4) Severe renal insufficiency (eGFR<30mL/min/1.73 m^2 or chronic dialysis); (5) Uncontrolled cancer; (6) Hepatic encephalopathy; (7) Lost to follow-up (Figure 1).

Ultimately, a total of 596 patients were included in the analysis. The patients were categorized into a MACCE (n=281) or no-MACCE (n=315) group according to the occurrence of MACCE during follow-up. After conducting receiver operating characteristic (ROC) curve analysis to identify the ideal threshold for the TyG index, patients were divided into the low group (n=292) and the high group (n=304) based on this categorization.

This study follows the principles of the Helsinki Declaration and has been approved by the Clinical Research Ethics Committee of the Dongfang Hospital of Beijing University of Chinese Medicine. All personal information regarding the patients' identities was de-identified.

Data collection and definitions

Data regarding demographics; vital signs; smoking (smoking was described as a total of more than 100 cigarettes in a patient's lifetime, regardless of whether they are currently quitting or not (25)); laboratory measurements (total cholesterol [TC], triglyceride [TG], high-density lipoprotein cholesterol [HDL-C], low-density

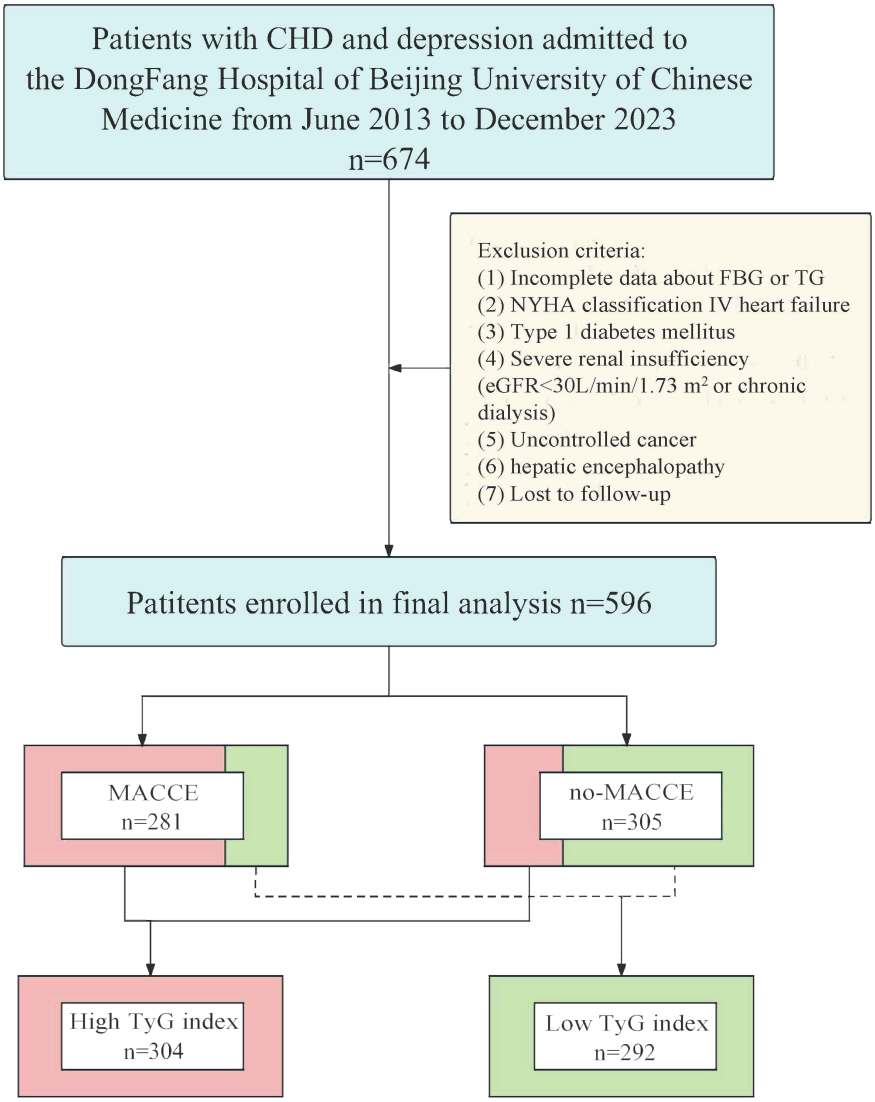

FIGURE 1
Flow chart of patients screening and grouping. CHD, coronary artery disease; FBG, fasting blood glucose; NYHA, New York Heart Association; TG, triglyceride; eGFR, estimated glomerular filtration rate; MACCE, major adverse cardiovascular and cerebrovascular event; TyG, triglyceride-glucose.

lipoprotein cholesterol [LDL-C], fasting blood glucose [FBG], and glycosylated hemoglobin A1c [HbA1c]); case history; a family history of CVDs; and use of medications. Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2 (26).

Follow-up and endpoints

All patients were followed up via telephone or outpatient visits by professionally trained personnel. The follow-up lasted until December 2023, unless detachment or death occurred. The primary endpoint of this study was the composite endpoint of MACCE, encompassing the occurrence of all-cause death, stroke, MI, or emergent coronary revascularization during the follow-up period (based on the first secondary endpoint event after discharge or the most severe event if multiple endpoint events occurred simultaneously, with the events prioritized as follows: all-cause death > stroke > MI > emergent coronary revascularization). End-point events were determined independently by two cardiovascular specialists who were not aware of the patient's TyG index scores or other baseline information. When there was disagreement regarding the determination of the endpoint event, a third expert was consulted, and a joint decision was made after discussion.

Statistical analysis

Statistical analyses in this study were calculated with SPSS software (version 26.0) and R software (version 4.2.3). The P-value <0.05 indicated a statistically significant difference. Continuous variables, including age, BMI and blood pressure were expressed as mean ± standard deviation (SD); continuous variables that did not follow a normal distribution, including TC,

LDL-C, HDL-C, FBG, and HbA1c, were presented as median and interquartile range. We used the independent samples t-test or Wilcoxon rank-sum test to compare continuous variables between the groups. The categorical variables, including sex, smoking, case history, and use of medications, are presented as frequencies (percentages). We compared categorical variables between groups by using Pearson's chi-square test or Fisher's exact test.

We conducted a systematic analysis of the relationship between the TyG index and MACCE in patients with depression and CHD. ROC curve analysis was employed to ascertain the ideal threshold value of TyG index in forecasting the occurrence of MACCE, and additionally evaluated the added discriminatory power of the TyG index group beyond the initial risk model. The Kaplan-Meier survival analyses were conducted to evaluate the incidence of endpoint events in both cohorts.

In order to determine if the TyG index score could function as an independent predictor of the incidence of MACCE, we performed univariate and multivariate Cox regression analyses, presenting results as hazard ratios (HR) and 95% confidence intervals (CI). In addition, four different Cox proportional risk models were developed to identify independent risk factors for MACCE in each model. Model 1 was adjusted for age, male sex, BMI, systolic blood pressure, diastolic blood pressure, and smoking; On the basis of Model 1, Model 2 was adjusted for hypertension, T2DM, dyslipidemia, prior CVDs, prior PCI, prior stroke and a family history of CVDs; Model 3 adds variables from clinical tests to Model 2: TC, LDL-C, HDL-C, and HbA1c; and Model 4 was adjusted for the variables included in Model 3 and the use of antiplatelet medication, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), calcium channel blocker (CCB), β-Blocker, antidiabetic agents, statins, antidepressants, and benzodiazepines. Furthermore, Model 4 adjustments were utilized to construct restricted cubic spline (RCS) curves, demonstrating the nonlinear or linear correlation between the TyG index score and MACCE.

In addition, subgroup analyses were conducted to explore the consistency of the TyG index score's predictive efficacy for MACCE among various subgroups. Besides, we employed the integrated discrimination improvement(IDI), net reclassification improvement (NRI) and concordance index (C-index) to examine the incremental benefit of the TyG index in forecasting MACCE.

Results

Baseline information

A total of 596 patients were ultimately involved in this study. The mean age was 71.71 ± 9.36 years, of which 212 (35.6%) were male. The baseline characteristics of the total population, grouped according to whether MACCE occurred or not, are shown in Table 1. The TyG index of patients with MACCE(9.10, 8.80–9.47) was significantly higher than that of patients without MACCE (8.48, 8.19–8.86) (P<0.01). In addition, patients in the MACCE group demonstrated substantially elevated levels of BMI, TC, TG, LDL-C, FBG, and HbA1c compared to those in the no-MACCE group. More patients in the MACCE group had diabetes as well as previous cerebral infarction than those in the no-MACCE group. Meanwhile, the proportion of patients in the MACCE group receiving ACEI/ARB, hypoglycemic agents, and statins was substantially higher than that in the no-MACCE group. The proportion of patients receiving antidepressants in MACCE group was similar to that in non MACCE group.

By ROC curve analysis (Figure 2), we found that the TyG index predicted MACCE with an area under the curve of 0.765 (0.726–0.804, P<0.01). It was determined that 8.80 was the best cut-off value for the TyG index in predicting MACCE (sensitivity: 75.4%; specificity: 70.8%). The participants was divided into the low group and the high group based on the best cut-off value of the TyG index. The baseline characteristics of the different groups are shown in Table 2. We observed that the BMI of patients in the high TyG group was significantly higher than that of patients in the low TyG index group. TG, TC, LDL-C, FBG, and HbA1c levels were significantly higher, and HDL-C was significantly lower in the high TyG index group. In addition, more patients in the high TyG index group were treated with ACEI/ARB, hypoglycemic agents, and statins.

Association of TyG Index with cardiovascular risk factors

Correlation analysis showed that the TyG index was associated with several cardiovascular risk factors. As shown in Additional file 1: Supplementary Table S1, TyG index was positively associated with BMI (P<0.01), TC (P<0.01), LDL-C (P<0.01), HbA1c (P<0.01), and history of T2DM (P<0.01), whereas it was negatively correlated with age (P=0.046), male sex (P=0.025), and HDL-C (P<0.01).

Predictive value of the TyG index for the occurrence of MACCE in patients with CHD and depression

During a median follow-up of 31 (15–62) months, 281 (47.15%) patients developed MACCE, including 111 (18.62%) all-cause deaths, 67 (11.24%) stroke, 63 (10.57%) MI, and 40 (6.71%) emergent coronary revascularization (Table 3). The incidence of MACCE in patients with high TyG index is significantly higher than that in patients with low TyG index, both in the overall incidence of MACCE and the incidence of each subgroup. The overall incidence of MACCE in the high TyG group (69.73%) was considerably higher than that in the low TyG group (23.63%). Moreover, compared with the low TyG group (13.36%), the high TyG group showed a higher incidence of all-cause death (23.68%). The incidence of stroke in the high TyG group (18.42%) was also significantly higher than that in the low TyG group (3.77%). Similarly, 16.12% of patients in the high TyG group had MI, which was higher than that in the low TyG group (4.79%); the incidence of emergent coronary revascularization was 11.51% in the high TyG group, which was higher than that in the low TyG group (1.71%). All the differences were statistically significant (P<0.01) (Table 3).

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TABLE 1 Baseline characteristics of population divided by MACCE-related situation.

Characteristics	Overall (n=596)	MACCE (n=281)	No-MACCE (n=315)	*P* value
Age (years)	71.71 ± 9.36	72.46 ± 9.76	71.05 ± 8.96	0.068
Male (n, %)	212(35.6%)	102(36.3%)	110(34.9%)	0.726
BMI (kg/m^2)	24.53 ± 3.64	24.87 ± 3.93	24.22 ± 3.33	0.031
Smoking (n, %)	147(24.66%)	77(27.40%)	70(22.22%)	0.143
SBP (mmHg)	133.56 ± 19.16	133.76 ± 19.02	133.37 ± 19.31	0.804
DBP (mmHg)	75.62 ± 11.21	75.03 ± 10.78	76.14 ± 11.58	0.229
Laboratory variables				
TC (mmol/L)	3.86(3.26~4.57)	4.05(3.34~4.86)	3.74(3.17~4.34)	<0.01
TG(mmol/L)	1.31(0.96~1.92)	1.63(1.20~2.16)	1.10(0.86~1.55)	<0.01
HDL-C(mmol/L)	1.22(1.00~1.47)	1.20(0.98~1.45)	1.23(1.02~1.49)	0.127
LDL-C(mmol/L)	2.26(1.72~2.87)	2.37(1.85~3.00)	2.20(1.66~2.73)	<0.01
FBG(mmol/L)	5.82(5.05~7.63)	6.59(5.34~8.81)	5.38(4.90~6.40)	<0.01
HbA1c(%)	5.80(5.40~6.80)	6.00(5.40~7.25)	5.60(5.30~6.40)	<0.01
TyG index	8.80(8.36~9.26)	9.10(8.80~9.47)	8.48(8.19~8.86)	<0.01
Case history				
Hypertension (n, %)	467(78.36%)	223(79.36%)	244(77.46%)	0.574
T2DM (n, %)	292(49.00%)	163(58.00%)	129(40.95%)	<0.01
Dyslipidemia (n, %)	388(65.10%)	184(65.48%)	204(64.76%)	0.854
Prior CVDs (n, %)	506(84.90%)	241(85.77%)	265(84.13%)	0.577
Prior PCI (n, %)	161(27.01%)	79(28.11%)	82(26.03%)	0.568
Prior stroke (n, %)	264(44.30%)	144(51.25%)	120(38.10%)	<0.01
Family history of CVDs (n, %)	183(30.70%)	78(27.76%)	105(33.33%)	0.141
Medications				
Antiplatelet medication (n, %)	565(94.80%)	262(93.24%)	303(96.19%)	0.105
ACEI/ARB (n, %)	262(43.96%)	155(55.16%)	107(33.97%)	<0.01
CCB (n, %)	334(56.04%)	155(55.16%)	179(56.83%)	0.683
β-Blocker (n, %)	351(58.89%)	173(61.57%)	178(56.51%)	0.210
Antidiabetic agents (n, %)	253(42.45%)	151(53.74%)	102(32.38%)	<0.01
Statins (n, %)	516(86.58%)	263(93.59%)	253(80.32%)	<0.01
Antidepressants (n, %)	405(67.95%)	189(67.26%)	216(68.57%)	0.732
Benzodiazepines (n, %)	214(35.91%)	102(36.30%)	112(35.56%)	0.850

MACCE, major adverse cardiovascular and cerebrovascular events; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TyG, triglyceride-glucose;T2DM, diabetes mellitus type 2; CVD, cardiovascular disease; PCI, percutaneous coronary intervention; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

According to Kaplan-Meier survival analysis, patients with a high TyG index exhibited an increased risk of MACCE (P<0.01). In the high TyG index group, there was a significantly higher occurrence of all-cause death, stroke, MI, and emergent coronary revascularization compared to the low TyG index group (P<0.01) (Figure 3).

To further assess the impact of the TyG index on MACCE, we used four distinct Cox proportional risk models incorporating different categories of confounders for separate analyses. The result revealed that as a continuous variable, the TyG index was independently associated with an elevated risk of MACCE for each unit increase in the index (Model 1: 2.27, 1.90–2.70, P<0.01; Model

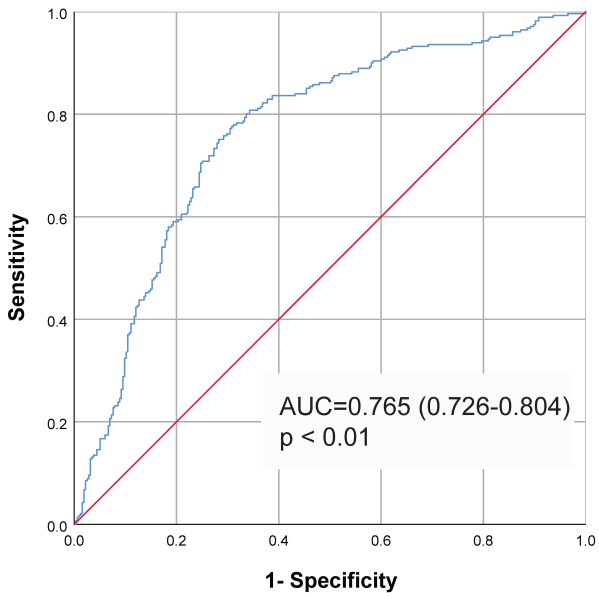

FIGURE 2
ROC curve to assess the diagnostic performance of the TyG index for MACCE. Cut-off value 8.80, AUC=0.765, 95% CI (0.726–0.804), *P*<0.01. Sensitivity: 75.4%; Specificity: 70.8%. ROC, receiver operating characteristic; AUC, area under the curve; TyG, triglyceride-glucose; MACCE, major adverse cardiovascular and cerebrovascular event.

2: 2.26, 1.85–2.75, *P*<0.01; Model 3: 2.44, 1.89–3.16 *P*<0.01; Model 4: 2.09, 1.59–2.74, *P*<0.01) (Table 4).

When the TyG index was examined as a categorical variable, a distinct correlation could also be observed between the high TyG index group and MACCE (Model 1: 3.84, 2.90–5.08, *P*<0.01; Model 2: 3.74, 2.79–5.01, *P*<0.01; Model 3: 3.56, 2.60–4.90, *P*<0.01; Model 4: 3.01, 2.16–4.21, *P*<0.01).

We examined the prognostic significance of the TyG index for all outcome events through both univariate and multivariate analyses. The results showed that the TyG index was independently associated with a high risk of MACCE when used as a continuous variable (2.09, 1.59–2.74, *P*<0.01), all-cause death (2.55, 1.65–3.93, *P*<0.01), stroke (2.79, 1.50–5.16, *P*<0.01),MI (2.54, 1.40–4.60, *P*<0.01), emergent coronary revascularization (4.37, 1.94–9.86, *P*<0.01). As a categorical variable, the TyG index could still serve as an independent predictor of both MACCE(3.01, 2.16–4.21, *P*<0.01) and all-cause death(2.99, 1.81–4.95, *P*<0.01), stroke (6.14, 2.86–13.15, *P*<0.01), MI(7.38, 3.36–16.18, *P*<0.01), or emergent coronary revascularization(10.10, 3.26–31.27, *P*<0.01) (Table 5).

The multivariate RCS curves generated according to Model 4 showed a nonlinear relationship between the TyG index and MACCE (nonlinear *P*<0.01, overall *P*<0.01). The HR value for distinguishing the presence of MACCE was closest to 1 when the TyG index was 8.80 (Figure 4).

TABLE 2 Baseline characteristics of population divided by TyG index-related situation.

Characteristics	Overall (n=596)	High TyG index (n=304)	Low TyG index (n=292)	*P* value
Age (years)	71.71 ± 9.36	71.19 ± 9.67	72.26 ± 9.01	0.161
Male, n (%)	212(35.57%)	101(33.22%)	111(38.01%)	0.222
BMI (kg/m^2)	24.53 ± 3.64	25.30 ± 3.72	23.72 ± 3.37	<0.01
Smoking n (%)	147(24.66%)	73(25.00%)	74(24.34%)	0.852
SBP (mmHg)	133.56 ± 19.16	134.10 ± 19.13	133.00 ± 19.20	0.486
DBP (mmHg)	75.62 ± 11.21	75.46 ± 11.20	75.78 ± 11.25	0.733
Laboratory variables				
TC (mmol/L)	3.86(3.26~4.57)	4.10(3.41~4.98)	3.64(3.13~4.21)	<0.01
TG(mmol/L)	1.31(0.96~1.92)	1.91(1.45~2.33)	0.97(0.80~1.18)	<0.01
HDL-C(mmol/L)	1.22(1.00~1.47)	1.15(0.95~1.36)	1.29(1.06~1.62)	<0.01
LDL-C(mmol/L)	2.26(1.72~2.87)	2.43(1.91~3.13)	2.13(1.65~2.64)	<0.01
FBG(mmol/L)	5.82(5.05~7.63)	7.14(5.68~9.31)	5.27(4.79~5.84)	<0.01
HbA1c(%)	5.80(5.40~6.80)	6.30(5.50~7.50)	5.50(5.30~6.00)	<0.01
TyG index	8.80(8.36~9.26)	9.25(8.98~9.58)	8.34(8.12~8.55)	<0.01
Case history				
Hypertension n (%)	467(78.36%)	239(78.62%)	228(78.08%)	0.874
T2DM n (%)	292(48.99%)	196(64.47%)	96(32.88%)	<0.01

(Continued)

TABLE 2 Continued

Characteristics	Overall (n=596)	High TyG index (n=304)	Low TyG index (n=292)	*P* value
Case history				
Dyslipidemia n (%)	388(65.10%)	204(67.11%)	184(63.01%)	0.295
Prior CVDs n (%)	506(84.90%)	250(82.24%)	256(87.67%)	0.064
Prior PCI n (%)	161(27.01%)	89(29.28%)	72(24.66%)	0.204
Prior stroke n (%)	264(44.30%)	144(47.37%)	120(41.10%)	0.123
Family history of CVDs n (%)	183(30.70%)	98(32.24%)	85(29.11%)	0.408
Medications				
Antiplatelet medication n (%)	565(94.80%)	285(93.75%)	280(95.89%)	0.239
ACEI/ARB n (%)	262(43.96%)	162(53.29%)	100(34.25%)	<0.01
CCB n (%)	334(56.04%)	175(57.57%)	159(54.45%)	0.444
β-Blocker n (%)	351(58.89%)	181(59.54%)	170(58.22%)	0.743
Antidiabetic agents n (%)	253(42.45%)	183(60.20%)	70(23.97%)	<0.01
Statins n (%)	516(86.58%)	277(91.12%)	239(81.85%)	<0.01
Antidepressants n (%)	405(67.95%)	198(65.13%)	207(70.89%)	0.132
Benzodiazepines n (%)	214(35.91%)	109(35.86%)	105(35.96%)	0.979

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TyG, triglyceride-glucose;T2DM, diabetes mellitus type 2; CVD, cardiovascular disease; PCI, percutaneous coronary intervention; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Subgroup analysis

The study participants were divided into subgroups based on age (<65 or ≥65 years); male sex(yes or no), BMI(< 24 or ≥ 24 kg/m^2), Somking(yes or no), Hypertension(yes or no), LDL-C(<1.8 or ≥1.8 mmol/L), HDL-C(<1.3 or ≥1.3 mmol/L), HbA1C(<7 or ≥7%), Prior stroke(yes or no), T2DM(yes or no), Dyslipidemia(yes or no) and Prior PCI (yes or no) for the purposes of further validating the TyG index's ability to predict MACCE in different subgroups (Figure 5).

The analysis results showed that TyG index has a good predictive effect on the prognosis of most patients with CHD complicated with depression. However, the predictive value of TyG index for MACCE in patients under 65 years old, smokers, patients with HDL-C ≥ 1.3 mmol/l and patients with HbA1c ≥ 7.0% had some limitations. The reasons might be as follows: patients who smoke often suffer from respiratory diseases; While patients with HbA1c ≥ 7.0% had poor long-term blood glucose control; These influencing factors might have adverse effects on the prognosis of patients with coronary heart disease complicated with depression. For patients under 65 years old or with HDL-C ≥ 1.3 mmol/l, their physical condition is relatively better, and the possibility of MACCE is lower. Even if there is metabolic abnormality, it is usually easier to be corrected, so it might be difficult to predict such patients through a single TyG index to some extent. For these people, it might be possible to make better prognosis prediction by combining TyG index with other influencing factors.

TABLE 3 Comparison of endpoint events between high and low TyG index groups.

Variable, n (%)	Total (n=596)	Low TyG index (n=292)	High TyG index (n=304)	*P* value
MACCE	281(47.15%)	69(23.63%)	212(69.73%)	<0.01
All-cause death	111(18.62%)	39(13.36%)	72(23.68%)	<0.01
Stroke	67(11.24%)	11(3.77%)	56(18.42%)	<0.01
MI	63(10.57%)	14(4.79%)	49(16.12%)	<0.01
Emergent coronary revascularization	40(6.71%)	5(1.71%)	35(11.51%)	<0.01

TyG, triglyceride-glucose; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction.

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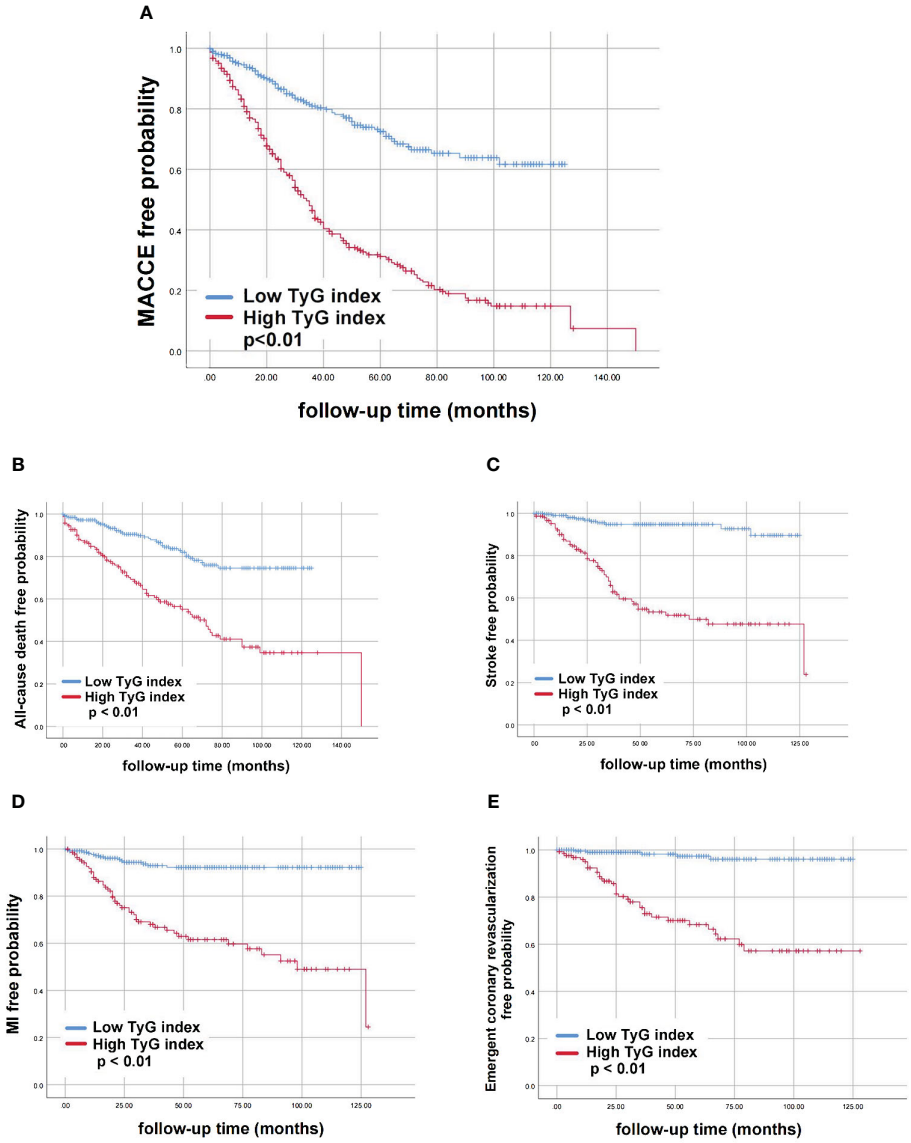

FIGURE 3
Kaplan-Meier curves for different groups of endpoint events. **(A)** MACCE; **(B)** All-cause death; **(C)** Stroke; **(D)** MI; **(E)** Emergent coronary revascularization. AUC; TyG, triglyceride-glucose; TyG, triglyceride-glucose; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction.

TyG index predicts the incremental effect of MACCE

The initial risk model of baseline incorporated diverse factors, including age, sex, BMI, SBP, DBP, smoking, TC, HDL-C, LDL-C, HbA1c, hypertension, T2DM, dyslipidemia, prior CVDs, prior PCI, prior stroke, family history of CVDs, and the use of antiplatelet medication, ACEI/ARB, CCB, β-Blocker, antidiabetic agents, statins, antidepressants, benzodiazepines. Upon integration into the baseline risk model, the TyG index significantly enhanced the precision of MACCE prediction, reclassification and discrimination, in comparison to TG or FBG alone (NRI: 0.028, 0.001–0.049; IDI:0.145, 0.011–0.193; C-Index: 0.698, 0.667–0.729; all P<0.01) (Table 6).

Discussion

TyG index is a surrogate marker of IR and metabolic abnormalities, which is closely related to the prognosis of a variety of diseases. Over the past few years, numerous studies have validated the strong correlation between the TyG index score and the occurrence and outcome of CVD. Nonetheless, the predictive significance of the TyG index in individuals with CHD complicated with depression is still uncertain. Our study showed that (1) The elevation of the TyG index was closely correlated with an increased risk of adverse events in patients with CHD complicated with depression. (2) The TyG index exhibited an independent association with the risk of all-cause death, stroke, MI, and emergency coronary revascularization, both as continuous

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TABLE 4 Predictive value of TyG index for MACCE in different Cox proportional risk models.

	TyG index as a continuous variable[a]			TyG index as a categorical variable[b]		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Crude model	2.18	1.85–2.58	<0.01	3.69	2.80–4.84	<0.01
Model 1	2.27	1.90–2.70	<0.01	3.84	2.90–5.08	<0.01
Model 2	2.26	1.85–2.75	<0.01	3.74	2.79–5.01	<0.01
Model 3	2.44	1.89–3.16	<0.01	3.56	2.60–4.90	<0.01
Model 4	2.09	1.59–2.74	<0.01	3.01	2.16–4.21	<0.01

Model 1 Age, sex, BMI, smoking, SBP, DBP.
Model 2 Add to Model 1: Hypertension, T2DM, Dyslipidemia, Prior CVDs, Prior PCI, Prior stroke, Family history of CVDs.
Model 3 Add to Model 2 the variable for clinical lab results: TC, HDL-C, LDL-C, HbA1c.
Model 4 Add to Model 3 the variable for clinical medication: Antiplatelet medication, ACEI/ARB, CCB, β-Blocker, Antidiabetic agents, Statins, Antidepressants, Benzodiazepines.
a. The HR was assessed with each 1-unit increase in the TyG index.
b. The HR was examined with the low TyG index group as the reference.

and categorical variables. (3) In patients with both CHD and depression, there existed a nonlinear relationship between the TyG index and the risk of MACCE, with the optimal cut-off value for predicting MACCE determined as 8.80.

Depression can lead to autonomic dysfunction and endocrine imbalance, exerting adverse effects on CVD through various mechanisms (27, 28). Specifically, depression induces dysregulation of the sympathetic–adrenomedullary system, which leads to the secretion of catecholamines, resulting in increased heart rate, blood pressure, and myocardial contraction, leading to increased cardiac load and risk of coronary artery spasm (4, 29, 30). In addition, depression leads to neuroendocrine disorders by activating the hypothalamic–pituitary–adrenal (HPA) axis and promoting the secretion of corticotropin-releasing hormone, which in turn promotes the secretion of adrenocorticotropic hormone, resulting in increased cortisol levels, abnormal cortisol rhythms, and fluctuating blood glucose (31).

Inflammation is a recognized risk factor for atherosclerosis and CHD (32). Depression can result in elevated levels of C-reactive protein, interleukin (IL)-1β, IL-6, and tissue necrotic factor-alpha, as well as an increase in the concentration of inflammatory molecules, such as NLRP3 inflammasomes (33, 34). It can also lead to an increase in oxidative stress markers (35), which in turn promote plaque formation and rupture, affect thrombosis formation, and have adverse effects on CV health (36).

TABLE 5 Predictive value of the TyG index for endpoint events in univariate and multivariate analyses.

	Univariate analysis			Multivariate analysis[a]		
	HR	95% CI	*P* value	HR	95% CI	*P* value
TyG index as a continuous variable[b]						
MACCE	2.18	1.85–2.58	<0.01	2.09	1.59–2.74	<0.01
All-cause death	2.30	1.77–2.98	<0.01	2.55	1.65–3.93	<0.01
Stroke	3.16	2.31–4.33	<0.01	2.79	1.50–5.16	<0.01
MI	2.61	1.90–3.59	<0.01	2.54	1.40–4.60	<0.01
Emergent coronary revascularization	3.58	2.46–5.22	<0.01	4.37	1.94–9.86	<0.01
TyG index as a categorical variable[c]						
MACCE	3.69	2.80–4.84	<0.01	3.01	2.16–4.21	<0.01
All-cause death	3.35	2.26–4.95	<0.01	2.99	1.81–4.95	<0.01
Stroke	9.15	4.78–17.50	<0.01	6.14	2.86–13.15	<0.01
MI	6.40	3.53–11.62	<0.01	7.38	3.36–16.18	<0.01
Emergent coronary revascularization	13.99	5.48–35.74	<0.01	10.10	3.26–31.27	<0.01

a. The variable factors included in the multifactor analysis are the same as in Model 4; b. The HR was assessed with each 1-unit increase in the TyG index; c. The HR was examined with the low TyG index group as the reference. TyG, triglyceride-glucose; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction.

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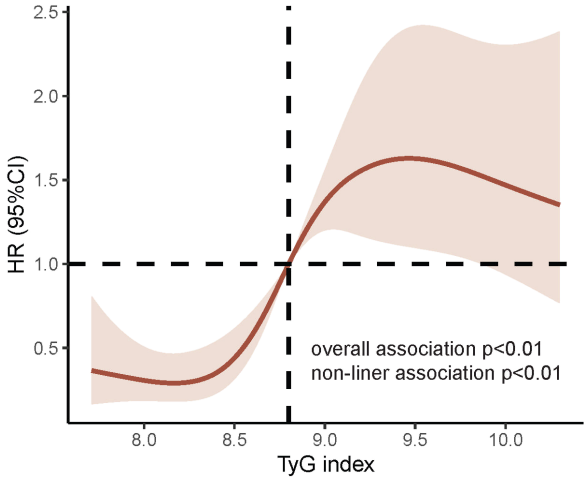

FIGURE 4
RCS curves for TyG index associated with MACCE. *P* value for nonlinear association<0.01; *P* value for overall association<0.01; the red line represents the references for HR, and the pink area indicates the 95% CI. RCS analysis was adjusted according to Model 4. RCS, Restricted cubic splines; TyG, triglyceride-glucose; MACCE, major adverse cardiovascular and cerebrovascular event; MI, myocardial infarction.

Depression also leads to disorders of lipid metabolism. Existing evidence suggests that high TC and LDL levels are closely associated with depressive symptoms, as well as severity and the expected course of depression (37). Similarly, depression can contribute to dyslipidemia and MetS, thereby affecting the development of CVD (38). In addition, depression can also induce an increase in platelet reactivity and secretion through the platelet-serotonin pathway and platelet adenosine response (39, 40). This further increases the susceptibility of patients with depression to acute thrombotic events and ischemic heart disease as well as the risk of mortality after MI (38). It can be seen that depression can make patients with cardiovascular disease more vulnerable, have a worse prognosis and a higher risk of cardiovascular events through a variety of ways (33).

The TyG index, a marker of IR, is strongly associated with not only the risk of adverse events in CHD but also depression. Individuals with higher TyG index are significantly more likely to experience depressive symptoms (21), and elevated IR and TyG index exacerbate depression and reduce the efficacy of antidepressant therapies (41, 42). On the other hand, depression can also lead to the aggravation of IR severity and the increase of TyG index (41) and TyG index (43). The specific mechanisms underlying this association may be related to altered dopamine signaling, 5-hydroxytryptaminergic transmission, the HPA axis, neurogenesis, neuroinflammation, opioid-mediated pathways, gut microbiome, and gut-brain signaling (41).

More importantly, IR, as characterized by the TyG index, can have a serious negative impact on the outcome of CHD comorbid with depression. Severe IR induces imbalances in glucose and lipid metabolism and elevates the TyG index while exacerbating the inflammatory response in the body (14, 44, 45); this further damages the already fragile vascular endothelium of this special population and induces atherosclerosis, as well as progression and rupture of coronary plaques (44). Additionally, it induces alterations in the fibrinolytic system and disrupts the balance of coagulation, leading to thrombosis (46). Persistent IR increases sympathetic nervous system activity, leading to blood pressure fluctuations and retention of water and sodium, thereby increasing cardiac load (47). It can also further affect the prognosis of patients with CHD complicated with depression by inducing high glycosylation to promote myocardial fibrosis (48). Our study confirmed that TyG, as a marker of IR, is an independent risk factor for MACCE in patients with CHD complicated with depression, especially when the TyG score is >8.80. Special attention should be paid to such patients in clinical practice.

Adopting a healthy lifestyle and diet is beneficial for improving IR, reducing the TyG index score, and promoting recovery of psychological health in patients with depression (49). Studies have demonstrated that exercise (50), vitamin supplementation, healthy diet, sun exposure, and sleep hygiene can effectively improve IR and depression (51). Therefore, a healthy lifestyle and diet are particularly important for patients with concomitant CHD and depression. Furthermore, this specific patient group should be regularly tested for blood glucose and lipids levels (52), for timely detection of changes in TyG levels, allowing for early interventions to prevent the occurrence of adverse events.

This study had some limitations. First, this is a single-center, retrospective, cohort study from China, which may have some external validity issues due to differences in culture, population, region, and healthcare system. Second, the TyG index included in this study was derived from a single calculation and failed to be studied with dynamically changing TyG index data. Third, the degree of patient depression was not accurately captured in this retrospective study, and future studies could further stratify patients with different levels of depression. Nevertheless, this study has clinical value as the first study to evaluate the prognostic factors of the TyG index in patients with CHD complicated with depression.

Conclusions

TyG index is highly correlated with the risk of MACCE in patients with CHD complicated with depression and may be a predictor of MACCE in this high-risk group, playing an important role in risk stratification and clinical management. The TyG index has an important prognostic value for patients with CHD complicated with depression. In the future, more in-depth prospective clinical studies can be conducted to further clarify the impact of the TyG index on endpoint events in this special population.

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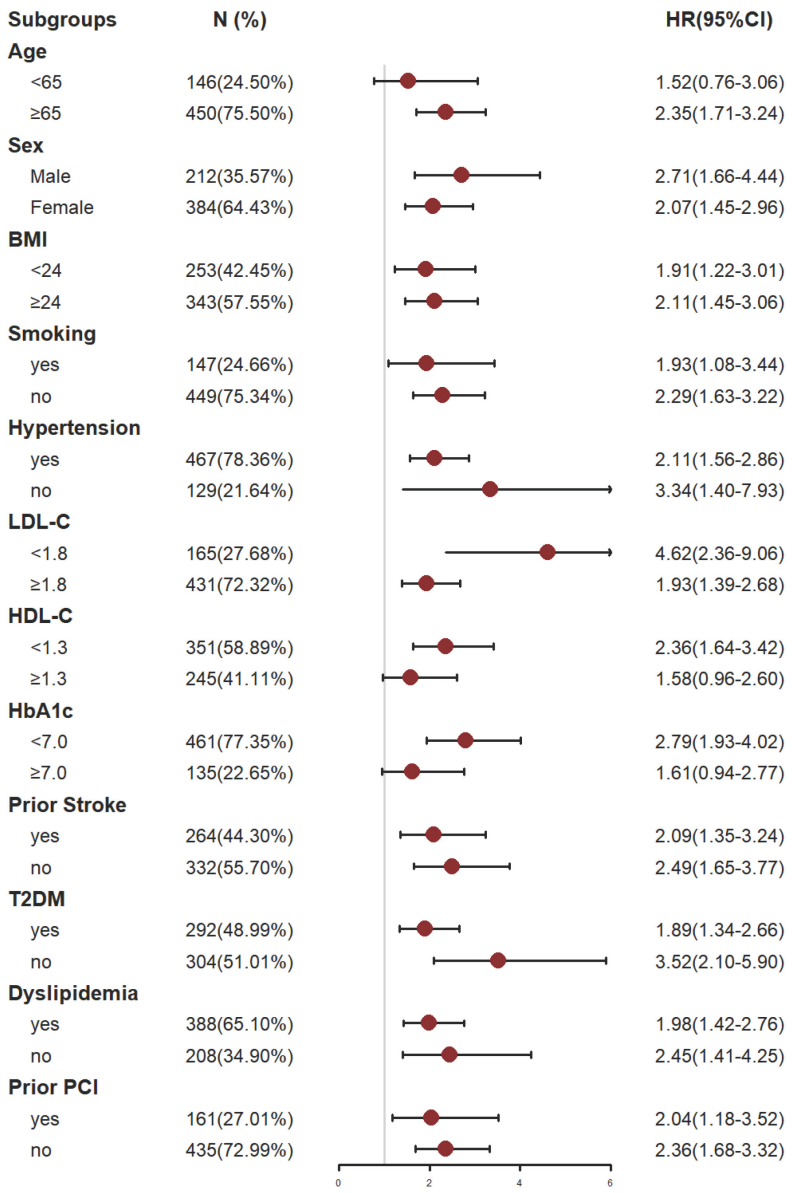

FIGURE 5
Subgroup analysis of the effect of the TyG index on MACCE. The gray vertical line represents an HR of 1. Subgroup analysis using Model 4. BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1C, glycosylated hemoglobin A1c; T2DM, type 2 diabetes mellitus; PCI, percutaneous coronary intervention.

TABLE 6 Incremental effect of TyG index and its components for predicting MACCE.

	NRI	95%CI	*P* value	IDI	95%CI	*P* value	C-Index	95%CI	*P* value
Baseline risk model	REF			REF			0.672	0.640–0.705	<0.01
+TG	0.006	0–0.022	<0.01	0.069	-0.027–0.168	0.545	0.677	0.645–0.709	<0.01
+FBG	0.007	0–0.018	0.182	0.075	0.005–0.149	<0.01	0.687	0.655–0.719	<0.01
+TyG index	0.028	0.001–0.049	<0.01	0.145	0.011–0.193	<0.01	0.698	0.667–0.729	<0.01

NRI, net reclassification improvement; IDI, integrated discrimination improvement; TG, triglyceride; FBG, fasting blood; TyG, triglyceride-glucose.

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 humans were approved by Clinical Research Ethics Committee of the Dongfang Hospital of Beijing University of Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this is a retrospective study. The data of all patients have been anonymous, so the written informed consent was waived.

Author contributions

WZ: Data curation, Formal analysis, Project administration, Writing – original draft, Conceptualization. JW: Data curation, Investigation, Writing – review & editing. DC: Formal analysis, Methodology, Writing – review & editing, Conceptualization. WD: Validation, Writing – review & editing. JH: Resources, Supervision, Writing – review & editing. YG: Investigation, Writing – review & editing. YL: Validation, Visualization, Writing – review & editing. RL: Investigation, Writing – review & editing. XL: Writing – review & editing, Project administration. ZS: Supervision, Writing – review & editing. HZ: Funding acquisition, Project administration, Resources, Writing – review & editing.

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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/fendo.2024.1416530/full#supplementary-material

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Association between ankle-brachial blood pressure index and erectile dysfunction in US adults: a large population-based cross-sectional study

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Background: Erectile dysfunction (ED) is a very common condition among adult men and its prevalence increases with age. The ankle-brachial blood pressure index (ABPI) is a noninvasive tool used to assess peripheral vascular disease (PAD) and vascular stiffness. However, the association between ABPI and ED is unclear. We aimed to explore the association between ABPI and ED in the US population.

Methods: Our study used data from two separate National Health and Nutrition Examination Survey (NHANES) datasets (2001-2002 and 2003-2004). Survey-weighted logistic regression models were used to explore the association between ABPI as a continuous variable and quartiles with ED. We further assessed the association between ABPI and ED using restricted cubic regression while selecting ABPI thresholds using two-piecewise Cox regression models. In addition, we performed subgroup analyses stratified by BMI, race, marital status, diabetes, and hypertension.

Main outcome measure: ABPI was calculated by dividing the mean systolic blood pressure at the ankle by the mean systolic blood pressure at the arm.

Results: Finally, 2089 participants were enrolled in this study, including 750 (35.90%) ED patients and 1339 (64.10%) participants without ED. After adjusting for all confounding covariates, logistic regression analyses showed a significant association between ABPI and ED (OR=0.19; 95% CI, 0.06-0.56, P=0.01); with ABPI as a categorical variable, compared with the lowest quartile, the OR and 95% CI for the second quartile were 0.58 (0.34-0.97; P = 0.04).Besides, splines indicated that there was an L-shaped relationship between ABPI levels and the risk of ED. Piecewise Cox regression demonstrated the inflection point at 1.14,

below which the OR for ED was 0.06 (0.02-0.20; P < 0.001), and above which the OR was 2.79 (0.17-4.53; P = 0.469).

Conclusion: In our study, lower ABPI was independently associated with ED risk. In addition, the lowest ABPI level associated with ED risk was 1.14, below this level, lower ABPI was associated with higher ED risk.

KEYWORDS

ankle-brachial blood pressure index, erectile dysfunction, peripheral vascular disease, national health and nutrition examination survey, logistic regression

Introduction

Erectile dysfunction (ED) is defined as the inability to attain or maintain a penile erection sufficient for successful vaginal intercourse (1). As a common condition, ED is prevalent in men over 40 years of age (2), and about half of men over 40 years of age are likely to have ED (3). The prevalence of ED increases gradually with age and will reach 50%-100% in men older than 70 years (4). In addition, the global prevalence of ED is estimated to reach 322 million by the year 2025 (5, 6). ED is a multifactorial disorder that can be divided into three specific categories, namely psychogenic, organic, and a mixture of both (2).

The close association between ED and cardiovascular disease (CVD) is well known (7). A number of studies have confirmed the existence of shared risk factors for ED and CVD, such as obesity, diabetes, metabolic syndrome, dyslipidemia, smoking, and sedentary lifestyle (8–10). It is widely accepted that ED is an early manifestation of CVD (11–13).

The ankle-brachial blood pressure index (ABPI) is a noninvasive tool used to assess peripheral vascular disease (PAD) and vascular stiffness (14), obtained by comparing the highest systolic blood pressure in the tibial artery with that in the brachial artery. An ABPI of < 0.9 is diagnostic of PAD (15), whereas an ABPI of > 1.3 is a reliable marker of arterial stiffness (16). First, patients with PAD are at higher risk for coronary heart disease and stroke (17), and are predictors of future cardiovascular events and mortality (18, 19). Second, arterial stiffness refers to the accumulation of plaque within the arteries, resulting in narrowing and hardening of the arteries (20), affecting multiple organs, including the brain, heart, kidneys, and lower limbs (21). Given the relationship between ED and CVD, there may be an association between ABPI and ED. In 2009, a study reported that ED was associated with PAD determined by screening ABPI testing (22). To date, no studies have explored the relationship between the overall range of ABPI and ED. However, a recent study found that the cardio-ankle vascular index of patients with ED was higher than that of healthy individuals, with no significant difference in ABPI between the two groups (23).

Is there really a correlation between ABPI and ED? Here, we conducted this study to further explore the specific association between the overall range of ABPI and ED through nationally representative data from the 2001-2004 National Health and Nutrition Examination Survey (NHANES) to provide more valuable evidence.

Methods

Participants

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional, stratified, multi-stage probability subgroup survey performed annually by the Centers for Disease Control and Prevention (CDC) that yields representative data (24). NHANES is used to obtain health and diet information of unstructured populations in the U.S (25). Additional details about the database have been previously reported (26). The participants in our study were collected using the NHANES database. The NHANES database is approved by the National Center for Health Statistics (NCHS) Research Ethics Review Committee, and all NHANES procedures are performed in compliance with the U.S. Department of Health and Human Services (HHS) Human Research Subjects Protection Policy. All participants provided written informed consent prior to the start of the study.

Our study used data from two separate NHANES datasets (2001-2002 and 2003-2004) because data on ED questionnaire information was only available for these years. During these two cycles, NHANES employed rigorous and standardized data collection methods to ensure consistency and reliability across different survey cycles. Therefore, the methods for measuring ABPI and the questionnaires for assessing ED were standardized, ensuring consistency between the cycles. From 2001 to 2004, a total of 4116 males had self-reported ED information in the NHANES database. Exclusion criteria were as follows: 1. unknown ABPI information (n=1854); 2. unknown educational status (n=2); 3. unknown family income information (n=124); 4. unknown body mass index (BMI) (n=23); 5. unknown marital information (n=2); 6. unknown smoking and alcohol use (n=3); 7. unknown hypertension, diabetes mellitus and CVD status (n=19). The specific process of participant selection is shown in Figure 1.

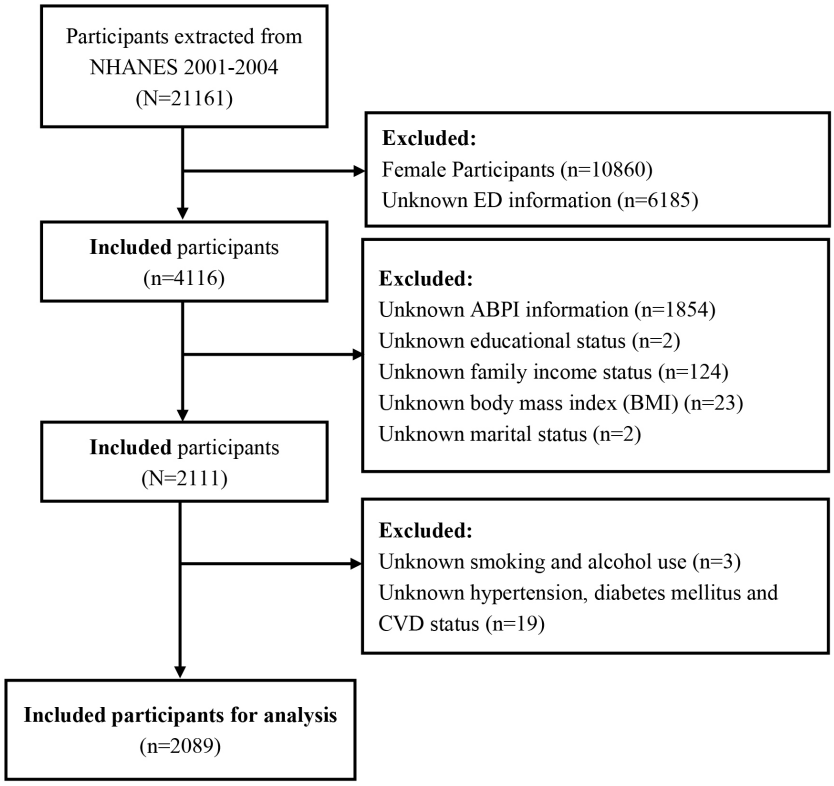

FIGURE 1
Flow chart of the study population identification from NHANES 2001 -2004.

Assessment of ED

Erectile function was assessed by the following questions from the Massachusetts Male Aging Study (MMAS) (27): "How would you characterize your ability to develop and maintain an erection adequate for satisfying sexual intercourse? " For this question, the following options are available: "never have the ability to maintain an erection," "sometimes able to develop and maintain an erection," "usually able to develop and maintain an erection," "almost often or almost always able to develop and maintain an erection." In this study, the responses "usually" and "almost often or almost always" were defined as normal erectile function, while the other two responses were defined as ED (28, 29). Moreover, the validity of the self-reported diagnostic approach to ED has been validated (30).

Ankle-brachial blood pressure index

Blood pressure measurements were taken by trained health technicians at the mobile medical examination centers. Systolic blood pressure was measured in both arms (brachial artery) and both ankles (posterior tibial artery) of supine subjects using an automated instrument. systolic blood pressure was measured twice at each site in participants aged 40-59 years, and once at each site in participants aged 60 years or older. the ABPI was calculated by dividing the mean systolic blood pressure in the ankles by the mean systolic blood pressure in the arms (Parks Mini-Laboratory IV, Model 3100). ABPI was calculated by dividing the mean systolic blood pressure at the ankle by the mean systolic blood pressure at the arm (Parks Mini-Laboratory IV, Model 3100).

Covariates

Confounding factors include basic characteristics: age (years), BMI, race, educational level, marital status (married or living with partner, living alone), poverty to income ratio (PIR, classified as <1.5, 1.5-3.5, and >3.5) (31). Alcohol use was categorized as (1) never alcohol use (<12 lifetime drinks); (2) former alcohol use (≥12 drinks in 1 year and no drinks in the last year, or no drinks in the last year but ≥12 lifetime drinks); (3) mild alcohol use (<2 drinks per day); (4) moderate alcohol use (≥2 drinks per day); (5) heavy alcohol use (≥3 drinks per day). The definition of smoking is when an individual smokes more than 100 cigarettes in their lifetime.

History of CVD was defined as previous coronary artery disease, angina pectoris, or heart attack; diabetes was defined as self-reported prior diagnosis of diabetes or fasting plasma glucose ≥126 mg/dL; and hypertension included systolic blood pressure ≥140 or diastolic blood pressure ≥90, or being on antihypertensive medication, or having been diagnosed with hypertension.

Statistical methods

We performed statistical analyses using survey-weighted techniques to account for the complex sampling design of the NHANES datasets (2001-2002 and 2003-2004). By dividing the 2-year weights for each cycle by 2, we derive the new sample weights for the combined survey cycle. We used the mean ± standard error ($\bar{x}$ ± SE) to describe the continuous variables, whereas categorical variables were expressed as percentage (%) ± SE. We used survey-weighted chi-square tests (for categorical variables) and survey-weighted linear regression (for continuous variables) to analyze the differences between the two groups. Weighted multivariate logistic regression models were used to explore the relationship between ABPI and ED. Three models were developed to assess the relationship between ABPI and ED: Crude model: no covariates were adjusted; Adjusted model 1: age, race, education, marital status, and PIR were adjusted; Adjusted model 2: Model 1+ BMI, alcohol intake, smoking, diabetes, CVD, and hypertension were adjusted. The strength of the correlation of the multivariate model was estimated using the ratio of ratios (OR) and 95% CI.

ABPI was converted from a continuous variable to a categorical variable based on quartiles (Q) for additional analysis. We further assessed the association between ABPI and ED using restricted cubic regression while selecting ABPI thresholds using two-piecewise Cox regression models. In addition, we performed subgroup analyses stratified by BMI, race, marital status, diabetes, and hypertension. Sensitivity analyses were conducted to verify the robustness of the findings by redefining ED using more stringent criteria. We used Empower software (www.empowerstats.com) as well as R version 4.0.2 (http://www.R-project.org, The R Foundation) to perform all statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Comparison of clinical characteristics of participants with and without ED

Finally, 2089 participants were enrolled in this study, including 750 (35.90%) ED patients and 1339 (64.10%) participants without ED. Table 1 shows the weighted distribution of baseline characteristics of the included population stratified by ED status. ABPI was significantly lower in the ED group (1.12 ± 0.01) than in the non-ED group (1.16 ± 0.00) (P<0.01). Non-ED participants (51.16 ± 0.28 years) were significantly younger than ED patients

TABLE 1 Baseline characteristics of study participants in NHANES 2001–2004, weighted.

Characteristics		History of erectile dysfunction (ED)		P-value
	Overall	No	Yes	
Number (n)	2089	1339	750	
ABPI	1.15(0.00)	1.16(0.00)	1.12(0.01)	<0.001
Age, years	54.44(0.28)	51.16(0.28)	63.60(0.47)	<0.001
Age, %				**<0.001**
<50	40.63(0.02)	51.06(2.00)	11.49(1.66)	
≥50	59.37(0.04)	48.94(2.00)	88.51(1.66)	
BMI, kg/m^2	28.47(0.16)	28.27(0.21)	29.05(0.27)	0.0436
BMI, %				**0.1573**
BMI ≤ 25	23.02(0.02)	23.43(1.91)	21.84(1.74)	
25<BMI<30	45.07(0.03)	46.21(1.44)	41.90(2.06)	
BMI≥30	31.91(0.02)	30.36(1.86)	36.26(2.51)	
Race, %				**0.268**
Mexican American	4.67(0.01)	4.88(0.78)	4.08(1.36)	
Other Hispanic	3.78(0.01)	3.35(0.88)	5.00(1.81)	
Non-Hispanic White	80.39(0.06)	80.13(1.92)	81.11(2.52)	
Non-Hispanic Black	8.51(0.01)	8.75(0.89)	7.86(1.13)	
Other races	2.65(0.01)	2.90(0.74)	1.94(0.49)	
Educational level, %				**<0.001**
Below high school	14.65(0.01)	11.36(1.03)	23.82(2.45)	

(Continued)

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TABLE 1 Continued

Characteristics		History of erectile dysfunction (ED)		P-value
	Overall	No	Yes	
Educational level, %				<0.001
High school	25.90(0.02)	26.92(1.25)	23.04(2.01)	
Above high school	59.46(0.03)	61.72(1.58)	53.14(2.55)	
Marital status, %				0.4258
Married or living with a partner	79.64(0.05)	79.19(1.52)	80.90(1.56)	
Living alone	20.36(0.01)	20.81(1.52)	19.10(1.56)	
PIR, %				<0.001
PIR<1.3	13.20(0.01)	12.17(0.99)	16.06(1.92)	
1.3≤PIR<3.5	31.64(0.02)	28.80(1.59)	39.59(2.50)	
PIR≥3.5	55.16(0.03)	59.03(1.95)	44.35(2.87)	
Alcohol intake, %				<0.001
Never	6.02(0.01)	5.82(1.18)	6.58(1.22)	
Former	21.94(0.02)	19.11(1.77)	29.83(2.44)	
Mild	43.90(0.03)	43.60(2.37)	44.72(2.25)	
Moderate	10.22(0.01)	11.53(1.18)	6.56(1.44)	
Heavy	17.92(0.01)	19.93(1.65)	12.31(1.88)	
Smoking, %				0.0805
No	76.45(0.04)	75.39(1.18)	79.43(2.08)	
Yes	23.55(0.02)	24.61(1.18)	20.57(2.08)	
History of diabetes, %				<0.001
No	86.00(0.04)	90.93(0.78)	72.22(1.55)	
Yes	14.00(0.01)	9.07(0.78)	27.78(1.55)	
History of CVD, %				<0.001
No	92.65(0.04)	95.42(0.59)	84.90(1.73)	
Yes	7.35(0.01)	4.58(0.59)	15.10(1.73)	
History of hypertension, %				<0.001
No	56.39(0.03)	62.53(2.19)	39.25(1.87)	
Yes	43.61(0.03)	37.47(2.19)	60.75(1.87)	

ED, erectile dysfunction; ABPI, ankle-brachial blood pressure index; BMI, body mass index; PIR, poverty income ratio; CVD, cardiovascular disease.

(63.60 ± 0.47) (p<0.001). Statistically significant differences in education level, PIR, and alcohol intake were found between the ED and non-ED groups (P < 0.05), and the prevalence of diabetes, CVD, and hypertension was higher in the ED group (P < 0.001).

Association between ABPI and ED

Table 2 showed the association of ABPI as a continuous variable and quartiles with ED. In fully adjusted Model 2, survey-weighted logistic regression analyses showed a significant association between ABPI and ED (OR=0.19; 95% CI, 0.06-0.56, P=0.01). Similarly, with ABPI as a categorical variable, compared with the lowest quartile, the OR and 95% CI for the second quartile were 0.45 (0.30-0.69; P < 0.001) in the crude model, 0.52 (0.33-0.82, P=0.01) in the partially adjusted Model 1, and 0.58 (0.34-0.97; P = 0.04) in the fully adjusted Model 2.

Restrictive cubic spline regression was employed to explore the dose-response relationship between ABPI and ED. The results indicated that there was an L-shaped relationship between ABPI levels and the risk of ED: as ABPI levels decreased, the risk of ED increased (Figure 2). Piecewise Cox regression (Table 3) demonstrated the inflection point at 1.14, below which the OR for ED was 0.06 (0.02-0.20; P < 0.001), and above which the OR was

TABLE 2 Weighted multivariable logistic regression for the association between ABPI and ED prevalence.

Exposure	Crude Model		Adjusted Model 1		Adjusted Model 2	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
ABPI (Continuous)	0.06(0.02,0.14)	<0.001	0.14(0.05, 0.36)	<0.001	0.19(0.06,0.56)	0.01
ABPI (Quartile)						
Q1	Ref		Ref		Ref	
Q2	0.45(0.30,0.69)	<0.001	0.52(0.33, 0.82)	0.01	**0.58(0.34,0.97)**	**0.04**
Q3	0.50(0.39,0.63)	<0.001	0.65(0.49, 0.87)	0.01	0.74(0.52,1.07)	0.10
Q4	0.47(0.31,0.70)	<0.001	0.56(0.34, 0.93)	0.03	0.62(0.34,1.12)	0.10
P for trend	0.001		0.056		0.214	

ABPI, ankle-brachial blood pressure index; ED, Erectile dysfunction; OR, odds ratio; CI, confidence interval; Q1-Q4, Quartile 1to 4; BMI, body mass index; PIR, poverty income ratio; CVD, cardiovascular disease.
Crude Model: no covariates were adjusted.
Model 1: age, race, education, marital status, and PIR were adjusted.
Model 2: Model 1+ BMI, alcohol intake, smoking, diabetes, CVD, and hypertension were adjusted.
The bold values provided indicate that the ABPI as quartiles in the fully adjusted model is meaningful only at Q2.

2.79 (0.17-4.53; P = 0.469). The study suggested that when ABPI< 1.14, ABPI was negatively correlated with the risk of ED.

Subgroups and sensitivity analysis

Subgroup analyses were used to explore the interaction between ABPI and ED. Figure 3 shows the results of the analysis of ABPI as a continuous variable, showing a significant association between ABPI and ED in the subgroups of BMI 25-30 (OR=0.13, 95%CI, 0.04-0.51), non-Hispanic whites (OR=0.15, 95%CI, 0.04-0.56), married or living with a partner (OR=0.18, 95%CI, 0.06-0.55), PIR ≥3.5 (OR=0.06, 95% CI, 0.01-0.35), hypertension-positive (OR=0.15, 95%CI, 0.04-0.59), and diabetes-negative (OR=0.17, 95%CI, 0.05-0.51). Table 4 presented the results of the analysis of ABPI as quartiles, showing that the risk of ED at ABPI levels in Q2 was lower than in Q1 in the subgroups of married or living with a partner (OR=0.53, 95%CI, 0.31-0.92), PIR ≥3.5 (OR=0.42, 95%CI, 0.22-0.79), and diabetes-negative (OR=0.55, 95% CI, 0.33-0.92). There was no interaction between subgroup analyses whether ABPI was used as a continuous variable or quartiles (P for all interaction > 0.05).

The results of the sensitivity analysis were generally consistent with the results of the main analysis (Supplementary Table 1). In the sensitivity analyses, we defined as ED participants who answered "never been able to get and keep an erection" to the question assessing erection, which used more stringent criteria. The results showed that there was a significant association between ABPI and ED prevalence in the fully adjusted Model 2 (Continuous variable, OR= 0.14; 95% CI, 0.05,0.42, P=0.003; Quartiles, Q2 vs Q1: OR= 0.68; 95% CI, 0.48-0.96, P=0.03).

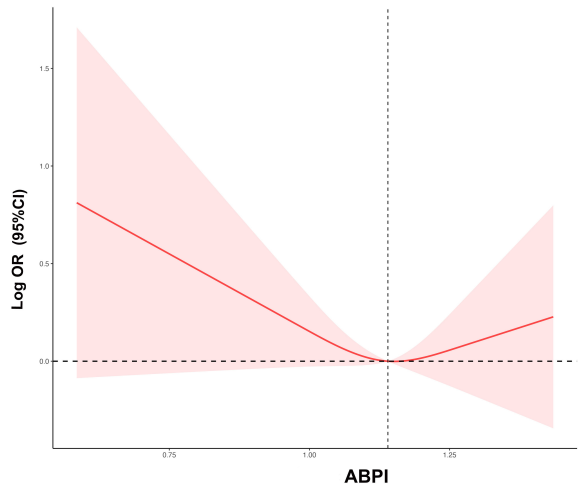

FIGURE 2
The restricted cubic regression between ABPI with ED.
ABPI, ankle-brachial blood pressure index; ED, erectile dysfunction; OR, odds ratio; CI, confidence interval.

Discussion

This study found that the second quartile was associated with a low risk of ed in men over 40 years of age. In addition, the relationship between ABPI and ED showed an L-shaped curve, with an ABPI value of 1.14 associated with the lowest ED risk, and an ABI value below 1.14

TABLE 3 Threshold Effect Analysis of Association of ABPI with ED Using Piecewise Cox Regression Models.

Outcome	OR (95%CI)	P value
Fitting model by two-piecewise linear regression Inflection point		
<1.14	0.06 (0.02,0.20)	<0.001
≥1.14	2.79 (0.17,4.53)	0.469
P for log likelihood ratio test		0.027

ABPI, ankle-brachial blood pressure index; ED, Erectile dysfunction; OR, odds ratio; CI, confidence interval.
Adjusted Model 2: Model 1+ BMI, alcohol intake, smoking, diabetes, CVD, and hypertension were adjusted.

increasing ED risk. Sensitivity analyses were consistent with the primary analysis, further determining the stability of the results. Our study is the first to assess the specific association between the overall range of the ABPI and ED through nationally representative data.

Previous studies have shown an association between lower ABPI and increased risk of malnutrition (32), diabetes (33) and CVD (34). An ABPI of < 0.9 is diagnostic of PAD (15), it is now generally accepted that an ABPI <0.9 in patients with chronic kidney disease (CKD) (35), diabetes (36), and cardio-cerebrovascular disease (37) predicts an increased risk of death. PAD is an independent predictor of mortality and morbidity due to the fact that it is usually accompanied by other atherosclerotic diseases (18, 19). In addition, a high value of ABPI > 1.3 indicates incompressible vascular calcification, reflecting arterial stiffness, which is associated with an increased risk of cardiovascular morbidity and mortality (38). Two recent NAHENS studies found that the lowest ABPI quartile in the normal range was associated with the highest risk of all-cause mortality and cardiocerebrovascular mortality, while higher ABPI were not significant (39, 40). However, there is little study on the relationship between ED and ABPI. In 2009, a study reported that ED was associated with PAD determined by screening ABPI testing (22). Consistent with that report, our findings also showed that the lowest ABI quartile was associated with risk of ED. However, a recent study found that the cardio-ankle vascular index of patients with ED was higher than that of healthy individuals, with no significant difference in ABPI between the two groups (23). The inconsistency in the findings could be attributed to the relatively small sample size of Bulbul's study (74 ED patients, 86 healthy controls), as well as differences in the inclusion and exclusion criteria. They excluded complications such as diabetes, hypertension, CVD, and PAD with ABPI < 0.9.

However, the association between ABPI and ED yields conflicting results. This study found no significant association between ABPI higher than 1.14 and the risk of ED. ABPI exhibits an L-shaped curve relationship with ED, possibly explained by certain atherogenic mediators and inflammatory cytokines, including high-sensitivity C-reactive protein, pentraxin 3, and soluble myeloid cell expression triggering receptor-1, which decrease with increasing ABPI (41). Additionally, high ABPI is often associated with arterial calcification (42, 43) and vascular stiffness (44), counteracting protective effects. The results of the subgroup analyses indicated a lower risk of ED at the Q2 level of ABPI compared with Q1. These subgroups included patients who were married or living with a partner, had a PIR ≥3.5, and were diabetes- negative. This can be explained as follows: Marriage or a stable partnership positively influences men's overall health and lifestyle, thereby improving their vascular health and erectile function; higher socioeconomic status is associated with better access to health resources, healthier lifestyles, and higher quality medical care; and in the absence of diabetes, maintaining good vascular health is crucial for preventing ED.

Subgroup	Adjusted OR (95% CI)	P value	P for interaction
BMI			0.15
>=30	0.35 (0.06, 2.16)	0.23	
<25	0.08 (0.01, 1.12)	0.06	
25-30	0.13 (0.04, 0.51)	0.01	
Race			0.83
Non-hispanic white	0.15 (0.04, 0.56)	0.01	
Mexican american	0.06 (0.02, 1.41)	0.08	
Non-hispanic black	0.22 (0.02, 2.62)	0.19	
Other hispanic	1.60 (0.04, 2.75)	0.91	
Other race	2.93 (0.05, 5.36)	0.47	
Marital status			0.79
Married or living with a partner	0.18 (0.06, 0.55)	0.01	
Living alone	0.13 (0.01, 1.85)	0.12	
PIR			0.07
>=3.5	0.06 (0.01, 0.35)	0.01	
1.3-3.5	0.24 (0.03, 1.71)	0.14	
<1.3	2.37 (0.18, 3.46)	0.46	
Hypertension			0.78
No	0.28 (0.03, 2.85)	0.25	
Yes	0.15 (0.04, 0.59)	0.01	
Diabetes			0.32
No	0.17 (0.05, 0.51)	0.01	
Yes	0.20 (0.02, 1.91)	0.14	

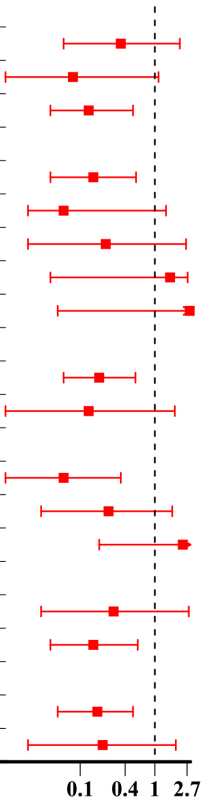

FIGURE 3
Subgroup analyses of the association between ABPI as a continuous variable and ED. ABPI, ankle-brachial blood pressure index; ED, Erectile dysfunction; OR, odds ratio, CI, confidence interval; BMI, body mass index; PIR, poverty income ratio.

As mentioned above, lower ABPI is associated with a variety of vascular diseases and may predict atherosclerosis (18, 19, 33, 34). The relationship between ED and atherosclerotic vascular disease is closely intertwined, which may also explain the association between lower ABPI and ED risk. Nitric oxide (NO) can mediate various anti-atherosclerotic properties, including effects on inflammation, platelet aggregation, and smooth muscle proliferation, and impaired NO levels are an early finding in atherosclerosis (45). Normal erectile function is particularly sensitive to reduce NO, and ED may be an early clinical manifestation of underlying vascular disease and NO deficiency (46). Additionally, penile arteries are relatively small, and with the progression of occlusive diseases, clinical manifestations may occur earlier in the penile vascular bed than in other vascular beds (47). In summary, lower ABPI predicts a possible risk of atherosclerotic lesions in the lower limb arteries, and ED symptoms may already be present at this stage. As Polonsky et al. suggest, ED may serve as an independent predictor of occult PAD identified through prospective ABPI testing (22). In addition, chronic inflammation is a common underlying pathology in both PAD and ED. Inflammatory cytokines such as C-reactive protein (CRP) and interleukins are elevated in patients with atherosclerosis and endothelial dysfunction. These inflammatory mediators contribute to the progression of vascular disease and directly affect erectile function by inducing vascular damage and impairing smooth muscle relaxation (45). The neurovascular interplay is crucial for erectile function. In conditions with compromised ABPI, there is often concurrent neurovascular dysfunction. The impaired neural regulation of blood flow, combined with vascular insufficiency, disrupts the normal erectile process (22, 47).

The present study has some limitations. First, this study was cross-sectional and could not provide a causal relationship between ABPI and ED. Second, due to the limitations of the NAHENS data, we were only able to study men in specific age groups. Third, the cross-sectional nature of our study captures ABPI at a single point in time, which may not fully reflect the dynamic nature of vascular health. As a result, the

TABLE 4 Subgroup analysis of the association between ABPI quartiles and ED (OR and 95%CI).

Subgroup	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend	P for interaction
BMI						0.25
Normal (<25 kg/m^2)	Reference	0.54(0.25, 1.15)	1.07(0.57, 2.03)	0.78(0.34, 1.77)	0.21	
Overweight (25-30 kg/m^2)	Reference	0.55(0.22, 1.37)	0.57(0.25, 1.32)	0.47(0.14, 1.53)	0.12	
Obese (≥30 kg/m^2)	Reference	0.69(0.36, 1.31)	0.73(0.42, 1.25)	0.63(0.34, 1.16)	0.97	
Race						0.33
Non-Hispanic white	Reference	0.53(0.27, 1.04)	0.70(0.44, 1.10)	0.54(0.27, 1.05)	0.14	
Mexican American	Reference	0.84(0.38, 1.89)	0.98(0.38, 2.57)	0.51(0.19, 1.35)	0.24	
Non-Hispanic black	Reference	1.11(0.46, 2.71)	0.85(0.22, 3.32)	0.79(0.25, 2.52)	0.62	
Other Hispanic	Reference	0.50(0.05, 5.16)	0.93(0.08, 10.44)	1.33(0.08, 21.48)	0.84	
Other race	Reference	7.65(7.1, 8.15)	0.02(0.00,0.05)	1.55(1.29,1.86)	0.19	
Marital status						0.52
Married or living with a partner	Reference	0.53(0.31, 0.92)	0.68(0.48, 0.96)	0.61(0.34, 1.09)	0.19	
Living alone	Reference	0.70(0.27, 1.82)	0.92(0.41, 2.04)	0.50(0.17, 1.48)	0.23	
PIR						0.23
PIR≥3.5	Reference	0.42(0.22, 0.79)	0.60(0.34, 1.06)	0.41(0.22, 0.76)	0.06	
1.3≤PIR<3.5	Reference	0.52(0.24, 1.13)	0.65(0.32, 1.31)	0.71(0.29, 1.75)	0.51	
PIR<1.3	Reference	1.63(0.59, 4.47)	2.22(0.75, 6.52)	1.42(0.60, 3.36)	0.26	
Hypertension						0.75
No	Reference	0.57(0.27, 1.22)	0.70(0.38, 1.28)	0.69(0.30, 1.58)	0.55	
Yes	Reference	0.57(0.29, 1.11)	0.86(0.44, 1.66)	0.58(0.28, 1.19)	0.21	
Diabetes						0.62
No	Reference	0.55(0.33, 0.92)	0.72(0.51, 1.03)	0.65(0.38, 1.13)	0.25	
Yes	Reference	0.62(0.25, 1.55)	1.04(0.31, 3.51)	0.47(0.15, 1.49)	0.28	

ABPI, ankle-brachial blood pressure index; ED, Erectile dysfunction; OR, odds ratio; CI, confidence interval; Q1-Q4, Quartile 1to 4; BMI, body mass index; PIR, poverty income ratio; CVD, cardiovascular disease.
Adjusted Model 2: Model 1+ BMI, alcohol intake, smoking, diabetes, CVD, and hypertension were adjusted.

observed associations between ABPI and erectile dysfunction (ED) might be influenced by these temporal variations. Longitudinal studies that track changes in ABPI and ED over time are needed to provide a more comprehensive understanding of the relationship. Additionally, although we adjusted for many confounding factors, there may still be residual confounding factors due to data limitations, such as lifestyle interventions and the use of certain medications (antihypertensives, lipid-lowering drugs, and antidepressants). Finally, while the MMAS questionnaire is a validated tool for assessing erectile function (30), it may have limitations compared to the more widely used International Index of Erectile Function (IIEF). The IIEF provides a more comprehensive assessment of erectile function, including domains such as orgasmic function, sexual desire, and overall satisfaction. The use of MMAS in this study, although validated, may not capture the full spectrum of ED symptoms as effectively as the IIEF.

However, our study could provide more detailed suggestions for future research. Future research should focus on longitudinal studies to establish a causal relationship between ABPI and ED. Tracking changes in ABPI and erectile function over time could provide valuable information on the progression and potential reversibility of vascular contributions to ED. Moreover, detailed mechanistic studies are needed to explore the specific biological pathways linking ABPI with ED. Investigating the roles of endothelial function, NO synthesis, and inflammation in larger, diverse populations could yield critical insights into the underlying mechanisms. Finally, clinical trials examining the impact of interventions targeting vascular health on erectile function are essential. Studies assessing the effects of lifestyle modifications, pharmacological treatments, or surgical interventions on both ABPI and ED outcomes could inform effective management strategies for patients with coexisting vascular diseases and ED.

Conclusion

In our study, lower ABPI was independently associated with ED risk. In addition, the lowest ABPI level associated with ED risk was 1.14, below this level, lower ABPI was associated with higher ED risk. This suggests that clinicians may consider assessing ABPI in individuals with ED and evaluating erectile function in those with lower ABPI levels. Clinicians should consider incorporating ABPI measurements into routine assessments, especially for patients with CVD risk factors. Early detection of vascular impairment can prompt timely interventions to prevent the progression of ED. Additionally, understanding the relationship between ABPI and ED can help in developing personalized treatment plans. Future studies should conduct longitudinal investigations to determine causality, as well as interventional studies to assess whether treatment of peripheral vascular disease improves ED.

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 NHANES database is open to the public and therefore the ethical review of this study was exempt. All participants provided written informed consent prior to the start of the study.

Author contributions

XW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. YZ: Methodology, Software, Supervision, Validation, Writing – review & editing. XZ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Project administration, Resources, Software, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1436043/full#supplementary-material

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Effects of sodium-glucose cotransporter 2 inhibitors on cardiovascular and cerebrovascular diseases: a meta-analysis of controlled clinical trials

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Objective: Evaluate the effects of sodium-glucose cotransporter 2 inhibitor (SGLT2i) on cardiovascular and cerebrovascular diseases.

Methods: Articles of SGLT2i on cardiovascular and cerebrovascular diseases were searched. Two authors independently screened the literature, extracted the data, assessed the quality of the study and performed statistical analyses using Review Manager 5.4.

Results: Random-effect model was used to merge the OR values, and the pooled effect showed that SGLT2i had significant preventive effects on cardiovascular death (OR=0.76, 95%CI 0.64 to 0.89), myocardial infarction (OR=0.90, 95%CI 0.84 to 0.96), heart failure (OR=0.69, 95%CI 0.64 to 0.74) and all-cause mortality (OR=0.65, 95%CI 0.58 to 0.73). Empagliflozin, dapagliflozin and canagliflozin all reduced the incidence of heart failure (OR=0.72, 95%CI 0.64 to 0.82; OR=0.56, 95%CI 0.39 to 0.80; OR=0.62, 95%CI 0.53 to 0.73), but only dapagliflozin displayed a favorable effect on inhibiting stroke (OR=0.78, 95%CI 0.63 to 0.98). SGLT2i could prevent stroke (OR=0.86, 95%CI 0.75 to 0.99), heart failure (OR=0.63, 95%CI 0.56 to 0.70) and all-cause mortality (OR=0.64, 95%CI 0.57 to 0.72) compared to DPP-4i. Furthermore, SGLT2i could reduce the incidence of heart failure (OR=0.72, 95%CI 0.67 to 0.77) and cardiovascular death (OR=0.72, 95%CI 0.54 to 0.95) in patients with high-risk factors.

Conclusions: SGLT2i affects cardiovascular death, myocardial infarction, heart failure and all-cause mortality. Only dapagliflozin displayed a favorable effect on inhibiting stroke. SGLT2i could prevent stroke, heart failure and all-cause mortality compared to DPP-4i. In addition, SGLT2i significantly reduced the development of heart failure and cardiovascular death in patients with high-risk factors.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42024532783.

KEYWORDS

sodium-glucose cotransporter 2 inhibitors, stroke, cardiovascular death, myocardial infarction, heart failure, all-cause mortality

1 Introduction

Diabetes mellitus is a class of metabolic diseases characterized by hyperglycemia. Type 2 diabetes caused by relative insulin deficiency or insulin resistance is prevalent in clinical practice. With the rapid development of the socio-economic conditions, the prevalence of type 2 diabetes has shown an increasing trend with each passing year. According to the study, there will be more than 640 million people with type 2 diabetes in 2024 (1). Hyperglycemia is often associated with disorders of lipid and protein metabolism, which induces and exacerbates oxidative stress and increases the risk of atherosclerotic vascular disease. Patients are highly susceptible to adverse outcomes such as cardiovascular disease, stroke or chronic renal insufficiency if they do not receive effective treatment at an early age (2–5). Cardiopathy and stroke are second only to cancer in terms of death and disability; the hyperglycemic state of the body results in a poor prognosis for cardiovascular disease. Currently, there is a limited range of antihyperglycemic agents (AHAs) available in the clinic and multiple drug loads may have adverse effects on the liver or kidney. So, it is crucial to choose a safe and effective class of glucose-lowering drugs.

Sodium-glucose cotransporter 2 inhibitor (SGLT2i) is a class of prescription drugs approved for the treatment of type 2 diabetes. SGLT2i reduces blood glucose without increasing the risk of hypoglycemia in patients with type 2 diabetes by blocking glucose and sodium reabsorption in renal proximal tubules (6). In addition, the mechanism of promoting urinary sodium excretion and diuresis by SGLT2i may allow it to decrease blood pressure and weight without increasing the heart rate, which has a preventive effect on the progression of atherosclerotic heart disease, heart failure or chronic kidney disease (6–9). Some findings suggested that SGLT2i could reduce the risk of stroke in Asian patients with type 2 diabetes (10); Zhou speculated that this favorable effect may be related to the reduction of atrial fibrillation/atrial flutter by SGLT2i (11). A meta-analysis found that although SGLT2i was more appropriate for type 2 diabetes patients who were at high risk of stroke compared to dipeptidyl peptidase 4 inhibitor (DPP-4i), the results of this study showed that SGLT2i did not reduce the risk of stroke (12). Therefore, we need to confirm the cardiovascular and cerebrovascular effects of SGLT2i in further clinical studies as well as to verify whether the effect is related to diseases or race/ethnicity.

Up to now, several clinical studies have reported the therapeutic effects of SGLT2i on cardiovascular and cerebrovascular diseases (10, 13–60); but the evidence needs to deepen due to the differences in search strategies, interventions, inclusion populations, sample sizes and other factors. In this study, we conducted a meta-analysis of clinical controlled trials on cardiovascular and cerebrovascular diseases with SGLT2i by systematically searching literature at home and abroad.

2 Materials and methods

2.1 Searching progress

We searched of the following databases: PubMed, Cochrane library and Sinomed for clinical controlled trials of SGLT2i on the effects of cardiovascular and cerebrovascular diseases. Reference lists of all eligible articles and related previous review articles were also manually searched. The literature search for this meta-analysis was restricted to published results. Databases were searched from the earliest data to 3 January 2024 with the search terms: ((SGLT2 inhibitors) OR (Sodium-Glucose Transporter 2 Inhibitors) OR (Sodium-glucose cotransporter-2 inhibitors) OR (Dapagliflozin) OR (Canagliflozin) OR (Empagliflozin) OR (Ipragliflozin) OR (Luseogliflozin) OR (Tofogliflozin)) AND ((acute cerebral infarction) OR (acute cerebral stroke) OR (ischemia stroke) OR (cerebral infarction)) AND ((cardiac failure) OR (acute cardiac failure) OR (heart failure) OR (acute heart failure) OR (cardiac insufficiency) OR (congestive cardiac failure) OR (congestive heart failure)) AND ((myocardial infarction) OR (acute myocardial infarction) OR (ST-segment elevation myocardial infarction) OR (ST elevated acute myocardial infarction) OR (non-ST-elevation myocardial infarction) OR (heart attack)).

Eligible studies were screened and selected based on the following criteria: (1) published in English or Chinese language; (2) evaluated the effect of SGLT2i intervention in cardiovascular and cerebrovascular diseases; (3) clinical controlled trial; (4) reported at least one outcome.

2.2 Study selection and data extraction

Two reviewers independently checked all titles and abstracts for studies that could potentially meet the inclusion criteria. We retrieved full reports of these potentially eligible studies for detailed assessment by two reviewers, who then independently extracted information on study design, drug use, study location, characteristics of participants, sample size and relevant outcomes on to a preformatted spreadsheet (10, 13–60). Any uncertainties or discrepancies between the two reviewers were resolved through consensus after rechecking of the source data and consultation with the third reviewer. We also contacted authors if any areas of uncertainty needed clarification.

2.3 Risk of bias in results of included studies

Two reviewers independently assessed the risk of bias in included studies to avoid conflicts of interest of study investigators or funders. Randomized controlled trials (RCTs) were evaluated using the revised version of the Cochrane tool, known as RoB 2. While cohort studies were evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, which is recommended for assessing risk of bias in a non-randomized study of interventions (NRSI) (61, 62). The articles were evaluated separately by two reviewers and disagreements were settled by discussion.

2.4 Statistical analysis

The primary outcomes were the incident rate of stroke, cardiovascular death, myocardial infarction, heart failure or all-cause mortality. The secondary outcomes were the incident rate of ischemic stroke, acute coronary syndrome (ACS) or revascularization. Subgroup analyses were carried out according to differences in interventions and population characteristics. The fixed-model was performed by odds ratio (OR) and 95% confidence intervals (CI) for dichotomous variables. The I^2 was calculated as an index of heterogeneity between studies. If a considerable heterogeneity exists, then the fixed-effects model is replaced by the random-effect model. The analyses were performed by Review Manager 5.4 (Cochrane Collaboration, United Kingdom, http://www.cochrane.org).

3 Results

3.1 Search results and characteristics of included studies

Our research yielded 368 articles in English or Chinese that were potentially relevant to this study. After screening the abstract, 121 articles were selected for full-text review. Of these, 49 articles were eligible and included in this meta-analysis (10, 13–60). Searching progress is shown in Figure 1. Nine of the included studies were RCT (14, 23, 40, 42–45, 48, 60), and the rest 40 trials were cohort studies. Nine trials were multi-center studies (14, 16, 23, 24, 31, 36, 40, 42, 43). Eight studies were published in Chinese (44–49, 59, 60), and the rest were published in English. There are 1270038 patients received SGLT2i treatment (dapagliflozin: 21145 patients (27, 36, 40, 41, 46, 47, 49, 60); empagliflozin: 110227 patients (20, 23, 27, 32, 39, 42, 43); canagliflozin:55950 patients

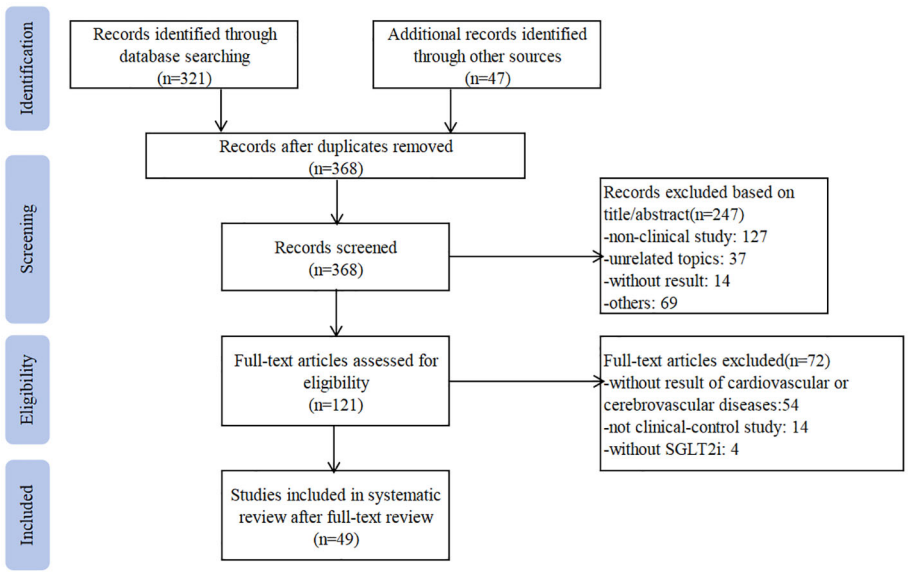

FIGURE 1
Flow chart of the systematic search process.

(33, 44, 45, 48, 59) and 1339802 assigned to the control group (glucagon-like peptide 1 (GLP-1RA): 427963 patients (15, 17, 20, 28, 30, 33–35, 37, 39, 53); DPP-4i: 469049 patients (10, 18, 20–22, 26, 27, 31–33, 36, 50, 53, 55–58). The sample size ranges from 30 to 133139 in the SGLT2i treatment group and the control group. Due to the large sample size and complex population characteristics of this meta-analysis, the exact dosage and frequency of treatment regimens were unclear. Only eleven trials reported the precise time of follow-up, and ranged from 1 month to 2 years (16, 20, 29, 37, 44, 45, 48–50, 56, 60). The detailed characteristics of the included studies are summarized in Supplementary Table 1.

3.2 Risk of bias

In this meta-analysis, only nine trials were RCTs (14, 23, 40, 42–45, 48, 60); one of which was found to be a high-risk trial after evaluating the quality of these studies with RoB 2 tool (45). The details are illustrated in Figure 2. The remaining cohort studies were evaluated in 7 dimensions for risk of bias using the ROBINS-I tool (10, 13, 15–22, 24–39, 41, 46, 47, 49–59). Figure 3 shows that 17 (42.5%) of the 40 papers had a low risk of bias (10, 15, 16, 19, 20, 24, 26, 32, 33, 36, 38, 39, 50, 51, 53, 57, 58), 16 (40%) had a medium risk of bias (13, 17, 18, 25, 27–31, 34, 35, 37, 52, 54–56) and 7 (17.5%) had a high risk of bias (21, 22, 41, 46, 47, 49, 59).

3.3 Main outcome

3.3.1 Incidence of stroke

Of these 49 included studies, 26 studies of SGLT2i with other AHAs reported the rate of incidence of stroke as an outcome (10, 14, 15, 18–24, 27, 30–33, 35–38, 41–43, 50, 56, 57, 59). A fixed-effect model was used for the pooled effect of these studies, which showed a significant heterogeneity (heterozygosity test, $Chi^2 = 76.74$, $P<0.00001$, $I^2 = 67\%$). Then, we used the random-effect model for comparison, which showed that SGLT2i did not reduce the incidence of stroke (OR=0.92, 95%CI 0.83 to 1.01, $P=0.07$) (Figure 4).

3.3.2 Incidence of cardiovascular death

Seventeen studies reported the effect of SGLT2i intervention on cardiovascular death (14, 17, 19, 21, 23, 25–28, 30, 31, 36, 40, 51, 56, 58, 59). Analyses using the fixed-effect model showed enormous heterogeneity (heterozygosity test, $Chi^2 = 95.37$, $P<0.00001$, $I^2 = 83\%$). So, the studies were instead analyzed using random-effect model and the merged OR value of the effect value was 0.76 (95%CI 0.64 to 0.89, $P=0.0007$) (Figure 5). Thus, the SGLT2i treatment group reduced the incidence of cardiovascular death compared to the non-SGLT2i control group.

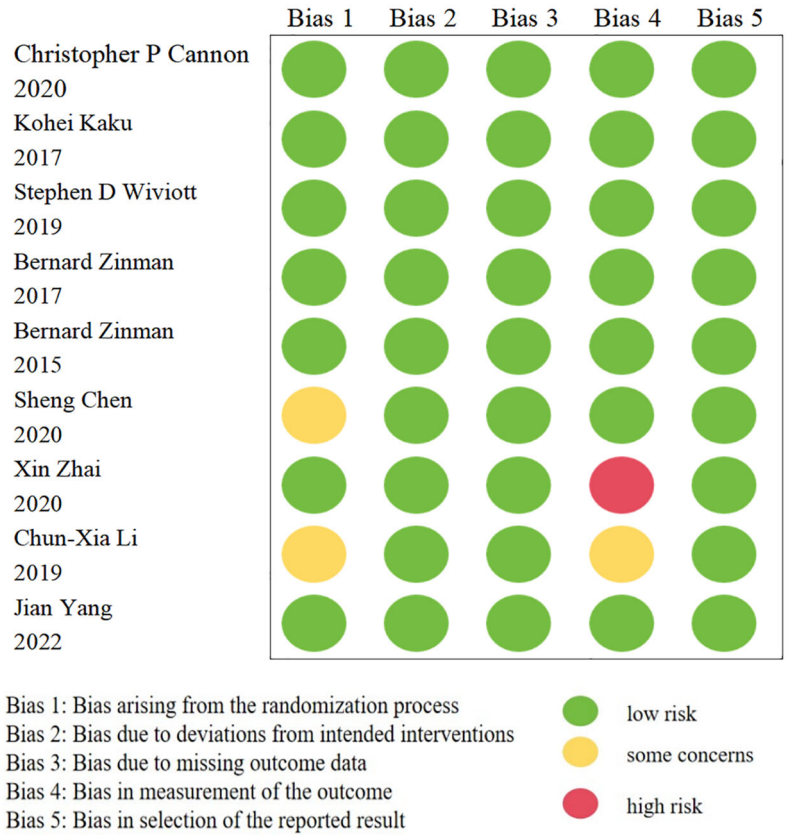

FIGURE 2
Risk of bias in RCTs.

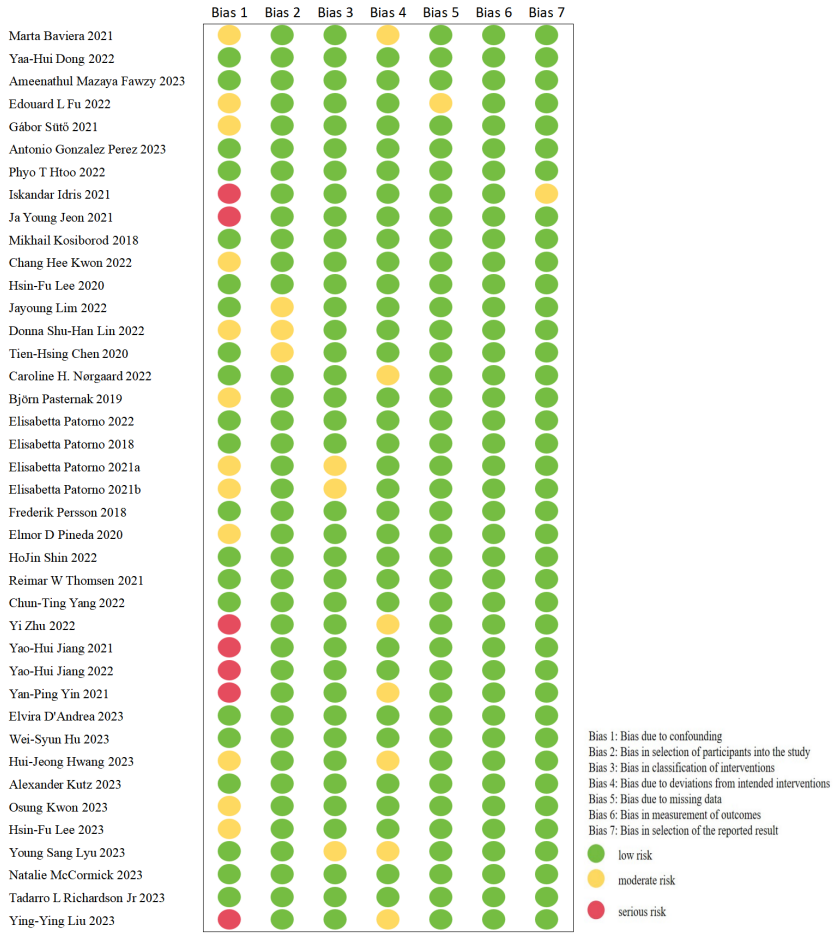

FIGURE 3
Risk of bias in cohort studies.

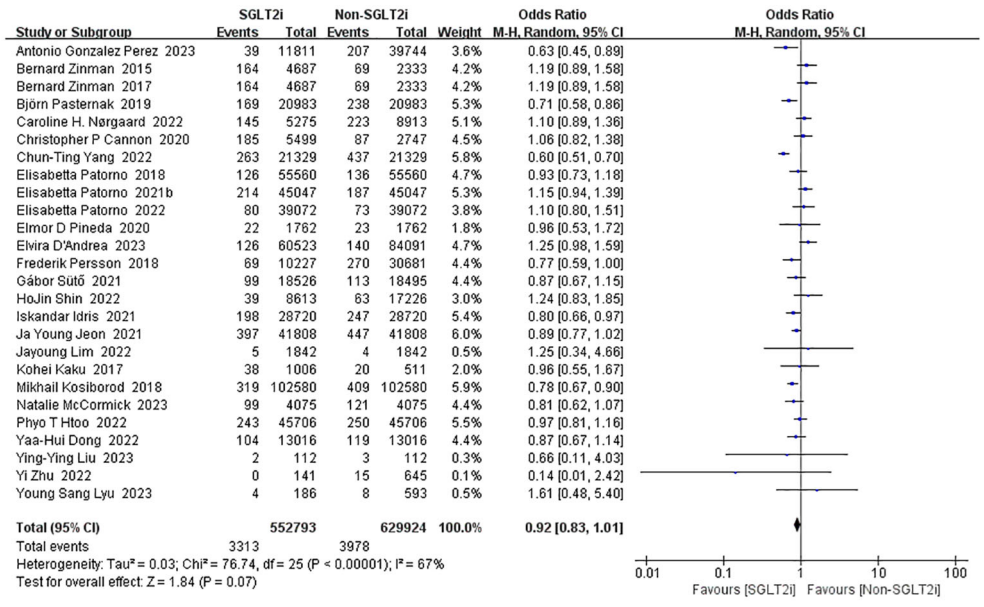

FIGURE 4
Forest plot of the incidence of stroke.

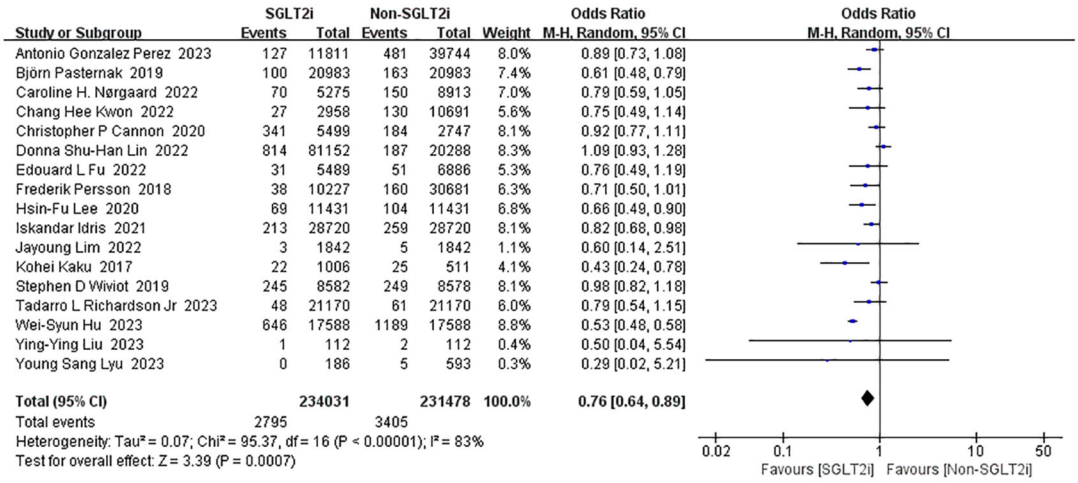

FIGURE 5
Forest plot of the incidence of cardiovascular death.

3.3.3 Incidence of myocardial infarction

A total of 33 studies reported the incidence of myocardial infarction with SGLT2i intervention (10, 14, 15, 17–26, 28, 30–33, 35–38, 40, 41, 43, 50–57). Heterogeneity was significant in the fixed-effect model analysis of these studies (heterozygosity test, Chi^2 = 95.61, P<0.00001, I^2 = 67%), after that, a random-effect model was used and pooled effect value was 0.90 (95%CI 0.84 to 0.96, P=0.002) (Figure 6). Thus, SGLT2i could reduce the incidence of myocardial infarction.

3.3.4 Incidence of heart failure

36 studies reported the incidence of heart failure (10, 13–18, 20–23, 25–41, 43, 50, 52–55, 58, 59). Heterogeneity analysis of these studies showed substantial heterogeneity (heterozygosity test, Chi^2 = 186.58, P<0.00001, I^2 = 81%). Therefore, the analysis was performed using the random-effect model with a pooled effect value of 0.69 (95%CI 0.64 to 0.74, P<0.00001) (Figure 7). It can be indicated that SGLT2i significantly reduced the occurrence of heart failure compared with non-SGLT2i.

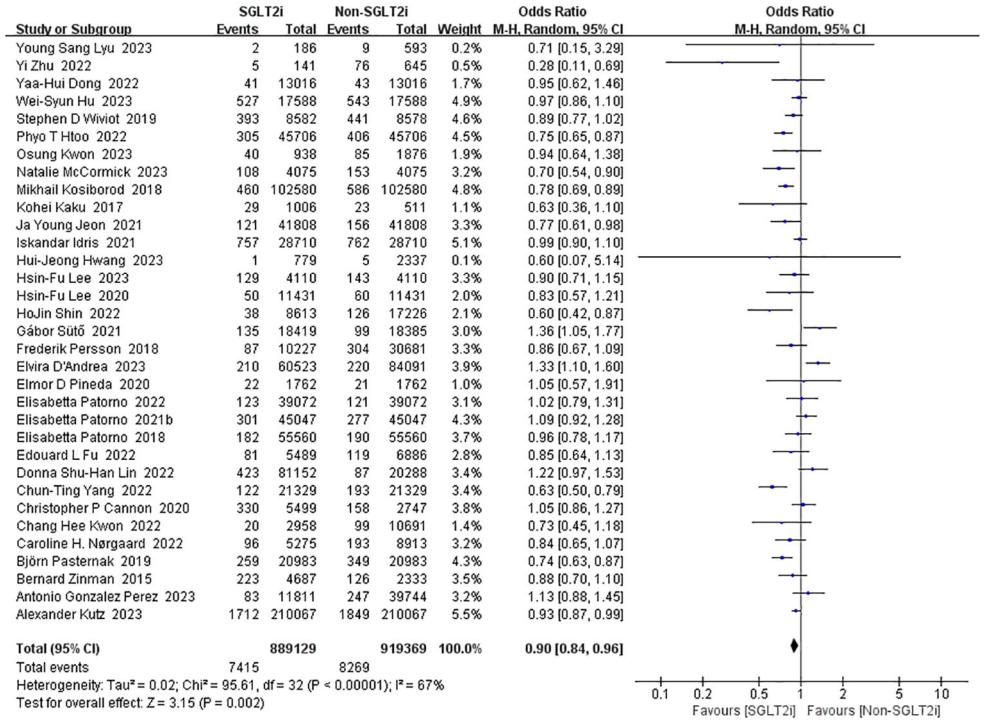

FIGURE 6
Forest plot of the incidence of myocardial Infarction.

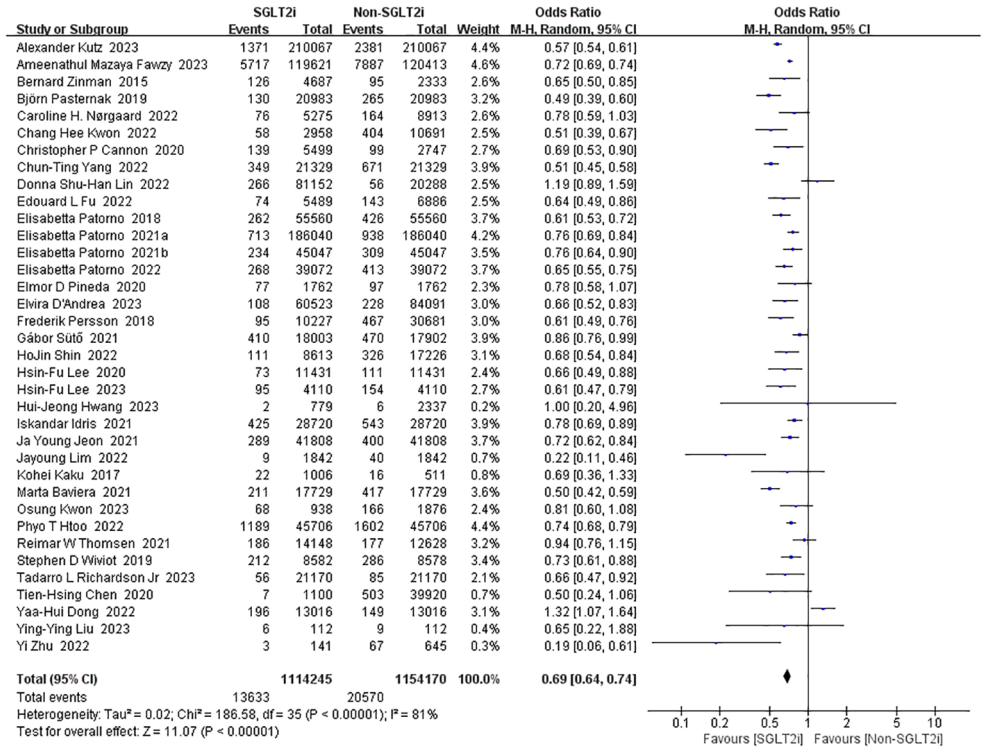

FIGURE 7
Forest plot of the incidence of heart failure.

3.3.5 Incidence of all-cause mortality

Among the intervention studies of SGLT2i, 32 studies reported all-cause mortality (10, 13, 14, 16, 18–23, 25–29, 31–33, 35, 36, 38–41, 43, 50–56). As there was substantial heterogeneity (heterozygosity test, Chi^2 = 635.84, P<0.00001, I^2 = 95%), pooled analyses using the random-effect model was instead which resulted in a favorable pooled effect value of 0.65 (95%CI 0.58 to 0.73, P<0.00001) for SGLT2i (Figure 8). In summary, SGLT2i could reduce all-cause mortality and improve survival.

3.4 Secondary outcome

3.4.1 Incidence of ischemic stroke

Fourteen studies reported the incidence of ischemic stroke between SGLT2i group and non-SGLT2i group (13, 15–17, 25, 26, 28, 29, 40, 51–55). Firstly, we pooled the OR value from these studies by fixed-effect model, as a result, a significant heterogeneity was found (heterozygosity test, Chi^2 = 47.65, P<0.00001, I^2 = 73%). Then the random-effect model was instead, and it was found that SGLT2i could not reduce ischemic stroke in patients (OR=0.95, 95%CI 0.87 to 1.05, P=0.32).

3.4.2 Incidence of revascularization

Only six studies reported the incidence of revascularization as an outcome (27, 33, 37, 43, 55, 56). A pooled analysis of outcome events from these studies using the fixed-effect model revealed tremendous heterogeneity of results (heterozygosity test, Chi^2 = 23.96, P=0.0002, I^2 = 79%). When analyzed using the random-effect model, the merged OR value was 0.85 (95%CI 0.65 to 1.11, P=0.23). In conclusion, SGLT2i did not reduce the occurrence of revascularization.

3.4.3 Incidence of acute coronary syndrome

Events of ACS in patients with SGLT2i have been reported in four studies (13, 27, 29, 59). However, a significantly and huge heterogeneity was found by fixed-effect model (heterozygosity test, Chi^2 = 19.53, P=0.0002, I^2 = 85%), then a random-effect model was used and pooled OR value was 0.98(95%CI 0.86 to 1.12, P=0.77). This means that SGLT2i is not beneficial in preventing the development of ACS. Detailed data for the above secondary endpoints are shown in Figure 9.

3.5 Subgroup analyses

3.5.1 Incidence of cardiovascular and cerebrovascular diseases under different interventions

Seven studies analyzed the effect of empagliflozin on cardiovascular and cerebrovascular diseases (20, 23, 27, 32, 39, 42, 43); eight studies analyzed the effect of dapagliflozin on it (27, 36, 40, 41, 46, 47, 49, 60); and only five studies analyzed the effect of canagliflozin on it (33, 44, 45, 48, 59). Appropriate effect models were selected based on the magnitude of heterogeneity. Pooling these studies about different types of SGLT2i revealed that dapagliflozin prevented stroke (OR=0.78, 95%CI 0.63 to 0.98, P=0.03), myocardial infarction

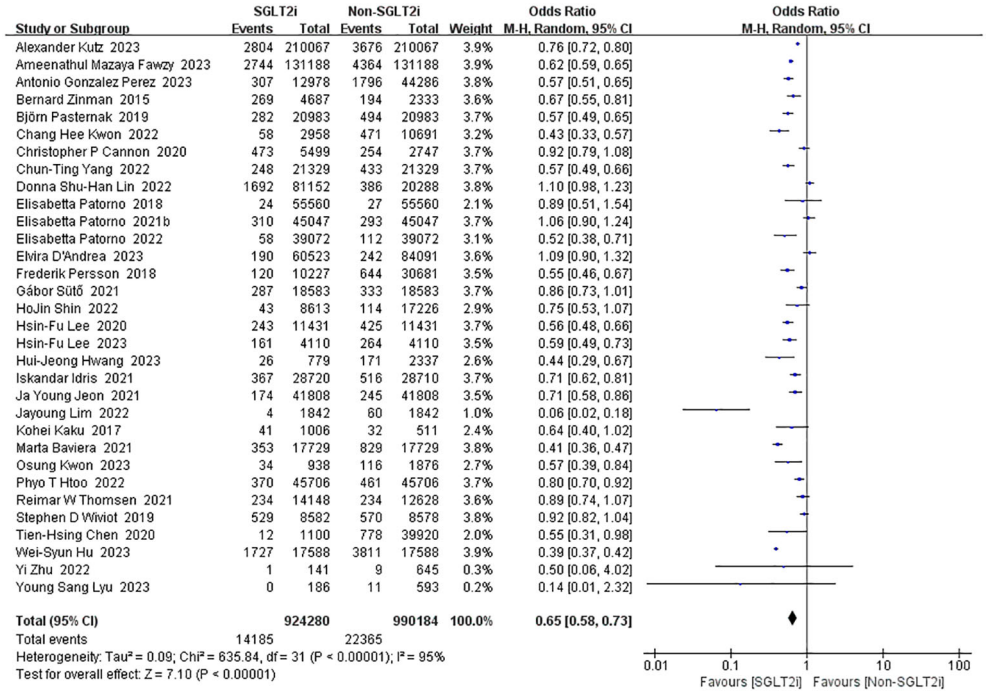

FIGURE 8
Forest plot of the incidence of all-cause mortality.

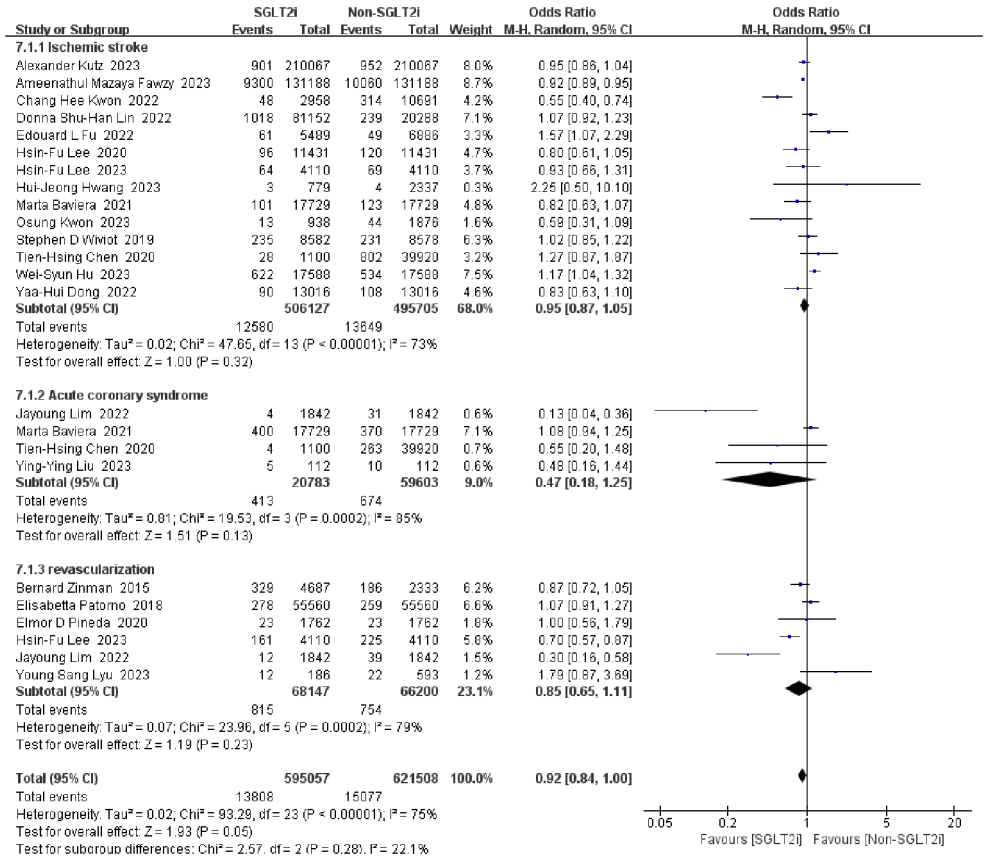

FIGURE 9
Forest plot of the incidence of secondary outcomes (ischemic stroke, revascularization, ACS).

(OR=0.83, 95%CI 0.74 to 0.93, *P*=0.002), heart failure (OR=0.56, 95% CI 0.39 to 0.80, *P*=0.002), and all-cause mortality (OR=0.50, 95%CI 0.30 to 0.82, *P*=0.006). At the same time, empagliflozin reduced the incidence of myocardial infarction (OR=0.82, 95%CI 0.73 to 0.91, *P*=0.0003), heart failure (OR=0.72, 95% CI 0.64 to 0.82, *P*<0.00001), and all-cause mortality (OR=0.68, 95%CI 0.55 to 0.84, *P*=0.0004); canagliflozin only had a positive effect on the occurrence of heart failure (OR=0.56, 95%CI 0.39 to 0.80, *P*=0.002).

Eleven studies reported the therapeutic effects of SGLT2i on cardiovascular and cerebrovascular diseases compared with GLP-1RA. These studies reported four diseases (including stroke, myocardial infarction, heart failure and all-cause mortality) and the details on the occurrence of each disease were provided (15, 17, 20, 28, 30, 33–35, 37, 39, 53). It was found that SGLT2i only had a significant preventive effect on heart failure (OR=0.83, 95%CI 0.74 to 0.93, *P*=0.002) compared to GLP-1RA.

Four diseases (including stroke, myocardial infarction, heart failure and all-cause mortality) were reported in seventeen studies (10, 18, 20–22, 26, 27, 31–33, 36, 50, 53, 55–58). What a pity, a considerable heterogeneity was found in all four subgroups by the fixed-effect model. Finally, a random-effect model was used and pooled OR value was 0.86 (95%CI 0.75 to 0.99, *P*=0.04) in the subset of stroke, 0.63 (95%CI 0.56 to 0.70, *P*<0.00001) in the subset of heart failure, and 0.64 (95%CI 0.57 to 0.72, *P*<0.00001) in the subset of all-cause mortality.

The details of the above are shown in Table 1. Summarily, in different types of SGLT2i, empagliflozin, dapagliflozin and canagliflozin all reduced the incident rate of heart failure, but only dapagliflozin could reduce the incident rate of stroke. Compared with DPP-4i, SGLT2i had a positive therapeutic effect on stroke, heart failure and all-cause mortality; however, compared with GLP-1RA, it only had a positive impact on heart failure.

TABLE 1 The incidence of cardiovascular and cerebrovascular diseases in different intervention measures.

Outcomes of different interventions	Sample size		OR	95%CI	P	Heterogeneity		Model
	Intervention	Control				I2 (%)	P	
Empagliflozin vs Non-Empagliflozin								
stroke	96079	92718	1.06	0.94,1.20	0.33	0	0.79	Fixed
Myocardial infarction	90471	87622	0.82	0.73,0.91	0.0003	44	0.15	Fixed
Heart failure	105540	103013	0.72	0.64,0.82	<0.00001	52	0.07	Random
All-cause mortality	105540	103013	0.68	0.55,0.84	0.0004	75	0.001	Random
Dapagliflozin vs Non-Dapagliflozin								
stroke	12561	36529	0.78	0.63,0.98	0.03	0	0.77	Fixed
Myocardial infarction	20222	42344	0.83	0.74,0.93	0.002	35	0.16	Fixed
Heart failure	19920	42715	0.56	0.39,0.80	0.002	66	0.02	Random
All-cause mortality	20393	43719	0.50	0.30,0.82	0.006	88	<0.00001	Random
Canagliflozin vs Non-Canagliflozin								
stroke	55750	55750	0.91	0.72,1.16	0.46	0	0.83	Fixed
Myocardial infarction	55756	55755	0.94	0.77,1.15	0.54	0	0.72	Fixed
Heart failure	55868	55867	0.62	0.53,0.73	<0.00001	0	0.98	Fixed
All-cause mortality	55756	55755	0.40	0.13,1.28	0.12	67	0.05	Random
SGLT2i vs GLP-1RA								
stroke	107718	111356	1.09	0.97,1.21	0.14	0	0.65	Fixed
Myocardial infarction	284224	228395	0.98	0.91,1.05	0.54	19	0.28	Fixed
Heart failure	484412	427063	0.83	0.74,0.93	0.002	79	<0.00001	Random
All-cause mortality	273645	211261	1.00	0.94,1.05	0.90	29	0.22	Fixed
SGLT2i vs DPP-4i								
stroke	267650	312048	0.86	0.75,0.99	0.04	72	<0.0001	Random
Myocardial infarction	401444	445839	0.89	0.80,1.00	0.04	76	<0.00001	Random
Heart failure	419779	463700	0.63	0.56,0.70	<0.00001	84	<0.00001	Random
All-cause mortality	399375	443804	0.64	0.57,0,72	<0.00001	83	<0.00001	Random

3.5.2 Incidence of cardiovascular and cerebrovascular diseases in different characteristics of patients

Furthermore, fifteen studies explicitly stated whether the subjects had cardiovascular and cerebrovascular diseases or were at other high risk (14, 15, 21, 23, 25, 27, 34, 40, 42, 43, 51, 54–56, 59). Firstly, four outcomes (including stroke, myocardial infarction, heart failure and cardiovascular death) in these studies were analyzed by using the fixed-effect model. However, some significantly and huge heterogeneity were found, then appropriate effect models were selected based on the magnitude of heterogeneity. It was found that SGLT2i demonstrated significant benefits in heart failure (OR=0.72, 95%CI 0.67 to 0.77, P<0.00001) and cardiovascular death (OR=0.72, 95%CI 0.54 to 0.95, P=0.02) in high-risk patients (Table 2).

3.6 Publication bias

Funnel plot was done to show the publication bias and results were shown in Figures 10, 11. Because of the complexity of population characteristics included in the study and the large gaps in sample sizes, some of the graphs show asymmetry; that is, there is publication bias.

4 Discussion

SGLT2i is a new class of insulin-independent drug for type 2 diabetes, which acts highly selectively on renal proximal tubules to block glucose reabsorption and increase the elimination of excess glucose from the body (63). In order to clarify the intervention effect of SGLT2i on cardiovascular and cerebrovascular diseases, researchers have prepared and conducted several clinical trials. EMPA-REG OUTCOME was a multi-center prospective study in which investigators found that the empagliflozin group could significantly reduce the risk of major adverse cardiovascular events in type 2 diabetes patients who were at high risk compared to the placebo group after following up for mean 3.1 years (23). This finding eventually caused SGLT2i was recommended by the American Diabetes Association and the European Association for the Study of Diabetes for the treatment of high-risk type 2 diabetes patients who suffer from arteriosclerotic cardiovascular disease (64). Current studies have found that SGLT2i does not reduce the incidence of stroke (42), and to some extent, it even increases the risk of ischemic stroke (65). The results of our study showed that SGLT2i does have great advantages in the prevention of cardiovascular and cerebrovascular diseases: SGLT2i could significantly reduce the incidence of myocardial infarction, heart failure, cardiovascular death and all-cause mortality; in subgroup analyses, the risk of heart failure was seen to be decreased by SGLT2i regardless of the type of SGLT2i; furthermore, in high-risk patients, SGLT2i exerted a positive effect in preventing the occurrence of heart failure and cardiovascular death. It was interesting to note that although SGLT2i reduced the risk of stroke compared to DPP-4i, but it had no preventative effect on the occurrence of stroke or ischemic stroke when comparing to non-SGLT2i.

At present, the mechanism of SGLT2i intervention in cardiovascular and cerebrovascular diseases is still being discovered and improved. Hemodynamic optimization and renal effect were thought to be the main two mechanisms (23, 66). Osmotic diuresis by SGLT2i reduces blood volume and cardiac load; in turn, sodium excretion decreases intraglomerular pressure by activating tubuloglomerular feedback (23, 67). On the other hand, SGLT2i has been shown to enhance endothelial cell function by reducing inflammation and oxidative stress (41, 68, 69), thereby improving coronary blood flow and myocardial energy metabolism (70). In contrast, SGLT2i is not as effective for stroke. Hypovolemia and elevated hematocrit from osmotic diuresis may be associated with an increased risk of stroke (42, 43), which seems to be a plausible explanation given that a meta-analysis has found that upright hypotension increases the risk of stroke (71).

GLP-1RA enhances insulin secretion by activating the GLP-1 receptor and inhibits glucagon secretion. It is able to delay gastric emptying and reduce the amount of food intake through central appetite suppression, ultimately achieving the effects of lowering

TABLE 2 The incidence of cardiovascular and cerebrovascular diseases in different characteristics of patients.

Outcomes of different population characteristics	Sample size		OR	95% CI	P	Heterogeneity		Model
	Intervention	Control				I2 (%)	P	
with cardiovascular and cerebrovascular risk factors								
stroke	27358	19403	1.00	0.88,1.13	0.95	44	0.11	Fixed
Myocardial infarction	56921	60394	0.95	0.89,1.01	0.08	0	0.63	Fixed
Heart failure	92160	95226	0.72	0.67,0.77	<0.00001	17	0.29	Fixed
Cardiovascular death	47298	52187	0.72	0.54,0.95	0.02	88	<0.00001	Random
without cardiovascular and cerebrovascular risk factors								
stroke	32211	32211	0.89	0.73,1.09	0.26	0	0.87	Fixed
Myocardial infarction	30369	30369	0.94	0.76,1.17	0.58	0	0.95	Fixed
Heart failure	165350	165350	0.73	0.47,1.13	0.15	<0.00001	90	Random
Cardiovascular death	19195	19195	0.85	0.61,1.19	0.35	0	0.62	Fixed

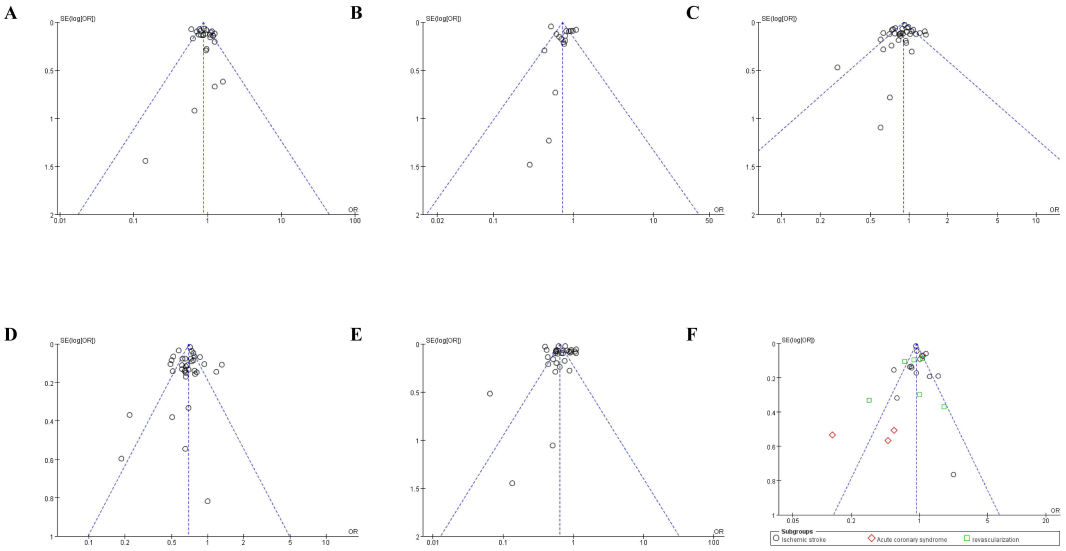

FIGURE 10
Funnel plot of publication bias on main and secondary outcomes. **(A)** Funnel plot of publication bias on stroke; **(B)** Funnel plot of publication bias on cardiovascular death; **(C)** Funnel plot of publication bias on myocardial Infarction; **(D)** Funnel plot of publication bias on heart failure; **(E)** Funnel plot of publication bias on all-cause mortality; **(F)** Funnel plot of publication bias on secondary outcomes.

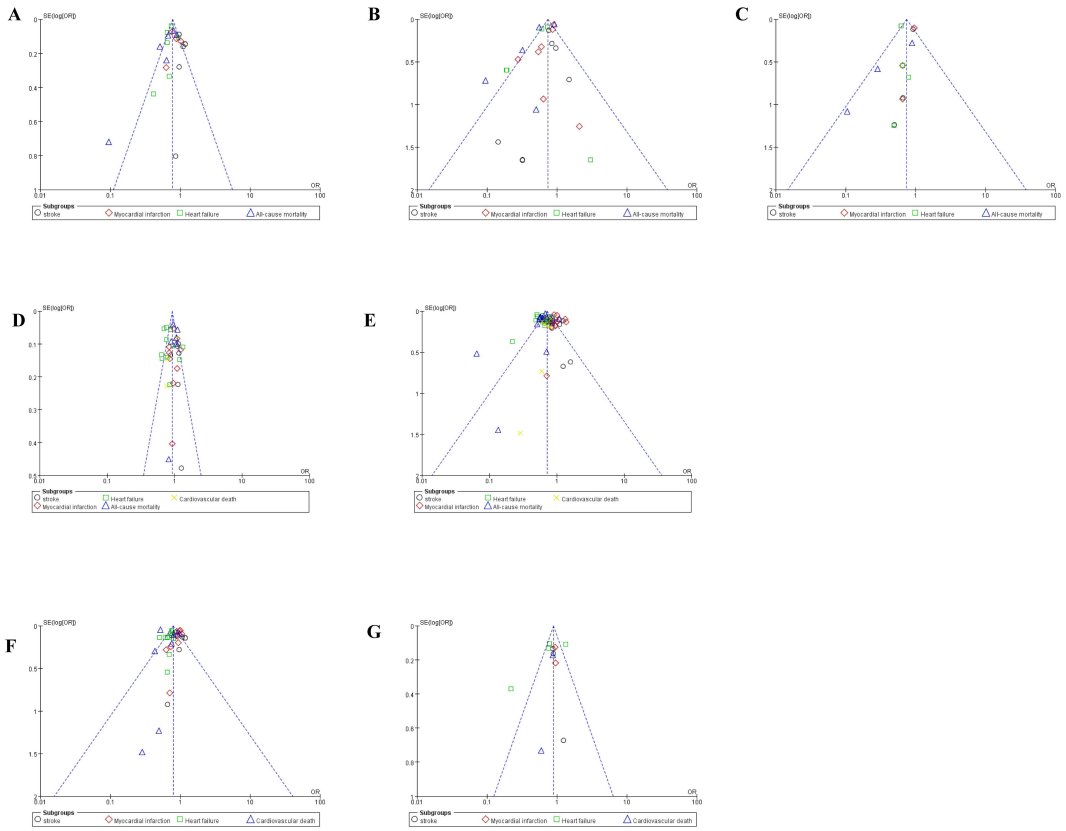

FIGURE 11
Funnel plot of publication bias on subgroup analysis. **(A)** Funnel plot of publication bias on subgroup analysis of Empagliflozin; **(B)** Funnel plot of publication bias on subgroup analysis of Empagliflozin Dapagliflozin; **(C)** Funnel plot of publication bias on subgroup analysis of Canagliflozin; **(D)** Funnel plot of publication bias on subgroup analysis of SGLT2i VS GLP-1RA; **(E)** Funnel plot of publication bias on subgroup analysis of SGLT2i VS DPP-4i; **(F)** Funnel plot of publication bias on subgroup analysis who were at high risk; **(G)** Funnel plot of publication bias on subgroup analysis who were not at high risk.

blood glucose and body weight (72). In recent years, with the in-depth studies of the drug, researchers have found that in addition to its hypoglycemic and weight-loss effects, it can improve mitochondrial dysfunction, reduce inflammatory mediators and leukocyte-endothelial interactions, which can prevent the onset and progression of atherosclerosis (73). DPP-4i promotes insulin release from pancreatic beta cells by reducing the inactivation of glucagon-producing polypeptide (74). A large number of studies have been conducted on the comparative clinical efficacy of these three classes of drugs, but the conclusions are conflicting (13, 17, 22, 30, 34, 36, 75). In addition, studies have found that empagliflozin improves sympathetic nerve activity and is more favorable for glycemic control and management of cardiometabolic parameters (76, 77); while dapagliflozin shows more benefits in heart failure (78, 79). In previous studies, investigators have found some heterogeneity in outcome comparisons, which depending on the presence of chronic cardiac and renal diseases in patients before inclusion in the study. With the above in mind, this study conducted a number of subgroup analyses to further analyze the clinical effects of SGLT2i from multiple perspectives.

Although a large number of articles have been published on the topic of SGLT2i and cardiovascular diseases, there are some unique aspects of our work. In this study, we added the keyword "stroke" to focus more on the cerebrovascular diseases which are controversial. We included more studies and larger sample than others, and got more results, what is a supplement to the previous meta-analysis. Patients with type 2 diabetes often have multiple comorbidities, such as microvascular disease and renal disease, which has led to high-risk bias when combining statistics. Therefore, researchers should design and carry out trials with high selectivity, high accuracy, rigorous design and large sample size, and conduct in-depth mechanism exploration to provide a more reliable basis for the application of SGLT2i.

The major limitation of this meta-analysis is the complex and diverse population characteristics of the included studies which may induce a racial heterogeneity. Secondly, among the 49 studies, only nine RCTs and the rest trials were cohort studies, this may lead to a reduction in the methodological quality of clinical controlled studies. Furthermore, when analyzing some results, there was a significant heterogeneity and publication bias due to the small number of included studies and the complexity of population characteristics. Therefore, more prospective clinical studies with a larger sample size may strengthen the evidence.

5 Conclusions

In conclusion, our meta-analysis summarized the efficacy of SGLT2i in cardiovascular and cerebrovascular diseases. The incidence of cardiovascular death, myocardial infarction, heart failure and all-cause mortality was reduced with the use of SGLT2i, but no significant preventive effect was seen for the occurrence of stroke, ischemic stroke, acute coronary syndrome and revascularization. Subgroup analyses showed that the different types of SGLT2i reduced the incidence of heart failure, but only dapagliflozin reduced the incident rate of stroke. SGLT2i had a positive preventive effect on the incidence of stroke, heart failure and all-cause mortality compared to DPP-4i. Furthermore, SGLT2i significantly reduced heart failure and cardiovascular mortality in patients who were at high risk. Further, more studies focusing on the mechanism still needs to be done.

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

FW: Data curation, Formal analysis, Software, Visualization, Writing – original draft. CL: Data curation, Formal analysis, Writing – original draft. LC: Data curation, Investigation, Writing – original draft. SG: Data curation, Software, Writing – original draft. JZ: Funding acquisition, Project administration, Supervision, Writing – review & editing. HW: Project administration, Supervision, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1436217/full#supplementary-material

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Association between cardiovascular health assessed by life's essential 8 and hyperuricemia in U.S. adults: the NHANES 2009-2020

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Background: This study presented the new Life's Essential 8 (LE8) framework for examining cardiovascular health (CVH) to analyze the potential relationship between the latter and hyperuricemia (HUA) in the U.S. population.

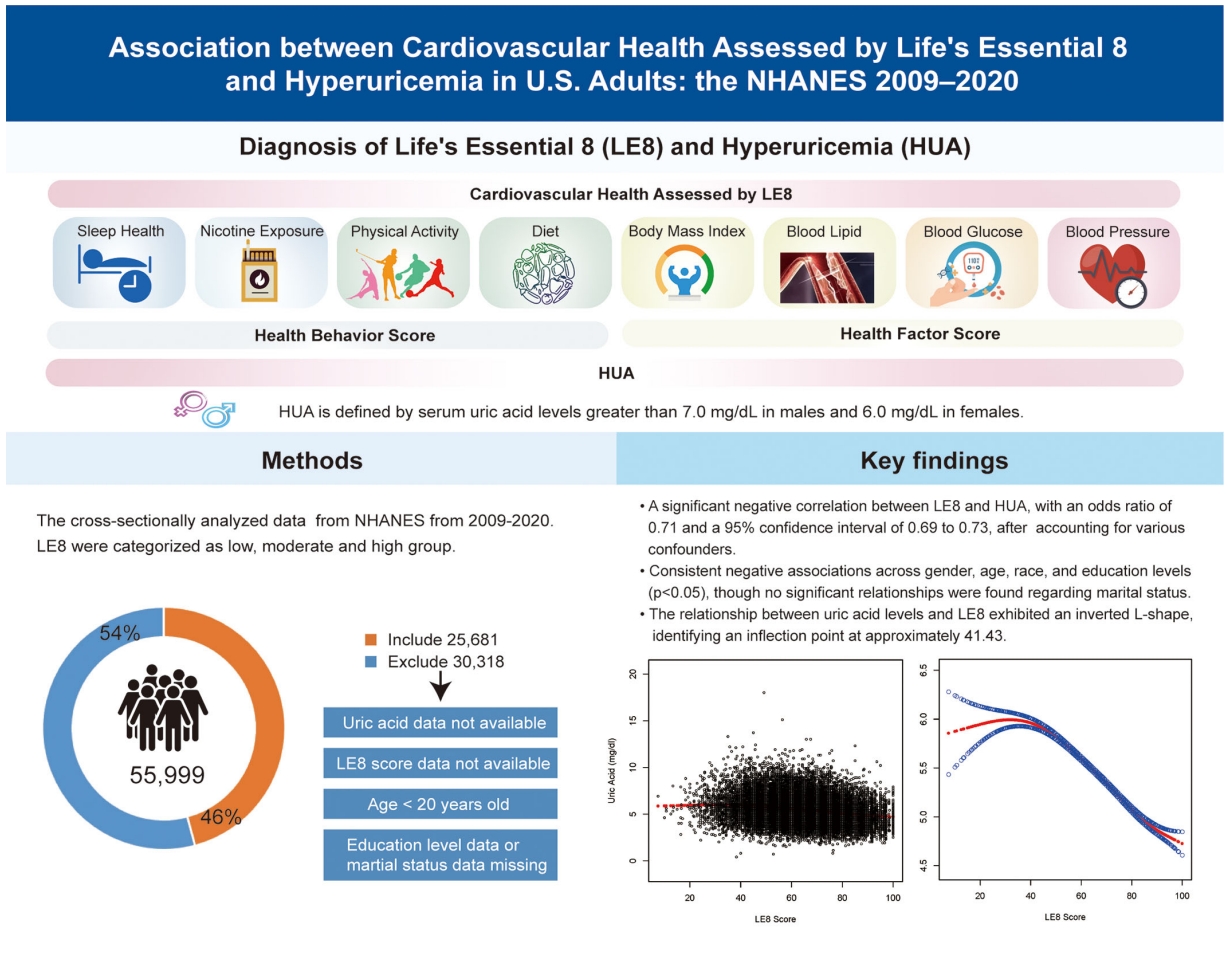
Methods: Data on individuals aged at least 20 years were collected from the National Health and Nutrition Examination Survey (NHANES) 2009-2020. Smoothed curve fitting and multivariate logistic regression analyses were then performed on a sample of 25,681 adults to explore the association between LE8 and HUA. A sensitivity analysis was conducted to examine the robustness of the research findings.

Results: The study found a strong negative association between LE8 and HUA, with an odds ratio (OR) of 0.71 and a 95% confidence interval (CI) from 0.69 to 0.73 after adjusting for multiple confounding factors. The sensitivity analysis further validated the robustness of this association. This analysis consistently showed negative associations across different genders, ages, races, and education levels ($p < 0.05$), but there were no significant relationships with marital status. The association between uric acid levels and LE8 displayed an inverted L-shaped curve, with an inflection point around 41.43.

Conclusions: The findings indicate a strong negative relationship between LE8 and HUA among the U.S. population, suggesting that higher scores on the LE8, which assesses CVH, were associated with reduced uric acid levels. The consistent negative association underscores the LE8 framework's potential as a valuable tool for understanding and managing HUA in CVH.

KEYWORDS

life's essential 8, hyperuricemia, cardiovascular health, NHANES, cross sectional study



GRAPHICAL ABSTRACT

1 Introduction

Hyperuricemia (HUA), a well-known metabolic disorder, is primarily caused by disruptions in purine metabolism. Globally, statistics indicate that 15 to 20% of the population is affected by HUA (1), and the prevalence of this condition is rising. During the 2015–2016 period, the prevalence of HUA was 20.2% among adult males and 20.0% among adult females in the US (2). Over time, HUA has become a significant global public health concern that is strongly associated with the formation and mortality of various diseases, including gout (3), severe kidney disease (4), and elevated plasma aldosterone concentration (5). Therefore, the management and prevention of HUA are crucially important in clinical practice.

Previous studies have demonstrated a correlation between cardiovascular disease (CVD) and HUA (6, 7), with CVD being the primary cause of morbidity and mortality worldwide (8). This underscores the necessity for epidemiological research and tertiary prevention efforts. In 2022, the American Heart Association (AHA) introduced "Life's Essential 8" (LE8), a framework comprising eight criteria to assess CVH (9). It includes a health behavior score (HBS) for diet, sleep health, physical activity, and nicotine exposure, as well as a health factor score (HFS) for blood pressure, blood glucose, lipid levels, and body mass index (BMI). The dynamic progression of CVD is widely identified, with smoking, hypertension, diabetes, and dyslipidemia being identified as primary risk factors (10). However, LE8 provides a broad analytical approach, resulting in a more precise evaluation of CVH. It also offers a comprehensive method for quantifying CVH than other single factors associated with HUA. Since its introduction, implementing the ideal CVH state as defined by LE8 has not only enhanced the prognosis for patients with CVD (11) but has also lowered the risk of stroke, diabetes, renal disease, and adult-onset asthma (12–14), among other conditions.

Some recent studies have confirmed that LE8 is associated with several metabolic diseases, such as diabetes mellitus (15) and osteoporosis (16). Moreover, as HUA is a metabolic disorder strongly associated with lifestyle factors, it may also correlate with LE8. Thus, the LE8 framework was used for this study to elucidate the influence of health behaviors on HUA. However, the association between HUA and LE8 has been underexplored, and no research has established this relationship within the U.S. adult population. These

findings suggested that individuals who maintain a reasonable LE8 score may have a lower risk of developing HUA, as a higher LE8 score indicates a healthier cardiovascular system. This cross-sectional study examined adults from the U.S. population to investigate the possible association between HUA and LE8. The data for this analysis was obtained from the National Health and Nutrition Examination Survey (NHANES), which lasted from 2009 to 2020.

2 Material and methods

2.1 Data source and participant cohort

This study used data from NHANES, accessible at https://www.cdc.gov/Nchs/Nhanes/. It is a nationally representative survey conducted by the National Center for Health Statistics (NCHS) that collects comprehensive health and nutrition data from households throughout the US population. This survey included a comprehensive questionnaire, demographic, dietary, examination, and laboratory data. The NCHS Research Ethics Review Board thoroughly reviewed and approved the research methodologies of NHANES, and all participants provided written informed consent.

A total of 55,999 individuals were included in the NHANES 2009-2020 datasets. This study was limited to adults with LE8 scores (i.e., those without > 2 missing variables out of the 8 in the LE8 score assessment), complete data on uric acid levels, and detailed demographic information. Participants who were missing standard biochemical profile data for uric acid (N = 20,888), those with missing LE8 scores (N = 6,204), those below the age limit (N = 3,195), and participants with insufficient details on education (N = 20) or marital status (N = 11) were excluded to ensure data integrity and consistency. This study included a final cohort of 25,681 participants (Figure 1).

2.2 Diagnosis of HUA

HUA is characterized by either urate overproduction or underexcretion. In this study, HUA was quantified using serum uric acid measurements from NHANES. According to diagnostic criteria from previous studies, HUA is defined as serum uric acid levels > 7.0 mg/dL in males and 6.0 mg/dL in females (17).

2.3 Calculation of LE8

The LE8, introduced by AHA, quantifies CVH through the HBS and HFS. It includes eight factors: sleep, nicotine exposure, physical activity, diet, blood pressure, blood glucose, lipid levels, and BMI. The total LE8 score is calculated by combining these eight factors, each rated from 0 to 100, without assigning any weights to the scores. Moreover, AHA guidelines classify LE8 scores into three categories: low CVH (0–49), moderate CVH (50–79), and high CVH (80–100). Data on sleep, nicotine exposure, physical activity, medication usage, and health history were obtained from self-reported participant questionnaires completed by participants. Dietary information was collected through two 24-hour dietary recall interviews at the mobile screening center and analyzed using the Healthy Eating Index 2015 (18). Exercise data included the total minutes of both moderate and high-intensity activities. Sleep duration was reported in hours.

Direct measurements included BMI, calculated as weight in Kg divided by the square of height in meters, and blood pressure, reported as diastolic and systolic values in mmHg. Lipid levels were quantified from blood samples, with non-HDL cholesterol reported in mg/dL, and blood glucose levels were expressed as a percentage of glycated hemoglobin. Supplementary Table S1 details the quantification methods for the eight factors, and Supplementary Table S2 illustrates the calculation of LE8 scores.

2.4 Covariates

Based on previous research (19, 20), the current multivariate logistic regression analysis examined potential covariates affecting the association between LE8 and HUA. Given that LE8 incorporates multiple lifestyle and health-related factors, this study limited the number of covariates to avoid model overfitting (21). The final covariates selected were gender, age, race, marital status, and educational attainment.

2.5 Statistical analysis

The multivariate logistic regression analysis observed a linear relationship between the independent variable (LE8) and the dependent variable (HUA). The stability of this relationship was also analyzed after adjusting for various confounding factors. Moreover, LE8 and HUA were explored *via* a multivariate logistic regression analysis. A total of 3 logistic regression models were constructed, each with varying levels of confounder adjustments:

Model 1 serves as a crude model without adjusting for any covariates; Model 2 adjusts for basic demographic characteristics, including gender, age, and race, while Model 3 adjusts for all covariates, which were further adjusted for marital status and education level based on Model 2. Furthermore, in light of ongoing debates concerning the definition of HUA, a sensitivity analysis was conducted to evaluate the robustness of the results across three models with different sets of adjusted confounding factors. A nonlinear association between LE8 and HUA was identified using smoothed curve fitting techniques and a threshold effects analysis to investigate potential thresholds across intervals. Further insights were obtained through subgroup analyses *via* stratified multivariate logistic regression, considering age, marital status, education level, race, and gender. Statistical analyses were performed with R software (v4.3.3), and statistical significance was set at a two-sided as $p < 0.05$. Descriptive analyses included complex weighting; continuous variables were expressed as mean ± standard deviation (SD), while categorical ones were reported as percentages and compared using the chi-square tests.

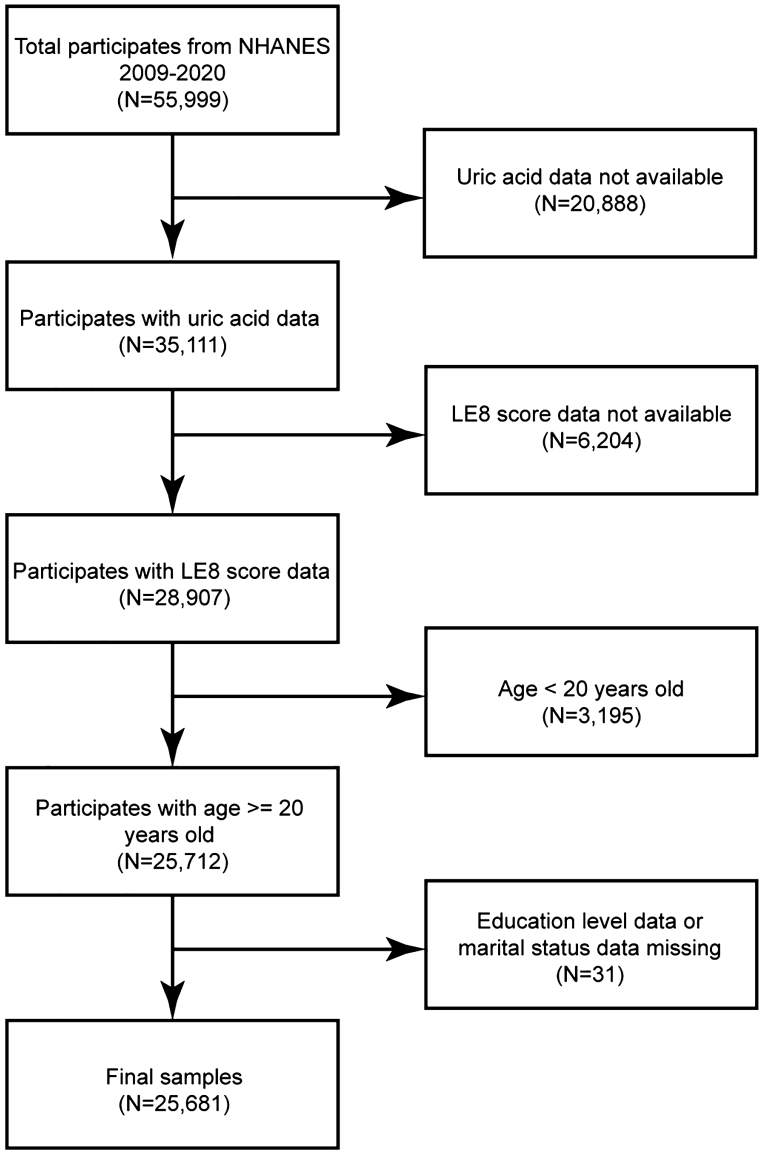


FIGURE 1
A flowchart for participant selection.

3 Results

3.1 Basic characteristics

This study comprises 25,681 participants, divided based on whether they had HUA. Table 1 presents the basic characteristics of the participants. In the sample, males represented 49.92%, and the average age of participants was 49.58 ± 17.50. The mean ± SD values for LE8, HBS, and HFS were 65.12± 14.75, 63.32± 20.43, and 66.70 ± 19.81, respectively. The LE8 group consisted of the following counts (%) of participants: low (3,840, 14.95%), moderate (17,389), and high (4,452, 17.34%) groups. Similarly, the HBS group's numbers (%) were 6,064 (23.61%), 13,624 (53.05%), and 5,993 (23.34%). For the HFS group, the percentages were as follows: 5,249 (20.44%), 12,996 (50.61%), and 7,436 (28.96%). A total of 4,663 participants (18.16%) were diagnosed with HUA. Individuals with HUA were shown to have a higher possibility of being non-Hispanic Black males aged ≥ 60, with a moderate education level, and a higher frequency of being widowed or divorced relative to those without HUA. Moreover, participants without HUA generally scored higher on the LE8, HBS, and HFS scales.

3.2 Relationship between LE8 and HUA

Table 2 illustrates the multivariate linear regression analysis, which examines the associations between LE8, its components HBS and HFS, and HUA. Collectively, it was found that LE8 and HUA were substantially and adversely correlated. The odds ratio (OR) for Model 1 (the unadjusted one) was 0.69 (95% CI: 0.67, 0.71). This negative association was consistent after adjusting for age, race, and gender (Model 2, OR = 0.71, 95% CI: 0.69, 0.73) and further adjustments for

TABLE 1 Basic characteristics of 25,681 participants.

Characteristics	Overall (N = 25,681)	Non-HUA (N = 21,018)	HUA (N = 4,663)	*p*-value
Gender (%)				<0.001
Male	12,821 (49.92)	10,217 (48.61)	2,604 (55.84)	
Female	12,860 (50.08)	10,801 (51.39)	2,059 (44.16)	
Age (years)	49.58 ± 17.50	48.54 ± 17.31	54.25 ± 17.63	<0.001
Age group (%)				<0.001
20~39	8,500 (33.10)	7,363 (35.03)	1,137 (24.38)	
40~59	8,643 (33.66)	7,218 (34.34)	1,425 (30.56)	
≥60	8,538 (33.25)	6,437 (30.63)	2,101 (45.06)	
Race (%)				<0.001
Mexican American	3,593 (13.99)	3,130 (14.89)	463 (9.93)	
Other Hispanic	2,664 (10.37)	2,297 (10.93)	367 (7.87)	
Non-Hispanic White	10,619 (41.35)	8,618 (41.00)	2,001 (42.91)	
Non-Hispanic Black	5,620 (21.88)	4,361 (20.75)	1,259 (27.00)	
Other Race - Including Multi-Racial	3,185 (12.40)	2,612 (12.43)	573 (12.29)	
Education level (%)				<0.001
Less than 9th grade	2,266 (8.82)	1,879 (8.94)	387 (8.30)	
9-11th grade (Includes 12th grade with no diploma)	3,332 (12.97)	2,714 (12.91)	618 (13.25)	
High school graduate/GED or equivalent	5,885 (22.92)	4,750 (22.60)	1,135 (24.34)	
Some college or AA degree	8,007 (31.18)	6,480 (30.83)	1,527 (32.75)	
College graduate or above	6,191 (24.11)	5,195 (24.72)	996 (21.36)	
Marital Status (%)				<0.001
Married	13,641 (53.12)	11,242 (53.49)	2,399 (51.45)	
Widowed	2,932 (11.42)	2,217 (10.55)	715 (15.33)	
Divorced	3,406 (13.26)	2,739 (13.03)	667 (14.30)	
Separated	633 (2.46)	523 (2.49)	110 (2.36)	
Never married	3,490 (13.59)	2,947 (14.02)	543 (11.64)	
Living with partner	1,579 (6.15)	1,350 (6.42)	229 (4.91)	
HBS	63.32 ± 20.43	63.58 ± 20.57	62.16 ± 19.74	<0.001
HBS group (%)				<0.001
Low	6,064 (23.61)	4,895 (23.29)	1,169 (25.07)	
Moderate	13,624 (53.05)	11,081 (52.72)	2,543 (54.54)	
High	5,993 (23.34)	5,042 (23.99)	951 (20.39)	
HFS	66.70 ± 19.81	68.96 ± 19.49	56.49 ± 17.94	<0.001
HFS group (%)				<0.001
Low	5,249 (20.44)	3,577 (17.02)	1,672 (35.86)	
Moderate	12,996 (50.61)	10,532 (50.11)	2,464 (52.84)	
High	7,436 (28.96)	6,909 (32.87)	527 (11.30)	
LE8	65.12 ± 14.75	66.54 ± 14.66	58.70 ± 13.36	<0.001

(Continued)

TABLE 1 Continued

Characteristics	Overall (N = 25,681)	Non-HUA (N = 21,018)	HUA (N = 4,663)	*p*-value
LE8 group (%)				<0.001
Low	3,840 (14.95)	2,697 (12.83)	1,143 (24.51)	
Moderate	17,389 (67.71)	14,150 (67.32)	3,239 (69.46)	
High	4,452 (17.34)	4,171 (19.84)	281 (6.03)	

marital status and education level (Model 3, OR = 0.71, 95% CI: 0.69, 0.73). According to Model 3, the possibility of developing HUA decreases by 29% for every ten-point increment in the LE8 score. Data also revealed that those in the high and moderate LE8 groups had a lower risk of experiencing HUA than those in the low LE8 group. Specifically, the high LE8 group had 80% lower odds of having HUA (OR = 0.20, 95% CI: 0.17, 0.23), with the moderate one being related to a 43% reduction in odds (OR = 0.57, 95% CI: 0.52, 0.61). Further, enhancing scores on seven components, while accounting for one factor, was associated with an overall improvement in scores, corresponding with lower chances of developing HUA.

HBS and HFS, the sub-scores of LE8, also showed a negative association with HUA. Model 3 indicated that the possibility of having HUA decreased by 3% for each ten-point increase in the HBS (OR = 0.97, 95% CI: 0.96, 0.99). Among the HBS categories, the high group had 19% lower odds of having HUA than the low one (OR = 0.81, 95% CI: 0.74, 0.90). Simultaneously, no statistical significance (p = 0.7451) was found for the results of the moderate group. The possibility of having HUA was 27% lower for each ten-point increment in the HFS (OR = 0.73, 95% CI: 0.71, 0.74). The moderate group experienced a 49% reduction in their chances of having HUA compared to the low HFS group (OR = 0.51, 95% CI: 0.47, 0.55), while the high group experienced a more significant 82% decrease in odds (OR = 0.18, 95% CI: 0.16, 0.20). The sensitivity analysis (Supplementary Table S3) found that all three models' results remained robust when applying the other three definitions of HUA.

3.3 Curve fitting and threshold effect analyses

To further investigate the nonlinear relationship between LE8 and uric acid levels, a smoothing curve fitting was used via a linear regression model, which revealed an inverted L-shaped association between uric acid levels and LE8 scores (Figure 2). Moreover, a threshold effect analysis, depicted in Table 3, identified 41.43 points as the crucial turning point in this relationship.

TABLE 2 Relationships between LE8, Its Sub-indices, and HUA.

	Model1		Model2		Model3	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Every ten-point increment for LE8	0.69 (0.67, 0.71)	<0.0001	0.71 (0.69, 0.73)	<0.0001	0.71 (0.69, 0.73)	<0.0001
LE8 group						
Low	Ref.		Ref.		Ref.	
Moderate	0.54 (0.50, 0.58)	<0.0001	0.57 (0.52, 0.61)	<0.0001	0.57 (0.52, 0.61)	<0.0001
High	0.16 (0.14, 0.18)	<0.0001	0.19 (0.17, 0.22)	<0.0001	0.20 (0.17, 0.23)	<0.0001
Every ten-point increment for HBS	0.97 (0.95, 0.98)	<0.0001	0.96 (0.95, 0.98)	<0.0001	0.97 (0.96, 0.99)	0.0010
HBS group						
Low	Ref.		Ref.		Ref.	
Moderate	0.96 (0.89, 1.04)	0.3107	0.96 (0.89, 1.04)	0.3548	0.99 (0.91, 1.07)	0.7451
High	0.79 (0.72, 0.87)	<0.0001	0.77 (0.70, 0.85)	<0.0001	0.81 (0.74, 0.90)	<0.0001
Every ten-point increment for HFS	0.72 (0.71, 0.73)	<0.0001	0.73 (0.71, 0.74)	<0.0001	0.73 (0.71, 0.74)	<0.0001
HFS group						
Low	Ref.		Ref.		Ref.	
Moderate	0.50 (0.47, 0.54)	<0.0001	0.50 (0.47, 0.54)	<0.0001	0.51 (0.47, 0.55)	<0.0001
High	0.16 (0.15, 0.18)	<0.0001	0.18 (0.16, 0.20)	<0.0001	0.18 (0.16, 0.20)	<0.0001

Model 1: Unadjusted for covariates. Model 2: Adjustments made for race, age, and gender. Model 3: Adjustments made for age, marital status, education level, race, and gender. Low groups represent scores of 0-49, moderate groups represent 50-79, and high groups represent scores of 80-100.

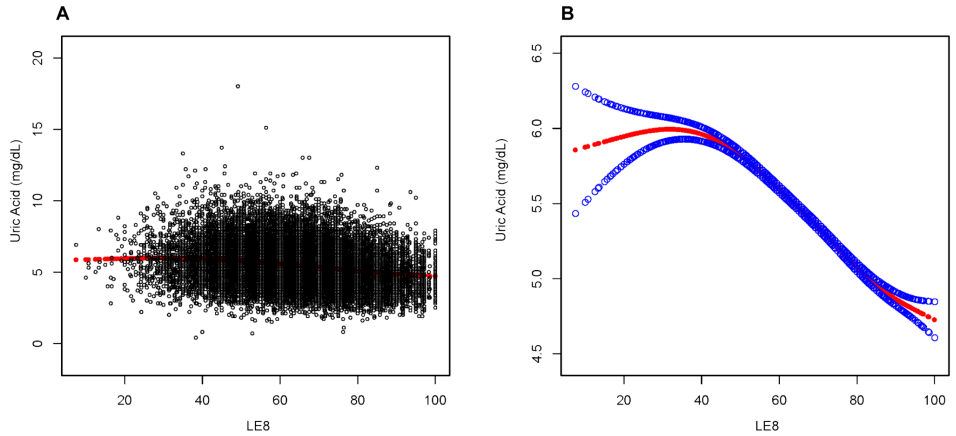


FIGURE 2
Association between LE8 and Uric Acid. **(A)** Each sample is represented by a black dot. **(B)** The smoothed curve, fitting the relationship between the two variables, is shown as a solid red line, with the 95% confidence interval for the curve indicated by the blue shaded area. This analysis has been adjusted for age, marital status, education level, race, and gender.

3.4 Subgroup analyses

Subgroup analyses were carried out in the study population to evaluate whether the relationship between LE8 and HUA remained consistent or differed among various demographic groups. As shown in Figure 3, a negative correlation between LE8 and HUA persisted across all subgroups, aligning with the findings from the overall analysis. Significant interactions ($p < 0.05$) were observed between LE8 and subgroups based on age, education level, race, and gender with HUA. Specifically, the study investigated a more pronounced negative correlation between HUA and LE8 in non-Hispanic Black females, adults aged 20 to 39, and those with a minimum college education.

3.5 Threshold effect analysis in Gender and Age Subgroups

Considering the significant clinical implications of age and gender differences in the association between HUA and different indicators (22–24), a comprehensive threshold effect analysis was carried out for subgroups stratified by gender and age. The inflection point for males was significantly higher than that for females. Similarly, the inflection point was higher in individuals aged 50 and older than those < 50 (Table 4).

TABLE 3 Analysis of the threshold effects for the association between uric acid levels and LE8 scores using linear regression.

Uric Acid(mg/dl)	Adjusted β (95% CI) P-value
Breakpoint	41.43
LE8 < Breakpoint	0.01(-0.00, 0.01) 0.1392
LE8 ≥ Breakpoint	-0.02(-0.03, -0.02) <0.0001
Log-likelihood ratio test	<0.001

Results are presented after adjusting for age, marital status, education level, race, and gender.

4 Discussion

This cross-sectional study analyzed a nationally representative sample of 25,681 U.S. adults, revealing a strong negative correlation between HUA and LE8 scores, including its sub-components. This association remained consistent across multiple demographic subgroups, including gender, age, race, and education level, but was not significant concerning marital status. Furthermore, a nonlinear relationship between uric acid levels and LE8 scores was identified *via* smoothing curve fitting, demonstrating that higher LE8 scores were associated with lower uric acid levels. These findings underscore the importance of maintaining healthy LE8 scores through appropriate lifestyle and physical health measures to reduce the prevalence of HUA.

In previous research, a Nested Case-Control Study (25) conducted on clinical data in England indicated that gout, a metabolic disease, was related to a temporary increase in cardiovascular events. However, studies examining the relationship between LE8 and HUA are limited. Currently, only one cross-sectional study (26) has investigated this association in underdeveloped ethnic minority regions in China. This study found a negative correlation between LE8 and HUA, which aligns with the current results.

A cross-sectional analysis from the UK Biobank (27) identified a nonlinear relationship between sleep duration and HUA, with significant gender variations. Moreover, a study covering 31 provinces in China found that smoking was a specific risk factor for HUA among women (28). A cohort study also conducted in rural Henan, China, documented that regular physical activity is associated with a reduced incidence of HUA (29). A review emphasized the direct impact of diet on HUA and gout, highlighting that obesity contributes to insulin resistance (30).

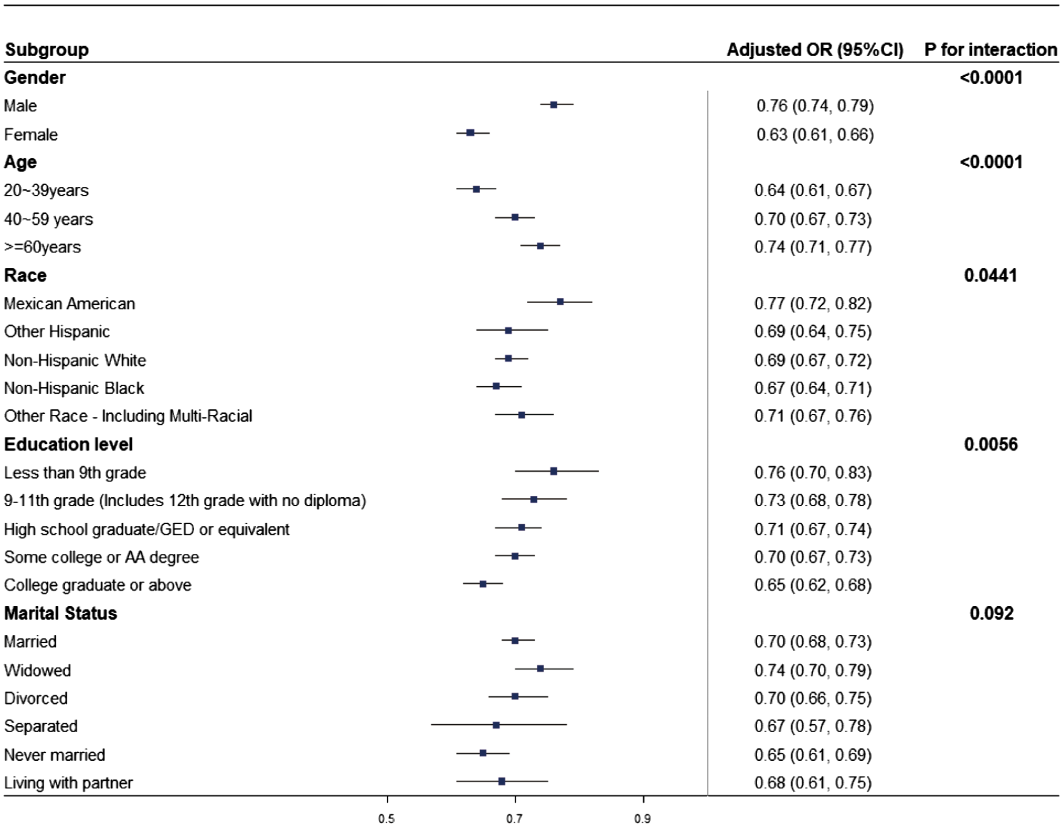


FIGURE 3
Subgroup analysis of the relationship between LE8 and HUA. The odds ratio (OR) was calculated for each 10-point increase in LE8. Each subgroup analysis was adjusted for age, marital status, education level, race, and gender.

Multiple studies have also reported a close association between blood pressure, blood glucose levels, lipid levels, and HUA (31–35). These factors, essential determinants of health and markers of healthful lifestyle choices, are all components of LE8. Therefore, it is imperative to adopt healthy lifestyles to prevent HUA (36). Although previous studies have typically focused on individual factors, LE8 presents a holistic and practical framework for fostering healthy behaviors and attaining optimal health metrics in clinical practice (37).

The precise mechanisms associated with LE8 and HUA remain incompletely understood, however, several hypotheses have been proposed. In subgroup analyses, LE8 showed a stronger association with HUA in women (OR = 0.63, 95% CI: 0.61, 0.66), indicating that the association between CVH indicators and lower uric acid levels might be more pronounced in females. This gender difference could originate from the conversion of testosterone to estrogens (38), the quantitative dependency of HUA on the concentration of sex hormones (39), and the protective effect of female sex hormones

TABLE 4 Threshold effect analysis of gender and age subgroups.

Uric Acid (mg/dl)	Adjusted β (95% CI) *p*-value			
	Gender		Age	
	Male (N = 12,821)	Female (N = 12,860)	Age ≤ 50 (N = 12,866)	Age>50 (N = 12,815)
Breakpoint	55	40.83	43.57	50
LE8 < Breakpoint	-0.01 (-0.01, -0.00) 0.0222	-0.00 (-0.01, 0.01) 0.8873	0.00 (-0.01, 0.01) 0.4845	-0.01 (-0.01, 0.00) 0.0503
LE8 ≥ Breakpoint	-0.02 (-0.03, -0.02) <0.0001	-0.02 (-0.03, -0.02) <0.0001	-0.02 (-0.03, -0.02) <0.0001	-0.03 (-0.03, -0.02) <0.0001
Log-likelihood ratio test	<0.001	<0.001	<0.001	<0.001

For the gender subgroups, adjustments were made for age, marital status, education level, and race. Adjustments were made for the age subgroups, including marital status, education level, race, and gender.

against HUA (40). Furthermore, gender differences in cardiovascular diseases may also affect the results, especially for women who are confronted with unique risk factors (41).

Age is a crucial factor in the relationship between LE8 and HUA, with a more significant correlation observed in younger individuals aged 20-39 years (OR = 0.64, 95% CI:0.61,0.67). This observation might be explained by the increased risk of developing other prevalent conditions like osteoporosis and thyroid dysfunction with advancing age, which could obscure the relationship between LE8 and HUA (42).

Specific living environments and lifestyles may influence ethnic differences. Moreover, genetic differences among ethnic groups, particularly in genes related to urate metabolism, might enhance or impair the function of urate transporters. Thus, these genetic variations could potentially affect the regulation of serum uric acid levels (43). More importantly, the differences in cardiovascular risk factors among different ethnic groups still exist, which may also impact the relationship between LE8 and HUA (44).

A stronger correlation between the LE8 and higher educational levels (OR = 0.65, 95% CI:0.62, 0.68) could be attributed to the association between higher education and a less healthy metabolic state (45), which is also associated with reduced susceptibility to cardiovascular risk factors (46). Moreover, individuals with higher educational attainment more closely follow medical recommendations and engage in disease prevention efforts.

This study has a nationally representative and substantial sample size, which is further strengthened by the incorporation of adjustments for confounding covariates, thereby increasing the reliability of the results. Comprehensive subgroup analyses were carried out to ensure the robustness and validity of the observed correlation. However, this study has certain limitations. Due to the cross-sectional study design, it was difficult to establish a direct cause-and-effect relationship between LE8 and HUA. This limitation underscores the need for more rigorous research methodologies to unravel the complex interaction between these factors. Future longitudinal studies on a broader scale are necessary to confirm the causal association between these factors. For example, the impact of LE8 scores on HUA risk will be monitored via longitudinal studies, while interventions will evaluate the efficacy of improvements in LE8-related factors in reducing HUA. Moreover, the data may contain potential biases. For example, potential biases (selection, information, recall) may affect NHANES data due to voluntary participation excluding some populations, misreporting of personal data, and inaccurate recall of past health behaviors, impacting the accuracy of LE8 score calculations. Lastly, despite adjusting for multiple confounding factors, it is feasible that this study did not fully account for all potential confounders. To enhance the generalizability of the current findings, future studies will aim to include more diverse population samples, facilitating a more comprehensive understanding of the relationship between LE8 and HUA across different populations and thereby providing more substantial evidence for its broader applicability and effectiveness.

5 Conclusions

Our study demonstrates a significant inverse association between LE8 and HUA, emphasizing the importance of maintaining a healthy lifestyle and favorable health metrics in managing HUA. Future longitudinal research will explore the causal relationships between HUA and LE8 scores over time, potentially enhancing the understanding of HUA progression and management.

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 below: https://www.cdc.gov/Nchs/Nhanes/.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

MW: Conceptualization, Data curation, Investigation, Methodology, Software, Visualization, Writing – original draft. HM: Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted without 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/fendo.2024.1445787/full#supplementary-material

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Evaluation of carotid artery elasticity and its influencing factors in non-obese PCOS patients using a technique for quantitative vascular elasticity measurement

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Objectives: To evaluate the intima-media thickness (IMT) and elasticity of the carotid artery in non-obese polycystic ovary syndrome (PCOS) patients using a quantitative technique for vascular elasticity measurement and to explore the influencing factors.

Methods: Sixty non-obese patients without metabolic and cardiovascular diseases who were diagnosed with PCOS in the Women and Children's Hospital of Chongqing Medical University from January to December 2022 were prospectively selected (case group), and 60 healthy volunteers matched for body mass index were included as the control group. Body weight, height, heart rate, blood pressure, and waist-to-hip ratio were recorded. Fasting blood samples were drawn from the elbow vein to measure hormone levels including total testosterone (TT), sex hormone-binding globulin (SHBG), fasting plasma glucose (FPG), fasting insulin (FINS), lipids, and homocysteine (Hcy). The insulin resistance index (HOMA-IR) and free androgen index (FAI) were calculated. Ultrasound elastography was used to measure the IMT and elastic function parameters of the right carotid artery, including vessel diameter, wall displacement, stiffness coefficient, and pulse wave velocity. Differences in various parameters between the two groups were analyzed, and correlations between the carotid stiffness coefficient and other serological indicators were assessed using Spearman correlation analysis.

Results: No significant differences in age, body mass index, heart rate, systolic blood pressure, and diastolic blood pressure were observed between the two groups (all P>0.05), while the waist-to-hip ratio (WHR) was higher in the case

group than in the control group (P<0.05).The hormone level serological indicators TT and FAI were higher in the case group than in the control group, and SHBG was lower in the case group than in the control group (all P<0.05). The metabolism-related serum indicators LDL-C, HDL-C, FPG, triglycerides, and total cholesterol levels were not statistically different between the two groups (all P>0.05), and serum FINS, HOMA-IR, and Hcy levels were significantly higher in the case group than in the control group (all P<0.05).No significant difference in carotid artery diameter was observed between the case group and control group (P>0.05). The carotid artery displacement in the case group was significantly smaller than that in the control group (P<0.05), and carotid IMT, hardness coefficient, and pulse wave propagation velocity were greater in the case group than in the control group (all P<0.05). The carotid elastic stiffness coefficient was positively correlated with WHR, TT, SHBG, FAI, FINS, HOMA-IR and Hcy to varying extents and negatively correlated with SHBG.

Conclusion: In non-obese PCOS patients with no metabolic or cardiovascular disease, the carotid stiffness coefficient was increased and correlated with indicators of hyperandrogenism, insulin resistance, and hyperhomocysteinemia.

KEYWORDS

polycystic ovary syndrome, body mass index, carotid artery elasticity, quantitative vascular elasticity, homocysteine, insulin resistance, hyperandrogenism

Introduction

Polycystic ovary syndrome (PCOS) is the most common gynecological disease in women of reproductive age, with an incidence of 5%–10%, and it leads to extremely complex endocrine and metabolic disorders, with vascular structural and functional abnormalities in the early clinical period and a significantly higher risk of complications in cardiovascular and cerebrovascular diseases in the long term (1). The prevalence of PCOS in women of reproductive age in China is 5.6%, and more than half of these patients are non-obese PCOS with a normal body mass index (BMI) (2). Because this population has a normal BMI and cardiovascular disease is not often present in the early stage, a method to assess cardiovascular and cerebrovascular disease risks early, comprehensively, and quantitatively represents an important clinical need.

The pathological basis of cardiovascular disease is atherosclerosis (AS), which can involve the arterial vascular beds of multiple organs throughout the body and cause different ischemic events (3). The carotid artery is the most commonly used ultrasound window for AS due to its superficial and fixed location and ease of detection. Two of the most important indicators assessed by ultrasound are the carotid medial intima-media thickness (CIMT) (4), which is a marker for predicting structural changes in the vascular wall, and the pulse wave propagation velocity (PWV) (5), which is important in evaluating the elasticity of large arteries.

Currently, many ultrasound techniques have been developed for evaluating the structure and elasticity of blood vessels, such as ultrafast pulse wave velocity (UFPWV), echo-tracking (ET), etc. However, the accuracy of the examination depends on the operator's skill and is affected by blood pressure, which limits the accuracy of the examination results (6–8). The ultrasound elasticity quantitative technology used in this study is a radio frequency data processing technology based on the current approaches used in the field of artificial intelligence and deep learning medical image recognition, and the main feature is the data acquisition frame frequency. The technology offers very high accuracy and fully automated measurement, which can avoid the limitations of the traditional measurement methods affected by data processing (9, 10). In this study, we applied the technique to assess the carotid artery elasticity in non-obese PCOS patients via ultrasound quantitative parameters and analyzed correlations with plasma Hcy, glucose-lipid metabolism, and sex hormones in order to identify AS risk factors independent of obesity in PCOS patients.

Materials and methods

Study participants

Sixty consecutive patients aged 20–40 years with confirmed PCOS who visited the Women and Children's Hospital of Chongqing Medical University from January to December 2022

were enrolled if they met the following inclusion criteria: normal body mass index (BMI <25 kg/m^2) (11) and PCOS diagnosed in accordance with the 2004 Rotterdam criteria (12). During the same period, 60 healthy volunteers who had regular menstruation, normal ovarian size and structure, and normal BMI were included as the control group. Participants were excluded from either group according to the following exclusion criteria: (1) presence of any other endocrine disease; (2) acute infection and glucocorticoid use in the previous 2 weeks; (3) intake of B vitamins and folic acid within the previous 6 months; (4) presence of hypertension or liver or kidney disease; or (5) CIMT >1.0 mm on ultrasound associated with carotid plaque formation.

Clinical data

The following data were recorded for all participants in both groups: age, heart rate, blood pressure, weight, height, waist-to-hip ratio (WHR), and BMI (weight/height^2). The WHR is the ratio of the waist circumference (smallest circumference of waist) to the hip circumference (largest circumference of buttocks). All measurements were performed with the participant in a natural standing position with the abdomen relaxed. Before blood pressure measurement, each participant rested quietly for approximately 15–20 min in a quiet environment and did not drink alcohol, coffee, or strong tea. Blood pressure was measured in the right upper arm using a Yutu brand XJ11D desktop standard sphygmomanometer (Shanghai Medical Device Company), and the data were averaged from three repeated measurements.

For serological testing of all participants, cubital venous blood was drawn in the morning after 8–12 h of fasting and on 3rd to 5th day of the participant's menstrual cycle (when no dominant follicles were detected by ultrasonography in amenorrhea patients). The blood samples were used to determine participants' levels of total testosterone (TT), sex hormone binding globulin (SHBG), fasting plasma glucose (FPG), fasting insulin (FINS), homocysteine (Hcy), and lipid levels, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). From these data, we calculated the homeostatic model assessment-insulin resistance (HOMA-IR), using the formula: HOMA-IR = FPG (mmol/L) × FINS (μU/mL)/22.5, as well as the free androgen index (FAI), using the formula: FAI = TT (nmol/L)/SHBG(nmol/L)×100%.

Ultrasound examination

Measurements were made with a Mindray Resona 8S color ultrasonic diagnostic apparatus (China), high-frequency linear array probe, frequency 2.5–9 MHz, and built-in digital system analysis software, including the RIMT and R-VQS systems. All participants underwent RIMT and R-VQS examination of the right carotid artery. When the acoustic beam was perpendicular to the anterior and posterior walls of the vessel and clearly showed the intima-media, the measurement points (region of interest: 15 mm) in the CIMT sampling frame were selected 1–2 cm below the bifurcation of the common carotid artery, and still images were obtained once the RIMT values were stable for six consecutive cardiac cycles. The instrument's built-in software automatically stored and analyzed the records to produce mean radial IMT values for the common carotid artery in six cardiac cycles, along with standard deviation (SD) values (Figures 1A, B). Using the same operating method, R-VQS analysis results were recorded, and the parameters obtained included carotid artery diameter (CADIA, mm), carotid artery wall displacement (CAWD, μm), the stiffness coefficient (VS), and PWV (m/s), as illustrated in Figures 2A, B.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 21.0 (IBM Corp. Armonk, NY, USA). Data conforming to a normal distribution were expressed as mean ± SD (x ± s). When the variance was equal, t-test of two independent samples was used for comparison between the two groups. Data that did not conform to a normal distribution were expressed as median (interquartile percentages [P25, P75]). The Mann–Whitney U test was used for comparison of non-normally distributed data between the two groups. Spearman correlation analysis was performed to identify correlations between the carotid stiffness coefficient and all parameters that showed a significant difference between the PCOS and control groups. Differences and correlations for which the *P* value was <0.05 were considered statistically significant.

Results

Comparison of clinical data between PCOS and control groups

Among the basic clinical data recorded, only the WHR differed significantly between the PCOS and control groups, with a higher WHR observed for PCOS patients ($P<0.05$; Table 1). Age, BMI, heart rate, SBP and DBP did not differ significantly between the two groups (all $P>0.05$).

Comparison of serological data between PCOS and control groups

Among the hormone levels and indices assessed in this study, TT and FAI were higher in the PCOS group than in the control group, and SHBG was lower in the PCOS group than in the control group (all P<0.05; Table 2). No statistical differences were detected in the metabolism-related serum indicators FPG, TC, TG, LDL-C, and HDL-C levels between the two groups (all $P>0.05$), whereas the serum FINS and Hcy levels as well as the HOMA-IR were significantly higher in the PCOS group compared with the control group (all $P<0.05$; Table 2).

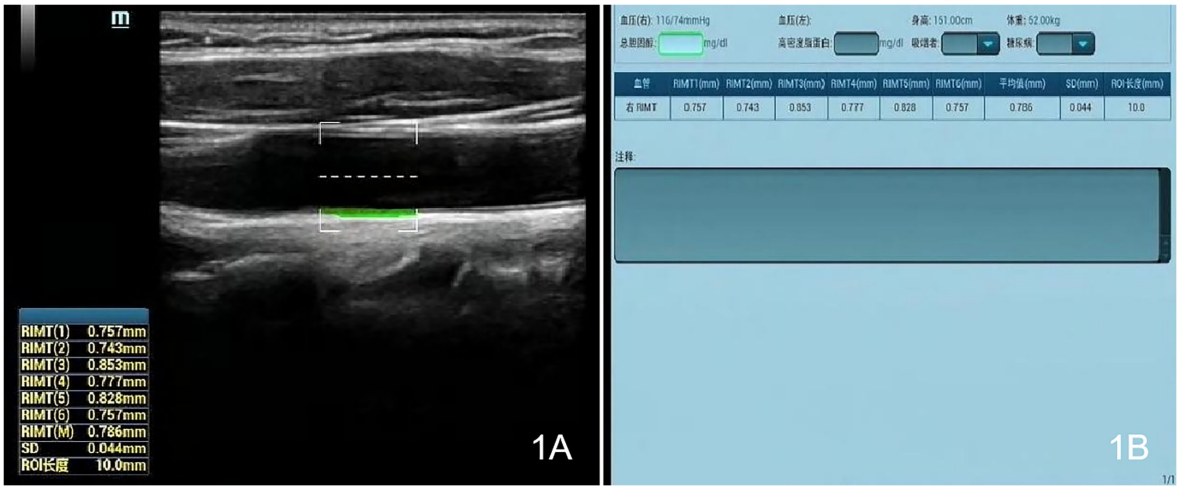

FIGURE 1
Each CIMT sampling frame was selected 1–2 cm below the bifurcation of the common carotid artery, and once the RIMT values were stable for six consecutive cardiac cycles, still images **(A)** and measurement data **(B)** were obtained.

Carotid artery elasticity in PCOS patients and correlation with clinical characteristics

Comparison of quantitative ultrasonographic results showed no significant difference in CADIA between the PCOS group and the control group (P>0.05). CAWD was significantly smaller in the PCOS group than in the control group (P<0.05), whereas the CIMT, VS, and PWV were greater in the PCOS group than in the control group (all P<0.05; Table 3).

From Spearman correlation analysis, the carotid elastic stiffness coefficient was positively correlated with WHR, TT, SHBG, FAI, FINS, HOMA-IR, and Hcy to varying degrees and negatively correlated with SHBG (Table 4 and Figure 3).

Discussion

This study investigated the changes in vascular elasticity in young, non-obese PCOS patients without traditional cardiovascular disease risk factors, and the results demonstrated that this group of patients still showed reduced vascular elasticity on carotid ultrasound elastography. Compared with an age- and weight-matched control group, the case group had significantly higher CIMT, PWV, and stiffness coefficient and significantly reduced vascular displacement (CAWD). We further explored the correlation between the stiffness coefficient and related serological indexes, and the results showed that vascular wall alterations were positively correlated with the accompanying hyperandrogenemia,

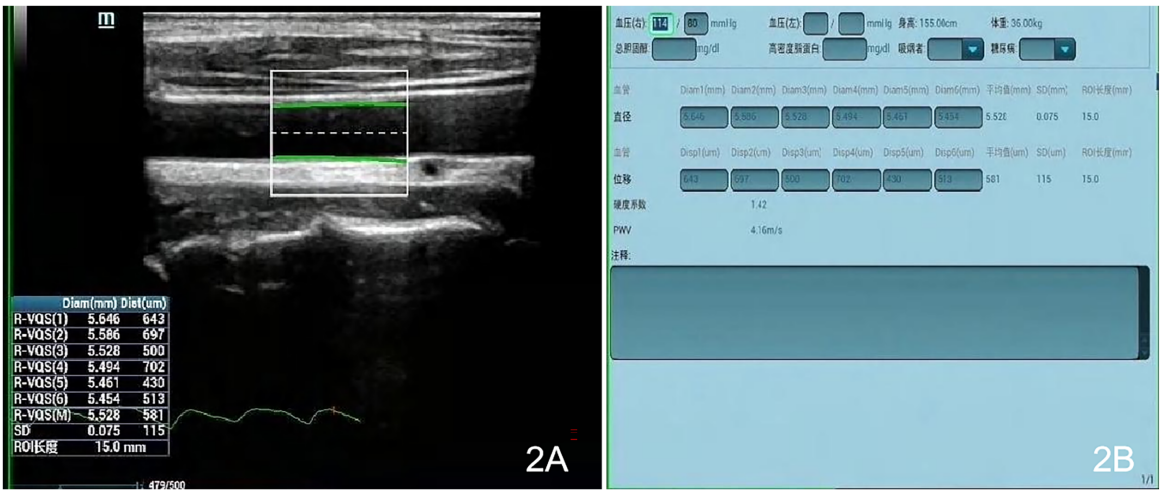

FIGURE 2
Each sampling frame was selected 1–2 cm below the bifurcation of the common carotid artery, and upon clicking the R-VQS system button, once the R-VQS analysis were stable for six consecutive cardiac cycles, the still images **(A)** and the parameters **(B)** were obtained including the carotid artery diameter (CADIA, mm), carotid artery wall displacement (CAWD, μm), stiffness coefficient (VS), and PWV (m/s).

TABLE 1 Basic clinical characteristics of PCOS patients and control participants.

	PCOS group (n=60)	Control group (n=60)	Z	*P*
Age (years)	28 (25.00, 30.00)	28 (26.00, 32.75)	-1.640	.101
BMI (kg/m^2)	22.31 (20.43, 23.29)	21.48 (20.76, 22.55)	-1.294	.196
WHR	0.76 (0.72, 0.81)	0.73 (0.69, 0.77)	-3.849	<.001
HR (bpm)	76.24 (67.25, 89.62)	83.36 (72.50, 89.70)	-1.265	.206
SBP (mmHg)	117.00 (110.00, 126.75)	114.96 (107.96, 125.95)	-.543	.587
DBP (mmHg)	76.00 (72.25, 86.00)	75.39 (68.96, 82.99)	-1.425	.154

BMI, body mass index; WHR, waist to hip ratio; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

insulin resistance, and hyperhomocysteinemia in PCOS patients to varying degrees. Thus, these indexes are clinically relevant for the early screening, evaluation, and follow-up of non-obese PCOS patients. This study explored the feasibility of utilizing vascular elasticity quantitative technology for non-invasive assessment of arterial vessel elasticity in non-obese patients with PCOS during the preclinical stage of atherosclerosis. The aim was to provide evidence-based clinical data to support the development of clinical preventive interventions.

Multiple studies (13–16) have demonstrated structural and functional abnormalities in the cardiovascular system in PCOS patients. The vascular changes associated with AS progress gradually, first appearing histologically as increases in collagen fibers and elastic fibers of blood vessels, with arterial wall thickening and arterial stenosis appearing later and eventually impairing the function of the perfused organs and leading to organ failure. Previous studies have suggested that the CIMT is the best ultrasound marker for detecting structural changes in the vascular wall in early AS (4). Accordingly, many studies have used the CIMT as an important indicator for evaluating the risk of AS in PCOS patients. However, Kim et al. (17) and other studies (18, 19) found that CIMT values in PCOS patients did not differ significantly from those in control groups. In a review by Alexandraki et al. (20), which retrospectively analyzed 71 studies that assessed IMT, 44 (62%) of the studies, including 2,761 patients with PCOS and 2,218 control participants, showed impairment in PCOS, whereas 27 studies, including 1,571 patients with PCOS and 1,286 control participants, did not show any difference between the groups. Such inconsistency in these findings may be related to the age of study participants, as the participants in studies that found no difference in CIMT between PCOS and control groups generally involved younger participants. Secondly, the CIMT is a marker of arterial structural change. Early changes are very small and become more significant in the later stage of AS progression. In the present study, the subjects were women of reproductive age (20–40 years old), and the CIMT values in these PCOS patients were higher than those in the control group. However, the difference was not as great as the differences in vascular elasticity parameters. In clinical studies, it is also recognized that vascular elasticity changes precede morphological changes. Thus, the detection of vascular elasticity by ultrasound is clearly more predictive in non-obese PCOS patients. The PWV in the quantitative ultrasound elasticity technique is the propagation velocity of the pressure wave in the blood vessel, and its size is directly related to the hardness of the blood vessel. This parameter was defined in the European Hypertension Guideline in 2003 (5) and holds an important

TABLE 2 Serological results for metabolism-related indicators in the PCOS and control groups.

	PCOS group (n=60)	Control group (n=60)	Z/t	P
TT(nmol/L)	2.50 (2.10, 2.88)	1.00 (0.80, 1.20)	-9.463	<.001
SHBG (nmol/L)	35.97 ± 8.59	44.26 ± 9.31	5.068	<.001
FAI	6.64 (5.36, 9.11)	2.26 (1.72, 2.93)	-9.353	<.001
FPG (mmol/L)	5.15 (4.73, 5.50)	4.90 (4.30, 5.58)	-1.587	.112
FINS (μIU/mL)	20.20 (13.05, 24.65)	6.45 (5.69, 7.59)	-7.912	<.001
Hcy (μmol/L)	11.40 (8.30, 15.98)	9.89 (7.10, 12.14)	-2.493	.013
TC (mmol/L)	4.19 (3.60, 4.78)	3.94 (3.39, 4.56)	-1.501	.133
TG (mmol/L)	2.05(1.61, 2.66)	2.03 (1.58, 2.34)	-.840	.401
LDL-C (mmol/L)	2.62 (2.32, 3.06)	2.59 (2.33, 3.06)	0.000	1.000
HDL-C (mmol/L)	1.40 (1.26, 1.57)	1.37 (1.16, 1.53)	-.916	.360
HOMA-IR	4.73 (2.76, 5.59)	1.44 (1.21, 1.69)	-7.810	<.001

TT, total testosterone; SHBG, sex hormone binding globulin; FAI, free androgen index; FPG, fasting plasma glucose; FINS, fasting insulin; Hcy, homocysteine; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance.

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TABLE 3 Carotid artery elasticity parameters in PCOS patients and control participants.

	PCOS group (n=60)	Control group (n=60)	Z	*P*
RCIMT (mm)	0.60 (0.57, 0.63)	0.57 (0.55, 0.60)	-3.223	.001
CADIA (mm)	6.15 (5.78, 6.65)	6.18 (5.94, 6.67)	-1.303	.193
CAWD (μm)	396.50 (354.25, 488.25)	640.00 (522.00, 690.00)	-7.372	<.001
VS	2.68 (2.29, 3.44)	1.53 (1.39, 1.89)	-8.260	<.001
PWV (m/s)	5.66 (5.18, 6.43)	4.11 (3.39, 4.44)	-8.389	<.001

RCIMT, right carotid intima-media thickness; CADIA, carotid artery diameter; CAWD, carotid artery wall displacement; VS, stiffness coefficient; PWV, pulse wave velocity.

position in the evaluation of the elasticity of large arteries. The CAWD can react to the degree of movement of the blood vessel, and with worsening elasticity, the displacement of the vessel is smaller. This key parameter in the quantitative ultrasound elasticity technique provides a quantitative and accurate means of measurement, that allows us to objectively assess subtle, early changes in vascular elasticity.

The findings in the present study of increased vascular stiffness are consistent with the results of most reported studies (20–23); however, a few studies still offer conflicting findings. Rees et al. (24) found that central arterial stiffness and diastolic dysfunction were not increased in young women with PCOS, whereas they were associated with both insulin resistance and central obesity. They both utilized distinct ultrasound indices to assess cardiovascular disease risk in PCOS patients, including the stiffness index (β), distensibility of the common carotid artery (CCA), and flow-mediated dilation (FMD) of the brachial artery. However, as the PCOS patients studied by these researchers had higher BMIs, arterial pressures, and basal insulinemia compared to the control participants, it remains ambiguous whether the presence of PCOS per se, rather than the comorbidities associated with this syndrome, was the primary contributor to this observed difference. This reduces the possibility that confounding factors are responsible for the differences between the populations studied, because the structure of the arterial wall slowly degrades with advancing age, hypertension, smoking, and coronary artery disease. Thus, the present study was designed to assess these markers in PCOS patients and a control population matched for age and BMI. In addition, all participants were young, normotensive, and nonsmokers with no signs or symptoms of cardiovascular disease. This study design aimed to reduce the biases stemming from population heterogeneity. Additionally, we employed advanced ultrasound imaging technology and more precise automated measurement software, thereby enhancing the accuracy and reliability of our data.

The cause of reduced arterial elasticity in PCOS is uncertain and appears to be related to the presence of individual cardiovascular risk factors. Insulin resistance plays a key role in the pathogenesis of PCOS, and while previous studies have suggested that obesity is one of the most important causes of insulin resistance, the present study found that non-obese patients with PCOS can also have insulin resistance. Insulin resistance in non-obese patients with PCOS may be related to a variety of factors such as genetics, endocrine abnormalities, inflammation, and other factors. In these patients, the cellular response to insulin becomes insensitive due to defective insulin receptors or abnormalities in the insulin signaling pathway. A chronic inflammatory state exacerbates this process and affects insulin efficacy and sensitivity. While insulin resistance is not only a metabolic abnormality in these patients, it is capable of directly leading to vascular endothelial and smooth muscle cell hypertrophy and differentiation, resulting in vascular endothelial dysfunction and vascular sclerosis (25). This is further supported by the study of Cussons et al. (26), who found that non-obese PCOS patients without concomitant insulin resistance did not have significantly altered arterial stiffness, implying an important role of insulin resistance in altered vascular stiffness.

Hyperandrogenemia is another distinguishing feature of patients with PCOS, especially in patients with a hyperandrogenemic phenotype, who have a higher prevalence of cardiovascular disease (27). Kilic et al. (28) suggested that androgen excess is independently

TABLE 4 Results of Spearman correlation analysis between VS and WHR, TT, SHBG, FAI, FINS, HOMA-IR, and Hcy.

			FINS	HOMA-IR	WHR	Hcy	TT	SHBG	FAI
VS	*r*		.609**	.607**	.211*	.525**	.608**	-.306**	.596**
	P		<.001	<.001	.021	<.001	<.001	.001	<.001
	95% CI	Lower Bound	.477	.471	.006	.366	.479	-.465	.467
		Upper Bound	.716	.715	.386	.652	.709	-.143	.711

**Confidence level of 0.01; the correlation is significant. *Confidence level of 0.05; there is a correlation.
FINS, fasting insulin; HOMA-IR, homeostatic model assessment-insulin resistance; WHR, waist to hip ratio; Hcy, homocysteine; TT, total testosterone; SHBG, sex hormone binding globulin; FAI, free androgen index.

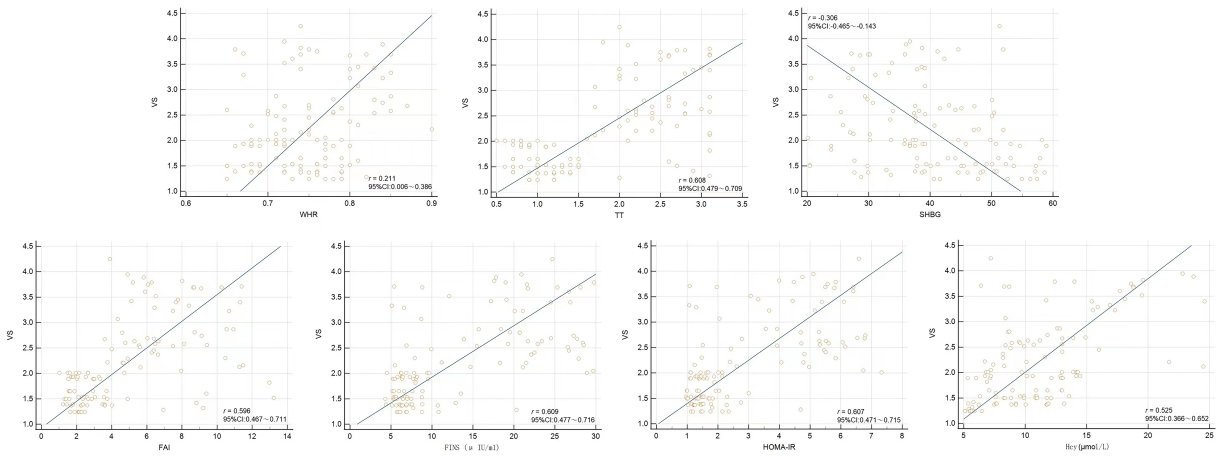

FIGURE 3
Scatter plots from Spearman correlation analysis between VS and WHR, TT, SHBG, FAI, FINS, HOMA-IR, and Hcy.

associated with increased arterial stiffness, an association that is attributed to the ability of excess androgens to affect vascular endothelial function and to promote smooth muscle cell proliferation and migration, thereby resulting in increased vascular stiffness. This idea that hyperandrogenemia is associated with an increased risk of cardiovascular disease is supported by the present study in nonobese PCOS patients.

Recent studies have focused on the role of chronic low-grade inflammation in the pathogenesis of PCOS (29, 30). Hcy is a sulfur-containing amino acid formed during methionine metabolism that has cytotoxic effects on the vascular endothelium (31). McCully et al. (32) first proposed that Hcy plays a role in the pathogenesis of arteriosclerosis, and this was subsequently confirmed by a large number of studies in diseases such as diabetes and hypertension. However, there are limited data on the association between high Hcy and AS in women with PCOS. One study (33) showed that high Hcy (H-Hcy) levels are positively and independently associated with elevated brachial and ankle pulse wave velocity (baPWV) in female patients with PCOS, suggesting that Hcy may play a role in the pathologic process of AS in women with PCOS. However, further studies in non-obese patients with PCOS were not conducted. We found that non-obese PCOS patients have a relatively higher Hcy that is positively correlated with the VS. Long-term high Hcy status increases oxidative stress and weakens the antioxidant response, which directly or indirectly damages vascular endothelial cells, promotes smooth muscle cell proliferation, changes blood coagulation status, and impairs platelet function, thus causing vascular damage and increasing the risk of long-term cardiovascular disease in PCOS patients (34, 35).

Obesity is also recognized as an independent risk factor for As. In the present study, the WHR was higher in non-obese PCOS patients than in control participants, indicating that even for patients with a normal BMI, abdominal obesity may still exist. Dumesic et al (36) suggested that intra-abdominal fat deposition in non-obese PCOS patients may be related to hyperandrogenism. Normal weight PCOS patients exhibit preferential intra-abdominal fat storage and have an increased number of small subcutaneous abdominal adipocytes, which could constrain subcutaneous adipose storage and promote metabolic dysfunction. For non-obese PCOS patients, the WHR can better reflect the obesity status and body fat distribution of non-obese PCOS patients compared with BMI, which may explain why it was found to be a more useful indicator for predicting the risk of AS. While healthy weight management may be important in treating PCOS patients, improving abdominal obesity should also be a goal in the health management of these patients.

The present study has some limitations. This study was a single-center, small-sample, cross-sectional study with possible bias, and there was no further categorization of different clinical phenotypes of patients with PCOS. Consequently, there remains a need for long-term, large-scale, prospective studies in PCOS patients, particularly focusing on cardiovascular outcomes across different PCOS phenotypes, to better understand the impact of PCOS on cardiovascular function. Future research could build upon the present findings by incorporating more datasets and expanding the sample size.

In summary, female patients with PCOS and normal BMI showed alterations in vessel wall thickness and elasticity even in the absence of traditional AS risk factors, indicating early signs of AS. These changes are associated with hyperandrogenism, insulin resistance, hyperhomocysteinemia, and abdominal obesity. Clinical attention should be paid to the risk factors for early-onset AS in non-obese PCOS patients and included in patient health management programs to slow the atherosclerotic process.

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 humans were approved by Clinical Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

YH: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. BC: Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation. YP: Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation. KX: Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation. ZX: Writing – review & editing, Resources, Project administration, Methodology, Formal analysis, Data curation. BS: Writing – review & editing, Validation, Supervision, Software, Project administration, Conceptualization. JL: Writing – review & editing, Validation, Supervision, Software, Project administration. HD: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Investigation, Funding acquisition, Formal analysis, Data curation. FL: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Data curation, Conceptualization.

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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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Associations between metabolic overweight/obesity phenotypes and mortality risk among patients with chronic heart failure

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Background: Metabolic disorders and overweight or obesity are highly prevalent and intricately linked in patients with chronic heart failure (CHF). However, it remains unclear whether there is an interactive effect between these conditions and the prognosis of heart failure, and whether such an interaction is influenced by stratification based on age and sex.

Methods: A total of 4,955 patients with CHF were enrolled in this study. Metabolic status was assessed according to the presence or absence of metabolic syndrome (MetS). BMI categories included normal weight and overweight or obesity (BMI < 24, ≥ 24 kg/m^2). Patients were divided into four phenotypes according to their metabolic status and BMI: metabolically healthy with normal weight (MHNW), metabolically unhealthy with normal weight (MUNW), metabolically healthy with overweight or obesity (MHO), and metabolically unhealthy with overweight or obesity (MUO). The incidence of primary outcomes, including all-cause and cardiovascular (CV) death, was recorded.

Results: During a mean follow-up of 3.14 years, a total of 1,388 (28.0%) all-cause deaths and 815 (16.4%) CV deaths were documented. Compared to patients with the MHNW phenotype, those with the MUNW (adjusted hazard ratio [aHR], 1.66; 95% confidence interval [CI], 1.38–2.00) or MUO (aHR, 1.42 [95% CI, 1.24–1.63]) phenotypes had a greater risk of all-cause death, and those with the MHO phenotype (aHR, 0.61 [95% CI, 0.51–0.72]) had a lower risk of all-cause death. Moreover, the above phenomenon existed mainly among males and elderly females (aged ≥ 60 years). In nonelderly females (aged < 60 years), the detrimental effects of MetS were lower (aHR, 1.05 [95% CI, 0.63–1.75] among MUNW group and aHR, 0.52 [95% CI, 0.34–0.80] among MUO group), whereas the protective effects of having overweight or obesity persisted irrespective of metabolic status (aHR, 0.43 [95% CI, 0.26–0.69] among MHO group and aHR, 0.52 [95% CI, 0.34–0.80] among MUO group). Similar results were obtained in the Cox proportional risk analysis of the metabolic overweight/obesity phenotypes and CV death.

Conclusions: In male and elderly female patients with CHF, the detrimental effects of MetS outweighed the protective benefits of having overweight or obesity. Conversely, in nonelderly females, the protective effects of having overweight or obesity were significantly greater than the adverse impacts of MetS.

KEYWORDS

chronic heart failure, mortality, metabolic syndrome, overweight or obesity, corhort study

Introduction

Cardiovascular disease (CVD) remains a significant global health challenge and is a leading cause of mortality and morbidity. According to statistics, the global incidence of CVD nearly doubled from 1990 to 2019, increasing from 217 million to 523 million cases, with corresponding deaths increasing from 12.1 million to 18.6 million (1). Chronic heart failure (CHF), a heterogeneous syndrome representing the end stage of various CVDs, is a significant contributor to global mortality, affecting 1–2% of adults worldwide (2). Factors such as population aging and increased life expectancy are driving the increasing prevalence of heart failure (HF) (3). CHF imposes a significant strain on health systems due to its high morbidity, high mortality rate, and negative influence on patient quality of life (4). Therefore, conducting an in-depth exploration of the prognostic factors and risk stratification for CHF is crucial to effectively reduce this ongoing burden.

Metabolic syndrome (MetS) encompasses a range of cardiovascular risk factors, including insulin resistance (IR), hypertension, dyslipidemia, and obesity, all of which heighten the risk of HF (5). Studies have shown that MetS is a significant risk factor for the onset and progression of HF and demonstrates a significant prevalence among patients with HF (5, 6). IR is the core feature of MetS, and numerous studies have established that IR significantly correlates with poor prognosis among patients with various CVDs, including HF (7–9). However, there remains controversy regarding the relationship between MetS and the prognosis of patients with HF. While some studies have indicated that MetS is linked to a worse prognosis of patients with HF (10–12), others have demonstrated no such association (13, 14). These discrepancies may stem from differences in the composition of the study populations and their metabolic profiles.

Obesity, as a key component of MetS, has a controversial impact on the prognosis of patients with HF, especially considering the obesity paradox. Some evidence supports the obesity paradox, which suggests that although having overweight or obesity is associated with a higher incidence of chronic diseases, it is closely related to better prognoses (15, 16). However, other studies challenge this idea, questioning its generalizability and applicability to specific groups (17–19).

Although MetS is frequently associated with overweight and obesity, it is important to note that not all individuals with MetS have overweight or obesity. Similarly, not every person with overweight or obesity has MetS; thus, this disease presentation demonstrates intersecting phenotypes. Few studies have specifically investigated the impact of metabolic overweight/obesity phenotypes on mortality outcomes in patients with CHF. Moreover, the complexities of the interaction between obesity and MetS and their impact on the prognosis of patients with HF remain incompletely understood (5). Therefore, this study aimed to bridge this significant knowledge gap by examining the relationship between different metabolic overweight/obesity phenotypes and mortality risk in patients with CHF. Additionally, considering that metabolic levels may be significantly influenced by age and sex (20, 21), we further conducted exploratory analyses according to sex–age stratification.

Abbreviations: CVD, cardiovascular disease; CHF, chronic heart failure; MetS, metabolic syndrome; IR, insulin resistance; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV death, cardiovascular death; MHNW, metabolically healthy with normal weight; MUNW, metabolically unhealthy with normal weight; MHO, metabolically healthy with overweight or obesity; MUO, metabolically unhealthy with overweight or obesity; WHO, World Health Organization; MAP, mean arterial pressure; BMI, body mass index; NYHA, New York Heart Association; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; ACEI/ARB/ARNI, angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitors; CCB, calcium channel blockers; SGLT2, inhibitors sodium-glucose co-transporter-2 inhibitors; CI, confidence interval; HR, hazard ratio.

Methods

Study design and population

In this study, we conducted a retrospective analysis of 6,384 patients with CHF admitted to The First Affiliated Hospital of Henan University of Science and Technology from July 1, 2017, to June 30, 2022. The definition of CHF followed the 2021 European Society of

Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2). Among the initial cohort of 6,384 patients, 1,429 were excluded in accordance with the following specified exclusion criteria: (1) age < 18 years or pregnancy; (2) severe hepatic or renal dysfunction; (3) advanced cancer or connective tissue diseases; (4) lacking data on body mass index (BMI), systolic blood pressure (SBP)/diastolic blood pressure (DBP), fasting blood glucose (FBG), triglyceride, or high-density lipoprotein cholesterol (HDL-C) at admission; and (5) in-hospital mortality or loss to follow-up. Ultimately, 4,955 patients were enrolled in this study. Furthermore, patients were categorized into four groups according to their metabolic status and BMI: metabolically healthy with normal weight (MHNW, n = 1398), metabolically unhealthy with normal weight (MUNW, n = 482), metabolically healthy with overweight or obesity (MHO, n = 1350), and metabolically unhealthy with overweight or obesity (MUO, n = 1725) (Figure 1).

Ethics statement

This retrospective study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the ethics committee of The First Affiliated Hospital of Henan University of Science and Technology (2023-03-K0026). Given the retrospective design of this research, the institutional review board exempted the requirement for informed consent and ensured that all patient-related information was anonymized.

Data collection and definitions

We gathered information on patient demographics, vital signs, medical history, laboratory test outcomes, echocardiographic data, and medication details from the electronic medical records system. Venous blood samples were collected for the analysis of laboratory indicators, including white blood cells (WBC), platelets, creatinine, serum lipid parameters, and N-terminal pro-brain natriuretic peptide (NT-proBNP), among others. The mean arterial pressure was calculated using the following formula: (SBP + 2 × DBP)/3. BMI was determined using the following formula: weight in kilograms divided by the square of height in meters, expressed as kg/m^2. Hypertension was defined as a history of hypertension or a diagnosis at admission. Chronic kidney disease was identified by an estimated glomerular filtration rate below 60 mL/min per 1.73 m^2,

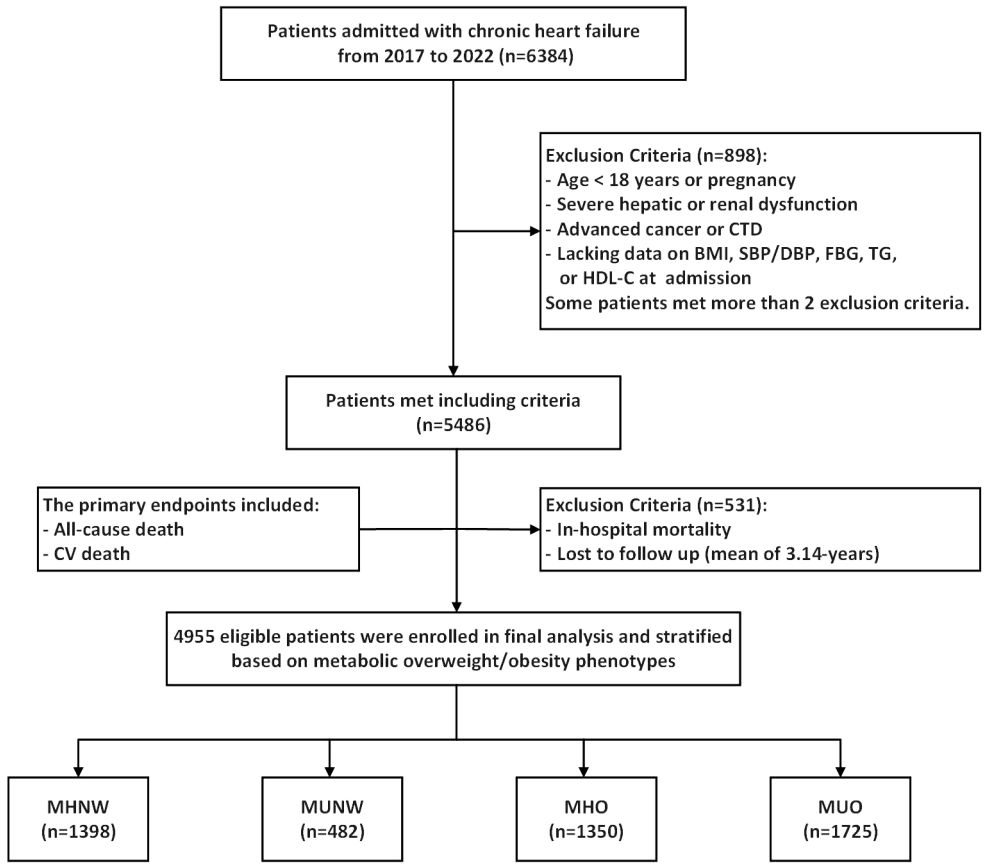

FIGURE 1
Flow diagram of patients selection. CTD, connective tissue diseases; BMI, body mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; CV death, cardiovascular death; MHNW, metabolically healthy with normal weight; MUNW, metabolically unhealthy with normal weight; MHO, metabolically healthy with overweight or obesity; MUO, metabolically unhealthy with overweight or obesity.

which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (22), or determined through medical history. Severe hepatic or renal dysfunction was defined as cirrhosis with ascites or chronic renal failure with dialysis treatment. To prevent the clinical missed diagnosis of diabetes, the diagnosis was further confirmed through the following criteria: a prior diagnosis of diabetes and/or FBG ≥7.0 mmol/L and/or random blood glucose ≥11.1 mmol/L and/or the use of hypoglycemic agents. Hypoglycemic medications included those prescribed at discharge as well as oral hypoglycemic drugs used during hospitalization, excluding SGLT2 inhibitors, as these were not exclusively used for patients with diabetes.

Metabolic status was evaluated by the presence or absence of MetS. According to the China Guidelines for Type 2 Diabetes (23) and the obesity criteria set by the Working Group on Obesity in China (24), which use BMI instead of waist circumference to assess obesity, MetS was identified by the presence of three or more of the following criteria: (1) obesity (BMI ≥ 28 kg/m^2); (2) hyperglycemia (FBG ≥ 6.1 mmol/L and/or clinically diagnosed diabetes by physician); (3) elevated blood pressure (blood pressure ≥ 130/85 mmHg and/or clinically confirmed hypertension); (4) fasting triglyceride ≥ 1.7 mmol/L; and (5) fasting HDL-C < 1.04 mmol/L. Obesity status was categorized as normal weight (BMI < 24 kg/m^2) or overweight/obesity (BMI ≥ 24 kg/m^2) by the definition of the Working Group on Obesity in China (24). According to the definition of the World Health Organization (WHO), overweight or obesity was classified as having a BMI of 25 kg/m^2 or higher, while obesity was classified as having a BMI of 30 kg/m^2 or higher (24).

Follow-up and outcomes

Prognostic data were acquired via telephone follow-ups or by examining pertinent electronic medical records over a mean follow-up duration of 3.14 ± 1.58 years. The primary outcomes of this study were all-cause mortality and cardiovascular death, with the latter primarily encompassing fatalities due to HF, sudden death, malignant arrhythmias, myocardial infarction, or other cardiac causes.

Statistical analysis

The characteristics of the participants were delineated according to metabolic overweight/obesity phenotypes. Continuous variables are reported as the mean ± standard deviation or median with interquartile range, depending on whether the distribution was normal. For continuous data, comparisons were made using one-way analysis of variance for normally distributed data and the Kruskal–Wallis test for skewed distributions. Categorical variables are presented as frequencies and percentages, with group differences evaluated using the chi-squared or Fisher's exact tests when appropriate.

The cumulative incidence of the primary endpoints was estimated using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. The relationship between metabolic overweight/obesity phenotypes and the incidence of primary outcomes was explored using Cox proportional hazards models. Predictors that achieved significance in univariate analyses ($P < 0.05$) (Supplementary Table S1) or were considered clinically important were selected as covariates in the multivariate Cox model. Furthermore, the multivariate analysis accounted for both collinearity and correlation among the variables. In addition to the unadjusted model, two other models were fitted: Model 1 controlled for age, sex, smoking status, and drinking status, and Model 2 included all variables from Model 1 with additional adjustments for New York Heart Association classification, left ventricular ejection fraction, NT-proBNP, creatinine, LDL-C, previous MI, atrial fibrillation, COPD, past CABG, ACEI/ARB/ARNI, β-blockers, diuretics, SGLT2 inhibitors, and other antidiabetic therapy. Multiple imputations with chained equations were utilized to handle missing covariates. The proportional hazards assumption was assessed through Schoenfeld residuals, revealing no observed potential violations. In this study, we conducted stratified analyses among different subgroups based on sex (male or female) and age (< 60 years or ≥ 60 years). Additionally, we performed sensitivity analysis, excluding the subset of the population potentially classified as having cardiac cachexia (BMI ≤ 20 kg/m^2) (25), to test the consistency of the results. Finally, we reclassified and further analyzed the metabolic overweight/obesity phenotypes based on the definition of overweight and obesity set by the WHO.

All the statistical analyses were performed using R software (version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria). A two-tailed P value <0.05 was considered to indicate significance.

Results

Participant characteristics

Table 1 details the baseline characteristics of the study population categorized by metabolic overweight/obesity phenotypes. In total, 4,955 eligible participants were included in the analysis.

The mean age was 65.4 years, and males accounted for 62.1%. Of these, 28.2% (n = 1398) were classified as MHNW, 9.7% (n = 482) as MUNW, 27.3% (n = 1350) as MHO, and 34.8% (n = 1725) as MUO.

Overall, the average age of the individuals in the metabolically unhealthy groups (MUNW and MUO) was greater than that of the individuals in the metabolically healthy groups (MHNW and MHO). Although there was a marginally greater proportion of females in the former groups than in the latter groups, this difference did not reach significance. The metabolic parameters, such as the mean arterial pressure, FBG, and lipid levels (excluding HDL-C), were elevated in the metabolically unhealthy groups compared to those in the metabolically healthy groups, whereas HDL-C exhibited an inverse association (all P <0.05). BMI levels were significantly greater in the overweight or obesity groups (MHO and MUO) compared to the normal weight groups (MHNW and MUNW). Regarding other laboratory parameters, the metabolically unhealthy groups exhibited higher WBC, platelets, and serum creatinine levels and lower eGFR

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TABLE 1 Baseline characteristics of the study population according to metabolic overweight/obesity phenotypes.

Characteristics	MHNW (n=1398)	MUNW (n=482)	MHO (n=1350)	MUO (n=1725)	*P* value
Demographics					
Age (years)	66.0 (55.2-74.0)	68.0 (57.0-77.0)	66.0 (55.0-74.0)	67.0 (57.0-77.0)	**<0.001**
Male (%)	869 (62.16%)	295 (61.20%)	850 (62.96%)	1062 (61.57%)	0.849
Medical measurements					
MAP (mmHg)	93.3 (84.0-101.0)	98.7 (93.0-107.2)	94.7 (87.0-102.3)	101.0 (92.7-109.0)	**<0.001**
HR (bpm)	77.0 (66.0-86.0)	76.0 (68.0-84.0)	76.0 (66.0-85.0)	76.0 (66.0-84.0)	0.076
BMI (kg/m^2)	21.4 (19.7-22.5)	21.5 (20.0-23.1)	26.3 (24.9-27.7)	28.4 (25.8-31.7)	**<0.001**
Current/ex-Smoker (%)	446 (31.90%)	157 (32.57%)	443 (32.81%)	573 (33.22%)	0.891
Current/ex-Drinker (%)	259 (18.53%)	82 (17.01%)	245 (18.15%)	348 (20.17%)	0.312
NYHA classification (%)					<0.001
I-II	723 (51.72%)	213 (44.19%)	630 (46.67%)	730 (42.32%)	
III	384 (27.47%)	153 (31.74%)	417 (30.89%)	572 (33.16%)	
IV	291 (20.82%)	116 (24.07%)	303 (22.44%)	423 (24.52%)	
Medical history (%)					
AF	363 (25.97%)	138 (28.63%)	344 (25.48%)	479 (27.77%)	0.343
CKD	362 (25.89%)	153 (31.74%)	356 (26.37%)	542 (31.42%)	**<0.001**
COPD	179 (12.80%)	70 (14.52%)	179 (13.26%)	287 (16.64%)	**0.010**
Diabetes	363 (25.97%)	319 (66.18%)	380 (28.15%)	1075 (62.32%)	**<0.001**
Hypertension	747 (53.43%)	370 (76.76%)	779 (57.70%)	1365 (79.13%)	**<0.001**
Previous MI	357 (25.54%)	158 (32.78%)	365 (27.04%)	568 (32.93%)	**<0.001**
Past PCI	386 (27.61%)	155 (32.16%)	409 (30.30%)	614 (35.59%)	**<0.001**
Past CABG	24 (1.72%)	8 (1.66%)	19 (1.41%)	35 (2.03%)	0.628
Laboratory measurements					
WBC (10^9/L)	6.30 (5.11-7.90)	6.65 (5.30-8.51)	6.24 (5.03-7.88)	6.51 (5.31-8.18)	**<0.001**
Platelets (10^9/L)	201.0 (160.0-242.0)	205.0 (163.2-246.0)	199.0 (162.0-245.0)	207.0 (167.0-254.0)	**0.007**
ALT (U/L)	24.0 (17.0-36.0)	24.0 (16.0-34.0)	24.0 (17.0-38.0)	25.0 (17.0-40.0)	0.227
AST (U/L)	23.0 (18.0-32.0)	22.0 (17.0-32.0)	24.0 (18.0-33.0)	23.0 (17.0-34.0)	0.320
Creatinine (umol/L)	70.5 (58.1-84.6)	72.5 (60.0-88.0)	70.5 (59.9-84.3)	73.0 (59.9-88.0)	**0.002**
eGFR (ml/min/1.73m^2)	89.2 (73.5-100.5)	85.9 (68.2-100.8)	89.7 (73.4-101.2)	86.8 (69.0-99.6)	**<0.001**
FBG (mmol/L)	5.19 (4.65-6.13)	6.74 (5.62-8.65)	5.38 (4.78-6.35)	6.46 (5.34-8.02)	**<0.001**
TC (mmol/L)	3.88 (3.24-4.72)	4.06 (3.34-4.88)	3.92 (3.29-4.64)	4.05 (3.32-4.83)	**0.002**
TG (mmol/L)	1.08 (0.81-1.46)	1.77 (1.24-2.36)	1.13 (0.84-1.52)	1.82 (1.12-2.20)	**<0.001**
LDL-C (mmol/L)	2.20 (1.68-2.84)	2.34 (1.72-2.95)	2.26 (1.70-2.83)	2.37 (1.82-3.02)	**<0.001**
HDL-C (mmol/L)	1.18 (1.05-1.38)	0.91 (0.79-0.98)	1.15 (1.06-1.35)	0.87 (0.76-1.08)	**<0.001**
Potassium (mmol/L)	3.92 (3.62-4.27)	3.89 (3.61-4.28)	3.91 (3.64-4.27)	3.91 (3.65-4.28)	0.830
Sodium (mmol/L)	141.1 (138.6-143.4)	140.6 (138.7-142.9)	141.3 (138.6-143.4)	141.3 (139.0-143.5)	0.211
NT-proBNP (pg/ml)	1415.5 (733.0-4431.5)	1687.0 (704.2-5535.8)	1405.0 (794.0-3482.5)	1567.0 (824.0-4567.0)	**<0.001**

(Continued)

TABLE 1 Continued

Characteristics	MHNW (n=1398)	MUNW (n=482)	MHO (n=1350)	MUO (n=1725)	*P* value
Echocardiography					
LVEF (%)	45.0 (36.0-57.0)	47.0 (36.0-59.0)	44.5 (35.0-57.0)	47.0 (36.0-58.0)	0.272
Medications (%)					
Antiplatelet agents	817 (58.44%)	324 (67.22%)	818 (60.59%)	1202 (69.68%)	**<0.001**
ACEI/ARB/ARNI	714 (51.07%)	265 (54.98%)	732 (54.22%)	982 (56.93%)	**0.013**
Beta-blocker	997 (71.32%)	381 (79.05%)	990 (73.33%)	1354 (78.49%)	**<0.001**
Statins	830 (59.37%)	336 (69.71%)	881 (65.26%)	1275 (73.91%)	**<0.001**
CCB	183 (13.09%)	92 (19.09%)	177 (13.11%)	349 (20.23%)	**<0.001**
Digoxin	194 (13.88%)	83 (17.22%)	222 (16.44%)	257 (14.90%)	0.162
Mineralocorticoid antagonists	958 (68.53%)	347 (71.99%)	929 (68.81%)	1230 (71.30%)	0.201
Diuretics	842 (60.23%)	326 (67.63%)	838 (62.07%)	1206 (69.91%)	**<0.001**
SGLT2 inhibitors	153 (10.94%)	111 (23.03%)	167 (12.37%)	360 (20.87%)	**<0.001**
Insulin	71 (5.08%)	64 (13.28%)	78 (5.78%)	205 (11.88%)	**<0.001**
Other oral antidiabetic agents	219 (15.67%)	177 (36.72%)	228 (16.89%)	608 (35.25%)	**<0.001**
Outcomes					
All-cause death	341 (24.39%)	180 (37.34%)	226 (16.74%)	641 (37.16%)	**<0.001**
CV death	199 (14.23%)	119 (24.69%)	128 (9.48%)	369 (21.39%)	**<0.001**

MHNW, metabolically healthy with normal weight; MUNW, metabolically unhealthy with normal weight; MHO, metabolically healthy with overweight or obesity; MUO, metabolically unhealthy with overweight or obesity; MAP, mean arterial pressure; HR, heart rate; BMI, body mass index; NYHA, New York Heart Association; AF, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; ACEI/ARB/ARNI, angiotensin converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitors; CCB, calcium channel blockers; SGLT2, inhibitors sodium-glucose co-transporter-2 inhibitors; CV, death cardiovascular death. P values <0.05 are presented in bold.

(all P <0.05). As expected, the risk of comorbidities, including chronic kidney disease, chronic pulmonary disease, diabetes, hypertension, previous myocardial infarction, and a history of PCI, was greater in the metabolically unhealthy groups compared to the metabolically healthy groups (all P <0.05). Although there were no discernible differences in left ventricular ejection fraction (P = 0.272) between the metabolically healthy and unhealthy groups, the latter demonstrated elevated New York Heart Association classification and NT-proBNP levels in comparison to the former (all P <0.05). Regarding medications, a greater proportion of patients in the metabolically unhealthy groups than in the metabolically healthy groups used antiplatelet agents, ACEIs/ARBs/ARNIs, beta-blockers, statins, calcium channel blockers, diuretics, or hypoglycemic agents (all P <0.05).

Association between metabolic overweight/obesity phenotypes and risk outcomes

After a mean follow-up of 3.14 years, there were 1,388 (28.0%) all-cause mortality events and 815 (16.4%) CV mortality events. The incidence rates (per 1,000 person-years) of the primary outcomes differed significantly between the metabolically healthy and unhealthy groups. Regarding all-cause mortality, the rates were 136.11 in the MUNW group and 118.54 in the MUO group, compared to 81.83 in the MHNW group and 48.38 in the MHO group. Similarly, CV mortality rates were also higher in the metabolically unhealthy groups, with rates of 89.98 in the MUNW group and 68.24 in the MUO group versus 47.75 in the MHNW group and 27.4 in the MHO group.

Figure 2 displays the Kaplan–Meier curves depicting the incidence of primary outcomes, including all-cause and CV mortality, across different metabolic overweight/obesity phenotypes. The results demonstrated that individuals identified as metabolically unhealthy (MUNW and MUO) exhibited a greater risk of primary events than did those in the MHNW group, irrespective of obesity status. Conversely, individuals in the MHO group displayed lower adverse outcome risk (log-rank test, both P < 0.001).

Table 2 shows the results of the univariate and multivariate Cox proportional hazards regression analyses in the four groups. According to an unadjusted model, compared to the MHNW group, which was used as the reference group, the metabolically unhealthy groups demonstrated significantly greater hazard ratios (HRs) for all-cause mortality, regardless of obesity status (HR, 1.66 [95% CI, 1.39–1.99] for the MUNW group and HR, 1.45 [95% CI,

1.27–1.66] for the MUO group). Conversely, the protective effects of having overweight or obesity were present in the MHO group (HR, 0.60 [95% CI, 0.51–0.71]) but dissipated in the MUO group (HR, 1.45 [95% CI, 1.27–1.66]). Even after adjusting for confounding variables in two different models, the results remained unchanged: patients in the metabolically unhealthy groups still faced a significantly greater risk of all-cause death (aHR, 1.66 [95% CI, 1.38-2.00] among MUNW group and aHR, 1.42 [95% CI, 1.24-1.63] among MUO group), while those in the MHO group continued to show a reduced risk (aHR, 0.61 [95% CI, 0.51-0.72]). Consistent outcomes were observed in the multivariate Cox proportional hazards analysis assessing the impact of metabolic overweight/obesity phenotypes on CV death. The aHRs and 95% CIs were 1.91 [1.51–2.41] for the MUNW group, 1.43 [1.19–1.71] for the MUO group, and 0.59 [0.47–0.73] for the MHO group.

Association of metabolic overweight/obesity phenotypes with mortality across age- and sex-stratified subgroups

We further conducted exploratory analyses in subgroups stratified by age and sex. Among both males and elderly females (aged ≥ 60 years), Kaplan–Meier analysis indicated that compared with individuals in the MHNW group, those in the MUNW and MUO groups had a greater risk of all-cause mortality, regardless of obesity status. However, individuals classified as MHO demonstrated a lower risk of all-cause mortality. In the subgroup of nonelderly females (aged < 60 years), we observed a different phenomenon: the detrimental effects of MetS were markedly diminished in the MUNW group or disappeared in the MUO group, while the protective effects of having overweight or obesity remained consistent across both the MHO and MUO groups, irrespective of metabolic status. The aforementioned findings remained consistent when CV death was used as the study endpoint (Supplementary Figure S1).

The results of the Cox proportional hazards analyses of the associations between metabolic overweight/obesity phenotypes and primary outcomes among different subgroups according to age and sex are presented in Supplementary Table S2. Consistent with the Kaplan–Meier analysis results, among males and elderly females, adverse prognostic risks persisted in the metabolically unhealthy groups (MUNW and MUO) compared to those in the MHNW group, irrespective of obesity status, even after multivariable adjustment (all $P < 0.05$). In contrast, individuals classified as MHO demonstrated a more favorable prognosis with MHNW as a reference in the aforementioned groups: for males under 60 years of age, the aHRs were 0.60 [0.41–0.87] for all-cause mortality and 0.52 [0.31–0.86] for CV mortality; for males aged 60 years and older, the aHRs were 0.64 [0.50–0.84] for all-cause mortality and 0.67 [0.48–0.94] for CV mortality; similarly, for females aged 60 years and older, the aHRs were 0.60 [0.42–0.84] for all-cause mortality and 0.52 [0.33–0.85] for CV mortality (Figures 3, 4).

However, different phenomena were observed among nonelderly females. First, the adverse prognostic effects of MetS were absent across all obesity statuses: the MUNW group exhibited aHRs of 1.05 [0.63–1.75] for all-cause mortality and 1.34 [0.68–2.63] for CV mortality (all $P > 0.05$); the MUO group displayed aHRs of 0.52 [0.34–0.80] for all-cause mortality and 0.52 [0.29–0.94] for CV mortality. Second, the protective effects of having overweight or obesity persisted and remained unaffected by MetS: the MHO group had an aHR of 0.43 [0.26–0.69] for all-cause mortality and 0.44 [0.23–0.85] for CV mortality; similarly, the MUO group had an aHR of 0.52 [0.34–0.80] for all-cause mortality and 0.52 [0.29–0.94] for CV mortality (Figures 3, 4, Supplementary Table S2). Additionally, we conducted a sensitivity analysis by excluding the population potentially characterized as having cardiac cachexia, identified by a BMI of ≤ 20 kg/m^2 (25). The results demonstrated that the

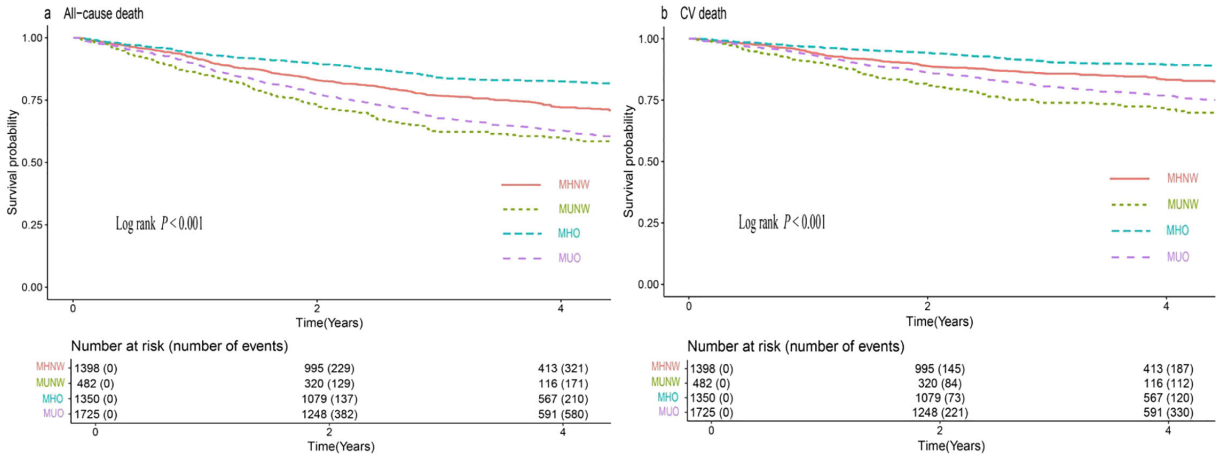

FIGURE 2
Kaplan-Meier estimation of **(A)** all-cause death and **(B)** CV death by metabolic overweight/obesity phenotypes in patients with HF. CV death, cardiovascular death; HF, heart failure; MHNW, metabolically healthy with normal weight; MUNW, metabolically unhealthy with normal weight; MHO, metabolically healthy with overweight or obesity; MUO, metabolically unhealthy with overweight or obesity.

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TABLE 2 HRs (95% CI) of primary outcomes according to metabolic overweight/obesity phenotypes.

Categories	Incidence/ 1000 person-y	Unadjusted		Model 1		Model 2	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause death							
MHNW (n=1398)	81.83	Ref.		Ref.		Ref.	
MUNW (n=482)	136.11	1.66 (1.39-1.99)	**<0.001**	1.64 (1.37-1.97)	**<0.001**	1.66 (1.38-2.00)	**<0.001**
MHO (n=1350)	48.38	0.60 (0.51-0.71)	**<0.001**	0.60 (0.51-0.72)	**<0.001**	0.61 (0.51-0.72)	**<0.001**
MUO (n=1725)	118.54	1.45 (1.27-1.66)	**<0.001**	1.43 (1.25-1.63)	**<0.001**	1.42 (1.24-1.63)	**<0.001**
CV death							
MHNW (n=1398)	47.75	Ref.		Ref.		Ref.	
MUNW (n=482)	89.98	1.88 (1.50-2.36)	**<0.001**	1.86 (1.48-2.33)	**<0.001**	1.91 (1.51-2.41)	**<0.001**
MHO (n=1350)	27.4	0.59 (0.47-0.73)	**<0.001**	0.58 (0.47-0.74)	**<0.001**	0.59 (0.47-0.73)	**<0.001**
MUO (n=1725)	68.24	1.44 (1.21-1.71)	**<0.001**	1.42 (1.20-1.70)	**<0.001**	1.43 (1.19-1.71)	**<0.001**

HR, hazard ratio; CI, confidence interval; MHNW, metabolically healthy with normal weight; MUNW, metabolically unhealthy with normal weight; MHO, metabolically healthy with overweight or obesity; MUO, metabolically unhealthy with overweight or obesity; CV death, cardiovascular death. P values <0.05 are presented in bold.
Model 1: adjusted for age, sex, smoking status, drinking status.
Model 2: adjusted for Model 1 + NYHA classification, LVEF, NT-proBNP, creatinine, LDL-C, previous MI, atrial fibrillation, COPD, past CABG, ACEI/ARB/ARNI, β-blocker, diuretics, SGLT2 inhibitors and other antidiabetic therapy.

conclusions remained unchanged both in the overall cohort and across all subgroups (Supplementary Table S3).

Association between metabolic overweight/obesity phenotypes based on the WHO definition and primary outcomes

We reclassified and conducted further analyses on the study population based on the WHO's definition of overweight and obesity. No substantial changes were observed within the overall population: for the MUNW group, the aHRs were 1.70 [1.45–1.98] for all-cause mortality and 1.87 [1.54–2.28] for CV mortality; for the MHO group, the aHRs were 0.61 [0.51–0.73] for all-cause mortality and 0.52 [0.41–0.66] for CV mortality; for the MUO group, the aHRs were 1.49 [1.30–1.70] for all-cause mortality and 1.46 [1.22–1.74] for CV mortality, with the MHNW group as a reference. In further analyses stratified by age and sex, the association of metabolic overweight/obesity phenotypes with either all-cause mortality or CV death remained consistent (Supplementary Table S4).

Discussion

In this study, we examined the association between metabolic overweight/obesity phenotypes and mortality among patients with CHF, with an additional focus on various subgroups delineated by age and sex. The findings suggest that MetS is closely associated with poor prognosis in patients with CHF independent of overweight or obesity status. In contrast, the influence of the obesity paradox was markedly affected by MetS, with the paradox only occurring in patients without MetS. These findings were primarily observed in males and elderly females. Interestingly, further observations revealed that in nonelderly females, the adverse effects of MetS were significantly diminished or entirely absent, whereas the protective effects of having overweight or obesity continued irrespective of metabolic status.

MetS represents a constellation of metabolic disorders with a high prevalence in the general population and is intricately linked with the development and progression of HF (5). Multiple studies have demonstrated that MetS is closely associated with the incidence of HF. Due to regional disparities, population characteristics, and variations in definitions, the prevalence of MetS among patients with HF ranged from 37% to 78.8%, indicating a generally high incidence trend (26). A Japanese cohort study of 3,603 patients showed that the incidence of MetS among patients with CHF is over twice that of the general population (6). The probability that MetS leads to HF may be linked to its core components and fundamental changes, particularly IR. First, long-term hypertension can result in HF through various mechanisms, including concentric hypertrophy, myocardial insult, eccentric hypertrophy, and imbalances in the neurohumoral regulation system of the body (27). Second, hyperlipidemia may induce HF by promoting oxidative stress and inflammatory cardiac fibrosis, reducing autophagy and microvascular density in cardiac myocytes, altering mitochondrial function in myocardial cells, and ultimately leading to cardiac dysfunction and electrophysiological alterations (28). Third, diabetes-induced hyperglycemia and hyperinsulinemia can cause capillary damage, myocardial fibrosis, and myocardial hypertrophy with mitochondrial dysfunction (29). Fourth, IR may lead to HF through several pathways, including mitochondrial dysfunction in myocardial cells, reduced cardiac efficiency, increased oxidative stress, inflammation, elevated apoptosis, and myocardial fibrosis (8). Similarly, HF can impair insulin sensitivity through mechanisms such as the excessive stimulation of β-adrenergic

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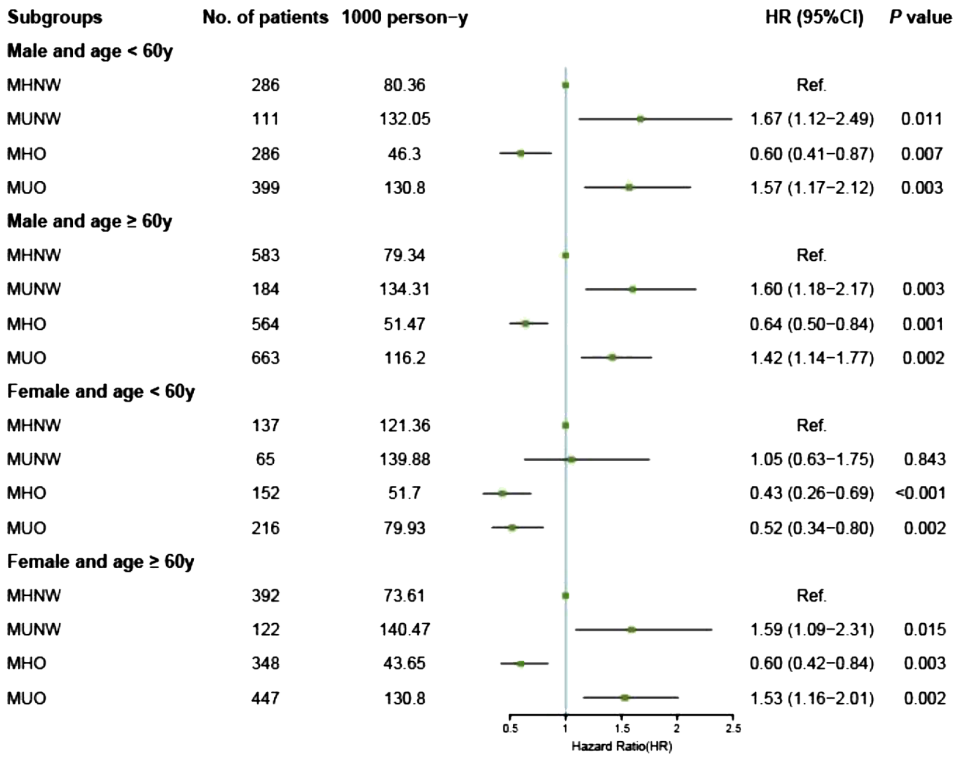

FIGURE 3
Forest plot of all-cause death according to metabolic overweight/obesity phenotypes in patients with HF adjusted for model 2. HR, hazard ratio; CI, confidence interval; HF, heart failure; MHNW, metabolically healthy with normal weight; MUNW, metabolically unhealthy with normal weight; MHO, metabolically healthy with overweight or obesity; MUO, metabolically unhealthy with overweight or obesity.

receptors, thereby triggering or exacerbating IR and creating a vicious cycle (30).

Although MetS is closely and significantly associated with the incidence and progression of HF, studies on the association between MetS and the prognosis of patients with HF have yielded inconsistent results. A cohort study of an Asian population included 4,762 patients with CHF, 41.3% of whom had MetS. Over a follow-up period of 3.2 ± 1.1 years, the study revealed that MetS was associated with an increased incidence of composite endpoints of all-cause mortality and atherosclerotic events in male patients in this cohort (aHR, 1.28 [95% CI, 1.06–1.54], $P = 0.011$) (10). Another study involving 865 indigent patients with HF revealed that during an average follow-up period of 2.6 ± 2.2 years, the mortality rate among those with MetS was 24%, compared to 16% among those without MetS. After multivariate adjustment, the relative risk of death associated with MetS was 1.5 (95% CI: 1.1–2.1) (11). However, other studies revealed different results. One study of HF in a Korean population indicated that although individuals with MetS face increased cardiovascular risk, their mortality rate from HF is relatively lower (13). A meta-analysis encompassing 10 studies with a total of 18,590 patients with HF indicated that MetS was not associated with all-cause mortality (HR, 1.04 [95% CI, 0.88–1.23]) but increased the risk of composite cardiovascular events (HR, 1.73 [95% CI, 1.23–2.45]) (31). The variations across study results may stem from differences in the definition of metabolic disturbances and the composition of study populations and their metabolic characteristics. Therefore, further research remains necessary to reach a consensus on these controversial phenomena.

Patients who have overweight or obesity exhibit increased susceptibility to various metabolic impairments (32) and are more likely to exhibit predispositions toward MetS. Additionally, numerous studies have confirmed that having overweight or obesity is a risk factor for the development of HF. A Mendelian randomization analysis incorporating two principal Danish cohorts and additional genetic data from extensive databases such as GIANT, HERMES, and the UK Biobank established a significant causal link between BMI and HF (18). The analysis revealed that every 1 kg/m^2 increase in BMI was associated with a 39% greater risk of HF, with a causal risk ratio of 1.39 [95% CI: 1.27–1.52]. Another study included 4,033 individuals with obesity who had no history of HF at baseline; 2,003 underwent bariatric surgery, and the remaining 2,030 received usual care. Over a median follow-up period of 22 years, the incidence of HF was significantly lower in the surgical group than in the usual care group (HR, 0.65 [95% CI, 0.54–0.79], $P < 0.001$) (33). This finding suggests that the risk of HF decreases with the extent of weight loss. The mechanisms by which individuals with elevated BMI are susceptible to HF are diverse and can be classified into indirect and direct pathways (34). Indirect pathways involve a heightened risk of conditions such as hypertension, diabetes, and hyperlipidemia associated with overweight and obesity (35). These conditions are intimately connected to cardiovascular diseases and significantly increase the

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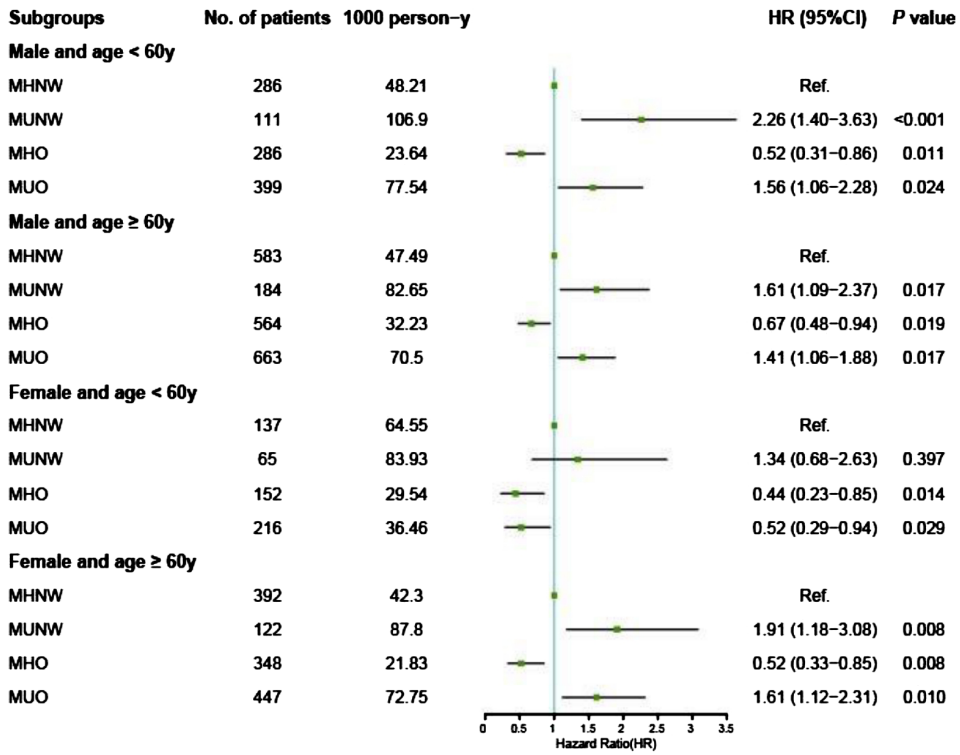

FIGURE 4
Forest plot of CV death according to metabolic overweight/obesity phenotypes in patients with HF adjusted for model 2. CV death, cardiovascular death; HR, hazard ratio; CI, confidence interval; HF, heart failure; MHNW, metabolically healthy with normal weight; MUNW, metabolically unhealthy with normal weight; MHO, metabolically healthy with overweight or obesity; MUO, metabolically unhealthy with overweight or obesity.

likelihood of HF. Direct mechanisms involve tissue inflammation, endothelial dysfunction, alterations in hemodynamics, and increased sympathetic nerve activity, which collectively lead to myocardial remodeling and the subsequent onset of HF (34).

Some studies have suggested the existence of an obesity paradox regarding the correlation between overweight or obesity and the prognosis of patients with HF. This obesity paradox posits that although elevated body weight is associated with an increased incidence of HF, it correlates with more favorable prognostic outcomes (5). Several possible mechanisms for the obesity paradox phenomenon have been proposed (36): it is suggested that patients with obesity may maintain higher levels of glucose and metabolic substrates, reduced sympathetic activity, and lower norepinephrine levels, which could compensate for the adverse effects of high metabolism and high energy expenditure caused by HF. However, some researchers have challenged the idea of this paradoxical phenomenon, suggesting that a higher BMI may be linked to increased mortality rates in patients with HF or raising doubts about the universality of the obesity paradox, proposing that it might only apply to certain specific subgroups (17–19).

Currently, the associations between metabolic dysregulation and overweight or obesity and the prognosis of patients with HF remain controversial and uncertain. Although MetS and overweight or obesity can influence each other and often coexist, this is not always the case. Many patients exhibit either isolated metabolic disorders or obesity, resulting in different metabolic overweight/obesity phenotypes. Previous studies on metabolically unhealthy phenotypes and their prognoses have primarily focused on populations with cancer or nonheart failure conditions (37–39), with few studies investigating the relationship between these phenotypes and the prognosis of patients with HF. Our research revealed that in the overall population with CHF, the adverse effects of MetS on prognosis do not change with alterations in obesity status, indicating that the MUNW and MUO phenotypes are closely associated with mortality risk. We observed that the obesity paradox is only present in the MHO phenotype. The primary reason behind this phenomenon is the higher metabolic compensation capacity in individuals with obesity, with skeletal muscle playing a crucial role. In patients with chronic diseases, skeletal muscle atrophy is significantly influenced by metabolic disorders (40), whereas in metabolically healthy patients with HF, the increased weight proportion is likely attributed to non-fat tissues such as skeletal muscle. As a major reservoir for glucose and protein, skeletal muscle plays an important role in energy and metabolic supplementation (41) and is closely associated with the prognosis of patients with HF (42). However, the obesity paradox is clearly influenced by metabolic status, disappearing within MetS presence. We propose that the following two factors might explain this phenomenon. First, patients with MetS exhibit elevated IR and may be in a state of chronic inflammation (43). Their energy metabolism expenditure could be more pronounced than that of patients without MetS, potentially offsetting the energy storage benefits associated with

overweight or obesity. Second, in the context of the obesity paradox, energy storage and the amelioration of chronic disease outcomes may be primarily facilitated by an increase in muscle mass or subcutaneous fat rather than visceral adipose tissue (VAT) (44, 45). However, MetS is closely associated with increased VAT (46). Therefore, in individuals with overweight or obesity and MetS, the increase may predominantly be in VAT content rather than muscle mass or subcutaneous fat. VAT can adversely affect cardiovascular diseases (47), leading to the disappearance of the obesity paradox in individuals with MetS.

Finally, given that metabolic levels may vary across different age and sex groups (20, 21), we conducted a stratified exploratory analysis by age and sex. The results of the exploratory analysis indicate that among males and elderly females, the following conclusions still hold: the adverse prognostic impacts of MetS are unaffected by obesity status, while the obesity paradox is significantly influenced by metabolic status. Interestingly, in nonelderly females, we observed a completely different phenomenon: the detrimental effects of MetS disappeared regardless of obesity status, and the obesity paradox persisted without being influenced by metabolic status. We speculated that the primary reason for this phenomenon may be associated with the relatively higher levels of estrogen in nonelderly females. First, the protective effects of estrogen on the cardiovascular system (48) could partially counterbalance the detrimental impacts of adverse metabolic conditions. Second, estrogen can influence fat distribution, notably by favoring peripheral rather than visceral fat accumulation (49), which may lessen or nullify the negative effects of MetS on visceral fat distribution. Third, although we hypothesize that estrogen levels may reduce the adverse effects of MetS and intensify the manifestations of the obesity paradox, we currently do not recommend estrogen supplementation for such patients due to the lack of support from large-scale clinical trial data and the potential risks of increased incidence of diseases such as breast and ovarian cancers (50). Finally, we reclassified and analyzed the study population based on the WHO definition, observing no significant changes in the outcomes. This supported the applicability of our findings across various ethnic groups.

Limitations

This study has several limitations. First, despite the large sample size, the investigation did not comprehensively track the evolution of metabolic status in the enrolled patients owing to insufficient information during the follow-up period. Second, the follow-up phase might be subject to some degree of recall or reporting bias, especially regarding the date and cause of death. Third, inherent to observational studies, unmeasured confounding factors could influence the outcomes, necessitating cautious interpretation of the results. Fourth, this study was fundamentally observational; hence, it was impossible to establish a causal relationship between the exposure factors and the observed outcomes. Fifth, we were unable to obtain measurements of skeletal muscle mass, thus precluding an evaluation of its prognostic value in patients with obesity. Finally, as this was a retrospective study relying on existing electronic medical records, the accuracy of baseline information was potentially limited. This could have affected the interpretation of results, and such limitations should have been considered when analyzing the findings. Future studies could consider employing a prospective design to enhance data quality.

Conclusions

In patients with CHF, the prognostic effects of MetS and overweight or obesity interact and are influenced by age and sex. In males and elderly females, the detrimental impacts of MetS surpass the protective advantages offered by overweight or obesity. Conversely, in nonelderly females, the protective effects of having overweight or obesity significantly outweigh the negative consequences of metabolic disorder. These findings emphasize the importance of prioritizing the management of metabolic disorders within specific populations. Additionally, in order to effectively improve patient outcomes, further research is necessary to understand the underlying mechanisms of the difference in the relationships between overweight or obesity and survival among patients with heart failure concomitant with MetS.

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to KH, kunlunhe_301@163.com.

Ethics statement

The studies involving humans were approved by The Ethics Committee of The First Affiliated Hospital of Henan University of Science and Technology. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YZ: Data curation, Formal analysis, Writing – original draft. YX: Data curation, Formal analysis, Writing – original draft. JD: Data curation, Methodology, Writing – original draft. KH: Supervision, Writing – review & editing.

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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/fendo.2024.1445395/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Kaplan–Meier estimation of all-cause death and CV death by metabolic overweight/obesity phenotypes among different subgroups: **(A1)** all-cause death in male and age < 60y group, **(A2)** CV death in male and age < 60y group, **(B1)** all-cause death in male and age ≥ 60y group, **(B2)** CV death in male and age ≥ 60y group, **(C1)** all-cause death in female and age < 60y group, **(C2)** CV death in female and age < 60y group, **(D1)** all-cause death in female and age ≥ 60y group, **(D2)** CV death in female and age ≥ 60y group. *CV death* cardiovascular death, *MHNW* metabolically healthy with normal weight, *MUNW* metabolically unhealthy with normal weight, *MHO* metabolically healthy with overweight or obesity, *MUO* metabolically unhealthy with overweight or obesity.

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Association of erectile dysfunction and peripheral arterial disease in NHANES 2001-2004: a cross-sectional study

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Objective: To evaluate the association between Erectile dysfunction (ED) and peripheral arterial disease (PAD) in adult American males using a large database.

Methods: The relationship between ED and PAD prevalence among participants in the 2001-2004 National Health and Nutrition Examination Survey (NHANES) database was assessed using a series of statistical analyses. ED was evaluated based on a single-item measure of self-reported erection problems from the Massachusetts Male Aging Study. PAD was defined as ankle-brachial index (ABI) < 0.9 in at least one leg. Multifactorial logistic regression models were used to investigate the association between ED and PAD.

Results: A total of 2394 participants were enrolled, of whom 905 individuals (37.8%) were diagnosed with ED. After adjusting for confounding variables, the association between ED and PAD remained positive, with an odds ratio of 2.05 (95% confidence interval 1.24-3.39). Subgroup analysis revealed that the relationship between ED and PAD was significant in patients aged >50 years old, without hypertension, without diabetes, without cardiovascular disease, without high cholesterol, former smokers, low physical activity levels, and a body mass index of 25-30 ($P < 0.05$). In addition, all subgroups analyzed were evaluated for any potential interaction, and no statistically significant association was discovered.

Conclusions: In a sample of US adults aged ≥40, this cross-sectional study found that ED is related to a higher occurrence of PAD. ED may be an independent predictor of PAD, and thus it should be considered in the treatment of patients with ED.

KEYWORDS

erectile dysfunction, peripheral arterial disease, ankle-brachial index, cross-sectional study, NHANES

1 Introduction

Erectile dysfunction (ED) is estimated to affect approximately 152 million males globally, with the prevalence projected to rise to 322 million cases by the year 2025 (1). Increasing evidence suggests a strong link between erectile dysfunction and atherosclerosis (2, 3). Several meta-analyses have shown that erectile dysfunction significantly increases the likelihood of experiencing a stroke, coronary heart disease (CVD), cardiovascular disease, and death from any cause (4, 5).

Peripheral arterial disease (PAD) is a significant cardiovascular condition caused by atherosclerosis, mainly affecting the arteries in the legs (6). The global prevalence of PAD continues to ascend annually, impacting over 200 million individuals, particularly middle-aged and elderly individuals (7). Nevertheless, PAD is often undiagnosed due to a lack of PAD-related knowledge and awareness and a high number of asymptomatic cases (8). Despite the established link between ED and atherosclerosis, the connection between ED and PAD is poorly understood. Reports on the association between ED and PAD are scanty, with only a few studies examining specific populations, such as diabetic individuals or those at elevated risk for CVD (9–11). Therefore, whether ED is a predictor of PAD or whether it can be utilized to identify individuals who would benefit from PAD screening remains elusive.

The study sought to investigate the link between ED and PAD by analyzing the National Health and Nutrition Examination Survey (NHANES) data collected between 2001 and 2004.

2 Materials and methods

2.1 Study population

The study utilized data from the NHANES database, a major program of the National Center for Health Statistics (NCHS), which is part of the Centers for Disease Control and Prevention (CDC). NHANES applies a sophisticated, multistage, probability sampling design to assess the dietary intake, health, and nutritional status of noninstitutionalized adults and children in the United States (12). Standardized interviews, physical exams, and laboratory tests are conducted to gain an understanding of various population demographics. NHANES data have been available for research since 1999 and are released biennially. Data from the 2001-2002 and 2003-2004 NHANES cycles were used in the present study. More details are available on the NHANES website (https://www.cdc.gov/nchs/nhanes/).

Only the data sets from the 2001-2002 and 2003-2004 NHANES cycles were chosen for cross-sectional analysis due to the lack of ED and ankle-brachial index (ABI) values in other NHANES cycles. Between 2001 and 2004, 21161 people participated in NHANES. Participants were excluded based on the following criteria: being female (n = 10860); missing ED data (n = 6185); previously diagnosed with prostate cancer (n = 36); missing ABI data (n = 1638); having an ABI ≥ 1.4 (n = 48). A total of 2394 cases were included in the final analysis, encompassing 905 individuals with ED and 1489 controls.

2.2 Data collection and definition

2.2.1 Assessment of ED

Private interviews were carried out at the MEC using audio computer-assisted self-interview (ACASI) methodology. Evaluating ED involved answering a specific question from the Massachusetts Male Aging Study: "How would you describe your ability to get and keep an erection adequate for satisfactory intercourse?" Response options included "always or almost always able", "usually able", "sometimes able", and "never able". Participants were categorized as having ED if they reported being 'sometimes able' or 'never able', while those who reported being 'always or almost always able' or 'usually able' were classified as not having ED (13).

2.2.2 Assessment of PAD

PAD was defined as ABI < 0.9 in one leg (14). Systolic blood pressure (SBP) was measured on the brachial artery of one arm, with a preference for the unaffected arm if there were doubts about the measurement on the right arm. Furthermore, the SBP in both ankles was assessed utilizing the posterior tibial artery. The ABI was calculated as the systolic ankle pressure divided by the systolic arm pressure on both sides.

2.3 Covariates of interest

Variables were chosen according to established confounding factors in prior research and medical practices. Various variables were analyzed, including age, ethnicity, level of education, marital status, family income, hypertension, diabetes, CVD, high cholesterol, smoking habits, alcohol consumption, physical activity, and body mass index (BMI) (15).

Individuals were categorized based on ethnicity (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and other ethnicities, including American Indian or Alaska Native, Native Hawaiian, other Pacific Islander, and individuals of mixed race), education levels (less than high school, high school, and more than high school), marital status (married/living with partners, widowed/divorced/separated, and never married), household poverty-to-income ratio (PIR) (low (≤1.3), medium (1.3-3.5), or high (≥3.5)), and blood pressure (SBP ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg). Diabetes was characterized by self-reported diabetes or glycated hemoglobin level of ≥6.5% (16). CVD was defined as individuals who were previously diagnosed with congestive heart failure, coronary artery disease, angina, or a heart attack. Those diagnosed with high blood cholesterol levels were given medication for hypercholesterolemia; individuals with a total cholesterol reading of ≥240 mg/dL were categorized as having elevated cholesterol. Individuals who had previously smoked a minimum of 100 cigarettes and were presently smoking during the survey were categorized as current smokers.

Those who had previously smoked at least 100 cigarettes in their lifetime and were not currently smoking during the survey were classified as former smokers. Meanwhile, males who had previously smoked less than 100 cigarettes in their lifetime were categorized as nonsmokers. Participants who had consumed at least 12 alcoholic beverages in their lifetime or within a year and had consumed alcohol within the previous year were classified as current drinkers. Participants were categorized into three groups based on their self-reported leisure-time physical activity levels: inactive, moderate, and vigorous. Additionally, the body mass index (BMI) was categorized into three groups: underweight/normal weight (<25.0 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30.0 kg/m^2).

2.4 Statistical analysis

Continuous variables were presented as weighted means with standard deviations and analyzed using either the independent samples T-test or the Mann-Whitney test. Categorical variables were expressed as weighted percentages along with 95% confidence intervals (95% CI) and assessed using the χ^2 test. Multivariate logistic regression was performed to investigate the relationship between ED and PAD. Three distinct models were employed: Model 1 without modifications, Model 2 with adjustments for age, race, and education level, and Model 3 with further adjustments for marital status, PIR, hypertension, diabetes, CVD, high cholesterol, smoking, alcohol consumption, physical activity, and BMI.

Subgroup analyses and interaction tests were also conducted. All data were analyzed using R software (The R Foundation, http://www.R-project.org) and Empower Stats (X&Y Solutions, Inc., Boston, MA, http://www.empowerstats.com). The sample weights were created to account for the complex survey design. Two-sided $P < 0.05$ was considered statistically significant.

3 Results

3.1 Characteristics of the participants

A total of 21161 individuals participated in 2001-2004 NHANES. After a meticulous screening procedure, 2394 participants met the eligibility criteria, of whom 905 individuals (37.8%) were diagnosed with ED. The specific selection process of study participants is depicted in Figure 1. The baseline characteristics of the participants and a weighted examination of the characteristics of the study group are displayed in Table 1. The prevalence of PAD in men with ED was >4 times higher than that in men without ED (11.4% vs. 2.6%, $P < 0.001$). Compared with the non-ED group, individuals in the ED cohort were typically older, with lower education levels, PIR, and physical activity levels, and a higher incidence of hypertension, diabetes, CVD, high cholesterol, and a history of smoking, as well as a higher BMI.

3.2 Association between ED and PAD

Multivariate logistic regression analysis was performed to elucidate the relationship between ED and the prevalence of PAD. Three models were constructed (Table 2). The crude model (Model 1) showed an odds ratio (OR) of 4.91 (95% CI 3.08-7.82). After partial adjustment of variables (Model 2), the OR decreased to 2.90 (95% CI 1.81-4.03). Despite full modification in Model 3, including the inclusion of additional variables, the correlation between ED and PAD remained significantly favorable, showing an OR of 2.05 (95% CI 1.24-3.39). Together, these findings suggest a robust association between ED and PAD, persisting even with adjustments for various factors.

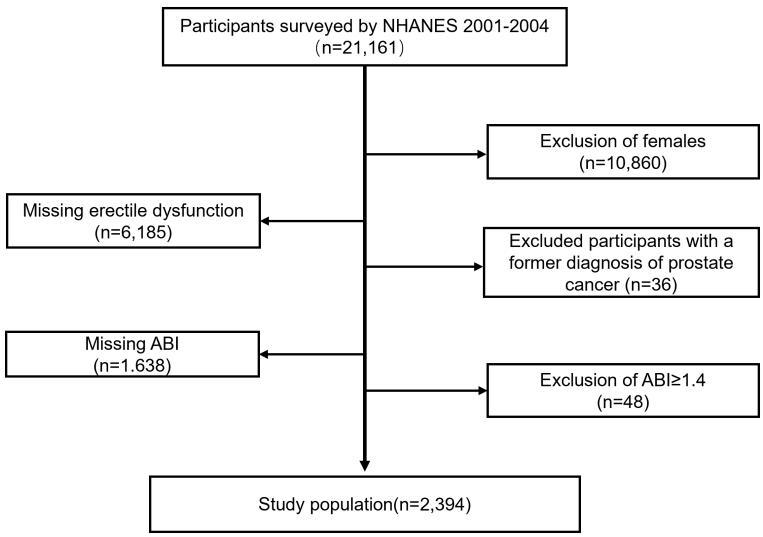

FIGURE 1
Flow chart of the screening process for the selection of study participants. ABI, ankle-brachial index.

TABLE 1 General characteristics of included participants (n = 2394) by the presence or absence of erectile dysfunction in the NHANES 2001-2004.

Characters	Total	NO (N=1489)	YES (N=905)	*P*-value
Age(years)	54.8 ± 11.4	51.3 ± 9.3	64.1 ± 11.4	<0.001
≤50	43.5 (40.3-46.7)	55.1 (51.4-58.8)	12.6 (9.5-16.4)	
>50	56.5 (53.3-59.7)	44.9 (41.2-48.6)	87.4 (83.6-90.5)	
Race/ethnicity				0.469
Mexican American	4.6 (3.2-6.7)	4.8 (3.5-6.5)	4.3 (2.2-8.1)	
Other Hispanic	3.7 (2.1-6.4)	3.2 (1.9-5.5)	4.8 (2.1-10.4)	
Non-Hispanic White	80.1 (76.1-83.7)	80.3 (76.2-83.8)	79.8 (74.3-84.4)	
Non-Hispanic Black	8.7 (7-10.9)	8.9 (7.2-11)	8.3 (6.3-10.9)	<0.001
Other Race[a]	2.8 (2-4)	2.8 (1.7-4.6)	2.8 (1.7-4.5)	
Education level				0.021
Less than high school	15.5 (13.5-17.7)	11.6 (9.8-13.7)	25.9 (21.6-30.6)	
High school	25.7 (23.8-27.7)	26.9 (24.4-29.6)	22.3 (18.9-26.2)	
More than high school	58.9 (55.5-62.1)	61.5 (58.2-64.7)	51.8 (47.5-56.2)	
Marital status				<0.001
Married/Living with partners	5.9 (4.5-7.7)	6.7 (5.1-8.8)	3.8 (2.4-6)	
Widowed/Divorced/Separated	79.1 (76.5-81.4)	78.7 (75.6-81.4)	80.1 (76.6-83.2)	
Never married	15 (13.1-17.2)	14.6 (12.1-17.6)	16.1 (13.7-18.8)	
Family poverty ratio				<0.001
<1.3	12.8 (10.8-14.9)	11.4 (9.7-13.5)	16.2 (12.5-20.9)	
1.3-3.5	30.9 (28.7-33.3)	28.1 (25.2-31.2)	38.4 (34.3-42.8)	
≥3.5	51.4 (47.8-54.9)	55.8 (51.9-59.5)	39.8 (34.8-44.9)	
Not recorded	4.9 (3.8-6.4)	4.7 (3.4-6.4)	5.6 (3.7-8.2)	
Hypertension				<0.001
No	64.6 (60.9-68)	71.3 (66.4-75.7)	46.8 (44-49.7)	
Yes	35.4 (32-39.1)	28.7 (24.3-33.6)	53.2 (50.3-56)	
Diabetes				<0.001
No	87.1 (85.5-88.6)	92 (90.3-93.4)	74.2 (70.9-77.2)	
Yes	12.9 (11.4-14.5)	8 (6.6-9.7)	25.8 (22.8-29.1)	
CVD				<0.001
No	86.6 (84.4-88.5)	91.6 (89.7-93.2)	73.2 (69.1-76.9)	
Yes	13.4 (11.5-15.6)	8.4 (6.8-10.3)	26.8 (23.1-30.9)	
High cholesterol				<0.001
No	52.9 (49.8-56)	55.1 (51.8-58.3)	47.1 (42.8-51.5)	
Yes	47.1 (44-50.2)	44.9 (41.7-48.2)	52.9 (48.5-57.2)	
Smoking				<0.001
Never	37.7 (34.6-40.9)	40.7 (36.9-44.6)	29.9 (26.4-33.7)	
Current	23.6 (21.4-25.9)	24.8 (22.5-27.4)	20.3 (16.1-25.3)	
Former	38.7 (36.2-41.2)	34.5 (31.2-37.8)	49.8 (45.2-54.4)	

(Continued)

TABLE 1 Continued

Characters	Total	NO (N=1489)	YES (N=905)	*P*-value
Alcohol intaking				<0.001
No	25 (21.3-29.1)	22.7 (19-27)	31 (26.3-36.2)	
Yes	75 (70.9-78.7)	77.3 (73-81)	69 (63.8-73.7)	
Physical activity				0.004
Inactive	34.3 (31.6-37.2)	30.8 (27.6-34.3)	43.6 (39.3-48.1)	
Moderate	32.7 (30.6-34.9)	30.8 (28.2-33.6)	37.6 (34-41.4)	
Vigorous	33 (30.3-35.7)	38.3 (35.2-41.5)	18.7 (15.4-22.6)	
BMI				<0.001
<25	22.4 (19.7-25.4)	22.7 (19-26.8)	21.8 (18.9-25.1)	
25-29.99	45 (42.7-47.4)	46.6 (43.7-49.5)	41 (37-45)	
≥30	31.6 (29.2-34)	30.1 (26.9-33.5)	35.5 (31.3-39.9)	
Not recorded	1 (0.6-1.6)	0.7 (0.3-1.4)	1.7 (0.9-3.3)	
PAD				<0.001
No	95 (93.9-96)	97.4 (96.3-98.3)	88.6 (85.7-91)	
Yes	5 (4-6.1)	2.6 (1.7-3.7)	11.4 (9-14.3)	

Values are weighted mean ± SD or weighted % (95% confidence interval). P values are weighted. [a]Other races include American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiracial persons.
BMI, body mass index; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral arterial disease.

3.3 Subgroup analysis

Additional analyses were conducted on subgroups based on different variables (Table 3). Results showed that ED was positively associated with PAD, with significant relationships found in patients aged >50 years old (OR = 2.32, 95% CI 1.34-4.03), without hypertension (OR = 2.18, 95% CI 1.08-4.40), without diabetes (OR = 2.10, 95% CI 1.14-3.86), without CVD (OR = 2.09, 95% CI 1.14-3.82), without high cholesterol (OR = 2.50, 95% CI 1.32-4.72), former smokers (OR = 3.15, 95% CI 1.36 -7.30), physically inactive individuals (OR = 2.59, 95% CI 1.19-5.61), and those with a BMI of 25-30 (OR = 3.21, 95%CI 1.77-5.84). However, no statistically significant correlation was found after analyzing all subgroups for interaction (all P > 0.05).

4 Discussion

The present cross-sectional study employed data from US adults aged ≥40 years old in 2001-2004 NHANES to investigate the possible link between ED and PAD. The study revealed a significant association between ED and the prevalence of PAD, suggesting that individuals with ED have a higher likelihood of also having PAD. Even after accounting for possible confounding variables, the association remained statistically significant.

Studies on the relationship between ED and PAD have received little attention. A recent meta-analysis found no significant association between ED and PAD. Considerable variability was found in the studies (17). A population-based study involving 614 volunteers found that ED was associated with higher carotid

TABLE 2 Association between peripheral arterial disease and erectile dysfunction.

Exposure	Model 1 OR (95%CI), *P*	Model 2 OR (95%CI), *P*	Model 3 OR (95%CI), *P*
Erectile Dysfunction			
NO	Reference	Reference	Reference
YES	4.91 (3.08-7.82) <0.001	2.90 (1.81-4.63) <0.001	2.05 (1.24-3.39) 0.007

CI, confidence interval; OR, odds ratio.
Model 1 was unadjusted.
Model 2 was adjusted for age, race, and education level.
Model 3 was adjusted for age, race, education level, marital status, family poverty ratio, hypertension, diabetes, cardiovascular disease (CVD), high cholesterol, smoking, alcohol intaking, physical activity and body mass index (BMI).

TABLE 3 Subgroup analysis for peripheral arterial disease and erectile dysfunction, weighted.

Characteristics	Model 1 OR (95%CI), *P*	Model 2 OR (95%CI), *P*	Model 3 OR (95%CI), *P*	P for interaction
Stratified by Age				0.156
≤50	0.74 (0.07-7.74) 0.795	0.75 (0.08-7.23) 0.799	0.19 (0.04-1.04) 0.055	
>50	3.30 (1.96-5.56) <0.001	3.14 (1.86-5.3) <0.001	2.32 (1.34-4.03) * 0.004	
Stratified by Hypertension				0.268
No	5.35 (2.65-10.8) <0.001	3.29 (2.04-5.28) <0.001	2.18 (1.08-4.40) * 0.015	
Yes	3.17 (1.55-6.45) 0.002	2.32 (1.2-4.49) 0.032	2.05 (0.93-4.54) 0.074	
Stratified by Diabetes				0.71
No	5.09 (2.89-8.95) <0.001	3.01 (1.71-5.29) <0.001	2.10 (1.14-3.86) * 0.019	
Yes	2.48 (1.02-6.03) 0.045	1.6 (0.59-4.32) 0.342	1.26 (0.53-3) 0.597	
Stratified by CVD				0.373
No	4.56 (2.49-8.33) <0.001	2.62 (1.56-4.39) 0.001	2.09 (1.14-3.82) * 0.019	
Yes	2.24 (1.18-4.27) 0.016	2.16 (1.03-4.53) 0.043	2.12 (0.97-4.65) 0.06	
Stratified by High cholesterol				0.133
No	6.21 (3.09-12.48) <0.001	3.51 (2.01-6.14) <0.001	2.50 (1.32-4.72) * 0.006	
Yes	3.93 (2.09-7.37) <0.001	2.39 (1.24-4.62) 0.011	1.71 (0.87-3.37) 0.115	
Stratified by Smoking				0.159
Never	2.82 (1.12-7.14) 0.03	1.62 (0.61-4.31) 0.32	0.86 (0.28-2.63) 0.79	
Current	3.92 (1.84-8.35) 0.001	2.25 (1.21-4.18) 0.012	1.76 (0.95-3.27) 0.07	
Former	6.54 (2.94-14.57) <0.001	4.02 (1.79-9.07) 0.001	3.15 (1.36-7.30) * 0.009	
Stratified by Alcohol intaking				0.837
No	3.47 (1.39-8.69) 0.01	2.95 (1.31-6.63) 0.011	2.43 (1.05-5.61) * 0.038	
Yes	5.58 (3.12-9.99) <0.001	2.99 (1.67-5.35) 0.001	2.15 (1.14-4.04) * 0.019	
Stratified by Physical activity				0.279
Inactive	5.11 (2.46-10.59) <0.001	2.83 (1.35-5.91) 0.007	2.59 (1.19-5.61) * 0.018	
Moderate	2.33 (1.12-4.87) 0.026	1.6 (0.8-3.2) 0.179	1.18 (0.59-2.33) 0.629	
Vigorous	7.71 (2.18-27.3) 0.003	5.46 (1.72-17.3) 0.005	2.01 (0.37-10.86) 0.403	
Stratified by BMI				0.993
<25	4.30 (1.66-11.15) 0.004	2.41 (0.98-5.95) 0.056	1.83 (0.67-5.02) 0.228	
25-29.99	7.47 (4.25-13.13) <0.001	4.3 (2.46-7.53) <0.001	3.21 (1.77-5.84) *<0.001	
≥30	3.22 (1.44-7.18) 0.006	2.09 (0.94-4.63) 0.07	1.29 (0.55-2.99) 0.546	

CI, confidence interval; OR, odds ratio.
Model 1 was unadjusted.
Model 2 was adjusted for age, race, and education level.
Model 3 was adjusted for age, race, education level, marital status, family poverty ratio, hypertension, diabetes, cardiovascular disease (CVD), high cholesterol, smoking, alcohol intaking, physical activity and body mass index (BMI). *'Inf' means that values can't be calculated. *$p < .05$.

atherosclerosis burdens but not lower extremity atherosclerosis rates. Nevertheless, ABI decreased and the prevalence of ABI < 0.9 increased with an increase in the severity of ED (9). This may be attributed to the limited sample sizes and a less accurate technique for identifying atherosclerosis in the lower limb arteries. Conversely, in the DIVA registry comprising 1366 type 2 diabetic patients, the incidence of abnormal ABI was significantly higher in patients with ED than in those without ED (18). Furthermore, a

study of the National Health Insurance Research Database involving 12825 patients who visited the Emergency Department found that men with ED had a 75% increased likelihood of PAD, even after accounting for cardiovascular risk factors and medication usage (19). However, there is a paucity of studies investigating the connection between ED and PAD. The current study utilized extensive and diverse data from 2001-2004 NHANES to investigate the connection between ED and PAD. The findings provide more insights into understanding the association of ED and PAD.

PAD is a chronic obstructive atherosclerotic disease of the arteries from the distal aorta to the foot that disrupts or obstructs blood flow to the feet. Similar to ED, PAD is closely linked to risk factors for atherosclerosis (20). However, PAD is underdiagnosed. Early detection of PAD can result in better cardiovascular results and decrease complications in the lower extremities, including critical limb ischemia and limb loss (21).

Since most risk factors for ED are identical to those for atherosclerotic disease, it can be partially considered a vascular disease (22). In line with previous findings, we discovered that ED was linked to common risk factors for atherosclerosis, including older age, diabetes, high blood pressure, elevated cholesterol levels, and tobacco use. Accumulating evidence indicates that ED is strongly linked to undiagnosed atherosclerotic vascular disease (23–25). According to the artery size hypothesis, all major vascular beds should be affected equally in the presence of atherosclerosis, given its systemic nature. However, symptoms rarely become evident at the same time (26). This implies that the identical typical disease progression could impact smaller blood vessels that provide blood to the penis before affecting larger blood vessels, resulting in the occurrence of ED symptoms before coronary artery disease or PAD symptoms.

The current study demonstrated that the association between ED and the prevalence of PAD was consistent across multiple sub-groups. Age is known to increase the risk of ED and PAD (27, 28). Our subgroup analysis confirmed the association between ED and PAD in older adults. Our subgroup analysis revealed some unexpected findings. A significant association between ED and PAD was observed in subjects without hypertension, diabetes, cardiovascular disease (CVD), and high cholesterol. In contrast, this association was not significant in subgroups with these conditions. This seemingly paradoxical phenomenon may be attributed to several factors: Firstly, individuals with these conditions may have already adopted more proactive health management strategies, such as lifestyle improvements or pharmacological interventions, which could influence the relationship between ED and PAD. Secondly, these conditions themselves might mask the potential association between ED and PAD. Lastly, this disparity may reflect complex pathological mechanisms or unidentified confounding factors. However, these explanations remain speculative and require validation through further research. Future studies should focus on exploring the potential mechanisms underlying the association between ED and PAD in these subgroups, as well as the impact of various interventions on this association. We reviewed all previous NHANES studies on PAD and found similar results in some subgroup analyses: there was a significant association between dietary magnesium intake and PAD in diabetes-negative and hypertension-negative subgroups (29); there was a significant association between the dietary inflammatory index and PAD in diabetes-negative, hypertension-negative, and CVD-subgroups (15).

Smoking has long been acknowledged as a major avoidable risk factor for PAD. Our findings demonstrated that former smoking habits may lead to a persistent increase in PAD risk, consistent with previous research (30). No significant relationships were observed between PAD and alcohol consumption. The relationship between drinking alcohol and CVD remains controversial (31). Epidemiological studies have revealed a U or J-shaped association between alcohol intake and cardiovascular conditions, such as heart attacks and strokes. This indicates an increased likelihood of CVD in individuals who do not drink alcohol and heavy drinkers, highlighting a beneficial impact linked to moderate alcohol intake (32, 33). Moreover, the current study confirmed the association between ED and PAD in physically inactive individuals, which aligns with previous reports. Kulinski found that exercise time was inversely associated with a low ABI (34).

Interestingly, our study uncovered an association between ED and PAD only in the overweight group. Obesity is a major public health issue and is strongly associated with atherosclerosis and heart problems. Despite frequent co-occurrence, the relationship between obesity and PAD remains controversial. Some studies suggest an unexpected protective effect of obesity, termed “obesity paradox” (35). A recent study discovered that obesity was primarily linked to PAD in women, while men showed only a minor correlation between higher BMI and PAD (36). Possible explanations include genetic factors, adipose tissue dysfunction, and differences in body fat distribution.

The present study possesses several strengths. Firstly, this study relies on NHANES data, offering the advantage of a large sample size. Secondly, this study allows for the adjustment of crucial PAD risk factors. Finally, we conducted subgroup analyses and adjusted for pertinent covariates, thereby augmenting the robustness of the study. Nevertheless, this study has some limitations. First, the cross-sectional study design does not allow for the determination of causality. Therefore, comprehensive longitudinal studies are warranted to validate our findings. Second, the lack of ABI data for participants aged <40 years old limited our ability to analyze this association across a broader age spectrum, despite PAD predominantly affecting older populations. Third, ED evaluation relied on self-reported assessment surveys, introducing inherent biases. Finally, the various impacts originating from eating disorders and PAD are complex. Although our adjustment model incorporated relevant covariates, fully mitigating the effects of other potential covariates remains challenging.

5 Conclusion

In summary, this large cross-sectional study suggests a significant association between ED and PAD in the US population ≥40 years old. ED may be an independent predictor of PAD and thus it should be considered in the treatment of patients with ED.

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

GW: Investigation, Software, Writing – original draft. CN: Conceptualization, Supervision, Writing – review & editing.

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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.

Publisher's note

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Evaluating atherogenic index of plasma as a predictor for metabolic syndrome: a cross-sectional analysis from Northern Taiwan

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Background: The rising global prevalence of metabolic syndrome (MetS), characterized by a constellation of cardiovascular risk factors, underscores the urgent need to identify reliable predictive biomarkers. We hypothesize that an elevated atherogenic index of plasma (AIP) predicts MetS risk through lipid imbalance, but population-specific variations in its predictive strength remain unexplored. Our study aimed to assess AIP), a ratio of triglycerides to high-density lipoprotein cholesterol, as a predictor of MetS.

Method: Between 2014 and 2018, our cross-sectional study collected and analyzed health examination data from 9,202 Northern Taiwan Medical Center employees without cardiovascular diseases, diabetes, and end-stage renal disease (ESRD). Our study classified AIP levels equally into three tertiles and evaluated their impact on MetS through a logistic regression model.

Results: After adjusting for age, gender, BMI, SBP, FPG, and LDL in our models, the ORs for MetS in the second and third tertiles of the AIP were 3.81 (95% CI: 2.33 to 6.21; OR: 37.14, 95%: 23.22 to 59.39). In addition, women have a higher MetS risk associated with elevated AIP than men across all models.

Conclusion: Our research identified the AIP as a significant predictive marker for the prevalence of MetS, suggesting its potential utility in clinical risk assessment and indicating the need for further research to explore its application in preventive strategies and therapeutic interventions.

KEYWORDS

atherogenic index of plasma, triglycerides, high-density lipoprotein cholesterol, metabolic syndrome, women

1 Introduction

Metabolic syndrome (MetS) represents a clustering of cardiovascular risk factors that significantly elevate the risk of developing heart disease, stroke, and diabetes. These factors include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. The prevalence of MetS has been rising globally, concomitant with the obesity epidemic, making it a critical focus for public health initiatives (1–3). Therefore, identifying biomarkers that can predict the development of MetS is paramount for early intervention strategies.

The atherogenic index of plasma (AIP), a logarithmic calculation based on the ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C), has emerged as a potent predictor of atherosclerosis and cardiovascular disease (CVD) (4–6). Recent studies suggest that the AIP could also be intricately linked to MetS, providing a simple yet effective tool for gauging metabolic health and the risk of cardiovascular complications (7–9). The relevance of the AIP as a predictive marker for MetS underscores the need for comprehensive research to further elucidate this relationship, which could lead to better predictive models for cardiovascular risk.

A 9-year longitudinal study in Taiwan highlighted AIP's strong predictive value for MetS, hypertension, and T2DM, particularly among middle-aged individuals, while a 15-year study confirmed its role as an independent predictor of MetS in men, showing a significant linear trend with increasing tertiles. In India, AIP demonstrated the highest diagnostic accuracy (AUC 0.954) for MetS, and studies in chronic kidney disease and schizophrenia populations further emphasized its robust association with MetS risk factors. A Moroccan study linked elevated AIP, TG levels, and reduced HDL-C to increased cardiovascular risk, surpassing lipid measures alone (7–9). In a cross-sectional analysis, the Atherogenic Index of Plasma (AIP) was highlighted as a predictive marker for Metabolic Syndrome (MetS). A study of chronic kidney disease patients on hemodialysis found a strong correlation between elevated AIP and MetS prevalence, emphasizing its potential in cardiovascular risk management. In schizophrenia patients, AIP showed high diagnostic accuracy for MetS, with an AUC of 0.845 and a cutoff of 0.4. Similarly, research among Moroccan women demonstrated stronger associations of lipid ratios and AIP with cardiovascular risks than individual lipids, suggesting AIP's vital role in identifying metabolic health risks across diverse populations (10–12). These findings underscore AIP's critical value in early detection, risk stratification, and intervention strategies across various clinical and demographic settings.

The relationship between AIP and MetS is essential to address the rising prevalence of MetS, a key contributor to cardiovascular diseases and diabetes. AIP, a biomarker derived from TG and HDL-C, shows promise in predicting MetS risk across populations. However, the predictive strength of AIP varies, and population-specific insights are limited. Investigating AIP's role in MetS can enhance early detection, risk stratification, and intervention strategies, bridging gaps in understanding its utility and offering a simple yet effective tool for managing cardiometabolic health across diverse clinical and demographic settings. This study aimed to explore the association between the AIP and MetS by leveraging a robust analytical approach to understand the extent of their correlation. Through a detailed analysis of the association between AIP and MetS, our research seeks to add a significant piece to the puzzle of metabolic health, with implications for clinical practices and public health policies.

2 Materials and methods

2.1 Data collection and population

In this longitudinal study, spanning from 2014 to 2018, we meticulously collected data from annual health examinations of 11,507 employees, encompassing both medical staff and general personnel, at a major medical center hospital located in Northern Taiwan. Following stringent exclusion criteria that removed participants with cardiovascular diseases, diabetes, and incomplete entries (n=2305) while ensuring privacy through encoding, a total of 9,202 employees aged between 20 and 80 years were included in the analysis. Detailed inclusion and exclusion criteria are shown in Figure 1.

2.2 General data collection

Vital sign assessments were systematically conducted by trained nursing staff. Waist circumference was measured at the umbilical level in a standing posture to the nearest centimeter using tape with constant tension. Body mass index (BMI) was calculated by dividing the weight of the subjects in kilograms by their height in meters squared (kg/m2) (13). Blood pressure readings, including both systolic blood pressure (SBP) and diastolic blood pressure (DBP), were taken with the participants in a seated position using standard mercury sphygmomanometers following a rest period of five minutes. To ensure accuracy, blood pressure was measured twice per session with a 30- to 60-second interval between measurements, and the average of these readings was recorded (14).

2.3 Laboratory measurements

Fasting blood samples were collected after a 12-hour fast in EDTA-containing tubes through venipuncture in a controlled setting. These samples were analyzed to determine the serum levels of total cholesterol, TG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), and fasting plasma glucose (FBG). TG and TC levels were analyzed using enzymatic methods with a Fuji Dri-Chem analyzer, while HDL-C and LDL-C concentrations were determined using cholesterol assays following dextran sulfate precipitation. FBG was measured using the glucose oxidase method, and ALT levels were assessed through the International Federation of Clinical Chemistry method. The AIP was subsequently calculated using the formula AIP = log10(TG/HDL-C), which is a critical measure for assessing cardiovascular risk by evaluating the balance between triglycerides

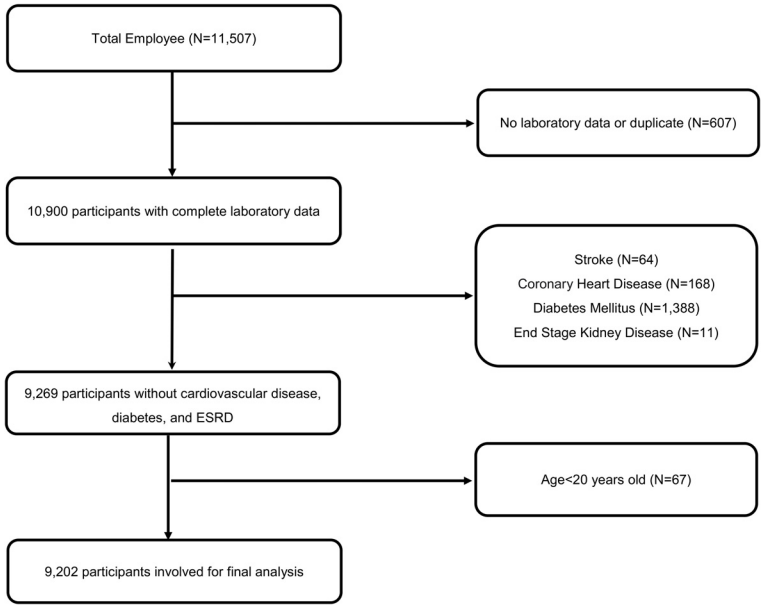

FIGURE 1
Flow chart of exclusion and inclusion in our study.

and HDL cholesterol. Metabolic syndrome is diagnosed based on the International Diabetes Federation Global Consensus Definition, which requires central obesity as a mandatory criterion, defined by WC with ethnicity-specific values, accompanied by any two of the following four factors: elevated TG (≥150 mg/dL or specific treatment for this lipid ab-normality), reduced HDL-C (<40 mg/dL in males and <50 mg/dL in females or specific treatment for this lipid abnormality), elevated blood pressure (SBP ≥130 or DBP ≥85 mm Hg or treatment of previously diagnosed hypertension), and elevated FBG (≥100 mg/dL or previously diagnosed type 2 diabetes) (15, 16).

2.4 Statistical analysis

The basic characteristics of categorical variables were expressed as counts and percentages, while those of continuous variables were described using means and standard deviations. AIP levels were categorized into three groups according to tertiles: T1 (≤ 33.3rd percentile), T2 (33.4th to 66.6th percentile), and T3 (> 66.6th percentile), with tertile comparisons conducted using ANOVA for continuous variables and the chi-square test for categorical variables. Pearson's correlation analysis was utilized to explore the relationship between AIP levels and metabolic syndrome risk factors. Adhering to the STROBE statement, our analysis implemented three models: a univariate logistic regression model (model 1), a model adjusted for age and gender (model 2), and a fully adjusted model incorporating additional adjustments for BMI, SBP, FPG, and LDL-C (model 3). Statistical significance was indicated by two-tailed p-values less than 0.05. All analyses were conducted using PASW SPSS Statistics for Windows, version 26.0 (SPSS Inc., Chicago, IL, USA).

To further justify the statistical methods employed, this study utilized a comprehensive approach to ensure robust and reliable analysis of the relationship between AIP and MetS. The use of ANOVA for continuous variables allowed for detecting significant differences across tertile groups of AIP, while the chi-square test effectively identified associations in categorical data. Pearson's correlation analysis was chosen to evaluate linear relationships between AIP and individual risk factors for MetS, including BMI, WC, TG, HDL-C, and fasting glucose. Logistic regression models were specifically selected to estimate odds ratios (ORs) for MetS across AIP tertiles, providing a clear understanding of risk magnitudes while adjusting for potential confounders in a stepwise manner. The univariate model (Model 1) identified baseline associations without adjustment, whereas Model 2 accounted for age and gender, addressing demographic variations. Model 3 further incorporated BMI, SBP, FPG, and LDL-C to control for metabolic and cardiovascular confounders, ensuring the robustness of the findings. Gender-specific subgroup analyses were performed to explore potential differences in AIP-MetS associations between men and women, providing critical insights into sex-based variations. The statistical software PASW SPSS Statistics version 26.0 was chosen for its reliability and advanced analytical capabilities, ensuring precise data handling, computation, and result presentation. Its comprehensive suite of statistical tools supported multivariate modeling, subgroup analysis, and hypothesis testing, aligning with the study's objectives. The use of two-tailed p-values less than 0.05 as the threshold for statistical significance ensured rigorous and conservative interpretations, minimizing the likelihood of Type I errors.

3 Results

Table 1 reveals the basic characteristics of the employees, equally stratified by AIP levels into three tertiles: T1 (<-0.3557),

T2 (-0.3557 to -0.0858), and T3 (>-0.0858). The prevalence of MetS and the percentage of men significantly increased with higher AIP levels, with MetS affecting 39.88% of the population in T3 and only 0.81% in T1, and the proportion of men increased to 49.69% in T3 from 9.04% in T1. Continuous variables such as SBP, DBP, BMI, WC, and FPG also demonstrated significant differences across tertiles. Particularly notable were the changes in HDL-C levels, which significantly decreased from 69.88 mg/dL in T1 to 47.02 mg/dL in T3, underscoring the atherogenic risk associated with higher AIP levels.

Table 2 elucidates the correlation between the AIP and MetS risk factors, utilizing Pearson's coefficient for analysis. Notably, BMI and WC demonstrated strong positive correlations with AIP, with coefficients of 0.48 and 0.55, respectively. Conversely, HDL-C exhibited a strong negative correlation with a coefficient of -0.73, indicating an inverse relationship with the AIP. TG had the highest positive correlation coefficient of 0.77, suggesting a significant link with AIP. These findings highlight the potential of the AIP as a significant marker for assessing metabolic syndrome risk, underscored by its strong associations with key risk factors such as BMI, WC, HDL-C, and TG.

Table 3 shows the associations between the AIP and MetS across the three models. According to the unadjusted Model 1, individuals in the second tertile (T2) of the AIP had an odds ratio (OR) of 6.78 with a 95% confidence interval (CI) of 4.43 to 10.36, and those in the third tertile (T3) had an OR of 81.18 with a 95% CI of 54.51 to 121.13, both of which were significant, with p values less than 0.001. When adjusted for age and gender in Model 2, the ORs slightly decreased to 6.28 for T2 and 76.91 for T3, with 95% CIs of 4.10 to 9.62 and 51.31 to 115.28, respectively, maintaining significance at p values less than 0.001. Further adjustments in Model 3 for BMI, SBP, FPG, and LDL resulted in reduced ORs to 3.81 for T2 and 37.14 for T3, with 95% CIs of 2.33 to 6.21 and 23.22 to 59.39, respectively; however, these values were still significant, with p-values less than 0.001. These findings underscore the strong association between higher AIP levels and increased odds of metabolic syndrome, even after adjusting for key demographic and clinical variables.

Table 4 reveals the gender-specific analysis of the association between the atherogenic index of plasma (AIP) and metabolic syndrome (MetS), showing distinct variations between men and women. For men in the highest AIP tertile (T3), the odds ratio (OR)

TABLE 1 Basic characteristics of the employee population at a medical center from 2014 to 2018.

			Atherogenic Index of Plasma						
	Total		T1		T2		T3		*p* value
Case number	9202		3085		3050		3067		
Cutoff value			<-0.3557		-0.3557 to -0.0858		>-0.0858		
Categorical variables									
MetS, N (%)	1408	(15.30%)	25	(0.81%)	160	(5.25%)	1223	(39.88%)	<0.001
Gender, N (%)									<0.001
Men	2592	(28.17%)	279	(9.04%)	789	(25.87%)	1524	(49.69%)	
Women	6610	(71.83%)	2806	(90.96%)	2261	(74.13%)	1543	(50.31%)	
Continuous variables									
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (years)	41.94	10.13	38.56	9.46	42.45	10.16	44.84	9.76	
SBP (mmHg)	124.66	16.20	118.24	13.68	124.18	15.35	131.58	16.61	<0.001
DBP (mmHg)	73.13	12.28	68.74	10.50	72.41	11.48	78.26	12.81	<0.001
BMI (kg/m^2)	24.22	4.08	22.07	3.11	23.87	3.57	26.73	4.07	<0.001
WC (cm)	78.53	10.45	72.29	7.68	77.62	8.86	85.71	9.93	<0.001
ALT (U/L)	23.50	19.77	17.07	12.40	21.22	15.86	32.24	25.38	<0.001
FPG (mg/dL)	89.02	18.13	83.77	11.83	87.67	13.13	95.63	24.51	<0.001
HDL-C (mg/dL)	58.57	13.73	69.88	11.42	58.73	9.74	47.02	8.84	<0.001
LDL-C (mg/dL)	115.79	30.43	103.70	25.73	116.76	28.11	126.98	32.46	<0.001
TC (mg/dL)	192.27	33.64	187.55	31.11	190.48	32.10	198.78	36.48	<0.001
TG (mg/dL)	98.00	83.31	49.67	12.07	80.00	16.67	164.52	115.36	<0.001

MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

TABLE 2 Correlation between the atherogenic index of plasma and associated risk factors for metabolic syndrome.

Risk factors	Atherogenic Index of Plasma					
	Total		Men		Women	
	Pearson's coefficient	p value	Pearson's coefficient	p value	Pearson's coefficient	p value
Age (year)	0.25	<0.001	0.10	<0.001	0.24	<0.001
SBP (mmHg)	0.34	<0.001	0.18	<0.001	0.30	<0.001
DBP (mmHg)	0.33	<0.001	0.21	<0.001	0.26	<0.001
BMI (kg/m^2)	0.48	<0.001	0.39	<0.001	0.46	<0.001
WC (cm)	0.55	<0.001	0.41	<0.001	0.47	<0.001
FPG (mg/dL)	0.30	<0.001	0.24	<0.001	0.27	<0.001
HDL-C (mg/dL)	-0.73	<0.001	-0.72	<0.001	-0.68	<0.001
LDL-C (mg/dL)	0.28	<0.001	0.11	<0.001	0.30	<0.001
TC (mg/dL)	0.16	<0.001	0.20	<0.001	0.12	<0.001
TG (mg/dL)	0.77	<0.001	0.73	<0.001	0.87	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

TABLE 3 The association between atherogenic index of plasma and metabolic syndrome.

		Model 1		Model 2			Model 3		
AIP	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
T1	1			1			1		
T2	6.78	4.43, 10.36	<0.001	6.28	4.10, 9.62	<0.001	3.81	2.33, 6.21	<0.001
T3	81.18	54.51, 121.13	<0.001	76.91	51.31, 115.28	<0.001	37.14	23.22, 59.39	<0.001

Model 1: unadjusted. Model 2: adjusted for age and gender. Model 3: adjusted for age, gender, BMI, SBP, FPG, and LDL.
AIP, atherogenic index of plasma; OR, odds ratio; CI, confidence interval.
T1, Tertile 1; T2, Tertile 2; T3, Tertile 3.

of developing MetS is significant across all models, decreasing from 42.24 in the unadjusted model to 22.58 in the fully adjusted model. Women, however, exhibit a stronger association, with an OR starting at 94.75 in the unadjusted model and decreasing to 37.18 in the fully adjusted model. The ORs for the second tertile (T2) also show significant differences, where men have lower ORs ranging from 2.53 in the unadjusted model to 1.50 in the fully adjusted model, whereas women's ORs range from 8.22 to 4.44, indicating a

TABLE 4 Gender subgroup analysis of the association between atherogenic index of plasma and metabolic syndrome.

AIP	Model 1			Model 2			Model 3		
	OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Men									
T1	1.00								
T2	2.53	0.88, 7.28	0.09	2.36	0.82, 6.80	0.11	1.50	0.46, 4.90	0.50
T3	42.24	15.66, 113.96	<0.001	39.48	14.62, 106.62	<0.001	22.58	7.42, 68.68	<0.001
Women									
T1	1.00								
T2	8.22	5.17, 13.08	<0.001	7.34	4.61, 11.68	<0.001	4.44	2.59, 7.61	<0.001
T3	94.75	60.96, 147.28	<0.001	81.62	52.44, 127.05	<0.001	37.18	22.13, 62.45	<0.001

Model 1: unadjusted. Model 2: adjusted for age and gender. Model 3: adjusted for age, gender, BMI, SBP, FPG, and LDL.
AIP, atherogenic index of plasma; OR, odds ratio; CI, confidence interval.
T1, Tertile 1; T2, Tertile 2; T3, Tertile 3.

consistently higher risk among women compared to men across all adjustments.

Figure 2 illustrates the prevalence of high levels (T3) of the atherogenic index of plasma (AIP) among individuals with and without metabolic syndrome (MetS). The data reveals a significant difference between the two groups. Among the 1,408 subjects diagnosed with metabolic syndrome, 86% exhibited a high AIP level, indicating a strong association between MetS and elevated AIP. In contrast, among the 7,794 sub-jects without metabolic syndrome, only 23% showed high AIP levels, suggesting a lower risk of atherogenic conditions in the absence of MetS. This disparity underscores the link between metabolic syndrome and cardiovascular risk factors.

4 Discussion

Our study elucidates the robust association between elevated levels of the AIP and the increased prevalence and risk factors for MetS, demonstrating a graded relationship where higher AIP tertiles significantly correlate with a higher prevalence of MetS and its components, thus reaffirming the potential utility of the AIP as a predictive marker for MetS in a clinical setting. Besides, women show a stronger association between high AIP and MetS risk compared to men, with notably higher odds ratios across all models.

The possible biological mechanisms linking higher AIP to increased MetS risk may involve dyslipidemia, with dyslipidemia's role in CVD highlighted by the critical diagnostic criteria of triglycerides and HDL-C in MetS and the demonstrated contribution of triglyceride-rich particles to the development and progression of atheromatous plaques (17–19). Triglyceride-rich lipoproteins, such as chylomicrons and very low-density lipoproteins (VLDL), play essential roles in lipid metabolism and energy homeostasis. These lipoproteins transport TG from the intestine and liver to peripheral tissues. The metabolism of these lipoproteins is significantly influenced by enzymes such as lipoprotein lipase, hepatic triglyceride lipase, and endothelial lipase (EL). LPL, anchored to the endothelial surface of capillaries, primarily in adipose tissue and muscle, hydrolyzes the triglycerides in chylomicrons and VLDL into free fatty acids and glycerol, which are then taken up by cells for energy production or storage. This hydrolysis process transforms chylomicrons into chylomicron remnants and VLDL into intermediate-density lipoproteins (IDL) and subsequently into LDL-C. HTGL, mainly found in the liver, further hydrolyzes triglycerides in IDL and chylomicron remnants, facilitating their conversion to LDL-C and their uptake by hepatic receptors, respectively. EL, while primarily hydrolyzing phospholipids, also influences the metabolism of TG-rich lipoproteins by modulating HDL metabolism and indirectly affecting plasma TG levels. Dysfunction in any of these enzymes can lead to elevated plasma triglyceride levels and contribute to metabolic disorders such as hypertriglyceridemia and CVD (20–26).

The observed gender-specific differences in the association between high AIP and MetS risk, as highlighted by notably higher odds ratios in women across all models, merit careful consideration. This variation may stem from inherent biological differences between men and women in lipid metabolism and cardiovascular risk profiles. Typically, women are known to have higher baseline levels of HDL-C, which could modulate the impact of AIP differently compared to men (27–30). Furthermore, hormonal differences, particularly the protective effects of estrogen, may influence lipid and glucose metabolism, altering the risk profile for MetS in premenopausal women (31, 32). However, this protective effect diminishes with age, aligning with an increased MetS risk as seen in the postmenopausal phase (33, 34). Additionally, genetic factors and lifestyle choices, which often vary between genders, might contribute to the observed disparities (35–37).

The strength of our study is its comprehensive approach and nuanced insights into the relationship between AIP and MetS. First, our robust data collection and longitudinal analysis span a significant period, from 2014 to 2018, capturing a large cohort of 9,202 employees with diverse backgrounds, ensuring a broad representation of the population. This extensive dataset allows for

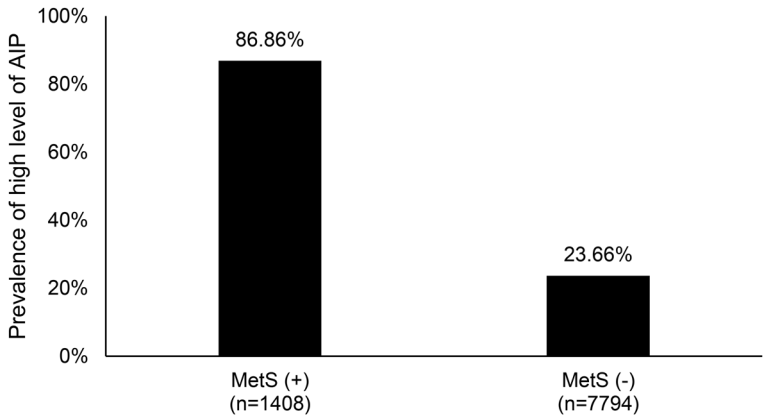

FIGURE 2
The prevalence of high level (T3) of atherogenic index of plasma between metabolic syn-drome patients and non- metabolic syndrome patients. MetS, metabolic syndrome; AIP, atherogenic index of plasma; T3, Tertile 3.

a detailed examination of trends and associations over time, enhancing the reliability of our findings. Second, the methodological rigor of categorizing AIP levels into tertiles and conducting a stratified analysis underscores the graded relationship between AIP and MetS, providing a nuanced understanding that higher AIP tertiles significantly correlate with an increased prevalence of MetS and its components. This stratification methodologically enriches the predictive utility of the AIP in a clinical setting. Third, our study benefits from a multivariable adjustment strategy that accounts for various confounding factors, including age, gender, BMI, blood pressure, and FBG levels. This approach ensures that the observed associations between AIP levels and MetS prevalence are not merely artifacts of these confounders but reflect a genuine underlying relationship. Last, the statistical analysis, grounded in Pearson's correlation and logistic regression models, offers a robust framework for evaluating the strength and significance of the association between AIP and MetS, providing compelling evidence of AIP's potential as a predictive marker for MetS in diverse clinical settings.

Our study has several inherent limitations. First, relying on a single medical center's employee cohort might not fully represent the broader population. To mitigate this, we carefully selected a diverse sample of employees, encompassing both medical staff and general personnel, to enhance the generalizability of our findings. Moreover, we applied stringent exclusion criteria to ensure the data's integrity and reliability, focusing on a well-defined and sizable cohort for analysis. Second, one of the primary constraints is the study's observational nature, which, despite the robust longitudinal design, may not fully account for all potential confounding variables. To address this issue, we performed a comprehensive statistical analysis, adjusting for a wide range of demographic and clinical factors, such as age, gender, BMI, blood pressure, and FBG levels, to ensure that the observed associations were as accurate as possible. Third, calculating the AIP itself, a recognized marker for cardiovascular risk, depends heavily on accurate triglyceride and HDL cholesterol measurements. Therefore, we ensured that all blood samples were collected and analyzed following stringent, standardized protocols to minimize variability and enhance the reliability of the AIP calculations. Fourth, while our study provides significant insights into the predictive utility of the AIP for MetS, the evolving nature of MetS definitions and criteria poses challenges for longitudinal research. We navigated this by adhering to the most current and widely accepted diagnostic guidelines, allowing for a consistent and relevant assessment of MetS across the study period. Fifth, our study lacks data on dyslipidemia therapies, particularly statins, which could impact the model's accuracy. Statin use may influence AIP levels and bias the results. According to a study using the Taiwan National Health Insurance Research Database (NHIRD), the use of statins has grown substantially over a decade. In 2011, approximately 6.3% of adults were identified as statin users (38). Sixth, our study highlights AIP's association with moderate and high-risk MetS cases; future research should include longitudinal designs to evaluate cardiovascular outcomes like myocardial infarction. Additionally, since our study population consists primarily of working adults aged 20 to 65, the lower expected rate of statin use in this group reduces the potential bias on the model's accuracy (39). Future research should further explore the mechanistic pathways linking AIP and MetS, with a focus on longitudinal and interventional studies to validate the predictive utility of AIP and explore potential therapeutic targets.

In conclusion, our research provides substantial evidence for the significant association between AIP and MetS, emphasizing its predictive value for MetS and related risk factors. The findings reinforce AIP's utility as a clinically accessible biomarker, facilitating early diagnosis and personalized risk stratification across diverse populations. This study underscores the critical need for longitudinal research to elucidate the mechanisms underlying AIP's role in metabolic pathways and its temporal relationship with cardiovascular outcomes, such as myocardial infarction. Future studies should incorporate larger, heterogeneous cohorts and advanced imaging techniques to explore AIP's impact on subclinical atherosclerosis and microvascular complications. Additionally, integrating AIP assessments with genetic, proteomic, and metabolomic profiles could further refine its application in precision medicine. Clinical implications of this work suggest incorporating AIP into routine metabolic health evaluations to enhance early intervention strategies, ultimately improving outcomes in patients at high risk for MetS and cardiovascular diseases. This research marks a pivotal step toward bridging gaps in the literature and advancing metabolic health management frameworks.

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 humans were approved by Institute Review Board of the Chang-Gung Memorial Hospital (IRB No: 201901599B0). The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from De-identified employee health examination database. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

L-SC: Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Y-RC: Data curation, Investigation, Writing – original draft. Y-HL: Formal analysis, Investigation, Methodology, Writing – original draft. H-KW: Investigation, Methodology, Writing – original draft. YL: Formal analysis, Investigation, Methodology, Writing – original draft. J-YC: Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing, Supervision.

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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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A Mendelian randomization study reveals a causal association between NASH and the risk of atrial fibrillation

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Background: Epidemiological evidence suggests that non-alcoholic fatty liver disease (NAFLD) may increase the risk of atrial fibrillation (AF). However, the findings are inconsistent, and the causality remains to be established.

Methods: We conducted two-step, two-sample Mendelian randomization (MR) analysis to assess the association between genetically predicted NAFLD (i.e. chronically elevated serum alanine aminotransferase levels [cALT], imaging-based and biopsy-confirmed NAFLD) and AF. Subsequently, we further performed Mendelian randomization to investigate the causal relationship between non-alcoholic steatohepatitis (NASH), a subtype of NAFLD, and AF. The inverse variance weighted (IVW) method was used as the primary approach to reveal the potential causation between the exposure and outcome.

Results: There was no significant causal association between NAFLD diagnosed based on cALT, confirmed by imaging, or verified by biopsy, and an increased risk of atrial fibrillation. Furthermore, the results of the IVW method revealed a positive causal effect of NASH on AF (OR=1.113, 95% CI=1.025-1.209, P = 0.011). In the reverse analysis, however, no evidence supported a significant genetic association between AF and NASH (OR=0.974, 95% CI=0.934-1.016, P = 0.214).

Conclusion: A causal relationship existed between NASH and the risk of AF. However, no significant genetic association has been observed between NAFLD and AF risk. This suggests that managing the progression of NAFLD may hold potential value in preventing the onset of AF.

KEYWORDS

atrial fibrillation, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, Mendelian randomization, causal relationship

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic metabolic liver disease, primarily encompassing simple steatosis and non-alcoholic steatohepatitis (NASH) (1). Simple steatosis is defined as the presence of ≥5% hepatic steatosis (HS) without evidence of hepatocellular injury in the form of hepatocyte ballooning. NASH is defined as the presence of ≥5% HS and inflammation with hepatocyte injury (e.g., ballooning), with or without any fibrosis. NASH represents a more severe pathological manifestation compared to steatosis alone and poses a heightened clinical risk of progressing to liver fibrosis, cirrhosis, and ultimately, hepatocellular carcinoma (2). Meanwhile, a growing body of evidence demonstrates that NAFLD, as a multisystemic disease, affects extrahepatic organs and regulatory mechanisms, thereby elevating the risk of cardiovascular diseases, type 2 diabetes, and other related conditions (3). Recently, the concept of metabolic association with fatty liver disease (MAFLD) has been proposed to better reflect the metabolic basis of the disease, emphasizing its association with obesity, insulin resistance, and cardiovascular risk (4).

As a cardiovascular disease with rapidly rising incidence and prevalence, atrial fibrillation (AF) significantly increases the global disease burden (5). Studies have shown that NAFLD is closely associated with the development of AF (6–8). NAFLD and AF share common risk factors, including obesity, insulin resistance, type 2 diabetes, systemic inflammation (9), and abnormal circadian rhythms (10–12), which can contribute to the development of both diseases. Additionally, the pro-inflammatory and pro-fibrotic states during the progression of NAFLD may contribute to atrial remodeling, thereby increasing the risk of atrial fibrillation (13). However, whether NAFLD is an independent risk factor for AF remains controversial.

Mendelian randomization (MR), a research method used to infer causal relationships between exposures and outcomes from a genetic perspective, is currently being widely applied in medical research (14). To further explore whether NAFLD is an independent risk factor for AF, our study employed the two-sample Mendelian randomization (TSMR) to clarify the potential causal relationships between NAFLD, particularly its advanced phenotype (NASH), and AF.

2 Methods

2.1 Study design

The genetic data pertaining to exposure and outcome variables in this study were derived from summary-level data of genome-wide association studies (GWAS). We performed TSMR analysis with publicly available summary-level data, which were derived from several large-scale cohorts (15–17). Declaration of Helsinki statement and informed consent procedure has been described in the original publications of these cohorts. In the first phase, we conducted two-sample Mendelian randomization analysis to investigate the causal relationship between NAFLD and AF. In the second phase, we employed the same two-sample Mendelian randomization approach to examine the causality between NASH (advanced phenotype of NAFLD) and AF. The flowchart of the study design is shown in Figure 1.

2.2 Data sources

Genetic data relating to NAFLD were derived from a recently published GWAS for cALT, in which NAFLD was defined as an elevated alanine transaminase (ALT) > 40 U/L for men or >30U/L for women during at least two time points at least 6 months apart within a 2-year period, after exclusion of other liver diseases (15). The study included 90,408 cases of cALT and 128,187 controls from the Million Veteran Program (MVP) database, predominantly composed of European Americans (EA, 75.1%) across four ancestral groups. Overall, 77 independent single-nucleotide polymorphisms (SNPs) were identified with significant associations (P < 5e-8) in the study. Among the SNPs, 22 were replicated in a subsequent imaging-confirmed NAFLD cohort (n=44,289), while 36 were replicated in a biopsy-defined NAFLD cohort comprising 7,397 cases and 56,785 controls. Therefore, NAFLD defined based on cALT, imaging, and biopsy was separately included in the MR analysis.

The SNPs associated with NASH are sourced from the FinnGen R10 dataset within the FinnGen study (16). The study is a large-scale genomics initiative that has analyzed over 500,000 Finnish biobank samples and correlated genetic variation with health data to understand disease mechanisms and predispositions. The project is a collaboration between research organisations and biobanks within Finland and international industry partners. The definition of NASH refers to clinically diagnosed non-alcoholic steatohepatitis (ICD-10 code K73.80). The study included a total of 175 NASH cases and 412,006 control subjects.

Genetic data associated with AF were extracted from the largest GWAS meta-analysis of 60,620 AF cases and 970,216 controls of European ancestry (17). This comprehensive dataset integrated information from notable studies such as the Nord-Trøndelag Health Study (HUNT), deCODE, the Michigan Genomics Initiative (MGI), DiscovEHR, UK Biobank, and the AFGen Consortium. AF cases were defined by clinically diagnosed atrial fibrillation or flutter (ICD-10 code I48 and ICD-9 code 427.3). A detailed description of the GWAS data involved in this study is shown in Table 1.

2.3 Screening for genetic instrumental variables

All instrumental variables included into the ultimate MR analysis are required to fulfill three fundamental assumptions.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; AF, atrial fibrillation; MR, Mendelian randomization; cALT, chronically elevated serum alanine aminotransferase; NASH, non-alcoholic steatohepatitis; IVW, inverse variance weighted; TSMR, two-sample Mendelian randomization; GWAS, genome-wide association studies; ALT, alanine transaminase; MVP, Million Veteran Program; EA, European Americans; SNPs, single-nucleotide polymorphisms; HUNT, Nord-Trøndelag Health Study; MGI, Michigan Genomics Initiative; FLI, fatty liver Index; IVs, instrumental variables.

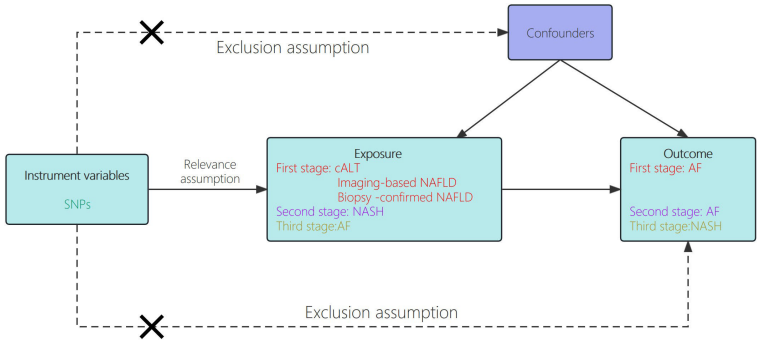

FIGURE 1
Schematic showing how Mendelian randomization was used to evaluate a causal association between NAFLD/NASH and AF in this study.

Firstly, SNPs that are significantly associated with exposure on a genome-wide scale are considered (specifically, $p < 5e\text{-}8$ for cALT, $p < 5e\text{-}6$ for Imaging-based NAFLD, Biopsy-confirmed NAFLD, and NASH, with 1.44e-9 representing 0.05/nSNPs for AF). Secondly, SNPs without linkage disequilibrium (kb = 10000, $r^2 < 0.001$) are extracted, and palindromic SNPs with intermediate allele frequencies are excluded. Proxy SNPs were not used in this MR analysis. The results from IVW will serve as the main outcomes for TSMR analysis. Significant associations identified by IVW will undergo further sensitivity analysis, and pleiotropy will be tested using MR-Egger to ensure the effects of horizontal pleiotropy. The strength of the selected genetic instrument was assessed using F statistics, with a mean F-statistic < 10 regarded as a weak set of instrumental variables.

3 Results

3.1 Causal effects of NAFLD-related traits on AF

We obtained 67 cALT-associated SNPs, 9 imaging-associated SNPs and 9 biopsy-associated SNPs after removing correlated SNPs (Supplementary Tables 1-3). According to the IVW result, no significant causal relationship between NAFLD-related traits and the risk of AF was found. Furthermore, other MR methods showed consistent results. Figures 2 and 3 present the detailed results of the MR analysis.

3.2 Causal effects between NASH and AF

3.2.1 The effect of NASH on AF

9 SNPs based on clinical diagnosis of NASH were used in MR analysis (Supplementary Table 4). IVW method showed a statistically significant association between genetically predicted NASH and the risk of AF (OR=1.113, 95% CI=1.025-1.209, P = 0.011). The result of Weighted median was consistent with IVW (p=0.045), while the remaining three methods were not statistically significant. Figures 4 and 5 present the detailed results of the MR analysis.

Cochran's Q statistic showed no significant heterogeneity in the estimates of included SNPs (Q=4.883, P=0.674). The intercept of MR-Egger was 0.013 (P = 0.350), which showed no significant horizontal pleiotropy. In addition, the MR-PRESSO Test also showed that there was no horizontal pleiotropy in this study (Global Test P= 0.769), and no potential outliers were found in the result, indicating that the result was robust and reliable (Supplementary Table 6).

TABLE 1 Detailed description table of GWAS data involved in this study.

Phenotype	PMID or GWAS ID	Years	Population	Sizes of sample	Consortium or cohort study
cALT	35654975	2022	European-American, African-American, Hispanic-American, and Asian-American	90,408 cases and 128,187 controls	–
Imaging-based NAFLD	35654975	2022	European-American, African-American, and Hispanic American	44,289	–
Biopsy-confirmed NAFLD	35654975	2022	European-American and Hispanic American	7,397 cases and 56,785 controls	–
NASH	–	2023	European	175 cases and 412,006 controls	FinnGen
AF	30061737	2018	European	60,620 cases and 970,216 controls	HUNT, deCODE, MGI, DiscovEHR, UK Biobank, and AFGen Consortium

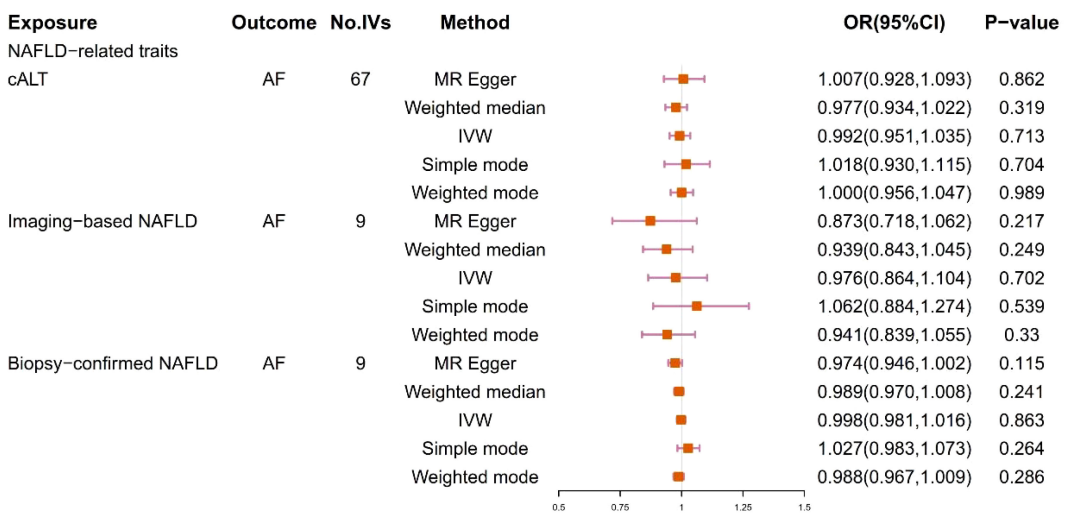

FIGURE 2
Odds ratios and p-value of MR analysis for the associations between NAFLD and AF. OR, odds ratio; 95% CI, 95% confidence interval.

3.2.2 The effect of AF on NASH

78 SNPs depending on the clinical diagnosis of AF were used in MR analysis (Supplementary Table 5). There was no significant causal relationship between AF and the risk of NASH according to the result of IVW (OR = 0.974, 95%CI = 0.934–1.016, P = 0.214). In addition, the results of MR Egger, Weighted median, Simple mode and Weighted mode were consistent with IVW. Figures 4 and 5 present the detailed results of the MR analysis.

4 Discussion

Although genetically predicted NAFLD based on cALT diagnosis, imaging and biopsy confirmation was not substantially

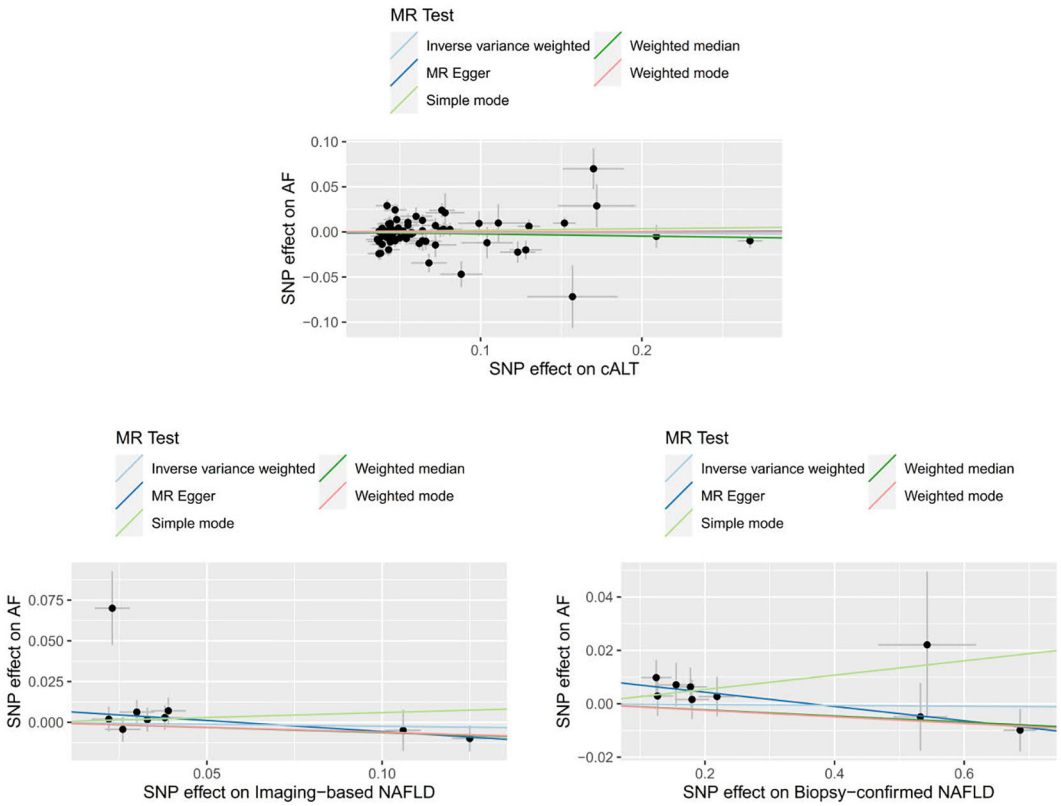

FIGURE 3
Scatter plots to assess causal associations between NAFLD-related traits and AF.

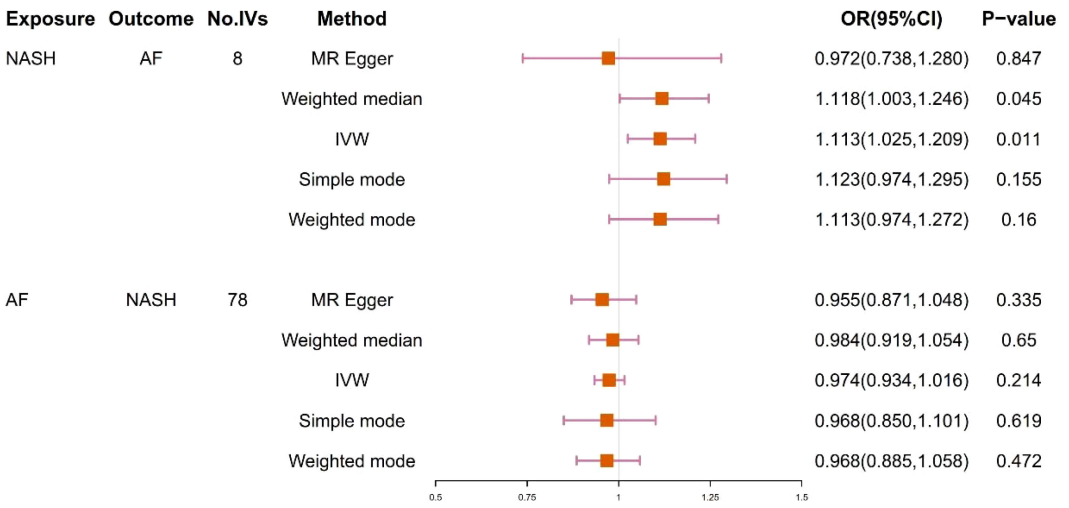

FIGURE 4
Odds ratios and p-value of MR analysis for the associations between NASH and AF. OR, odds ratio; 95% CI, 95% confidence interval.

related to an increased risk of AF, further analysis revealed that NASH, the advanced phenotype of NAFLD, was associated with the risk of developing AF.

4.1 The relationship between NAFLD/NASH and atrial fibrillation

Previous clinical studies have shown that NAFLD is closely related to the occurrence of AF. Käräjämäki et al. (18) reported an elevated incidence of AF in NAFLD patients from the OPERA study, which persisted after adjusting for confounding factors. Roh et al. (7) found an independent link between NAFLD (defined by FLI) and increased AF risk in a healthy Korean cohort. Meta-analyses further confirmed a strong correlation between NAFLD and higher AF risk (6, 19–22). As an advanced phenotype of NAFLD, NASH have risk factors for the development of cardiac abnormalities. Whitsett et al. (23) pointed out that AF is highly prevalent in patients with biopsy-proven Nonalcoholic Steatohepatitis (NASH). However, the Framingham Heart Study showed no association between AF and either computerized tomography or ultrasound-diagnosed hepatic steatosis (24).

Mendelian randomization explored the relationship between NAFLD/NASH and AF from the perspective of genetics. Two previous Mendelian randomization studies have explored the relationship between NAFLD and its subtype NASH and AF (Their exposure data originated from the same GWAS study). Their results showed that there was no significant causal relationship between NAFLD and AF, which is consistent with our Mendelian randomization study of NAFLD and AF. Simultaneously, these two investigations probed the causative association between NASH and AF, and the findings indicated the absence of a causal relationship (25, 26). We conducted a Mendelian randomization analysis based on the newly published FinnGen R10 database to further explore the causal relationship between NASH and AF, and the result revealed that genetically predicted NASH was causally associated with an increased risk of AF(OR=1.113, 95% CI=1.025-1.209, P = 0.011). Subsequently, heterogeneity tests and pleiotropy evaluations suggested the causal relationship was robust and reliable(both P >

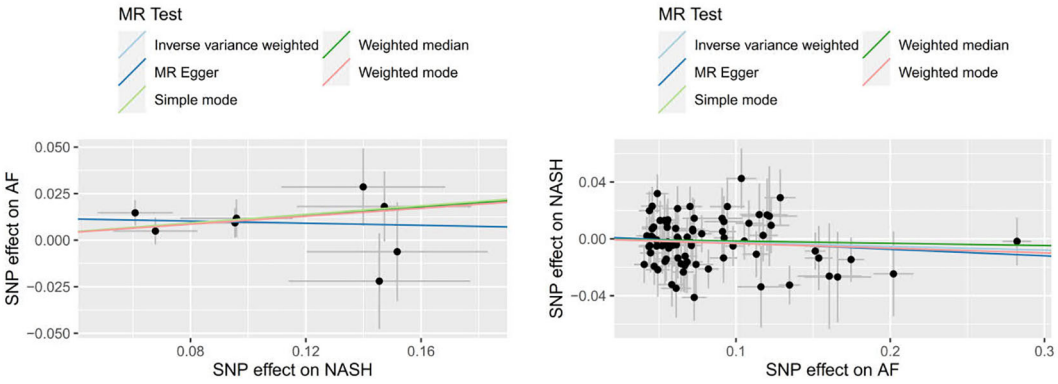

FIGURE 5
Scatter plots to assess causal associations between NASH and AF.

0.05). Although the increase in odds ratio may not appear substantial, it still holds important epidemiological and clinical implications. Furthermore, reverse MR analysis suggested that AF was not associated with an increased risk of NASH. The larger sample size and updated genetic information in FinnGen R10 may provide a more robust interpretation of the relationship between NASH and AF.

4.2 Possible mechanisms associated with NASH and atrial fibrillation

The mechanism of AF induced by NAFLD remains unclear, but it is suggested that chronic inflammation, insulin resistance, lipid deposition, and oxidative stress may be involved in the development of AF in NAFLD patients (27). Mild systemic inflammation is a key factor in NAFLD (28). The Pro-inflammatory environment and oxidative stress lead to an increased release of inflammatory factors, ultimately resulting in an elevated risk of AF (29, 30). Furthermore, as NAFLD progresses to the stage of NASH, lipid deposition leads to the occurrence of lipotoxicity, causing further release of inflammatory factors and exacerbating the inflammatory response (31). During the NASH stage, the degree of liver fibrosis progresses significantly compared to the early stage of NAFLD (simple steatosis). Study have shown that the severity of liver fibrosis in NAFLD patients is associated with an increased risk of atrial fibrillation (AF), potentially mediated through mechanisms such as systemic inflammation, metabolic disturbances, and atrial remodeling (32). Furthermore, Hui et al. reported that high TNF-α levels and hypoadiponectinemia are IR-independent features of NASH, and these two factors synergistically exacerbate insulin resistance, oxidative stress, and lipotoxicity, potentially serving as underlying mechanisms linking NASH to AF risk (33).

4.3 The role of NASH in the prevention and treatment of atrial fibrillation

The pathogenesis of atrial fibrillation is still not fully understood, and effective treatment strategies remain limited. Our study provides genetic evidence supporting a causal relationship between NASH and AF risk, which may have implications for clinical practice. When NASH is recognized as a risk factor for atrial fibrillation, patients with NASH, especially those with obesity or metabolic syndrome, should be encouraged to undergo regular screening for atrial fibrillation. In addition, interventions for NASH, such as lifestyle changes (such as weight loss, dietary changes) and anti-inflammatory or anti-fibrotic treatments, may help reduce the risk of atrial fibrillation.

5 Conclusion

In conclusion, this MR study reveals a causal relationship between genetically determined NASH and an elevated risk of AF, while there is no apparent causal relationship between NAFLD and AF. This suggests that controlling the further progression of NAFLD may hold potential value in preventing the occurrence of AF.

6 Limitation

Although our study had enough statistical power to evaluate the causal relationships, the findings should be interpreted with prudence. Furthermore, this study also has some limitations. Firstly, the selected instrumental variables (IVs) capture only a relatively small proportion of the phenotypic genetic variation, potentially leading to bias from weak IVs. Additionally, the standard for the independence test P-value is relatively lenient ($P < 5e\text{-}6$), which could introduce some bias into the results. Secondly, the definition of NAFLD is partially based on cALT levels rather than the presence of NAFLD itself. Thirdly, a possible limitation of the study is the lack of further stratification for the severity of NAFLD and other factors such as gender and age. The absence of subgroup data for NAFLD limits the extension of these stratified analyses. While our study did not stratify by gender due to data limitations, future research should explore gender-specific associations, particularly in postmenopausal women, to better understand the underlying mechanisms. Finally, our focus was primarily on individuals of European descent, which may reduce the generalizability of our study results.

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

All the summary-level GWAS data used in the analyses are publicly available, and therefore ethical approval was not imperative for this study. Ethical approval for the GWASs can be found in the corresponding GWAS publications cited in the manuscript.

Author contributions

BC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. XS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. JH: Visualization, Writing – review & editing. YG: Conceptualization, Project administration, Software, Supervision, Writing – review & editing. MC: Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. YW: Investigation, Methodology, Software, Supervision,

Validation, Writing – review & editing. YY: Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. PC: Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. XL: Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. TL: Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. CX: Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. BL: Conceptualization, Project administration, Software, Supervision, Writing – review & editing. QL: Conceptualization, Project administration, Software, Supervision, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1390259/full#supplementary-material

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Metabolic syndrome, left ventricular diastolic dysfunction and heart failure with preserved ejective fraction

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Metabolic syndrome (MetS) encompasses a cluster of interrelated conditions, including obesity, hyperglycemia, hyperlipidemia, and hypertension, and has been established as a significant risk factor for cardiovascular events and heightened mortality. At its core, insulin resistance serves as the primary underlying mechanism driving the development of MetS. The prevalence of MetS is rising at an alarming rate, posing a significant public health challenge worldwide. Even in the absence of overt obstructive coronary artery disease or valvular heart disease, patients with MetS often exhibit adverse cardiac remodeling and myocardial dysfunction. Left ventricular hypertrophy (LVH) and left ventricular diastolic dysfunction (LVDD) are the leading manifestations of heart failure with preserved ejection fraction (HFpEF). Abnormal myocardial substrate utilization, neurohormonal activation, interstitial fibrosis, coronary microvascular dysfunction, and metabolic inflammation have all been implicated in the development and progression of adverse cardiac remodeling associated with MetS. However, despite the tremendous research produced on this subject, HFpEF remains highly prevalent in such a population. The early diagnosis of abnormal cardiac remodeling would enable optimal effective therapies to prevent the progression of the disease to the symptomatic phase. HFpEF encompasses a diverse range of pathological processes. In these patients, LVDD and elevated left ventricular filling pressure are the primary manifestations. Echocardiography remains the popular imaging modality for the assessment of LVDD and LV filling pressure. The article aims to review recent articles covering the association between MetS components or MetS and LVDD in HFpEF.

KEYWORDS

metabolic syndrome, left ventricular diastolic dysfunction, heart failure with preserved ejective fraction, hypertension, diabetes mellitus

1 Introduction

Metabolic syndrome (MetS) appears to be important in the development of left ventricular diastolic dysfunction (LVDD) and its progression towards heart failure with preserved ejection fraction (HFpEF), as the increasing prevalence of obesity, hypertension, chronic kidney disease, and diabetes is closely associated with the incidence of HFpEF. HFpEF is commonly defined as a condition in which a person with heart failure (HF) has a left ventricular (LV) ejection fraction (EF) of ≥50%. The European Society of Cardiology (ESC) provides a more detailed definition: HFpEF is characterized by symptoms and signs of heart failure, evidence of structural and/or functional cardiac abnormalities, and/or elevated natriuretic peptides (NPs), along with an LVEF of ≥50% (1). Findings from previous studies have suggested a novel paradigm. In the new paradigm, multiple comorbidities, including obesity, hypertension, hyperlipidemia, diabetes, and insulin resistance, cause a systemic pro-inflammatory state that leads to oxidative stress, endothelial dysfunction, ectopic fat accumulation, and coronary microvascular dysfunction. Eventually, these disease mechanisms contribute to LVDD and, ultimately, HFpEF.

Throughout this review, we will focus on the association between MetS and its components with changes in LVDD to offer updated information on this emerging issue. Using the following keywords, we searched PubMed, Medline, OVID, and EMBASE databases for English-language studies published from January 1963 to December 2024: "left ventricle diastolic dysfunction", "metabolic syndrome", "arterial hypertension", "systemic hypertension", "obesity", "overweight", "central obesity", "body mass index", "diabetes", "increased glucose level", "dyslipidemia", "triglycerides", and "high-density lipoprotein cholesterol", and "heart failure with preserved ejective fraction".

2 Definitions of MetS

There have been several definitions proposed for the MetS so that clinicians and researchers can use the tool effectively. An international consultation group on the definition of diabetes for the World Health Organization (WHO) proposed the first formalized definition of metabolic syndrome in 1998 (2). Several insulin resistance markers and two additional risk factors, including obesity, hypertension, high triglyceride level, reduced high-density lipoprotein (HDL) cholesterol level, or microalbuminuria, could be used to diagnose the syndrome by the WHO criteria. Based on the National Cholesterol Education Program-Third Adult Treatment Panel (NCEP ATP III) definition (3), a diagnosis is based on the presence of three of the following five factors: abdominal obesity, elevated triglyceride, reduced HDL cholesterol, elevated blood pressure (BP), and elevated fasting glucose (impaired fasting glucose or diabetes). In 2005, according to the International Diabetes Federation (IDF) (4), abdominal obesity was one of five factors that must be taken into account in the diagnosis of diabetes, with waist measurement serving as the primary screening tool. The remaining criteria were essentially the same as those in ATP III. While the American Heart Association (AHA)/National Heart, Lung, and Blood Institute (AHA-NHLBI) definition (5) slightly modified the ATP III criteria, abdominal obesity was not mandated as a risk factor. In 2009 (6), both the IDF and AHA/NHLBI recognized abdominal obesity as one of five criteria for a diagnosis, but not a prerequisite. As a result, the presence of three of five risk factors constitutes a diagnosis of MetS. Table 1 shows the common definition.

3 Echocardiographic variables for evaluating LVDD

LVDD is primarily assessed using echocardiography. The methodology is the most extensively validated, and it has the highest temporal resolution. We have summarized the main advantages, disadvantages, and indications for utilizing different echo parameters in Table 2. LVDD is widely evaluated with echocardiography due to its availability and relative low cost. The first recommendations for LVDD by echocardiography were published in 2009 (7). In patients with abnormal diastolic

TABLE 1 Criteria for the clinical diagnosis of metabolic syndrome.

Measure	Categorical cut-off points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in men; <50 mg/dL (1.3 mmol/L) in women
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	100 mg/dL

HDL-C, high-density lipoprotein cholesterol.
*It is recommended that the IDF cut-off points be used for non-Europeans and either the IDF or AHA/NHLBI cut-off points be used for people of European origin until more data are available.
†The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose Omega-3 fatty acids presumes high triglycerides.
‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

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TABLE 2 Echocardiographic variables for evaluating left ventricular diastolic function.

Variable	Hemodynamic determinants	Advantages	Limitations
Mitral E/A ratio	E velocity is dependent on LA-LV pressure gradient in early diastole and therefore LV relaxation and LA pressure. A-wave velocity depends on LA-LV pressure gradient during late diastole, and therefore LV stiffness and LA contractility. The mitral inflow E/A ratio is used to identify the following filling patterns: normal, impaired relaxation, pseudonormal (PN), and restrictive filling.	1. Feasible and reproducible. 2. It provides diagnostic and prognostic information. 3. In patients with dilated cardiomyopathy, filling patterns correlate better with filling pressures, functional class, and prognosis than LVEF. 4. A restrictive filling pattern in combination with LA dilation in patients with normal EFs is associated with a poor prognosis similar to a restrictive pattern in dilated cardiomyopathy.	1. The U-shaped relation with LV diastolic function makes it difficult to differentiate normal from PN filling, particularly with normal LVEF, without additional variables. 2. If mitral flow velocity at the start of atrial contraction is >20 cm/s, the E/A ratio will be reduced due to fusion. 3. Not applicable in atrial fibrillation/atrial flutter patients. 4. Age dependent (decreases with aging).
DT of mitral E velocity (ms)	In patients with impaired LV relaxation, IVRT <70 ms is usually associated with increased LA pressure	1. Feasible and reproducible. 2. A short DT in patients with reduced LVEFs indicates increased LVEDP with high accuracy both in sinus rhythm and in atrial fibrillation.	1. DT does not relate to LVEDP in normal LVEF 2. Should not be measured with E and A fusion due to potential inaccuracy. 3. Age dependent (increases with aging). 4. Not applied in atrial flutter.
IVRT (ms)		1. Overall feasible and reproducible. 2. IVRT can be combined with other mitral inflow parameters, such as the E/A ratio, to estimate LV filling pressures in patients with HFrEF 3. It can be applied in patients with mitral stenosis in whom the same relation with LV filling pressures described above holds. 4. In patients with MR and in those after MV replacement or repair, it can be combined with E/e' to estimate LV filling pressures	1. IVRT duration is in part affected by heart rate and arterial pressure. 2. It is more challenging to measure and interpret with tachycardia. 3. Results differ on the basis of using CW or PW Doppler for acquisition.
Pulmonary vein systolic-to-diastolic (S/D) velocity ratio	S/D is inversely related to LA pressure and is most reliable in patients without mitral valve disease and with depressed LVEF.	1. Reduced S velocity, S/D ratio < 1, and systolic filling fraction. 2. In patients with AF, DT of diastolic velocity (D) in pulmonary vein flow can be used to estimate mean PCWP.	1. The feasibility of recording PV inflow can be suboptimal, particularly in ICU patients. 2. The relationship between PV systolic filling fraction and LAP has limited accuracy in patients with normal LVEF, AF, mitral valve disease, and HCM.
Pulmonary vein atrial reversal duration minus mitral A velocity duration (Ar-A) (ms)	In patients with normal LA systolic function, the time difference between the duration of pulmonary vein flow and mitral inflow during atrial contraction is directly related to LV pressure rise with LA contraction and LV end-diastolic pressure.	1. PV Ar duration > mitral A duration by 30 msec indicates an increased LVEDP. 2. Independent of age and LVEF. 3. Accurate in patients with MR and patients with HCM.	1. Adequate recordings of Ar duration may not be feasible by TTE in several patients. 2. Not applicable in AF patients. 3. Difficult to interpret in patients with sinus tachycardia or first-degree AV block with E and A fusion
LA maximum volume index	LA volume is directly but weakly related to LV filling pressure.	1. Feasible and reproducible. 2. It provides diagnostic and prognostic information about LV diastolic dysfunction and chronicity of disease. 3. Apical four-chamber view provides visual estimate of LA and RA size, which confirms LA is enlarged.	1. LA dilation is seen in bradycardia, high-output states, heart transplants with biatrial technique, atrial flutter/fibrillation, and significant mitral valve disease, despite normal LV diastolic function. 2. LA dilatation occurs in well-trained athletes who have bradycardia and are well hydrated. 3. Suboptimal image quality, including LA foreshortening, in technically challenging studies precludes accurate tracings. 4. It can be difficult to measure LA volumes in patients with ascending and descending aortic aneurysms as well as in patients with large interatrial septal aneurysms
Peak velocity of tricuspid regurgitation jet by continuous-wave Doppler (m/s)	In patients without pulmonary disease, there is a direct relation between pulmonary artery systolic pressure and LA pressure.	Systolic PA pressure can be used as an adjunctive parameter of mean LAP. Evidence of pulmonary hypertension has prognostic implications.	1. Indirect estimate of LAP. 2. Adequate recording of a full envelope is not always possible, though intravenous agitated saline or contrast increases yield. 3. With severe TR and low systolic RV-RA

(Continued)

TABLE 2 Continued

Variable	Hemodynamic determinants	Advantages	Limitations
			pressure gradient, the accuracy of calculation is dependent on a reliable estimation of systolic RA.
e' (cm/s), acquired by pulse tissue Doppler (recommended to measure at septal and lateral annulus)	The hemodynamic determinants of e' velocity is LV relaxation, restoring forces, and filling pressure.	1. Feasible and reproducible. 2. LV filling pressures have a minimal effect on e' in the presence of impaired LV relaxation. 3. Less load dependent than conventional blood-pool Doppler parameters.	1. Limited accuracy in patients with CAD and regional dysfunction in the sampled segments, significant MAC, surgical rings or prosthetic mitral valves and pericardial disease. 2. Need to sample at least two sites with precise location and adequate size of sample volume. 3. Different cut-off values depending on the sampling site for measurement. 4. Age dependent (decreases with aging).
Mitral E/e' ratio	e' is dependent on LV relaxation. As e' corrects for the effect of LV relaxation on E, the E/e' ratio relates directly to LA pressure.	1. Feasible and reproducible. 2. Values for average E/e' ratio < 8 usually indicate normal LV filling pressures, values > 14 have high specificity for increased LV filling pressures.	1. E/e' ratio is not accurate in normal subjects, patients with heavy annular calcification, mitral valve and pericardial disease. 2. "Gray zone" of values in which LV filling pressures are indeterminate. 3. Accuracy is reduced in patients with CAD and regional dysfunction at the sampled segments. 4. Different cut-off values depending on the site used for measurement.
LA reservoir strain	Reflects LA reservoir function and is related inversely to LA pressure. In conjunction with LA pressure, it can be used as an index of LA stiffness.	1. Feasible and reproducible 2. LA reservoir strain may be used as additional markers of LV filling pressure.	1. Lower accuracy with tachycardia as it relates to frame rate. 2. Limited data on its accuracy in the presence of atrial arrhythmias, mitral valve disease, and MAC; dependent on LV systolic function, which, if reduced, can be associated with reduced LA reservoir strain in the presence of normal LA pressure.

LVEF, left ventricular ejection fraction; LA, left atrium; LV, left ventricular; E, early filling; DT, E peak deceleration time; LVEDP, left ventricular end-diastolic pressure; MR, mitral regurgitation; MV, mitral valve; CW, continual wave Doppler; PW, pulse wave Doppler; PCWP, pulmonary capillary wedge pressure; PV, pulmonary vein; LAP, left atrium pressure; HCM, hypertrophic cardiomyopathy; RA, right atrium; ICU, intensive care unit; AV, atrium ventricular; e', early diastolic; IVRT, isovolumic relaxation time; MV, mitral valve; TR, tricuspid regurgitation; CAD, coronary artery disease; MAC, mitral annular calcification; LVDD, left ventricular diastolic dysfunction.

function, the severity of LVDD was determined by comparing the maximum diastolic velocity of the early(E) and late(A) waves, E/A ratios, E-wave deceleration time, diastolic velocities (tissue Doppler) in the mitral annulus (e' and a'), and pulmonary vein inflow. More recently, updated recommendations from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) for the evaluation of diastolic function by echocardiography were published in 2016 (8). These recommendations tried to apply the most feasible and reproducible measurements from the 2009 recommendations to simplify the evaluation of LVDD. The 2016 recommendations proposed a new algorithm to assess LVDD, as shown in Figure 1. A recent study has revealed a new LVDD indicator, left atrial (LA) reservoir strain, which has excellent feasibility of ~95% and can detect LV diastolic alterations and elevated LV filling pressure even when LA volume index (LAVI) is normal (9, 10).

4 Hypertension and LVDD

A link between LVDD and hypertension was found (11), in which insulin resistance, LV concentric remodeling/hypertrophy (12), abnormalities of the renin–angiotensin–aldosterone system (RAAS) (13), endothelial dysfunction, and changes of coronary microcirculation (14) were factors. High sodium intake may affect BP parameters and arterial wall damage in hypertensive individuals, contributing to LVDD impairment (15). Sympathetic nerve system (SNS) activity causes LVDD in hypertension patients, and sympathoinhibition prevents the development or delays the progression of LVDD. Diastolic dysfunction was presumed to be a surrogate marker of myocardial fibrosis in hypertensive patients who were untreated. Matrix metalloproteinases type I (TIMP-1) tissue inhibitors correlate with diastolic dysfunction (16).

LVDD can occur across a range of blood pressure states, including normal blood pressure, hypertension, or masked hypertension. Grade 1 DD was more frequent in subjects with prehypertension, and grade 2 DD was significantly frequent in hypertension. Asymptomatic and newly diagnosed hypertensive patients showed reduced E/A and lower e' velocity compared to normal BP individuals. Inter-visit systolic blood pressure (SBP) variability was more correlated with LVDD than mean SBP. Hypertensive patients have high pulse pressure and arterial stiffness, with significant effects on LVDD through ventricle-arterial coupling. Using the 2009 recommendations, Grade 1 DD was documented in 24.4%, grade 2 DD in 19.3%, and no patients were diagnosed with grade 3 LVDD. After applying the 2016 recommendations, LVDD was documented in 12.3% of patients (17). The prevalence of LVDD is 1.2%–2.7% in adults. An early

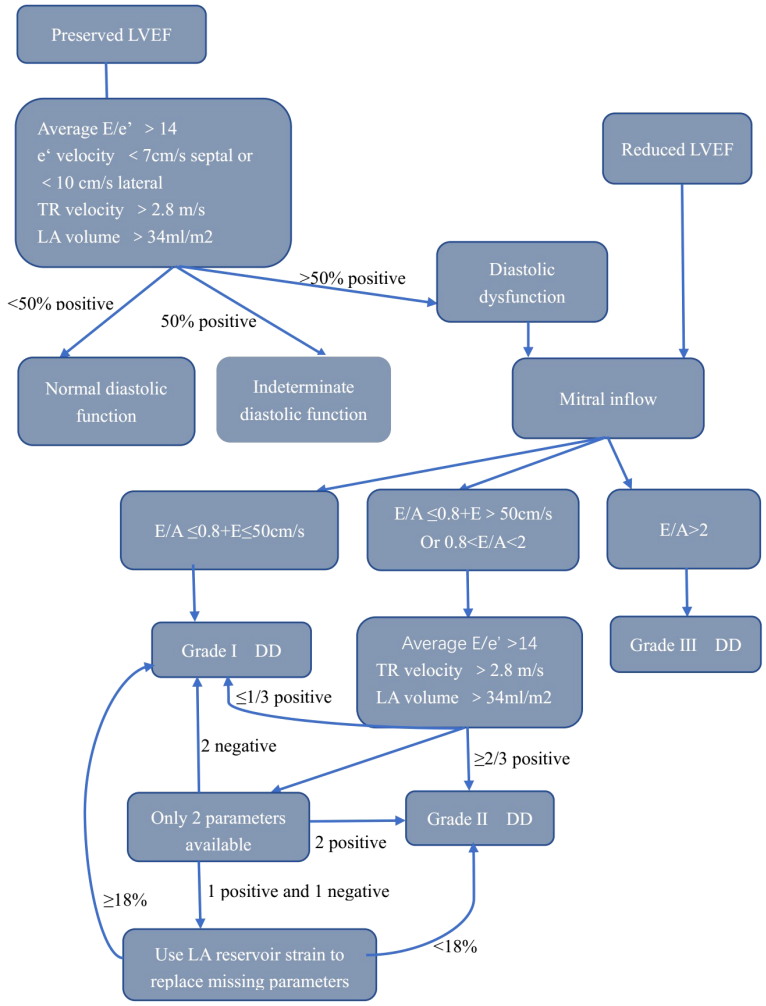

FIGURE 1
Algorithm for estimation of LVDD. LVEF, left ventricular ejection fraction; E, early filling; e', early diastolic; LA, left atrium; TR, tricuspid regurgitation; LVDD, left ventricular diastolic dysfunction.

stage of impaired glucose metabolism and diabetes in hypertensive patients may specifically deteriorate diastolic function. Obesity-related insulin resistance amplifies the effect of hypertension on LVDD. In elderly hypertensive women, LVDD occurs earlier and estimated filling pressures are higher, which indicates a greater likelihood of HFpEF. Primary hypertension patients experience a decrease in LA strain conduit and reservoir function before the diagnosis of LVDD is established.

Due to their ability to reduce both preload and afterload, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) are conceptually the most effective treatments for LVDD. Furthermore, these drugs reverse the concentric geometry of the left ventricle and reduce myocardial fibrosis and LV hypertrophy (LVH). Recent studies have examined the clinical effect of ARBs on LVDD. The E/e′ ratio of uncomplicated hypertensives was reduced by irbesartan (18). Angiotensin receptor-neprilysin inhibitors (ARNI) are recommended for the treatment of HFpEF. In addition to LVH regression, telmisartan therapy induced a parallel decrease in LAV and a shortening of IVRT (19). LV filling time is prolonged when the heart rate is lower, which counterbalances the resistance of a stiffened left ventricle to the diastolic inflow. In hypertension patients with LVDD, controlling heart rate is therefore an important objective. There was a strong correlation between e′ velocity and the extent of SBP reduction (SBP target <130 mm Hg or <140 mm Hg), and patients with the lowest achieved SBP values tended to have the highest velocity (20).

5 Diabetes and glucose intolerance and LVDD

Even patients with well-controlled diabetes without overt macrovascular complications, LV structural changes, and systolic and diastolic dysfunction have all been observed. It may be triggered by insulin resistance, abnormal substrate utilization by the myocardium, and uncoupling of mitochondrial oxidative phosphorylation. Researchers have identified decreased

cardiomyocyte function in diabetic animal models, caused by impaired mitochondrial calcium handling and decreased levels of free matrix calcium, as a key mediator of heart failure. Inflammatory signaling and collagen metabolism are also affected by hyperglycemia via oxidative stress, protein kinase C activation, and advanced glycosylation end-products (AGEs). Additionally, insulin resistance may contribute to SNS activity. As a result of SNS activity, the RAAS may be stimulated and may promote LVDD via adrenergic-mediated hypertrophy and fibroblast growth, as well as apoptosis and necrosis in myocytes. A high level of insulin resistance, hyperglycemia, and increased metabolism of free fatty acids (FFAs) may contribute to diabetes-related altered cardiac phenotypes (21). Diabetic patients who had microvascular complications were most likely to develop cardiomyopathy, and several of them displayed alterations within the coronary arteries of the myocardium. Diabetic hearts in humans also display thickened capillary basement membranes and capillary microaneurysms (22). In a study by Zoneraich et al. (23) in type 1 diabetic patients with normotensive blood pressure levels, small vessel disease was present in 72%, but it was not found in non-diabetic patients with normal blood pressure levels.

Glucose interacts with collagen to form AGEs, and in diabetes, the process is accelerated, leading to interstitial fibrosis. In chronic hyperglycemia, vascular and membrane proteins are non-enzymatically glycated, resulting in reactive oxygen species (ROS) and AGEs. As a result of diabetes, AGEs of collagen are formed more frequently in the myocardium of the heart, which causes stiffness. Furthermore, glucose enhances the production of the extracellular matrix in fibroblasts by activating the collagen gene promoter sequence and increasing the level of angiotensin II type 1 receptors (24). The RAAS and SNS are major neurohormonal systems that affect cardiac remodeling; therefore, drugs that affect them are vital in preventing or reversing it (24). Diabetes-related changes in the heart include hypertrophy of myocytes, the addition of extracellular collagen, interstitial fibrosis, and microangiopathy within the myocardium (25).

In individuals with type 1 or 2 diabetes, LVDD is considered to be the first manifestation of diabetic cardiomyopathy, especially in patients with poorer glycemic control. In the Strong Heart Study, which enrolled 2,411 Native Americans, type 2 diabetes was frequently associated with an abnormal LV relaxation pattern, independent of age, BP, LV mass, and LV systolic function. There is a greater degree of abnormal LV relaxation in the diabetes-hypertension combination. HbA1c concentrations correlate with abnormal LV relaxation (26). In the context of LVDD, microalbuminuria is an independent risk factor, perhaps as a marker for intramyocardial microangiopathy. It appears that LVDD is more commonly associated with aging and chronic diabetes in patients with well-controlled diabetes than hypertension or LV hypertrophy. Diabetes patients' E/A ratios in their 40s were not significantly different from those of control subjects, but in their 50s, 60s, and 70s, the ratio was significantly lower. Diabetes patients without overt heart disease are more susceptible to diastolic function deterioration when they are older, have retinopathy, and have increased BP over time (27). Diabetes duration was strongly and positively associated with larger LAVI. Worsening in e' (5.4 vs. 7.3 cm/s) and E/e' ratio (13.6 vs. 10.3) was observed in patients with diabetes or impaired glucose tolerance who also had cardiovascular autonomic neuropathy (28). Impaired LV longitudinal systolic and diastolic strains were documented in diabetes. One study found the diabetes susceptibility locus, HNF1B, is associated with prevalent diastolic dysfunction and incident cardiovascular disease. This may provide future drug targets (29). Those with a higher HbA1c level and obesity status showed a high prevalence of LVDD (30). Decreased LA reservoir, conduit, and booster strain was found in adolescents and young adults with obesity and diabetes, although LA volume was normal (31). Peak diastolic strain rate from cardiovascular magnetic resonance feature tracking was decreased in diabetes (32).

Glycemic control can partially prevent or reverse LVDD. Canagliflozin can improve LV diastolic function within 3 months, and those with significantly improved hemoglobin values showed the greatest benefit (33). Animal research found that PPAR-α (fenofibrate) or -γ agonists (pioglitazone) prevented LVDD, possibly by improving the fatty acid metabolism in the myocardium or by modifying hyperglycemia and/or hyperlipidemia (34). After 4 years of treatment with pioglitazone on LVDD in diabetes, a study found an increase in both E/e' and LAVI (35). Liraglutide therapy had favorable effects on E/e' regardless of body weight. The DPP-4 inhibitor, alogliptin, prevents cardiac diastolic dysfunction by inhibiting ventricular remodeling, which can be explained by enhanced mitochondrial function and increased mitochondrial biogenesis in diabetic rabbits (87). LVEF and E/e' in individuals with diabetes improved after 6 months of treatment with tofogliflozin, a sodium-dependent glucose transporter 2 (SGLT2) inhibitor. A previous study has indicated that empagliflozin improves diastolic function, preserves calcium handling and growth signaling pathways, and reduces myocardial insulin resistance in obese mice (36). SGLT2 inhibitors (SGLT2is) are efficacious and safe in treating HFpEF in patients with comorbid chronic kidney disease with and without T2DM (37). SGLT2is work by inhibiting the sodium-glucose co-transporter 2 in the proximal renal tubules, reducing glucose reabsorption and increasing glucose excretion in urine. This leads to lower blood glucose levels, improved insulin sensitivity, and additional benefits such as reduced sodium retention, blood pressure, and cardiac workload, which are particularly beneficial in managing heart failure and diabetic conditions. The ESC 2023 HF guideline update has given SGLT2is for chronic HFpEF a class 1a recommendation (38). However, in patients with diabetes and hypertension without overt heart failure, metformin treatment did not affect LV mass or diastolic function after 1 year (39).

6 Obesity and LVDD

Previous histological analysis showed that the capillary length density of obese patients was lower (40), cardiomyocyte width was reduced, and the pulmonary capillary wedge pressure was greater. A reduction in phosphocreatine/adenosine triphosphate (ATP) is

further exacerbated in obese individuals during inotropic stress, leading to continuing diastolic dysfunction. There is evidence that myocardial energetics may play a key role in obesity-related diastolic dysfunction. The obesity-related increase in LV filling pressure was associated with a lower coronary microvascular density, which could account for the lower maximal myocardial blood flow, impaired myocardial metabolism impairment, LVDD, and a greater risk of HF in obese individuals. Excess adipose accumulation in peripheral obesity increases total and central blood volume, resulting in an increase in cardiac output. Peripheral vascular resistance is decreased, which facilitates this process. An increased amount of visceral adipose tissue is associated with low-grade inflammation (serum C-reactive protein) (41). Obesity is associated with various neurohormonal and metabolic abnormalities that may alter cardiac morphology in humans. Obesity is associated with LVH (42), which alters cardiac morphology. The combination of insulin resistance and hyperinsulinemia has been linked to increased LV mass in obese animals and humans. LVH contributes the most to LV diastolic function. In obesity, RAAS activation may increase sympathetic tone and directly affect the LV myocardium, which can lead to LVH (43). LVDD and myocardial fibrosis were also exacerbated by obesity and hypertension in a synergistic manner (44). It is often difficult to determine whether obesity is independently responsible for LVDD in obese patients due to the presence of insulin resistance, impaired glucose tolerance, or overt diabetes (43).

Impairment of LV diastolic filling or relaxation in obesity was revealed. LVDD appears to be related to obesity level and fasting insulin levels and reduced exercise capacity (45, 46), however, obesity duration was not considered (47). Elderly patients with severe prolonged obesity had elevated plasma volume, eccentric LVH, and systolic and diastolic dysfunction. HF is more likely to develop in obese women. The adverse effect of central adiposity on LV diastolic function was independent of general adiposity and more prominent among women (48). Only visceral fat, other than total body fat, was significantly associated with LVDD. The relationship between LV diastolic function and visceral fat was significantly mediated by triglycerides and sex hormone-binding globulin, possibly through a metabolic pathway that involves blood lipids and ectopic fat accumulation (49). A significant association exists between adipocyte fatty acid-binding protein (FABP4) levels and LVDD in obese subjects who have MetS. FABP4 may thus play a role in obesity and cardiometabolic disorders (50). In morbidly obese individuals, the growth-differentiation factor (GDF)-15 level, a marker of inflammation, was better correlated with diastolic dysfunction. GDF-15 levels increase in relation to different degrees of LVDD (51). One study showed obese patients with a reduced diffusing capacity of the lungs for carbon monoxide had an increased prevalence of moderate or severe LVDD (52). Sarcopenic obesity was associated with impaired diastolic function and decreased exercise capacity (53, 54).

Weight loss, whether achieved through diet and exercise or bariatric surgery, can improve myocardial metabolism, left ventricular structure, and diastolic function, all of which are affected by obesity. As BMI decreased longitudinally, LAVI decreased significantly, and e' velocity increased significantly. Surgical weight loss resulted in a 23% decrease in LV mass, a 33% increase in E/e, and a 28% improvement in relaxation. A reduction of BMI, insulin resistance, total oxygen consumption of the heart, and LV mass was associated with an improvement in LV relaxation but not the reduction of fatty acid utilization. These changes can be reversed more effectively by bariatric surgery than by diet and exercise alone. Bariatric surgery, which is primarily used for severely obese patients, results in significant weight loss and improves the neurohormonal and metabolic milieu to a greater extent than the weight loss modalities of diet and exercise alone (55).

High- and moderate-intensity training can prevent diet-induced obesity-related LV remodeling with diastolic and systolic dysfunction in mice, which suggests that physical activity can alleviate obesity-related cardiac disorders. An obese, insulin resistance, and hypertension rodent model showed that nebivolol attenuated diastolic dysfunction and myocardial remodeling by blunting myocardial oxidative stress and promoting insulin metabolic signaling (56). Recent evidence indicates that GLP-1 RA may play a significant role in preventing HFpEF in patients with obesity, MS, or obesity and T2DM (57). According to a recent study, Epithelial Sodium Channel (EnNaC) activation induces endothelium permeability, which promotes macrophage infiltration and oxidative stress, resulting in cardiac fibrosis and LVDD in female mice with diet-induced obesity. Western diet-induced impairments of left ventricular filling rate and relaxation time were attenuated by amiloride, an EnNaC antagonist (58). A significant reduction in cardiomyocyte area, interstitial and perivascular fibrosis, and collagen deposition was observed after clostazol treatment. The inflammatory milieu in the hearts of obese mice was also reduced by cilostazol. There may be a therapeutic role for clostazol in treating obesity-related diastolic dysfunction and preventing overt heart failure (59).

7 Hyperlipidemia and LVDD

There is an association between LVDD and increased myocardial lipid storage. Diastolic dysfunction can be induced by lipid intermediates, which generate ROS. Mitochondrial dysfunction and impaired energetics may lead to cardiac dysfunction since the heart requires most of its ATP from mitochondrial oxidative phosphorylation. Reduced ATP availability may be caused by mitochondrial dysfunction but could also be caused by myocardial lipid buildup. It has been discussed previously that mitochondrial dysfunction leads to an increase in mitochondrial ROS, which damages cellular components and causes subsequent dysfunction (60). Increased oxidative stress and inflammation in a high-fat and high-cholesterol diet in rats led to cardiac fibrosis, endothelial dysfunction, and LVDD (61).

Intramyocardial fat deposition may partly contribute to LVH and impaired diastolic function in humans. When all components of the MetS and visceral adiposity tissue were adjusted for, an increase in hepatic triglyceride content was associated with a change

in mean E/A in obese individuals. In healthy subjects or those with diabetes, a short-term very low-calorie diet (VLCD) induced the accumulation of myocardial triglycerides and was associated with a decrease in LV diastolic function (62, 63). An increase in intramyocardial triglycerides is associated with LVDD. Myocardial steatosis is associated with accelerated deterioration of left ventricular diastolic function over time. In children with heterozygous familial hypercholesterolemia (FH), reduced e' and higher E/e' ratios were observed (64). In one Mendelian randomization (MR) analysis, HDL cholesterol showed no significant connection with any LV parameter. LDL cholesterol and triglycerides were independently associated with adverse changes in LV mass in another MR analysis (65).

There is controversy regarding the effect of lipid-lowering therapy on improving diastolic function. Compared with healthy volunteers, patients with hypercholesterolemia showed lower E/A ratios, higher Tei indexes, and lower e'/a' ratio in both the septum and laterally. After 6 months of rosuvastatin (RSV) treatment, a significant improvement of longitudinal global systolic and diastolic function (Tei index) was registered (66). The subjects received treatment with RSV or pitavastatin (PTV) for 24 weeks, however, the result showed statin treatment did not significantly alter the E/e′ ratio (67). Multiple diastolic parameters should be included in this research to avoid bias. In rabbits, HDL cholesterol infusions accompany a rapid improvement of LVDD with reductions of LV macrophage accumulation, coronary atherosclerosis, cardiomyocyte apoptosis, and remodeling (68).

8 MetS and LVDD

Although the effect of the MetS on LV remodeling has been extensively studied, the effect of MetS on LVDD has been less studied (69–73) (Table 3). Previous studies have revealed that patients with MetS have LVDD independent of LV mass (74, 75). In patients with MS, insulin resistance plays a key role in LVDD and HFpEF (76). Additionally, SNS excitement, RAAS activation, oxidative stress, endothelial dysfunction, and inflammation, which are common symptoms of MetS, could also explain the worsening of LVDD in these patients. In MetS, excess salt induces LVDD through the upregulation of mineralocorticoid receptor signals and increased oxidative stress. Myocardial fibrosis is a key contributor to subclinical LVDD and HFpEF in patients with MetS. In patients with MetS, those with increased abdominal fat deposition exhibited higher levels of procollagen peptides and cardiac fibrosis and more severe LVDD manifested by lower myocardial remodeling and e' and higher E/e' ratios (77). MetS and higher insulin resistance were significantly related to impaired diastolic function in one study using cardiac magnetic resonance imaging (CMR), independent of the myocardial extracellular matrix (ECV). The severity of LVDD was strongly related to the abundance of MetS components. Importantly, diabetes and obesity affect LV function even in the absence of coronary artery disease and hypertension (78). LVDD was more pronounced in individuals with obesity and MS than in those without (79). LVDD can also occur in patients with MetS without hypertension. Impaired LV diastolic and systolic

TABLE 3 The impact of MetS on LVDD.

Reference	Study population (n)		e' cm/s		E/e'		LAVI		E/A		LVDD	
	MS+	MS-	MS+	MS-	MS+	MS-	MS+	MS-	MS+	MS-	MS+	MS-
Lisa de las Fuentes (74)	186	110	9.0 ± 2.1	11.5 ± 2.4*	–	–	–	–	1.2 ± 0.5	1.6 ± 0.5*	7-9%	29-35%
Nir Ayalon (91)	90	26	9.0 ± 2.0	11.7 ± 3.0*	9.2 ± 2.4	6.6 ± 1.7*	–	–	1.1 ± 0.3	1.6 ± 0.5*	–	–
Parvanescu, T (69).	150	150	–	–	–	–	–	–	0.81 ± 0.21	1.47 ± 0.23*	52%	39%*
Chung, J. W (70).	20	17	4.7 ± 0.8	5.5 ± 1.5*	–	–	32.8 ± 6.8	45.1 ± 20.0*	0.55 ± 0.09	0.67 ± 0.17*	–	–
Jorgensen,P.G (71).	345	80	6.5 ± 1.8	8.4 ± 2.7*	11.6 (9.6, 14.9)	7.7 (6.6, 9.9) *	26 (22, 32)	25 (20, 31) *	0.87 (0.75, 1.06)	1.11 (0.85,1.38) *	–	–
Burroughs Pena, M (72).	399	861	6.8 ± 0.1	7.5 ± 0.1*	10.0 ± 0.2	9.3 ± 0.2*	22.7 ± 0.5	23.2 ± 0.03*	1.0± 0.02	1.1 ± 0.01*	–	–
Aksoy, S (81).	30	30	7.3 ± 0.4	14 ± 3*	8.9 ± 2.2	6.6 ± 1.3*	31.5 ± 9	23.1 ± 9.4*	0.9 ± 0.3	1.4 ± 0.1*	–	–
Crendal, E (73).	92	50	8.7 ± 1.5	10.6 ± 1.8*	6.9 ± 1.9	5.7 ± 1.5*	–	–	1.1 ± 0.3	1.3 ± 0.4*	–	–
Kosmala, W (77).	172	61	6.0 + 1.9	9.4 + 2.5*	10.9 + 3.3	8.1 + 2.4*	–	–	1.17 + 0.42	1.38 + 0.44*	–	–
Hwang, Y.-C (92).	331	1228	6.2 ± 1.5	7.4 ± 1.8*	9.7 ± 2.5	8.4 ± 2.0*	21.9 ± 5.5	20.2 ± 5.8*	0.90 ± 0.25	1.09 ± 0.34*	–	–

MetS, metabolic syndrome; LVDD, left ventricular diastolic dysfunction.
* Subjects with metabolic syndrome vs. control group ($p < 0.05$).

synchronization were found in patients with MS, in which obesity, hyperglycemia, and age play key roles, whereas hypertension was not a contributor to impaired synchronicity. A previous study has shown that the impact of the MetS on preclinical myocardial abnormalities were not accounted for by differences in age, gender, or 24-h BP and can be reasonably ascribed to the interplay of MetS components, making MetS in itself a relevant clinical problem in non-diabetic patients or in those never treated with antihypertensive or lipid-lowering drugs (80). Additionally, the coexistence of MS with hypertension or diabetes can further worsen LVDD (81, 82).

A previous study confirmed a significant improvement in LVDD after a 1-year lifestyle intervention program in abdominally obese men with MS, which worked through improved exercise tolerance, enhanced heart rate variability (HRV), and decreased insulin levels (83). One study showed that adding spironolactone to standard angiotensin II inhibition therapy significantly improved myocardial fibrosis in patients with MS (84). In a rat model of metabolic syndrome, improving endothelial dysfunction could improve LVH and diastolic function (85, 86). The DPP-4 inhibitor linagliptin reduces left ventricular stiffness and improves LV relaxation, which was related to decreased cardiac fibrosis and cardiomyocyte passive stiffness in MetS rats (87). In MetS rats, calorie restriction alleviates the incidence of obesity, hypertension, LV remodeling, and diastolic dysfunction by reducing cardiac oxidative stress and inflammation (88). Statins treatment reverses myocardial remodeling and enhances ventricular relaxation via AMPK (amplifier-activated protein kinase)-mediated

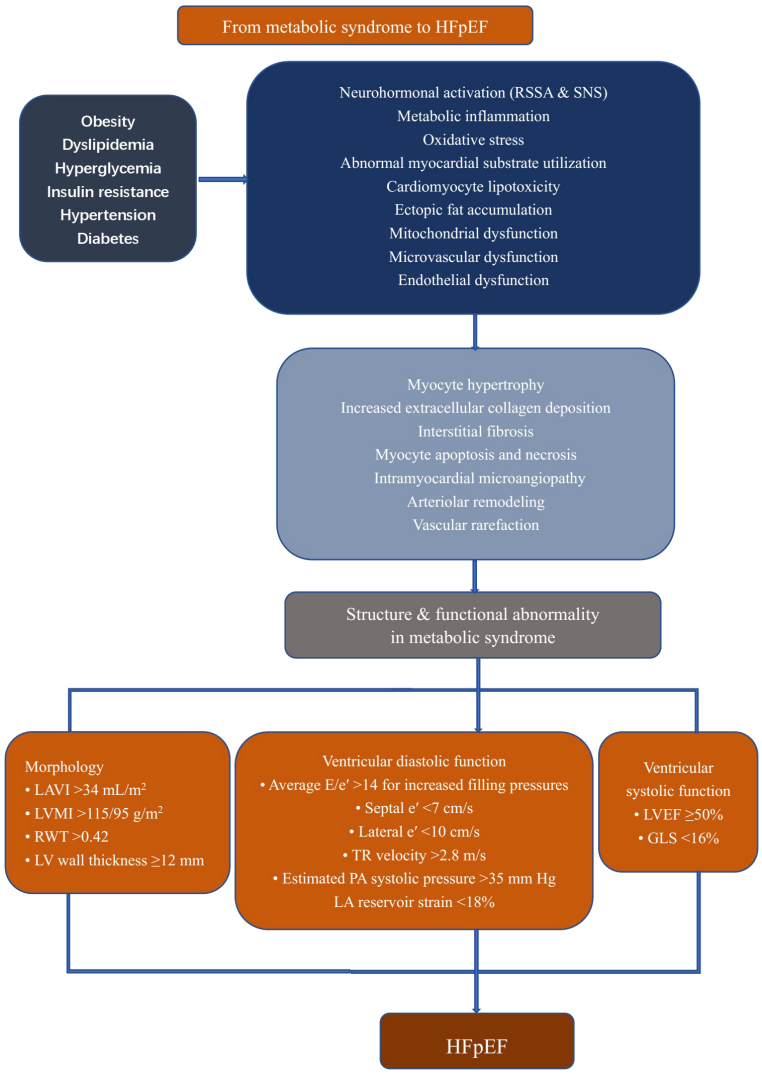

FIGURE 2
Cardiac remodeling in patients with metabolic syndrome. All components of metabolic syndrome can induce cardiac alteration to some extent. Their sum activates several pathophysiological pathways in the vessels and heart, including neurohormonal activation, mitochondrial dysfunction, and increased oxidative and inflammatory stress, leading to adverse cardiac remodeling. LVEF, left ventricular ejection fraction; E, early filling; e', early diastolic; LA, left atrium; LAVI, left atrium volume index; LVMI, left ventricular mass index; RWT, relative wall thickness; TR, tricuspid regurgitation; PA, pulmonary artery; GLS, Global Longitudinal Strain; HFpEF, heart failure with preserved ejection fraction; RSSA, Renin Angiotensin Aldosterone System; SNS, sympathetic nervous system.

antifibrotic effects (89). Attenuation of the inflammatory and oxidative stress process, reduced insulin levels, and decreased cardiac fibrosis may provide a novel therapeutic strategy in treating metabolic cardiomyopathy.

9 Clinical consequences of LVDD in individuals with metabolic syndrome

LVDD is an independent predictor of adverse cardiovascular events in hypertensive patients. Of importance, the prognostic value of e′ and the E/e' ratio for heart failure has been recognized in the hypertensive setting with normal EF. The Framingham Heart Study also provided the earliest evidence of diabetes and heart failure independent of coronary artery disease (90). In individuals with overt cardiovascular diseases, MetS increases the risk of adverse events; however, in HF patients, MetS was not an independent predictor for all-cause mortality or cardiovascular mortality. Few studies have investigated the prognostic value of LVDD in patients with MetS. The coexistence of MetS with diastolic dysfunction showed obvious incremental value in predicting cardiac events. Overall, few prospective studies have explored the association between LVDD and HFpEF in patients with MetS. Much of the current evidence is based on the characterization of patients with HFpEF. MetS refers to a group of interrelated disorders. More studies have explored the prognosis of LVDD in patients with hypertension or diabetes. Along with an aging population and rising rates of cardiometabolic comorbidities, HFpEF has a tremendous global burden and is poised to increase in prevalence, particularly the MetS phenotype. Future research should focus on the prognostic value of LVDD in patients with metabolic syndrome. A previous study revealed that the number of MetS criteria fulfilled and the presence of 4–5 criteria was associated with incident HF, implying that metabolic disturbances also contribute to an elevated risk of HF through pathways other than insulin resistance (76).

10 Conclusion

The prevalence of MetS is constantly growing. MetS-related LVDD or HFpEF also leads to a high risk of cardiac events in this population. Echocardiography diagnosis techniques are rapidly developing, allowing for the early detection of cardiac structural or functional alterations, as summarized in Figure 2. Although the underlying mechanisms of HFpEF pathogenesis remain controversial, insulin resistance and subsequent changes in both cardiomyocytes and the myocardial interstitium and coronary microcirculation play critical roles in mediating LVDD in MetS. Considering this, in individuals with MetS, improving LVDD may serve as the therapeutic strategy to prevent or ameliorate HFpEF, especially for the MetS phenotype. Improving metabolic abnormalities associated with MetS, particularly through controlling insulin levels and reducing oxidative stress and inflammation, may help slow down or reverse the progression of LVDD, thereby improving the prognosis of HFpEF. Although lifestyle interventions (such as weight loss and exercise) and pharmacological treatments (such as statins and liraglutide) have been shown to have certain effects on improving LVDD, there is significant individual variability among patients with MetS, and the universality and long-term effects of these interventions are still unclear. The lack of standardized treatment guidelines and evidence-based support makes it difficult to implement clinical treatments broadly. With the continuous development of personalized medicine, future research should focus more on how to tailor treatment plans based on different MetS subtypes and patient characteristics (such as gender, age, and comorbidities). Further prospective large population studies are needed to integrate clinical data and optimize intervention strategies to enhance treatment outcomes.

Author contributions

DZ: Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. SL: Conceptualization, Investigation, Writing – original draft. ZL: Conceptualization, Investigation, Writing – original draft. JY: Conceptualization, Investigation, Writing – original draft. HR: Conceptualization, Investigation, Writing – review & editing. HT: Conceptualization, Investigation, Writing – review & editing. YG: Conceptualization, Investigation, Writing – review & editing. XJ: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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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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Development and validation of an AMR-based predictive model for post-PCI upper gastrointestinal bleeding in NSTEMI patients

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Background: Upper gastrointestinal bleeding (UGIB) is a common complication in patients with non-ST-segment elevation myocardial infarction (NSTEMI) after percutaneous coronary intervention (PCI), and the aim of our study is to construct a nomogram for predicting the occurrence of UGIB within 1 year after PCI in NSTEMI patients.

Methods: In this study, 784 patients with NSTEMI after PCI in the Affiliated Hospital of Xuzhou Medical University between September 1, 2017 and August 31, 2019 were included as the training group, and 336 patients from the East Affiliated Hospital of Xuzhou Medical University were included as the external validation group. Classical regression methods were combined with a machine learning model to identify the independent risk factors. These factors based on multivariate logistic regression analysis were then utilized to develop a nomogram. The performance of the nomogram was evaluated using the area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analysis (DCA).

Results: The nomogram consisted of six independent predictors, including HASBLED, triglyceride glucose index, alcohol drinking, red blood cell count, use of proton pump inhibitor, and angiographic microvascular resistance of culprit vessel. Training and validation groups accurately predicted the occurrence of UGIB (AUC, 0.936 and 0.910). The calibration curves showed that the nomogram agreed with the actual observations and the DCA also demonstrated that the nomogram was applicable in the clinic.

Conclusion: We developed a simple and effective nomogram for predicting the occurrence of UGIB within 1 year in NSTEMI patients after PCI based on angiographic microvascular resistance.

KEYWORDS

angiographic microvascular resistance of culprit vessel, upper gastrointestinal bleeding, non-ST-segment elevation myocardial infarction, nomogram, percutaneous coronary intervention

Introduction

Coronary artery disease (CAD) is the leading major cause of death and loss of healthy life in society, both in terms of morbidity, mortality, and disease progression (1). Non-ST-segment elevation myocardial infarction (NSTEMI) is a severe type of CAD and in NSTEMI, coronary atherosclerotic plaque erosion, rupture or subsequent thrombosis causes partial obstruction of the coronary arteries, which can lead to myocardial necrosis (2). In myocardial infarction, NSTEMI accounted for 63.1% and 4.2% of NSTEMI patients died in the hospital (3).

With advances in antiplatelet and percutaneous coronary intervention (PCI) therapies, cardiovascular morbidity and mortality in patients with NSTEMI have decreased significantly (4). However, the occurrence of gastrointestinal bleeding (GIB) after PCI remains a major problem. The most common bleeding after PCI was GIB, which accounted for 61.7% of all bleeding (5). A study indicated that the incidence of upper gastrointestinal bleeding (UGIB) in patients with ACS was 8.9% within 30 days of PCI, 4.7% within 1 year, and rose to 10.1% beyond 1 year (6). Yasuda et al. found that the incidence of UGIB at 1 and 2 years after PCI was 2.5% and 5%, respectively, whereas the incidence was higher in patients who did not use the proton pump inhibitor (PPI), at 4.5% and 9.2%, respectively (7). And patients with acute coronary syndrome (ACS) had a 62% mortality rate for UGIB compared to patients with UGIB only (8). This caused a certain burden on both the cost of hospitalization and medical insurance. Thus, early screening for UGIB in ACS patients is necessary.

Coronary microcirculatory disorders (CMD) is disease that affect the structure and function of the coronary microcirculation. There were various methods of assessing CMD, categorized as invasive and non-invasive. Positron emission computed tomography (PET) was considered the gold standard for noninvasive assessment of CMD by quantifying myocardial blood flow (MBF) and assessing myocardial perfusion reserve (9). Cardiac magnetic resonance imaging (CMR) and myocardial contrast echocardiography could also noninvasively quantify MBF (10). Invasive assessment methods such as coronary angiography could assess microvascular dilatation by coronary flow reserve (CFR) (10). The index of microcirculatory resistance (IMR) was the gold standard for measuring CMD and was obtained by measuring the product of distal coronary artery pressure and the mean passage time of saline push during maximal congestion induced by adenosine or opioid (11). In recent years, angiographic microvascular resistance (AMR) has been proposed for the assessment of CMD and was mainly calculated by quantitative flow ratio (QFR) (12). Compared with invasive methods, AMR did not rely on drug induction such as adenosine and require additional operations in clinical applications, providing simplicity and maneuverability. And it enabled accurate numerical assessment of microvascular function at a lower cost than non-invasive methods. Hence, it was considered an emerging method to CMD assessment.

Some chronic diseases (e.g., heart failure, hypertension, diabetes, metabolic syndrome, cardiac hypertrophy, and CAD) and post-PCI were risk factors for CMD (13–16). We pondered whether CMD affected systemic microcirculation and would increase the risk of having UGIB. Therefore, we constructed an AMR-based nomogram to predict UGIB within 1 year in NSTEMI patients after PCI.

Materials and methods

Study population and design

This study was approved by the Medical Research Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2023-KL043-01), which was conducted following the Declaration of Helsinki. Because our study was retrospective, the committee waived the requirement for written informed consent. Based on inclusion and exclusion criteria, we included patients with NSTEMI who underwent PCI from September 1, 2017, to August 31, 2019 in the Affiliated Hospital of Xuzhou Medical University (training group, n=784), and the East Hospital of Xuzhou Medical University (validation group, n=336). The flow chart of the study is shown in Figure 1.

Inclusion criteria: (1) Diagnosis of NSTEMI; (2) Successful implantation of the drug-eluting stent; (3) Readmission for UGIB within 1 year after PCI; and (4) over 18 years old.

Meanwhile, exclusion criteria: (1) Restenting within 1 year; (2) Bleeding from esophageal or fundal varices ; (3) Patients with severe hepatic or renal insufficiency or tumors; (4) excessive lack of clinical

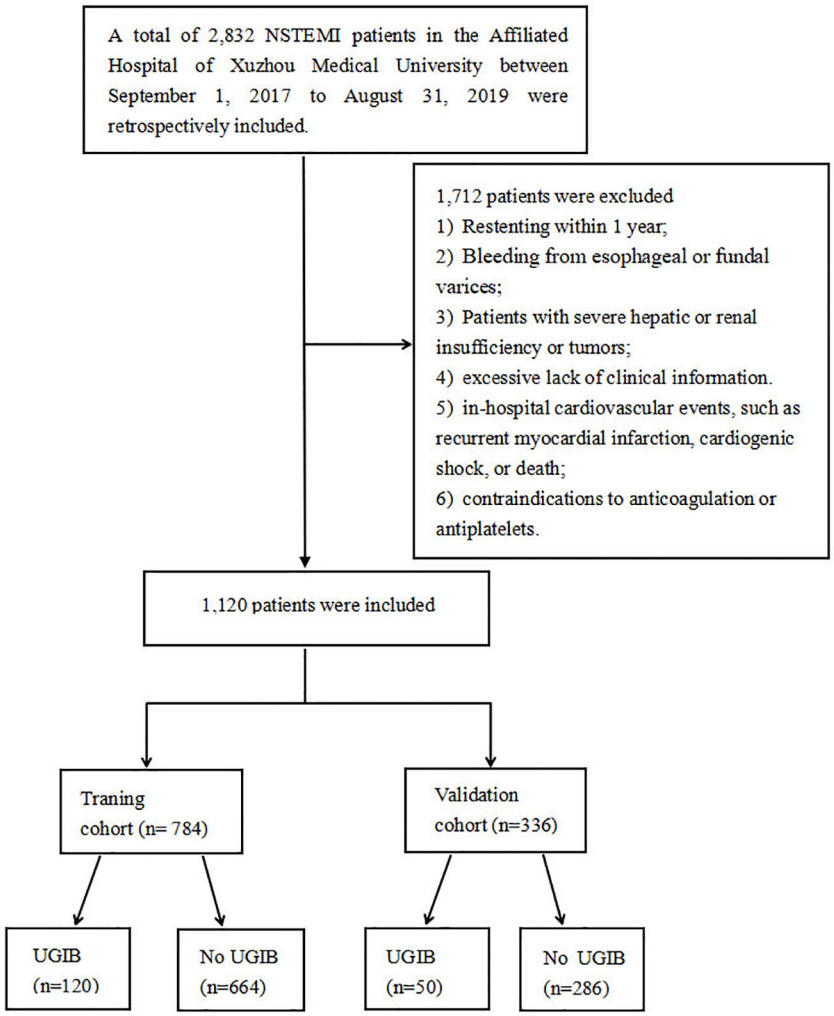

FIGURE 1
The study flowchart for developing and validating nomogram.

information; (5) in-hospital cardiovascular events, such as recurrent myocardial infarction, cardiogenic shock, or death; (6) contraindications to anticoagulation or antiplatelets.

Clinical treatment process

All patients with NSTEMI in this study underwent PCI in the digital subtraction angiography (DSA) suite, and patients were anticoagulated with heparin subcutaneously and given 300 mg of aspirin, 300 mg of clopidogrel, or 180 mg of ticagrelor orally as a loading dose before PCI. The various devices, instruments, and adjunctive medications (nitroglycerin, sodium nitroprusside, tirofiban, atropine, etc.) used during the procedure were determined by the operator based on the patient's intraoperative condition.

Postoperatively, medications were prescribed according to guidelines. These therapies included (1) dual antiplatelet therapy (DAPT), including aspirin (100 mg once daily) in combination with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily) (2); statin (3); beta-blocker; and (4) angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist (ACEI/ARB).

Collection of variables

Demographic data included age, sex, smoking, and drinking status. Previous history contained heart failure (HF), diabetes, stroke, hypertension, chronic kidney disease (CKD), bleeding, peripheral vascular disease (PVD), atrial fibrillation (AF), and peptic ulcer. In the history of bleeding, 16 patients had nosebleeds and 12 patients had cerebral hemorrhage before PCI. Physical examination contained body mass index (BMI), diastolic blood pressure (DBP), heart rate (HR), and systolic blood pressure (SBP). Laboratory tests contained white blood cell (WBC) count, hemoglobin (Hb), lymphocyte count, red blood cell (RBC) count, platelet (PLT) count, neutrophil, serum uric acid (sUA), C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), glucose,

glycated hemoglobin (HbA1c), serum creatinine (sCr), low-density lipoprotein (LDL), total cholesterol (TC), high-density lipoprotein (HDL), lipoprotein a (LPa), triglycerides (TG), N-terminal pro-brain natriuretic peptide (NT-proBNP), international normalized ratio (INR), left ventricular ejection fraction (LVEF), creatinekinase-MB (CKMB), fibrinogen (FIB), and total bilirubin (TBIL). Image data during PCI contained the culprit vessels (right coronary artery (RCA), left anterior descending branch (LAD), left circumflex branch (LCX)), multivessel disease, the number of stents, stent length, stent diameter, and Killip grade. Postoperative medications comprised of angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist (ACEI/ARB), calcium antagonist (CCB), Low molecular weight heparin (LMWH), diuretics, proton pump inhibitor (PPI), beta-blockers, and nonsteroidal anti-inflammatory drug (NSAID).

Triglyceride glucose index (TyG) was calculated as Ln[TG(mg/dL) × FBG(mg/dL)/2]. HAS-BLED scores up to 9 points including hypertension, stroke, history of bleeding, abnormal liver/kidney function, labile INR, elderly, and drug/alcohol.

Computation of AMR

AMR analysis was performed independently by certified technicians using commercial software (AngioPlus Core, Pulse Medical Imaging Technology Co., Ltd., Shanghai, China), who were blinded to the clinical data. Coronary artery image analysis was performed using the above system. The blood flow velocity was derived by dividing the vessel centerline length by the contrast fill time. Using high blood flow as a boundary condition, the pressure drop was calculated from the hydrodynamic equations. Distal coronary pressure (Pd) was calculated from the pressure drop, and μQFR was calculated by dividing Pd by mean aortic pressure (Pa). Angiography microvascular resistance (AMR) is computed as Pd divided by the hyperaemic flow velocity $Velocity_{hyp}$ (17).

$$AMR = \frac{P_d}{Velocity_{hyp}} = \frac{P_a * \mu QFR}{Velocity_{hyp}}$$

Clinical endpoints and definitions

The clinical endpoint was NSTEMI patients who were readmitted with UGIB symptoms within 1 year after the PCI. The definition of UGIB was clinical signs of coffee-ground vomiting, hematemesis, melena, or endoscopic findings of active bleeding from upper gastrointestinal sites.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test. Continuous variables are expressed as mean ± standard deviation. Normally distributed variables were compared using the t-test for comparison, while non-normally distributed variables were compared using the Mann-Whitney U-test. The percentage of missing values were less than 20%, and multiple imputation was used to impute the missing data for the covariates. We first used univariate analysis and random forest to predict independent risk factors. The random forest algorithm generated the mean decreased Gini (MDG) that was used to reflect the contribution of each independent variable to the dependent variable. In the random forest algorithm, Ntree specifies the number of decision trees in the random forest and Brenneman suggests that the optimal number of decision trees is 500. Optimal mtry parameter was selected by grid search method, and then combined with different ntree to find the lowest out-of-bag error (OOB) rate. Finally, we included independent risk factors that were statistically significant in the univariate analysis ($P< 0.01$) and the top ten variables of the random forest MDG in the analysis. The variables were screened and used to perform the multivariate logistic regression model. The least absolute shrinkage and selection operator (LASSO) regression was then performed to ensure that the model was not overfitted. Finally, a nomogram of the multivariate model based on optimal predictors was developed to predict the probability of UGIB within 1 year after PCI. The consistency index (C-index) is the area under the curve (AUC) of the receiver operating characteristic curve (ROC) in logistic regression analysis for the discrimination capacity of the nomogram. The nomogram's predictive accuracy was evaluated using calibration plots and the consistency between predicted and actual probabilities was assessed by the Hosmer-Lemeshow test. Clinical efficacy was evaluated using decision curve analysis (DCA). Data were analyzed using R Studio (Version 4.2.3, https://www.Rproject.org). P values < 0.05 were significant for all statistical tests.

Ethics approval and consent to participate

This study was approved by the Medical Research Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2023-KL043-01), which was conducted following the Declaration of Helsinki. Because our study was retrospective, the Medical Research Ethics Committee of the Affiliated Hospital of Xuzhou Medical University waived the requirement for written informed consent.

Results

Participants characteristics

Our study included 1,120 NSTEMI patients after PCI from September 1, 2017, to August 31, 2019, from the Affiliated Hospital of Xuzhou Medical University and the East Affiliated Hospital of Xuzhou Medical University. Baseline characteristics were shown in Table 1. The average age of this study was 68.88 years old and most of the patients (68.8%) were male. There were 120 and 50 UGIB participants in the training and validation groups, respectively.

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TABLE 1 Patient characteristics.

Variables	Validation Cohort (N=336)	Training Cohort (N=784)	P value
UGIB, n (%)			
No	286 (85.1)	664 (84.7)	0.856
Yes	50 (14.9)	120 (15.3)	
Age, years	68.56 (10.81)	69.02 (10.91)	0.516
Sex (%)			
Male, n (%)	237 (70.5)	533 (68.0)	0.399
Female, n (%)	99 (29.5)	251 (32.0)	
BMI, kg/m^2	25.12 (3.62)	25.41 (3.68)	0.234
SBP, mmHg	129.94 (22.35)	133.29 (22.09)	0.021
DBP, mmHg	77.93 (12.92)	79.00 (13.52)	0.216
HR, times/min	75.68 (12.99)	74.95 (12.10)	0.362
Smoking, n (%)			
No	225 (67.0)	528 (67.3)	0.901
Yes	111 (33.0)	256 (32.7)	
Drinking, n (%)			
No	241 (71.7)	571 (72.8)	0.704
Yes	95 (28.3)	213 (27.2)	
Hypertension, n (%)			
No	167 (49.7)	370 (47.2)	0.441
Yes	169 (50.3)	414 (52.8)	
Diabetes, n (%)			
No	250 (74.4)	557 (71.0)	0.251
Yes	86 (25.6)	227 (29.0)	
CKD, n (%)			
No	319 (94.9)	747 (95.3)	0.808
Yes	17 (5.1)	37 (4.7)	
AF, n (%)			
No	319 (94.9)	757 (96.6)	0.202
Yes	17 (5.1)	27 (3.4)	
HF, n (%)			
No	297 (88.4)	658 (83.9)	0.053
Yes	39 (11.6)	126 (16.1)	
Stroke, n (%)			
No	265 (78.9)	636 (81.1)	0.384
Yes	71 (21.1)	148 (18.9)	
Bleeding, n (%)			
No	330 (98.2)	762 (97.2)	0.316
Yes	6 (1.8)	22 (2.8)	
HASBLED	2.67 (1.14)	2.65 (1.14)	0.814
Peptic Ulcer, n (%)			
No	295 (87.8)	714 (91.1)	0.093
Yes	41 (12.2)	70 (8.9)	
PVD, n (%)			
No	330 (98.2)	773 (98.6)	0.631
Yes	6 (1.8)	11 (1.4)	
Laboratory test			
WBC, ×10^9/L	8.81 (2.85)	9.03 (3.55)	0.315
N, ×10^9/L	6.67 (2.86)	7.04 (5.18)	0.221
L, ×10^9/L	1.51 (0.81)	1.54 (0.83)	0.654
RBC, ×10^9/L	4.40 (0.65)	4.33 (0.72)	0.182
Hb, g/L	136.13 (17.09)	135.19 (18.15)	0.421
PLT, ×10^9/L	206.59 (62.46)	205.99 (65.70)	0.886
CRP, mg/dl	10.50 (26.78)	12.13 (31.10)	0.402
sCr, mmol/L	75.18 (77.57)	74.70 (75.88)	0.923
sUA, umol/L	309.89 (95.49)	311.26 (124.31)	0.857
eGFR, mL/min/ 1,73m^2	107.49 (23.58)	108.13 (24.01)	0.679
Glucose, mmol/L	6.71 (3.00)	6.68 (2.74)	0.877
HbA1c (%)	6.56 (1.57)	6.57 (1.49)	0.968
TyG	7.26 (0.64)	7.27 (0.65)	0.698
TC, mmol/L	2.99 (1.74)	3.09 (1.80)	0.380
TG, mmol/L	1.48 (1.20)	1.54 (1.21)	0.473
HDL, mmol/L	2.19 (1.27)	2.19 (1.18)	0.991
LDL, mmol/L	119.72 (224.42)	117.40 (200.45)	0.803
LPa, mg/L	131.28 (199.53)	148.17 (247.39)	0.269
INR	0.97 (0.11)	0.99 (0.12)	0.053
LVEF, (%)	55.06 (8.47)	55.37 (8.37)	0.567
CKMB, ng/mL	50.06 (79.99)	48.73 (79.91)	0.799
NT-proBNP, pg/mL	1656.43 (3361.16)	2086.81 (4646.60)	0.125
FIB, g/L	3.25 (1.46)	3.66 (10.43)	0.470
TBIL, umol/L	15.10 (9.61)	15.10 (8.73)	0.999

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TABLE 1 Continued

Variables	Validation Cohort (N=336)	Training Cohort (N=784)	P value
Angiographic features			
Killip grade			
Grade I, n (%)	320 (95.2)	748 (95.4)	0.480
Grade II, n (%)	13 (3.9)	22 (2.8)	
Grade III, n (%)	1 (0.3)	8 (1.0)	
Grade IV, n (%)	2 (0.6)	6 (0.8)	
LAD, n (%)	158 (47.0)	351 (44.8)	0.488
LCX, n (%)	139 (41.4)	340 (43.4)	0.536
RCA, n (%)	114 (33.9)	274 (34.9)	0.742
Multivascular disease, n (%)			
No	291 (86.6)	689 (87.9)	0.554
Yes	45 (13.4)	95 (12.1)	
Stent diameter, mm	2.87 (0.45)	2.88 (0.47)	0.826
Stent length, mm	26.15 (7.23)	26.12 (7.12)	0.943
Number of stents, n (%)	1.49 (0.82)	1.39 (0.72)	0.040
Culprit Vessel AMR	2.23 (0.86)	2.23 (0.87)	0.988
Medication			
ACEI/ARB, n (%)			
No	176 (52.4)	370 (47.2)	0.111
Yes	160 (47.6)	414 (52.8)	
Beta-blocker, n (%)			
No	73 (21.7)	185 (23.6)	0.496
Yes	263 (78.3)	599 (76.4)	
LMWH, n (%)			
No	109 (32.4)	286 (36.5)	0.195
Yes	227 (67.6)	498 (63.5)	
CCB, n (%)			
No	290 (86.3)	648 (82.7)	0.128
Yes	46 (13.7)	136 (17.3)	
Diuretics, n (%)			
No	187 (55.7)	464 (59.2)	0.273
Yes	149 (44.3)	320 (40.8)	
PPI, n (%)			
No	51 (15.2)	116 (14.8)	0.869
Yes	285 (84.8)	668 (85.2)	
NASID, n (%)			
No	320 (95.2)	754 (96.2)	0.470
Yes	16 (4.8)	30 (3.8)	

(Continued)

TABLE 1 Continued

UGIB, upper gastrointestinal bleeding; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CKD, chronic kidney disease; AF, atrial fibrillation; HF, heart failure; HASBLED, including hypertension, abnormal liver/kidney function, stroke, history of bleeding, labile INR, elderly, and drug/alcohol; PVD, Peripheral vascular disease; WBC, white blood cell; N, neutrophils; L, lymphocytes; RBC, red blood cell; Hb, hemoglobin; PLT, platelets; CRP, C-reactive protein; sCr, serum creatinine; sUA, serum uric acid; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; TyG, triglyceride glucose index; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low density lipoprotein; INR, international normalized ratio; LVEF, left ventricular ejection fraction; CKMB, creatine kinase isoenzyme-MB; NT-proBNP, N-terminal pro-brain natriuretic peptide; FIB, fibrinogen; TBIL, total bilirubin; LAD, left anterior descending; LCX, left circumflex branch; RCA, right coronary artery; AMR, angiography-derived microcirculatory resistance; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; LMWH, low molecular weight heparin; CCB, calcium channel antagonist; PPI, proton pump inhibitor; NASID, nonsteroidal anti-inflammatory drug.

Potential predictors of UGIB and construction of the nomogram

The results of the univariate analyses and random forest were displayed in Table 2. The default value of Ntree was 500. After testing and adjusting, mtry=6 and ntree=300 had the lowest rate of OOB (2.81%). These variables (HASBLED, TyG index, Alcohol drinking, RBC count, PPI use, and AMR of culprit vessel) not only had a significant difference in the univariate analysis ($p< 0.01$) but also obtained high MDG (top ten) in the random forest. Therefore, these six variables were included in further multivariate logistic regression model.

Six potential risk factors were included in the multivariate logistic regression model (Table 3). In the training set model, a high HASBLED, TyG index, and AMR of the culprit vessel were correlated with developing the risk of UGIB (OR: 2.615, 95% CI: 1.940-3.620, P< 0.001; OR: 4.482, 95% CI: 2.813-7.366, P< 0.001; OR: 3.251, 95% CI: 2.216-4.899, P< 0. 001). Alcohol drinking was positively associated with the occurrence of UGIB (OR: 2.985, 95% CI: 1.584-5.665, P< 0.001). While taking PPI and higher RBC count played a protective role (OR: 0.179, 95% CI: 0.090-0.350, P< 0. 001; OR: 0.293, 95% CI: 0.188-0.439, P< 0. 001).

Subsequently, these predictors were determined using the least absolute shrinkage and selection operator (LASSO) method for screening non-zero coefficient characteristics (Figures 2A, B). We used tenfold cross-validation to select the appropriate tuning parameters (λ) for the LASSO model. The optimal reconciliation coefficients λ.min at the minimum MSE and λ.1se at one standard MSE error were 0.004 and 0.031, respectively. The advantages of the Lasso regression were highly predictive and robust and minimized the effects of multicollinearity. Finally, the nomogram model was constructed using these six independent factors to predict the occurrence of UGIB within 1 year after PCI (Figure 3).

TABLE 2 Univariate logistic regression analysis in the training group.

Variables	OR (95%CI)	P value	MDG
HASBLED	3.410 (2.720,4.274)	<0.001	14.055
RBC, $\times10^9$/L	0.269 (0.197,0.367)	<0.001	11.639
TyG	3.631 (2.617,5.038)	<0.001	8.655
Culprit Vessel AMR	2.374 (1.843,3.059)	<0.001	8.568
CRP, mg/dl	0.980 (0.964,0.996)	0.017	7.429
CKMB, ng/mL	0.998 (0.995,1.001)	0.201	7.398
Drinking, n (%)	7.621 (4.996,11.624)	<0.001	6.682
PPI, n (%)	0.139 (0.090,0.217)	<0.001	5.944
WBC, $\times10^9$/L	0.921 (0.860,0.985)	0.017	5.531
FIB, g/L	1.003 (0.988,1.018)	0.688	5.042
LAD, n (%)	6.416 (3.994,10.305)	<0.001	4.666
NT-proBNP, pg/mL	1.000 (1.000,1.000)	0.001	4.663
N, $\times10^9$/L	0.848 (0.785,0.918)	<0.001	4.492
LVEF, (%)	1.044 (1.018,1.071)	0.001	4.422
LDL, mmol/L	0.995 (0.992,0.997)	<0.001	4.413
HbA1c (%)	1.148 (1.023,1.288)	0.019	4.342
sCr, mmol/L	1.004 (1.001,1.006)	0.007	4.136
Hb, g/L	0.975 (0.965,0.986)	<0.001	3.728
eGFR, mL/min/1,73m^2	0.984 (0.976,0.992)	<0.001	3.605
LPa, mg/L	1.001 (1.000,1.001)	0.085	3.492
TG, mmol/L	1.063 (0.925,1.221)	0.389	3.384
sUA, umol/L	1.001 (1.000,1.002)	0.120	3.355
TBIL, umol/L	0.968 (0.941,0.996)	0.027	3.316
BMI, kg/m^2	0.922 (0.871,0.977)	0.006	3.184
TC, mmol/L	1.161 (1.043,1.293)	0.006	3.072
PLT, $\times10^9$/L	1.001 (0.998,1.004)	0.511	3.046
HR, times/min	0.991 (0.975,1.008)	0.285	2.983
INR	2.991 (0.627,14.275)	0.169	2.864
Age, years	1.014 (0.995,1.033)	0.153	2.746
LMWH, n (%)	0.279 (0.187,0.419)	<0.001	2.740
HDL, mmol/L	0.753 (0.621,0.902)	0.003	2.511
Glucose, mmol/L	1.006 (0.938,1.079)	0.870	2.398
L, $\times10^9$/L	0.724 (0.549,0.956)	0.023	2.320
Number of stents, n (%)	1.846 (1.467,2.322)	<0.001	2.294
Stent length, mm	1.010 (0.982,1.038)	0.485	2.203
NASID, n (%)	8.265 (3.915,17.847)	<0.001	2.071
SBP, mmHg	1.007 (0.998,1.016)	0.121	2.004
DBP, mmHg	1.003 (0.988,1.017)	0.727	1.943
Stent diameter, mm	0.761 (0.494,1.171)	0.214	1.877
CKD, n (%)	6.751 (3.427,13.299)	<0.001	1.273
Multivascular disease, n (%)	3.469 (2.145,5.610)	<0.001	1.167
AF, n (%)	6.614 (3.025,14.462)	<0.001	1.036
Smoking, n (%)	0.439 (0.271,0.710)	0.001	0.666
RCA, n (%)	0.960 (0.637,1.446)	0.845	0.647
Stroke, n (%)	2.008 (1.290,3.126)	0.002	0.607
Beta-blocker, n (%)	0.466 (0.307,0.705)	<0.001	0.597
ACEI/ARB, n (%)	0.613 (0.414,0.908)	0.015	0.507
Male, n (%)	1.171 (0.771,1.811)	0.468	0.485
HF, n (%)	1.758 (1.094,2.824)	0.020	0.484
Diuretics, n (%)	0.656 (0.435,0.991)	0.045	0.465
Diabetes, n (%)	1.112 (0.729,1.697)	0.622	0.446
CCB, n (%)	1.393 (0.862,2.251)	0.176	0.446
Bleeding, n (%)	3.316 (1.360,8.088)	0.008	0.414
LCX, n (%)	0.634 (0.422,0.952)	0.028	0.403
Hypertension, n (%)	1.813 (1.209,2.718)	0.004	0.361
Peptic Ulcer, n (%)	1.161 (0.603,2.234)	0.655	0.279
PVD, n (%)	6.937 (2.082,23.109)	0.002	0.257
Killip grade			0.202
Grade I, n (%)	Reference		
Grade II, n (%)	1.688 (0.610,4.668)	0.313	
Grade III, n (%)	3.443 (0.811,14.613)	0.094	
Grade IV, n (%)	1.148 (0.133,9.918)	0.900	

OR, Odds Ratio; MDG, mean decreased Gini; UGIB, upper gastrointestinal bleeding; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CKD, chronic kidney disease; AF, atrial fibrillation; HF, heart failure; HASBLED, including hypertension, abnormal liver/kidney function, stroke, history of bleeding, labile INR, elderly, and drug/alcohol; PVD, Peripheral vascular disease; WBC, white blood cell; N, neutrophils; L, lymphocytes; RBC, red blood cell; Hb, hemoglobin; PLT, platelets; CRP, C-reactive protein; sCr, serum creatinine; sUA, serum uric acid; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; TyG, triglyceride glucose index; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low density lipoprotein; INR, international normalized ratio; LVEF, left ventricular ejection fraction; CKMB, creatine kinase isoenzyme-MB; NT-proBNP, N-terminal pro-brain natriuretic peptide; FIB, fibrinogen; TBIL, total bilirubin; LAD, left anterior descending; LCX, left circumflex branch; RCA, right coronary artery; AMR, angiography-derived microcirculatory resistance; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; LMWH, low molecular weight heparin; CCB, calcium channel antagonist; PPI, proton pump inhibitor; NASID, nonsteroidal anti-inflammatory drug.

Validation of the nomogram

The AUC of training and external validation groups was 0.936 and 0.910 in the ROC curve (Figures 4A, B), which demonstrated an outstanding discrimination of the nomogram. Calibration plots identified good consistency between the nomogram (Figure 5A) and the validation cohort (Figure 5B). The Hosmer-Lemeshow test indicated that the probability of UGIB after PCI predicted by the

TABLE 3 Multivariate logistic regression analysis in training group.

Variables	OR	95%CI	P value
HASBLED	2.615	(1.940;3.620)	<0.001
TyG	4.482	(2.813;7.366)	<0.001
Drinking	2.985	(1.584;5.665)	<0.001
RBC	0.293	(0.188;0.439)	<0.001
PPI	0.179	(0.090;0.350)	<0.001
Culprit vessel AMR	3.251	(2.216;4.899)	<0.001

TyG, triglyceride glucose index; PPI, proton pump inhibitor; AMR, angiography-derived microcirculatory resistance.

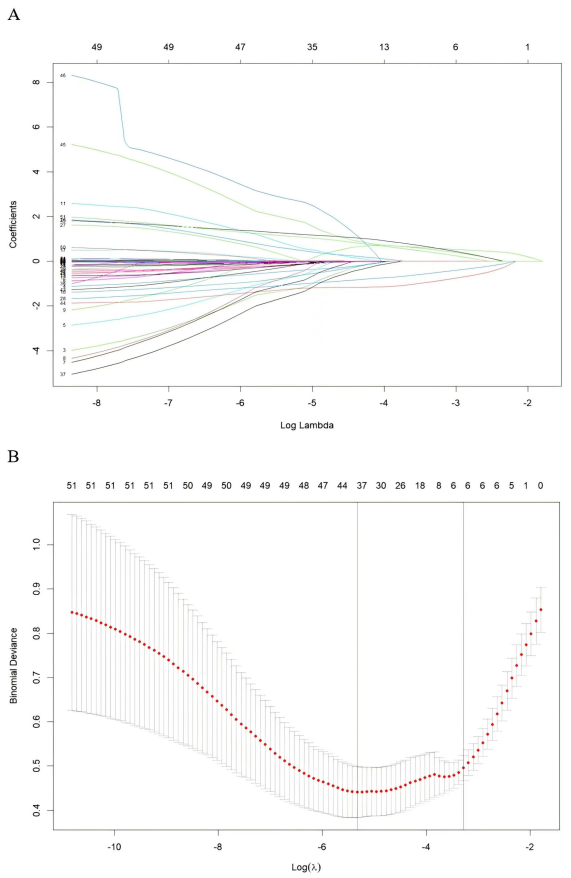

FIGURE 2
Variable screening based on lasso regression. **(A)** Characterization of the variation of variable coefficients; **(B)** The process of selecting the optimal value of the parameter λ in the Lasso regression model by the cross-validation method.

nomogram was consistent between the training set (P = 0.728) and the validation set (P = 0.269).

Clinical use

The applicability and utility of the model in the training and external validation sets were evaluated by DCA. The DCA curves for both sets showed a significantly higher net benefit than the two extremes, indicating that the nomogram had good clinical benefits (Figures 6A, B).

Discussion

UGIB is a common cause of bleeding after PCI, and in-hospital occurrence of UGIB has a high mortality rate (18). Some patients are more susceptible to have UGIB in one year of dual antiplatelet therapy applied after PCI (19). Consequently, a prediction model that accurately predicts UGIB is beneficial in obtaining a better clinical significance in patients with NSTEMI after PCI. In this study, 1,120 NSTEMI patients with post-PCI were included for analysis and AMR of culprit vessel (≥ 2.5 mmHg*s/cm) were diagnosed with CMD. The results showed that AMR of culprit vessel was an independent predictor of UGIB. In addition, the nomogram constructed by six factors, including HASBLED, TyG index, Alcohol drinking,RBC count, PPI use, and AMR of culprit vessel, can be used to assess the likelihood of UGIB within 1 year in NSTEMI patients undergoing primary PCI.

The mechanisms of CMD may be closely related to inflammation, microvascular spasm, or endothelial dysfunction (20). There is growing evidence that patients with chronic inflammatory diseases (without clinically evident CVD), including psoriasis, psoriatic arthritis, rheumatoid arthritis, and inflammatory bowel disease, have a higher incidence of endothelial and coronary microcirculatory dysfunction (21). In contrast, presence of CMD in NSTEMI patients after PCI may be related to inflammation. In patients with early CAD, coronary segments with macrophage infiltration and vascular proliferation showed a greater response to acetylcholine (ACh) than those without macrophage infiltration and vascular proliferation, suggesting an important role for inflammation and vascular proliferation in the pathogenesis of CAD (22). In addition, the complexity of CMD is further compounded by the possibility of microvascular obstruction (MVO) in patients with acute coronary syndromes (ACS) (23). The causative mechanisms of MVO include distal atherosclerotic thromboembolism, ischemia-reperfusion injury with endothelial cell death along the myocardial cell death, myocardial edema and/or inflammation, which may ultimately result in persistent angina symptoms, despite the fact that the patient has undergone PCI or coronary artery bypass grafting (CABG) (23).

AMR has recently been proposed as a simple way to measure CMD (12). Fan et al. showed a good correlation between AMR and IMR (r=0.83) and found that the accuracy of AMR (≥ 2.5 mmHg*s/cm) for the diagnosis of CMD was high (87.2%) using IMR (≥ 25 U) as the standardized reference (12). In addition, several studies have shown that AMR is not only strongly associated with CMD, but also has a significant association with the prognosis of cardiovascular events. Ma et al. found that AMR was a valid indicator for assessing CMD in patients with obstructive hypertrophic cardiomyopathy, and high microvascular resistance (3 vessel AMR ≥ 7.04) was correlated with poor prognosis (24). And a retrospective study found that AMR could predict the risk of all-cause death or heart

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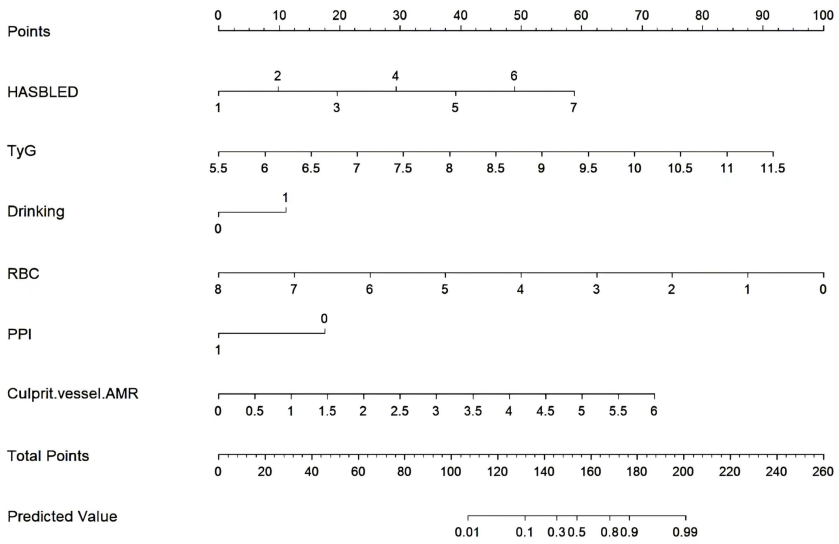

FIGURE 3
Nomogram for predicting the possibility of UGIB in NSTEMI patient after PCI.

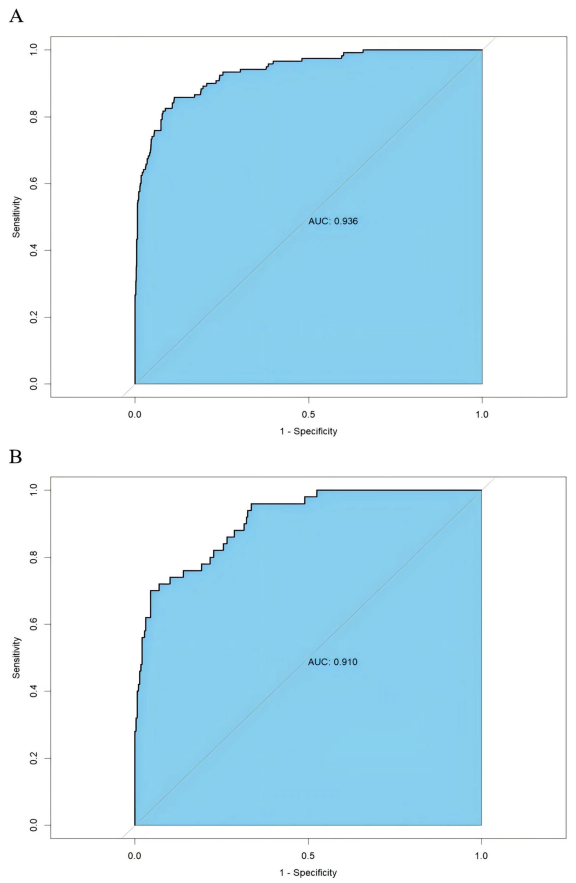

FIGURE 4
Receiver operating characteristics curve of the nomogram in the training group **(A)** and the validation group **(B)**.

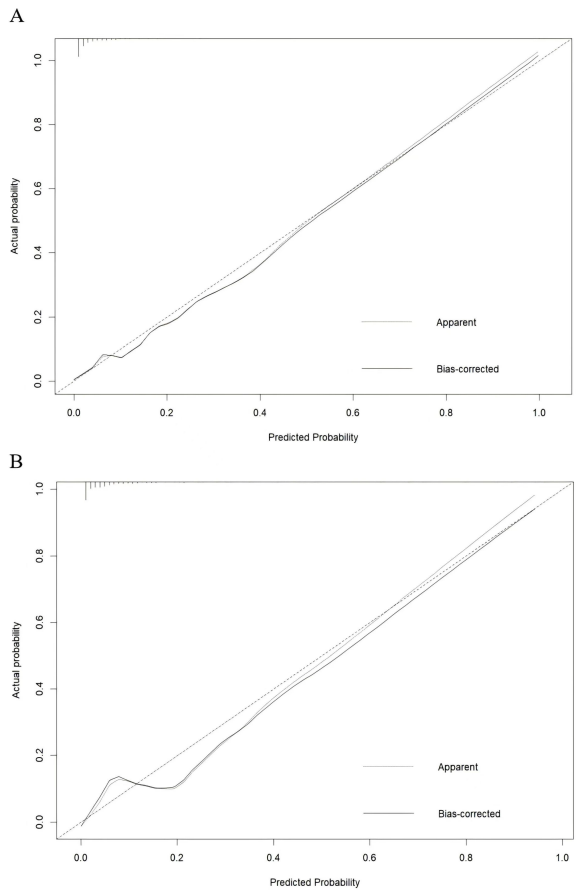

FIGURE 5
Calibration curve for the training group **(A)** and the validation group **(B)**, the horizontal axis denotes the overall predicted probability of UGIB in NSTEMI patients after percutaneous coronary intervention, and the vertical axis displays the actual probability.

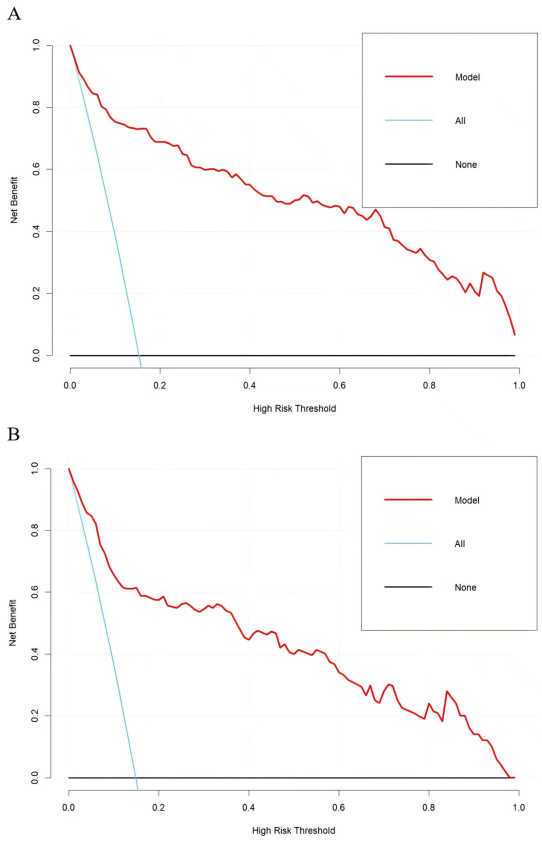

FIGURE 6
Decision curve analysis for the training group **(A)** and the validation group **(B)**.

failure readmission after PCI in STEMI patients (25). Therefore, AMR, as a surrogate measurement tool for CMD, has an equally important clinical value in the assessment of patient prognosis.

It has been proposed that patients with CMD may not only manifest in the heart, but rather a systemic microvascular disease that may manifest in multi-system disorders including dementia, renal dysfunction, and retinopathy (26). Ohura-Kajitani et al. demonstrated that, in the absence of inhibitors, patients with MVA (Microvascular Angina) and those with both VSA (Vasospastic Angina) and MVA had little or no significant response in resistance arteries to vasodilator drugs compared with patients with VSA alone (27). Overall, the findings support the idea that MVA is not only a microvascular disease limited to the heart, but may also be a systemic microvascular dysfunction, and that MVA can be considered a cardiac manifestation of systemic microvascular disease (27). In patients with CMD, the problem is not limited to the coronary microcirculation and microvascular function can be abnormal throughout the body. Particularly in patients with NSTEMI, one of the possible causes of UGIB after PCI is dysfunction of the GI microcirculation, which may weaken the defenses of the GI mucosa against the acidic environment, thereby increasing the risk of bleeding. Secondly, dysfunction of the heart as a pumping organ may lead to reduced peripheral blood flow, which in turn exacerbates microcirculatory disturbances in the GI tract, leading to decreased mucosal defenses against acidic environments, and ultimately to bleeding. This mechanism provides a potential pathologic explanation for AMR as an independent predictor of UGIB.

Recently, the TyG index has attracted a lot of attention. Several studies have found that the TyG index was an indicator of insulin resistance (IR) and also reflected systemic metabolism (28, 29). A meta-analysis showed an association between a higher TyG index and the risk of developing CAD (30). Shi et al. found a linear positive correlation between TyG index and the occurrence of ischemic stroke (31). Zhao et al. found that the risk of arterial stiffness and renal microcirculatory injury increased with the TyG index (32). In conclusion, a high TyG index was not only a cardiovascular risk factor, but was also associated with cerebrovascular and renal vascular diseases. Although the exact biological mechanisms linking TyG index to disease were unknown, key pathways may be associated with IR. Chronic hyperglycemia and dyslipidemia induced by IR triggers oxidative stress, exacerbates inflammatory responses, promotes foam cell formation, impairs endothelial function, and contributes to smooth muscle cell proliferation (28, 29). In addition, persistent IR increases sympathetic nervous system activity, renal sodium retention, and elevated blood pressure, which increases cardiac load and leads to vascular and renal injury (33). Finally, IR may affect coronary microcirculation, and is strongly associated with myocardial injury and myocardial reperfusion (34). However, few studies have explored the association between TyG index and gastrointestinal circulation. In our study, we found that the TyG index was a predictor of UGIB in NSTEMI patients after PCI, which implied that gastrointestinal circulation was similarly affected in high TyG populations.

Secondly, Feit et al. found that patients with anemia had almost double the risk of all types of bleeding, including a fourfold increase in the risk of GIB, compared to patients without anemia (35). In a two-center study of patients with atrial fibrillation treated with PCI, severe GIB occurred in 12.4% of patients with anemia compared with 3.1% of patients without anemia (36). Similarly, we found that low red blood cell count had a high risk of developing GIB, probably because patients with low red blood cell count were anemic. Patients with anemia often have poor systemic microcirculation, which may affect gastrointestinal microcirculation. In the context of the above discussion, we believe that it is not just damage to the circulation of one organ, but more likely some degree of damage to the systemic microcirculation, of which gastrointestinal hemorrhage is a manifestation.

The HASBLED score was a tool used to assess the risk of bleeding in patients with atrial fibrillation who were receiving anticoagulation therapy (37). In recent years, the application of the HASBLED score has gradually expanded beyond assessing bleeding risk in patients with atrial fibrillation. Konishi et al. and Castini et al. found that the HASBLED score could predict bleeding risk (including GIB) and mortality in patients without atrial fibrillation after PCI (38, 39). HASBLED score incorporated multiple risk factors for GIB (e.g., gender, age, hepatic and renal insufficiency) and we also found that the HASBLED score could be

used to predict the occurrence of UGIB after PCI in patients with NSTEMI. A study of patients with CAD treated with dual antiplatelet therapy showed that the higher incidence of UGIB was due to non-administration of PPI and found proton pump inhibitor (PPI) to be more protective than H2 receptor antagonists (H2RA) (40). And in our study, the protective effect of PPI after PCI in patients with NSTEMI was consistent with previous studies. The reason may be that PPI use could selectively inhibit the H+/K+ ATP enzyme in gastric wall cells, significantly reducing gastric acid secretion. This reduction in acid alleviates gastric mucosal damage caused by antiplatelet drugs, as excessive acid secretion could exacerbate mucosal irritation and damage (41).

In summary, we utilized the combination of the classical regression methods and machine learning model to found that HASBLED, TyG index, alcohol drinking, RBC count, PPI use, and AMR of culprit vessel were independent indicators for having UGIB. The model about the relationship between independent factors and UGIB was presented graphically, which had a simple and intuitive effect and the results of this study showed that our prediction model had good performance. While model simplicity reduced the risk of overfitting and improved generalization, the good performance of our current model may not only be a result of the simplicity of the model, but also of the insufficient sample size.

Our study had several limitations. Firstly, this study was a retrospective study and the external data were from the branch hospital. Although AMR is a predictor of UGIB, future prospective studies with large samples are needed to investigate the association between AMR and UGIB and its potential mechanisms. Secondly, not all patients presented to the hospital promptly when signs or tendencies related to bleeding were detected. Thirdly, the collection of UGIB-related risk variables was not comprehensive enough.

Conclusion

The nomogram clinical prediction model constructed by six factors, including HASBLED, TyG index, alcohol drinking, RBC count, PPI use, and AMR of culprit vessel, can be used to assess the likelihood of UGIB within 1 year in NSTEMI patients undergoing primary PCI, and the nomogram could help clinicians to stratify risk and individualize management for postoperative patients. Secondly this nomogram could also reflect the state of microcirculation throughout the body.

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 Research Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2023-KL043-01), which was conducted following the Declaration of Helsinki. Because our study was retrospective, the Medical Research Ethics Committee of the Affiliated Hospital of Xuzhou Medical University waived the requirement for written informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because our study was retrospective, the Medical Research Ethics Committee of the Affiliated Hospital of Xuzhou Medical University waived the requirement for written informed consent.

Author contributions

ZW: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. SY: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. CZ: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. CL: Data curation, Formal Analysis, Writing – original draft. CC: Data curation, Formal Analysis, Writing – original draft. JC: Writing – review & editing. DL: Writing – review & editing. LL: Writing – review & editing. TX: Writing – review & editing.

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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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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Decoding the mystery between hyperuricemia and atrial fibrillation: new causal links through mediating proteomics

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Background: Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with high incidence and mortality rates. Recent studies have confirmed a close correlation between hyperuricemia and the onset of AF, though the mechanisms remain unclear. Consequently, this study employs Mendelian randomization based on proteomics and mediation analysis to investigate the potential mechanisms by which hyperuricemia induces AF.

Methods: A two-step mediation MR analysis was conducted to determine whether plasma proteins mediate atrial fibrillation induced by serum urate. The Reactome database was subsequently utilized to analyze the list of significant mediating plasma proteins to identify enriched pathways.

Results: Mediation Mendelian randomization analysis suggested that hyperuricemia may promote the development of atrial fibrillation (AF) through 17 plasma proteins, includeing hepatocyte nuclear factor 4-alpha (HNF4α), identified as key mediators. Subsequent enrichment analysis of these proteins revealed 9 metabolic or signaling pathways potentially involved in this pathological process. Central mediator proteins such as HNF4α appear to drive AF through metabolic and inflammatory pathways.

Conclusion: There is a close correlation between hyperuricemia and the onset of atrial fibrillation.

KEYWORDS

atrial fibrillation, hyperuricemia, mediation mendelian randomization, proteomics, mediation analysis

1 Introduction

Atrial fibrillation (AF), as the most common cardiac arrhythmia, has seen an annual increase in global incidence and prevalence. According to data from the Framingham Heart Study (FHS), the prevalence of AF has tripled over the fifty years from 1958 to 2007 (1). From 2010 to 2060, the number of adults aged 55 and over with AF in the European Union is

expected to more than double (2).The primary risk factors for AF include advanced age, hypertension, obesity, diabetes, heart failure, valvular heart disease, and myocardial infarction, among others (3).Besides significantly impacting patients' quality of life, AF also substantially increases the risk of morbidity and mortality from conditions such as heart failure, thromboembolism, and stroke (4).Current management of atrial fibrillation primarily involves controlling heart rate and rhythm to improve symptoms and prevent strokes, while also managing comorbidities and lifestyle factors. Although ablation and risk management strategies for AF have yielded some improvement, the prevalence of AF continues to rise. Given the complexity, progressive nature, and limited detectability of atrial fibrillation, coupled with a high incidence of treatment ineffectiveness, the prevention and treatment of atrial fibrillation face increasing challenges (5, 6).Hyperuricemia is a metabolic syndrome caused by a disorder in purine metabolism, with uric acid being the final product of purine catabolism in the body. Under physiological conditions, the synthesis and excretion of uric acid are balanced. Once this balance is disrupted, hyperuricemia will ensues. In recent years, extensive clinical research has confirmed the association between hyperuricemia and atrial fibrillation (7–11). Numerous studies indicate that hyperuricemia promotes the development of cardiovascular diseases through mechanisms such as the modulation of inflammatory responses (12–14), oxidative stress (15), insulin resistance (16), endothelial dysfunction (17), and endoplasmic reticulum stress (18, 19). Although the relationship is widely recognized, the mechanisms by which hyperuricemia induces or sustains atrial fibrillation remain incompletely elucidated. The level of evidence from Mendelian Randomization (MR) studies lies between that of randomized controlled trials (RCTs) and observational studies (20). It utilizes lineage-specific genetic variants as instrumental variables (IVs) to explore the causal relationships between exposure phenotypes and outcome phenotypes (21). According to Mendel's laws, alleles are randomly distributed from parents to offspring, and the genotype precedes exposure temporally (22).

Consequently, MR studies can minimize confounding factors to the greatest extent and eliminate reverse causation. This study aims to investigate the underlying mechanisms by which hyperuricemia leads to AF, using proteomic Mendelian randomization and mediation analysis methods. It identifies the link between purine metabolism disorders and the onset of AF, thereby determining potential therapeutic targets for AF.

2 Methods

2.1 Data source

As shown in Table 1, the GWAS summary data related to serum urate levels were published by Köttgen et al. in 2013 (23). This research measured serum urate levels and performed whole-genome sequencing on 110,347 individuals from 48 studies, followed by GWAS and meta-analysis. Prior to all meta-analyses, monomorphic SNPs were excluded. If the genomic inflation factor of the study exceeded 1, all study-specific results were corrected using the genomic inflation factor, calculated by dividing the median of the observed GWAS chi-square distribution by the median of the expected chi-square distribution under the null hypothesis of no association. GWAS data associated with atrial fibrillation were published by Nielsen et al. in 2018 (24). This study conducted a genome-wide association analysis on over 1,000,000 individuals, including 60,620 cases of atrial fibrillation and 970,216 controls. Atrial fibrillation patients were identified based on ICD-10 code I48 and ICD-9 code 427.3 in electronic medical records. Plasma proteome-based GWAS data were released by Sun et al. in 2018. The study, conducted from mid-2012 to mid-2014, recruited donors aged 18 and above at 25 centers of the National Health Service Blood and Transplant (NHSBT) in England, excluding those with a history of major diseases such as myocardial infarction, stroke, cancer, HIV, and hepatitis B or C, or recent illness or infection. A multiplex aptamer-based approach (SOMAscan assay, with standardized and normalized data) was utilized to measure the relative concentrations of 3,622 plasma proteins or protein complexes, using 4,034 modified aptamers (25). The aforementioned data have each passed an ethical review and include European populations of both genders, effectively mitigating biases introduced by population stratification. Details regarding cohort recruitment and the ethical approval of the original studies can be found in Supplementary Files 1, 2.

2.2 Selection of instrumental variables

Extraction of valid instrumental variables is key to conducting MR analysis; these variables must meet the relevance, independence, and exclusion criteria of the MR assumptions. Initially, we extracted exposure-related SNPs at a genome-wide significance level (*P*-value less than $5 \times 10^{\wedge -8}$). In the mediation MR analysis, due to varying associations between different plasma proteins and genetic variants, extracting too many SNPs would increase heterogeneity, while extracting too few would result in insufficient explained variance. Therefore, a second threshold was established (*P*-value less than $1 \times 10^{\wedge -5}$). SNPs exhibiting linkage disequilibrium (LD) were removed based on an $r^{\wedge 2} < 0.001$ and a window size > 10,000 kb. Data on SNPs associated with outcomes are extracted based on SNP identifiers in the outcome datasets. Ambiguous SNPs and palindromic SNPs were eliminated in this process, aligning the SNP data from both datasets. The F statistic was calculated for each SNP (26). The F statistic, an intermediate measure in analysis of variance, quantifies the associative strength of the instrumental variable SNPs with risk factors. SNPs with an F statistic below 10 were considered weak instrumental variables and were excluded. The MR-PRESSO test was conducted to identify and exclude potential pleiotropic SNPs. The MR-Stiger test was applied to examine the directional causality of each SNP, excluding those with incorrect directions (27). Finally, the PhenoScanner test was used to determine if any SNPs were associated with confounding factors, removing those that potentially violated the independence assumption (28). Following the aforementioned filtering, the remaining SNPs were deemed compliant with the three major MR assumptions and considered valid instrumental variables.

TABLE 1 Information on the included data sets.

Trait	Case	Sample size	Year	Author	Gender	Population	NSNP
Atrial fibrillation	60620	1030836	2018	Nielsen JB	Males and Females	European	33519037
Urate	110347	110347	2013	GUGC	Males and Females	European	2450548
3282 plasma proteome	3301	3301	2018	Sun BB	Males and Females	European	10534735

2.3 Mendelian randomization analysis

Classical Mendelian Randomization requires the use of Inverse Variance Weighting (IVW). To evaluate the robustness of the results, we also employed MR Egger regression, Weighted Median (WM), Mode-based estimation, and MR Robust Adjusted Profile Score (MR-raps) to comprehensively assess potential biases in the study findings. The IVW method consolidates causal estimates of individual SNPs using a variance inverse-weighted form of the Wald ratio (29). The Wald ratio estimates measure the impact of a single SNP on the outcome relative to its effect on the risk factor, assuming that all associations conform to a log-linear relationship (30). MR-Egger regression, a valuable tool in MR analysis, is used to establish a weighted linear regression between the outcome and exposure coefficients (31). MR-Egger regression, similar to the IVW method, allows for the assessment of horizontal pleiotropy through the significance level of its intercept term. The MR-Egger method is based on the No Measurement Error (NOME) assumption. We also calculated the $I^{\wedge 2}$ statistic to quantify the extent to which MR-Egger violates the NOME assumption. When $I^{\wedge 2}$ is less than 90%, the results should be adjusted (31, 32). When multiple variants are ineffective, the results of the aforementioned method may lack robustness, in which case the WM method and the weighted mode demonstrate greater robustness. The WM method calculates normalized inverse-variance weights for each genetic variant, then combines these weights to generate an estimate. Importantly, as long as at least 50% of the weights used in the analysis come from valid instrumental variables, the WM method can provide reliable estimates of causal effects. Even in the presence of some invalid instrumental variables, the WM method can accurately estimate causal relationships, enhancing precision. The weighted mode remains robust even with a greater number of invalid instrumental variables. Furthermore, this study employs the newly developed MR-RAPS technique, which directly simulates the pleiotropic effects of genetic variants using a random-effects distribution. Compared to traditional Mendelian randomization techniques, this novel strategy offers enhanced robustness. When the *P*-value is less than 0.05, the final results are statistically significant.

2.4 Sensitivity analysis

Pleiotropy encompasses both horizontal and vertical dimensions; typically, vertical pleiotropy does not compromise the reliability of the conclusions; however, horizontal pleiotropy should be eliminated. The primary method employed for estimating the magnitude of horizontal pleiotropy is the MR-Egger approach. If the *P*-value of the MR-Egger intercept is less than 0.05, the instrumental variables are considered to be significantly affected by horizontal pleiotropy, rendering the results unreliable. When pleiotropy is present, MR-Egger regression is utilized as the principal analytical method.

In MR analysis, even if all SNPs are valid instrumental variables, they may exhibit heterogeneity. The presence of substantial heterogeneity can compromise the reliability of the findings; thus, heterogeneity tests are conducted to enhance the credibility of the results. The IVW method is used to calculate heterogeneity among SNPs, assessed with Cochran's Q test. A *P*-value less than 0.05 indicates heterogeneity; in such cases, an IVW random effects model is applied alongside the weighted median method. If no heterogeneity is present, the IVW random effects model remains the main analytical approach (33). Additionally, as per convention, the leave-one-out method is employed, and a funnel plot is constructed. A comprehensive MR-Steiger test was conducted to verify the correct overall causal direction. Finally, we calculated the statistical power to ascertain the reliability of negative results (34).

2.5 Proteomic mediation analysis and enrichment analysis

Two-step mediation MR analyses using GWAS summary data were conducted to determine whether plasma proteins are intermediary factors in serum urate-induced atrial fibrillation. The first step involved a two-sample MR analysis between serum urate and the plasma proteome, followed by a second two-sample MR analysis between the plasma proteome and atrial fibrillation. Proteins significant in both analyses exhibited partial mediation effects, those only significant in the two-step mediation analyses showed complete mediation effects, and proteins not consistently significant displayed no mediation effects. Indirect effects were calculated using the formula $\beta 1^{*}\beta 2$, and direct effects were determined by subtracting indirect effects from the total effects. The Reactome knowledgebase (35) was utilized to analyze the list of mediating plasma proteins to understand enriched pathways. Reactome is a peer-reviewed database of human biological pathways and reactions. Overrepresentation analysis was conducted to determine whether specific Reactome pathways were enriched in the gene list, generating probability scores and significance *P*-values.

2.6 Statistical software and visualization

For the visualizations in the conclusion section, this study generated scatter plots for each SNP, illustrating the relationship

with exposure factors and outcome effects, accompanied by regression curves to present causal estimates. A significance heatmap for the MR analysis was created to display the results. Funnel plots were utilized to assess potential directional effects and pleiotropy, as well as to examine the distribution of data. The final causal estimates were used to create forest plots, which displayed the results for each SNP and the overall MR analysis outcomes. All statistical analyses in this study were conducted using R (version 4.2.3) and the R packages "TwoSample MR", "MR-PRESSO", and "mr.raps".

3 Results

3.1 Selection of instrumental variables

In the MR analysis, initially 27 SNPs associated with exposure were screened, and no weak instrumental variables were identified; no SNPs were excluded from the outcome database due to missing data. 2 SNPs were identified as ambiguous or palindromic, and 2 SNPs were excluded after screening with Phenoscanner due to their association with confounding factors. The MR-PRESSO test identified 2 SNPs with horizontal pleiotropy; the MR-Steiger test found no SNPs with incorrect causal direction. No SNPs directly related to the outcome were identified; ultimately, 21 eligible SNPs were included in the study. In the mediation MR analysis, initially, 193,706 exposure-related SNPs were screened without detecting any weak instruments; 3,171 SNPs were excluded from the outcome database due to missing data. A total of 21,886 ambiguous and palindromic SNPs were removed during the dataset consolidation. The MR-PRESSO test detected no SNPs with horizontal pleiotropy; the MR-Steiger test revealed no SNPs with erroneous causal directions. Following Bonferroni correction, 12,469 SNPs directly related to the outcome were removed, leaving 156,180 eligible SNPs included in the study.

3.2 Mendelian randomization analysis

In the Mendelian Randomization analysis, an increase in serum urate levels was found to promote the onset of atrial fibrillation (OR (95% CI): 1.045 (1.007 ~ 1.083), P=0.019, see Figure 1D). There was no evidence of pleiotropy or heterogeneity in these results.

In the mediation MR analysis, we initially discovered that serum urate exerted a causal effect on 348 proteins (Figures 1B, E), and 269 proteins causally influenced the onset of atrial fibrillation (Figures 2B, E). Subsequently, a protein-protein interaction

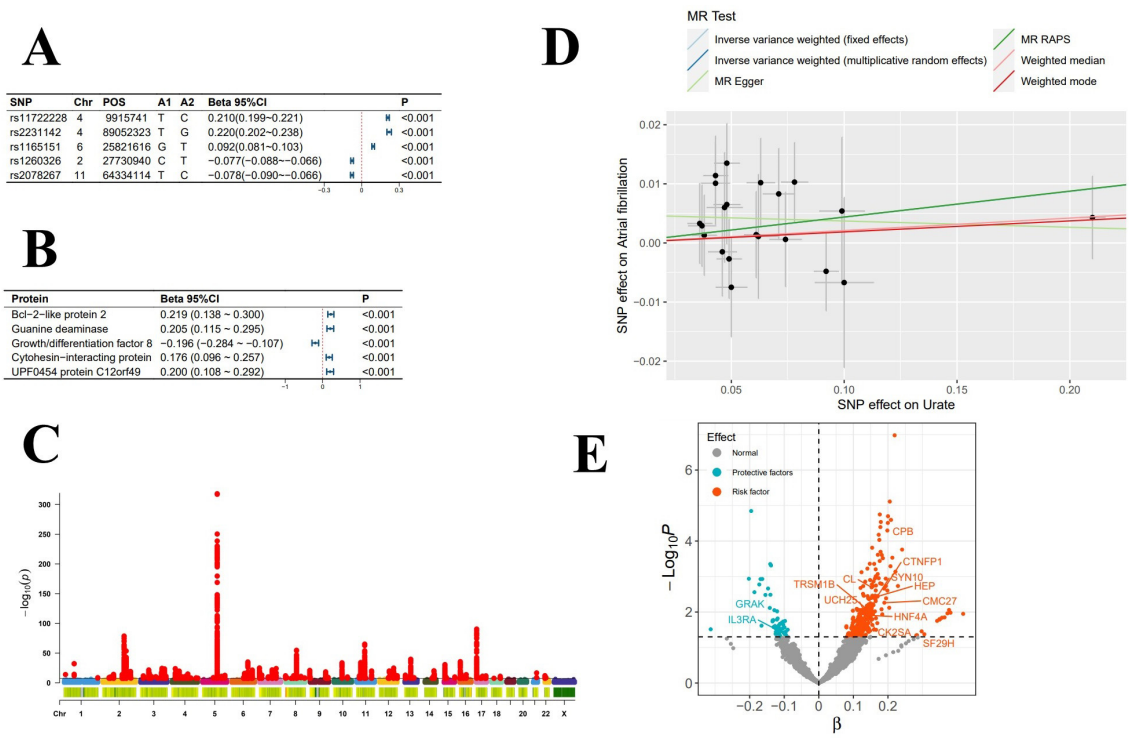

FIGURE 1
Exposure-Related Analysis Graphs. **(A)** Top 5 single nucleotide polymorphisms (SNPs) most significantly associated with serum urate levels; **(B)** Top 5 plasma proteins most significantly impacted by serum urate levels; **(C)** Manhattan plot of genome-wide association study summary data for serum urate levels; **(D)** Scatter plot and regression curve from Mendelian randomization exploring the causal relationship between serum urate levels and atrial fibrillation; **(E)** Scatter plot of the significance levels of serum urate effects on plasma proteins, with specified proteins indicating mediation.

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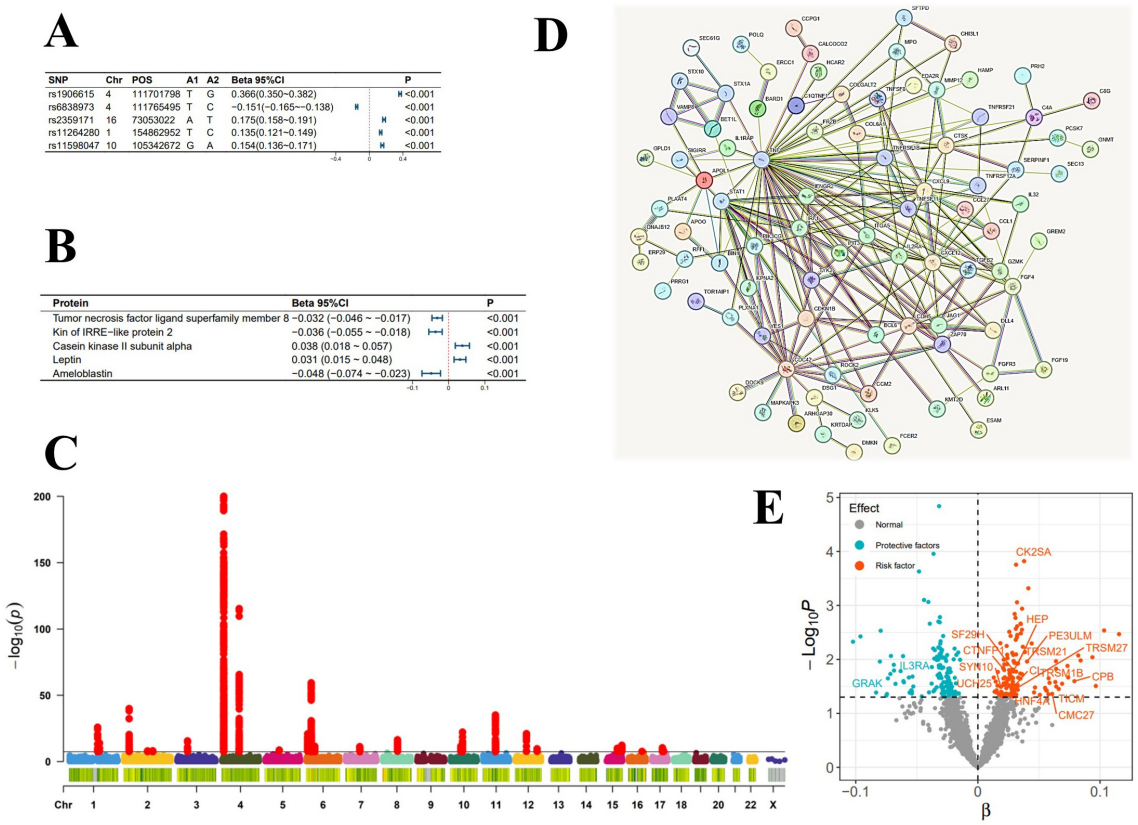

FIGURE 2
Analysis Graphs Related to the Incidence of Atrial Fibrillation. **(A)** Top 5 SNPs most significantly influencing the incidence of atrial fibrillation; **(B)** Top 5 plasma proteins most significantly associated with the incidence of atrial fibrillation; **(C)** Manhattan plot of genome-wide association study summary data for atrial fibrillation; **(D)** Diagram of plasma protein interactions affecting the incidence of atrial fibrillation; **(E)** Scatter plot of the significance levels of plasma protein effects on the incidence of atrial fibrillation, with specified proteins indicating mediation.

analysis was conducted on plasma proteins that induce atrial fibrillation (Figure 2D). Ultimately, we identified 17 plasma proteins with mediating effects, including Hepatocyte nuclear factor 4-alpha (Table 2, Figures 3A, B), which mediated the promotion of atrial fibrillation by serum urate, with mediation effect ratios ranging from 0.05% to 0.36%.

3.3 Enrichment analysis

In the enrichment analysis, we identified 10 significant pathways mediating the increased levels of serum urate in promoting the onset of atrial fibrillation, with evidence remaining for 2 significant pathways after correction for the false discovery rate. Specifically, the pathways 'Regulation of gene expression in beta cells' (Reactions: 1/12; Entities: 3/23; Adj. P=0.003) and 'Regulation of beta-cell development' (Reactions: 1/26; Entities: 3/44; Adj. P=0.009) significantly mediated the influence of serum urate on the onset of atrial fibrillation; eight signal transduction pathways including 'TNFs bind their physiological receptors' potentially mediated this effect. Table 3 and Figure 3C display the enrichment information for the mediating pathways, with detailed data available in the Supplementary Materials.

4 Discussion

Atrial fibrillation, as the most common cardiac arrhythmia, severely impacts the quality of life of patients and significantly increases the risk of developing conditions such as heart failure, thromboembolism, and stroke, thereby elevating mortality rates. Although numerous studies have confirmed the association between hyperuricemia and atrial fibrillation (9–11, 36), the precise mechanisms by which hyperuricemia induces atrial fibrillation remain unclear. It is widely believed that atrial remodeling is a prerequisite for the onset of atrial fibrillation, with oxidative stress and inflammation being the most critical mechanisms (37). Mediators of inflammation can alter atrial electrophysiology and structural matrix, as well as regulate calcium homeostasis and connexins, thereby promoting the onset of atrial fibrillation (38). Studies have demonstrated that activation of the NLRP3 inflammasome in atrial myocytes is a potential pathogenic mechanism for atrial fibrillation (12). In a hyperuricemic state, activation of the NLRP3 inflammasome can also promote inflammation, closely resembling the pathogenic mechanism of atrial fibrillation. Additionally, uric acid (UA)-induced upregulation of Kv1.5 expression may represent a novel mechanism for the induction of atrial fibrillation: UA enhances

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TABLE 2 Significant results of two-step mediation analysis.

Mediator	X-Y		X-M		M-Y		Mediating direction	Mediating effect	Mediating ratio
	OR 95%CI	*P*	OR 95%CI	*P*	OR 95%CI	*P*			
Complement C1q tumor necrosis factor-related protein 1	1.045 (1.007~1.083)	0.019	1.214 (1.075~1.372)	0.002	1.022 (1.004~1.040)	0.002	TRUE	Partial	0.10%
SAGA-associated factor 29 homolog	1.045 (1.007~1.083)	0.019	1.357 (1.035~1.779)	0.042	1.029 (1.005~1.053)	0.042	TRUE	Partial	0.20%
C-C motif chemokine 27	1.045 (1.007~1.083)	0.019	1.209 (1.057~1.382)	0.005	1.063 (1.005~1.124)	0.005	TRUE	Partial	0.26%
Carboxypeptidase B	1.045 (1.007~1.083)	0.019	1.221 (1.112~1.341)	<0.001	1.082 (1.016~1.153)	<0.001	TRUE	Partial	0.36%
Corticoliberin	1.045 (1.007~1.083)	0.019	1.165 (1.057~1.284)	0.002	1.028 (1.002~1.055)	0.002	TRUE	Partial	0.10%
Casein kinase II subunit alpha	1.045 (1.007~1.083)	0.019	1.155 (1.029~1.295)	0.014	1.039 (1.018~1.059)	0.014	TRUE	Partial	0.12%
Tumor necrosis factor receptor superfamily member 27	1.045 (1.007~1.083)	0.019	1.132 (1.002~1.278)	0.046	1.021 (1.000~1.043)	0.046	TRUE	Partial	0.06%
Granzyme K	1.045 (1.007~1.083)	0.019	0.868 (0.782~0.963)	0.008	0.929 (0.877~0.984)	0.008	TRUE	Partial	0.24%
Hepcidin	1.045 (1.007~1.083)	0.019	1.172 (1.052~1.305)	0.004	1.033 (1.007~1.060)	0.004	TRUE	Partial	0.12%
Hepatocyte nuclear factor 4-alpha	1.045 (1.007~1.083)	0.019	1.154 (1.032~1.292)	0.012	1.047 (1.004~1.092)	0.012	TRUE	Partial	0.15%
Interleukin-3 receptor subunit alpha	1.045 (1.007~1.083)	0.019	0.893 (0.804~0.992)	0.035	0.968 (0.941~0.995)	0.035	TRUE	Partial	0.09%
Probable E3 ubiquitin-protein ligase MID2	1.045 (1.007~1.083)	0.019	1.109 (1.001~1.228)	0.047	1.041 (1.009~1.074)	0.047	TRUE	Partial	0.10%
Syntaxin-10	1.045 (1.007~1.083)	0.019	1.185 (1.057~1.329)	0.004	1.019 (1.002~1.037)	0.004	TRUE	Partial	0.07%
Tumor necrosis factor receptor superfamily member 1B	1.045 (1.007~1.083)	0.019	1.147 (1.037~1.270)	0.008	1.066 (1.009~1.127)	0.008	TRUE	Partial	0.20%
Tumor necrosis factor receptor superfamily member 21	1.045 (1.007~1.083)	0.019	1.131 (1.011~1.265)	0.031	1.029 (1.005~1.054)	0.031	TRUE	Partial	0.08%
Troponin I, cardiac muscle	1.045 (1.007~1.083)	0.019	1.090 (1.003~1.184)	0.042	1.068 (1.009~1.131)	0.042	TRUE	Partial	0.13%
Ubiquitin carboxyl-terminal hydrolase 25	1.045 (1.007~1.083)	0.019	1.142 (1.033~1.262)	0.010	1.015 (1.001~1.030)	0.010	TRUE	Partial	0.05%

OR, Odds ratio; CI, Confidence interval; X-Y, Total effect; X-M, step 1 mediating effect; M-Y, step 2 mediating effect.

Kv1.5 protein expression by activating the ERK pathway and promoting the expression of Heat Shock Protein 70 (Hsp70) in mouse atrial myocytes (HL-1 cells), thereby increasing the ultra-rapid delayed rectifier K+ current and shortening the duration of action potentials (39, 40). Oxidative stress is also a significant cause of atrial fibrillation in hyperuricemia. In a hyperuricemic state, enhanced oxidative stress responses lead to excessive production of reactive oxygen species (ROS), which by affecting ion channels and the propagation of action potentials, promote atrial fibrillation (41): Hydrogen peroxide induces triggered activity by enhancing late Na + currents, leading to early afterdepolarizations (EAD) and delayed afterdepolarizations (DAD); Additionally, excessive ROS upregulates L-type Ca2+ channels, altering intracellular calcium homeostasis to promote EADs (41), activates calcium/calmodulin-dependent protein kinase II (CaMKII), increases the opening probability of RYR2 (calcium release channel 2), leading to calcium overload and the formation of multiple waves, thereby inducing atrial fibrillation (42).

Furthermore, oxidative stress can induce atrial fibrillation through atrial structural remodeling, where hydroxyl radicals (OH-) alter the structure and function of myofibrillar proteins, contributing to myocardial damage and the onset of atrial fibrillation (43).

In this study, employing proteomic Mendelian randomization and a two-step mediation analysis, we explored the underlying

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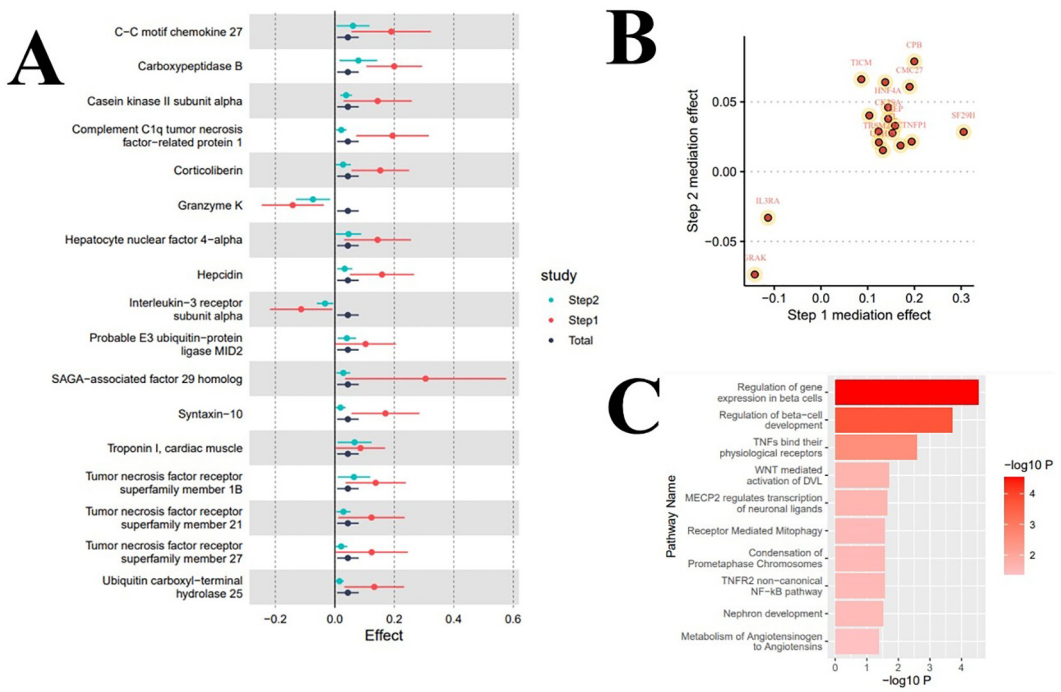

FIGURE 3
Results of mediation analysis and enrichment analysis. **(A)** Forest plot of total effect and two-step mediation effects; **(B)** Scatter plot of two-step effects of mediating proteins; **(C)** Mediating pathways of metabolic or signal transduction related to serum urate levels in the onset of atrial fibrillation.

TABLE 3 Activated mediating metabolism or signal transduction pathways.

Pathway name	Reactions found	Reactions ratio	Entities found	Entities ratio	*P*Value	FDR	Mapped proteins
Regulation of gene expression in beta cells	1/12	0.0008	3/23	0.0020	<0.001	0.003	Hepatocyte nuclear factor 4-alpha
Regulation of beta-cell development	1/26	0.0018	3/44	0.0037	<0.001	0.009	Hepatocyte nuclear factor 4-alpha
TNFs bind their physiological receptors	2/13	0.0009	2/30	0.0025	0.003	0.083	Tumor necrosis factor receptor superfamily member 27;Tumor necrosis factor receptor superfamily member 1B
WNT mediated activation of DVL	1/4	0.0003	1/8	0.0007	0.020	0.301	Casein kinase II subunit alpha
MECP2 regulates transcription of neuronal ligands	1/8	0.0006	1/9	0.0008	0.023	0.301	Corticoliberin
Condensation of Prometaphase Chromosomes	1/4	0.0003	1/11	0.0009	0.028	0.301	Casein kinase II subunit alpha
Receptor Mediated Mitophagy	1/7	0.0005	1/11	0.0009	0.028	0.301	Casein kinase II subunit alpha
TNFR2 non-canonical NF-kB pathway	9/44	0.0030	2/102	0.0087	0.028	0.301	Tumor necrosis factor receptor superfamily member 27;Tumor necrosis factor receptor superfamily member 1B
Nephron development	1/17	0.0012	1/12	0.0010	0.030	0.301	Hepatocyte nuclear factor 4-alpha
Metabolism of Angiotensinogen to Angiotensins	1/18	0.0012	1/17	0.0014	0.042	0.337	Carboxypeptidase B

mechanisms by which hyperuricemia induces atrial fibrillation. We identified 17 proteins playing significant roles in this process, with enrichment analysis revealing that abnormalities in HNF4α leading to beta-cell impairment in the pancreas are critical in the onset of AF driven by hyperuricemia. Hepatocyte nuclear factor 4 alpha (HNF4α) is a nuclear transcription factor (TF) predominantly expressed in the liver, intestines, kidneys, and pancreas (44). It plays a crucial role in transcriptional regulation in hepatocytes and pancreatic cells and is closely associated with carbohydrate and lipid metabolism, and inflammatory responses (45–47). Hyperuricemia may affect transcription factors' DNA-binding capacity and activity through oxidative stress responses. Additionally, the release of inflammatory cytokines can interfere with the expression and activity of HNF4α. Furthermore, signal transduction activated by inflammatory pathways may indirectly influence the expression or functionality of HNF4α via pathways (48). Abnormal activity and status of HNF4a affect its regulation of downstream genes, ultimately leading to developmental and functional dysfunctions in pancreatic β-cells. Initially, HNF4a plays a crucial role in pancreatic β-cells, influencing the synthesis and secretion of insulin, as well as other functions related to glucose metabolism. Abnormalities in HNF4a are commonly associated with a high incidence of maturity-onset diabetes of the young (MODY), with MODY1 patients exhibiting defects in insulin secretion stimulated by glucose and arginine, indicating a progressive loss of pancreatic β-cell function (49). This also demonstrates that abnormalities in HNF4a lead to the loss of pancreatic β-cell function, exacerbating disorders in glucose metabolism, resulting in persistent hyperglycemia, and further intensifying oxidative stress and inflammatory responses within the body. Moreover, the absence of HNF4α in the liver leads to the dysregulation of multiple genes involved in lipid metabolism, resulting in severe lipid disorders, further intensifying oxidative stress and inflammatory responses in the body (46). Furthermore, increasing evidence suggests a strong link between transcription factor modifications mediated by HNF4α and inflammation/oxidative stress. For instance, the *PARA* gene is one of the known direct target genes of HNF4α (50). Upon activation by HNF4a, the *PPAR* gene not only exerts its anti-inflammatory activity by stimulating the catabolic metabolism of pro-inflammatory arachidonic acid (51), but also inhibits the activation of inflammatory response genes (such as cytokines, metalloproteinases, and acute-phase proteins) through the suppression of the NF-κB signaling pathway, thereby reducing the production of inflammatory mediators (52). Therefore, aberrant expression of HNF4a contributes to the onset of atrial fibrillation by exacerbating metabolic dysregulation, oxidative stress, and inflammatory responses. Besides its effects on pancreatic β-cells, Hou et al. discovered that Peli1-mediated ubiquitination of HNF4α leads to impaired fatty acid oxidation (FAO), a notable metabolic remodeling found in pathological cardiac hypertrophy (53). Such structural changes may also be a causative factor in atrial fibrillation induced by HUA. At the metabolic level, HNF4α maintains myocardial energy homeostasis by regulating genes involved in fatty acid oxidation (FAO); its dysfunction may lead to electrical remodeling (e.g., impaired calcium handling) and structural remodeling (e.g., fibrosis) (53). In addition, HNF4α acts as a transcriptional activator of TGF-β1, promoting atrial matrix remodeling by upregulating TGF-β1 expression, which in turn suppresses the miR-29 family and facilitates CDK2-mediated fibroblast proliferation (54). Moreover, the protein stability of HNF4α is modulated by ubiquitination—such as Peli1-mediated modification at K307/K309 residues—and by stress-responsive signaling pathways including AMPK and JNK2. Aberrant degradation of HNF4α may contribute to AF pathogenesis by exacerbating metabolic imbalance and autophagy overactivation (55).

In addition to the aforementioned pathways, we have identified potential activations of 17 plasma proteins along eight metabolic and signaling pathways: TNFs binding their physiological receptors, WNT-mediated activation of DVL, MECP2 regulation of neuronal ligands transcription, Condensation of Prometaphase Chromosomes, Receptor-Mediated Mitophagy, TNFR2 non-canonical NF-kB pathway, Nephron development, and Metabolism of Angiotensinogen to Angiotensins. As an inflammatory cytokine with multiple biological effects, TNF exerts its biological activity by binding and activating two distinct receptors, TNFR1 and TNFR2 (56). Previous research has confirmed that the binding of TNF to TNFR1 can promote inflammatory responses. This study suggests that TNF may also activate the atypical NF-κB pathway through binding to TNFR2, further enhancing the expression of inflammatory genes and the production of various inflammatory cytokines and chemokines, thus initiating and amplifying inflammatory responses (57). Additionally, TNF receptors and casein kinase II (CK2) contribute to atrial fibrosis, ion channel dysfunction, and electrical conduction abnormalities by activating inflammatory signaling pathways (such as NF-κB) and profibrotic cascades. Both also induce oxidative stress, which activates the NLRP3 inflammasome and promotes the release of proinflammatory cytokines such as IL-1β, thereby exacerbating myocardial injury and fibrosis. Together, these mechanisms drive atrial structural remodeling and electrical instability, facilitating the initiation and progression of atrial fibrillation (55).We have also found a correlation between the occurrence of atrial fibrillation and the WNT signaling pathway. Previous studies have confirmed the association of this pathway with myocardial fibrosis (58–60). Dishevelled protein (DVL) plays a critical regulatory role in both the canonical Wnt/β-catenin signaling pathway and the non-canonical Wnt/planar cell polarity (PCP) signaling pathway. By promoting the differentiation of myofibroblasts, this leads to myocardial fibrosis and subsequently the occurrence of atrial fibrillation (61). The RAS system is also one of the factors by which hyperuricemia promotes the occurrence of atrial fibrillation. Hyperuricemia can directly or indirectly activate the RAS system's ACE/AII/AT1 axis (62), stimulating oxidative stress and cytokine release, promoting inflammatory responses, and also participating in cardiac electrical remodeling, inducing morphological changes in atrial cardiomyocytes. Additionally, it may stimulate epicardial fat accumulation and inflammation, thereby directly or

indirectly affecting the occurrence of atrial fibrillation (63). Moreover, clinical evidence has shown that classical RAS inhibitors (ACE-Is and ARBs) can reduce the incidence Additionally, MECP2 regulation of transcription of neuronal ligands, condensation of prometaphase chromosomes, and receptor-mediated mitophagy may play a role in the onset of atrial fibrillation induced by hyperuricemia, but the specific mechanisms remain unknown and require further investigation. Through protein-level analysis, we have unveiled the potential mechanisms by which HUA induces AF, identifying a link between purine metabolic disorder and the onset of AF, potentially offering new targets for the prevention and treatment of atrial fibrillation with significant clinical implications.

In recent years, accumulating studies have elucidated the association between hyperuricemia and AF. Mechanistically, activation of the NLRP3 inflammasome has emerged as a key contributor to AF pathogenesis. Hyperuricemia promotes the release of proinflammatory cytokines such as IL-1β by activating the NLRP3 inflammasome, leading to atrial fibrosis and structural remodeling (55, 64). Additionally, xanthine oxidase (XO)–mediated oxidative stress contributes to autophagy dysregulation and impaired calcium handling, further enhancing AF susceptibility (65). From a clinical intervention perspective, urate-lowering therapies—such as allopurinol and febuxostat—have become a focus of AF-related research. Both drugs are XO inhibitors but act via distinct mechanisms. While allopurinol has shown potential in reducing AF risk among older adults, febuxostat has been associated with an increased risk of AF in the same population, suggesting the need for individualized treatment decisions (66). Moreover, the impact of hyperuricemia on AF appears to vary significantly by ethnicity, potentially linked to polymorphisms in the URAT1 gene. A stronger association observed in female patients may be attributable to estrogen-mediated regulation of XO activity (67, 68). These findings underscore the importance of conducting mechanistic studies in more diverse, multi-ethnic cohorts to better understand the relationship between uric acid and AF. Targeting key nodes within the NLRP3 inflammasome or purine metabolism pathways may provide a theoretical foundation for developing more selective therapeutic strategies.

From a translational medicine standpoint, the 17 mediator proteins identified in this study offer promising utility as blood-based biomarkers for early diagnosis and risk stratification. Moreover, these key proteins may serve as targets for novel therapeutics or the repurposing of existing drugs. Stratified intervention strategies could also be developed based on protein expression profiles. Future research should focus on validating the clinical utility of these biomarkers through multicenter cohort studies and elucidating the causal mechanisms of candidate proteins using organoid models or gene-editing technologies, thereby providing an experimental basis for rational target selection.

This study is innovative in the following ways. To our knowledge, this is the first study to apply mediation analysis to explore the causal relationship between serum uric acid levels and the onset of atrial fibrillation, including the mediation pathways involved. Furthermore, this study was conducted using large-sample pooled data from genome-wide association studies. Confounding-related SNPs were eliminated from the statistical model, and multiple sensitivity analysis techniques were employed to ensure the robustness and reliability of the causal conclusions. Our conclusions are subject to the following limitations. Initially, our study population focused on Europeans; hence, the conclusions are presently not generalizable to a broader demographic. Furthermore, the use of aggregate data rather than individual-level data precludes stratification by variables such as gender. This limitation is particularly important given that multiple studies have demonstrated a positive association between HUA and AF risk in both men and women, with significant sex-specific differences (68, 69), underscoring the need for future sex-stratified investigations. The assumption of a linear causal relationship inherent in the ratio estimation method means that a non-linear relationship between hyperuricemia and the incidence of AF cannot be dismissed. Lastly, individual channeling is an unavoidable aspect of Mendelian Randomization (MR) studies. However, it is important to note that the conclusions of the MR study remain valid as long as the SNPs used in this research satisfy the three assumptions of an instrumental variable.

Overall, our innovative findings indicate that impairments in β-cells due to abnormal states and activities of transcription factor HNF4α are a significant cause of atrial fibrillation induced by hyperuricemia, indirectly corroborating the frequent co-occurrence of atrial fibrillation in diabetic patients.

5 Conclusion

Hyperuricemia is closely associated with the incidence of atrial fibrillation. Seventeen plasma proteins, including Hepatocyte nuclear factor 4-alpha with mediating effects, play a critical role in the process by which hyperuricemia promotes atrial fibrillation, elucidating the potential link between purine metabolic disorder and AF pathogenesis, and offering potential targets for future prevention and treatment of atrial fibrillation.

Data availability statement

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

Author contributions

MZ: Data curation, Formal Analysis, Methodology, Visualization, Writing – original draft. LS: Data curation, Writing – original draft. CQ: Visualization, Writing – original draft. MP: Writing – original draft, Writing – review & editing. ZZ: Conceptualization, Supervision, Writing – original draft.

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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/fendo.2025.1429465/full#supplementary-material

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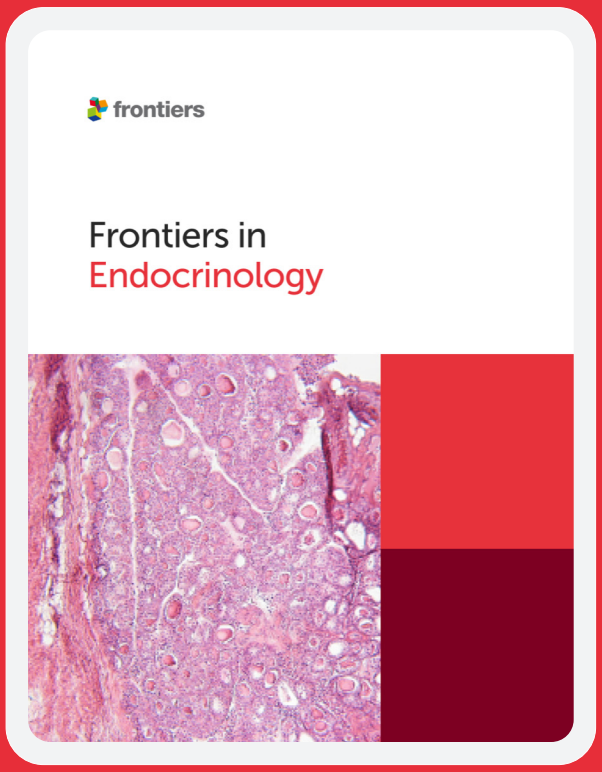

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