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Metabolic pathways to multiple long-term conditions (multimorbidity): focusing on cardio-metabolic multimorbidity (CMM)

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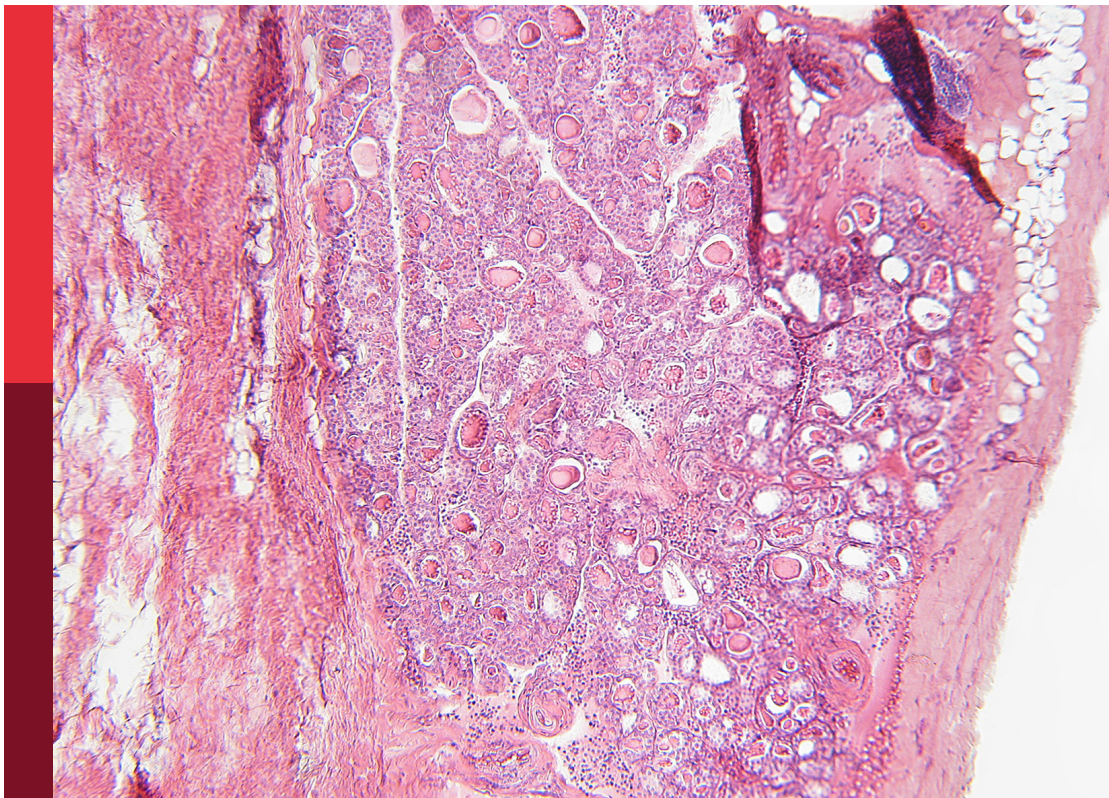

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Metabolic pathways to multiple long-term conditions (multimorbidity): focusing on cardio-metabolic multimorbidity (CMM)

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Table of contents

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Editorial: Metabolic pathways to multiple long-term conditions (multimorbidity): focusing on cardio-metabolic multimorbidity (CMM)

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KEYWORDS

cardiometabolic multimorbidity, MAFLD, metabolic disease, morbidity measures, multimorbidity

Editorial on the Research Topic

Metabolic pathways to multiple long-term conditions (multimorbidity): focusing on cardio-metabolic multimorbidity (CMM)

Multimorbidity is the presence of two or more long-term health conditions, which could be a non-communicable disease, chronic mental condition or even chronic infectious diseases (HIV, Hepatitis B), in an individual. This stands separate from co-morbidity which is any distinct additional entity that has existed or may occur during the clinical course of a patient on therapy for an index disease.

Multimorbidity is an issue that clinicians grapple with, especially given the global demographic transition to an increasingly aging population. The pathways to multimorbidity are often shared setting scope for prevention in the at-risk groups. The Research Topic in multimorbidity focusses on cardiometabolic multimorbidity (CMM), covering the themes of epidemiological patterns across various settings globally; pathophysiology and pathways to multimorbidity and CMM; and the therapeutic aspects including challenges at the community level.

Shen et al. did a cross-sectional analysis based on a sample size of 3,779,756 medical records. A network analysis and community classification were performed to illustrate disease networks and patterns of multimorbidity in the elderly population of Shanghai.

Guo et al. cluster analysed multimorbidity patterns in older adults in Shenzhen, China. They analysed data from the Shenzhen aging-related disease cohort, including 8,911 people aged 60 and above after exclusion of missing and abnormal values. The study found that multimorbidity is prevalent among the older adult in Shenzhen and explored their patterns, and found a high prevalence of cardiometabolic comorbidities, reaching 15.83%, and detailed the distribution of specific comorbidity combinations.

Zhou and Yi studied CMM and frailty in middle-aged and the elderly using data from four international cohorts – HRS, CHARLS, ELSA and SHARE – to examine the correlation between frailty and cardiometabolic diseases (CMD). The used the frailty index w for assessing frailty and statistical analyses were performed as a means of analysing the correlation between the number of cardiometabolic conditions and frailty severity. The study found that as the number of cardiometabolic diseases increased, the frailty index rose significantly, with stroke having the most pronounced impact on frailty.

Gao et al. analysed the association between metabolic-associated fatty liver disease and risk of cardiometabolic multimorbidity from a disease trajectory analysis using the data from the UK Biobank. From a median follow-up of 13.85 years, 4,622 new-onset CMM cases emerged among participants free of CMD at baseline. MAFLD was significantly associated with an increased risk of incident CMM independently elevating the risk of incident CMM, emphasizing the necessity of targeted MAFLD interventions for CMM prevention.

Liu et al. studied 4676 eligible participants from the China Health and Retiremuent Longitudinal Study (CHARLS) database, wherein they looked at the association between hemoglobin glycation index (HGI) and the risk of cardiovascular disease in early-stage cardiovascular-kidney-metabolic syndrome (CKM). From their analysis they concluded that HGI is associated with an elevated risk of CVD in participants with early-stage CKM syndrome. Additionally, they opined that HGI could serve as an independent biomarker for guiding clinical decision-making and managing patient outcomes.

Li et al. studied cardiometabolic multimorbidity (CMM) and the risk of sudden cardiac death (SCD) among geriatric community dwellers using longitudinal EHR-derived data. An analysis of records of 55130 elderly population revealed a rate of CMM of 25.3%. Older adults were categorized into different CMM patterns according to the cardiometabolic disease (CMD) status at baseline. Cox proportional hazard models were used to evaluate associations between CMM and SCD. They concluded the risk of SCD varied by the pattern of CMM, and increased with increasing number of CMM among geriatric community dwellers.

Banerjee and Mani explore the molecular pathways linking adipose tissue expansion to multimorbidity and its heterogenous outcomes. Their review explores key pathways, including inflammation, insulin resistance, adipokine dysregulation, and complement system activation, that link obesity to diabetes, cardiovascular diseases, and metabolic syndrome. They go on to analyse of how these pathways drive two major obesity-related conditions: type 2 diabetes and cardiovascular disease, with particular emphasis on the pathophysiology leading to heart failure.

Ma et al. study the association between peripheral thyroid sensitivity defined by the FT3/FT4 ratio and composite adverse outcome among patients with heart failure. Their single centre prospective cohort of 402 patients of heart failure revealed that maintaining or restoring higher FT3/FT4 levels improve outcomes. They opine that regular monitoring of this ratio, coupled with tailored interventions based on thyroid functional status, could enhance risk stratification and therapeutic decision-making.

Guo and Du look at the osteogenic differentiation in vascular smooth muscles with hyperglycaemic. Sustained hyperglycemia drives VSMCs to undergo a phenotypic transition from contractile state to osteo-/chondrogenic lineages through multiple pathophysiological mechanisms. Specifically, hyperglycemia stimulates metabolic reprogramming. This includes enhancing advanced glycation end products (AGEs), trigger vesicles-mediated mineralization (including matrix/extracellular vesicles), oxidative stress, inflammatory cascades, and an imbalance between autophagy and apoptosis.

Yu et al. study the association of pan-immune-inflammation value (PIV) and atherogenic index of plasma (AIP) with chronic coronary syndrome (CCS) in non-alcoholic fatty liver disease patients (NAFLD). They conclude from their assessment of 459 individual with NAFLD that lnPIV and AIP are independent biomarkers for CCS in NAFLD patients. Eight independent variables were used to construct a nomogram which showed values as a tool for CCS risk stratification and personalized management.

Shen et al. studied the expression profiles and roles of microRNAs in cardiac glucose metabolism and to explore their potential as biomarkers for glucose metabolism disorders in diabetic cardiomyopathy (DCM). Their systematic review helped identified 20 consistently dysregulated miRNAs associated with myocardial glucose metabolism. Six dysregulated miRNAs, including miRNA-199a, let-7, miRNA-21, miRNA-133, miRNA-503 and miRNA-378, have potential as candidate miRNA biomarkers of glycometabolism in the heart.

Zhu et al. explored the role of oral microbiome and metabolic profiling in CVD risk stratification and risk prevention as a part of the Suzhou cardiometabolic health study protocol. Their study introduced oral (tongue coating) microbiota as a metabolic marker for the first time, in combination with multiple metabolic factors, to explore their potential in assessing subclinical target organ damage and optimizing cardiovascular risk stratification, in order to provide a new path for the early identification and intervention of CVD.

He et al. investigated the association of body roundness index (BRI) with the risk of CVD and its components including congestive heart failure (CHF), coronary heart disease (CHD), angina, heart attack, and stroke in patients with cardiometabolic syndrome (CMS). At the same time, we hypothesized that BRI would identify CVD better than BMI or waist circumference (WC). They used logistic regression models to evaluate the relationship between BRI and CVD in patients with CMS, using data from the 2009-2018 National Health and Nutrition Examination Survey (NHANES) datasets.

Lekha et al. explored the challenges healthcare providers (HCPs) face in managing people with multiple-long-term conditions (MLTCs) in a south Indian primary care setting, as a qualitative exploratory study. They conducted 33 in-depth, semi-structured interviews with HCPs in four districts of Kerala, India.

The study highlights Our study sub-optimal health system preparedness and highlights the challenges for a transitioning primary care for managing people with MLTCs in one of India's states with a well-developed healthcare system.

Multimorbidity especially CMM is now a norm in clinical practise, especially in the elderly. Understanding the epidemiology and the patterns of multimorbidity becomes crucial for therapy, prevention and for policy-makers and planners. Pathways to multimorbid conditions are often shared, making its identification crucial for effective prevention. Multimorbidity also needs be assessed with a different therapeutic lens for both medications and in the context of morbidity measures. Certain common patterns of multimorbidity would add to disability weights of more than 1 which represents deaths. It makes a case of assigning commoner dyads and triads a disability weight with multimorbidity rather than for the individual conditions. These, and the pathways to multimorbidity need be explored more deeply so as to ensure a more personalised/customised care and not therapy for individual morbid conditions.

Author contributions

JM: Conceptualization, Writing – original draft, Writing – review & editing. SP: Conceptualization, Writing – review & editing, Writing – original draft.

Conflict of interest

The author(s) declared that this work 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 body roundness index with cardiovascular disease in patients with cardiometabolic syndrome: a cross-sectional study based on NHANES 2009-2018

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Background: Cardiometabolic syndrome (CMS), marked by abdominal obesity and metabolic dysregulation, is associated with a heightened risk of cardiovascular disease (CVD). Compared to the traditional anthropometric predictors represented by body mass index (BMI) and waist circumference (WC), body roundness index (BRI) appears to provide a more accurate reflection of the abdominal fat distribution associated with metabolic diseases. Therefore, this study intends to investigate the association of BRI with the risk of CVD and its components including congestive heart failure (CHF), coronary heart disease (CHD), angina, heart attack, and stroke in patients with CMS. At the same time, we hypothesized that BRI would identify CVD better than BMI or WC.

Methods: Data from the 2009-2018 National Health and Nutrition Examination Survey (NHANES). Logistic regression models were mainly utilized to evaluate the relationship between BRI and CVD in patients with CMS, including smooth curve analysis, threshold effects analysis, subgroup analysis and multiple imputation. In addition, receiver operating characteristic (ROC) curves were used to assess the ability of BRI to predict CVD.

Results: The logistic regression model showed a positive association between the BRI and CVD. The highest quartile of BRI (Q4) showing the strongest association with CVD. The smoothed curve revealed a linear relationship between BRI and CVD, but a U-shaped association between the BRI and CHF. For CVD, stratified analyses did not show significant difference between strata. For CHF, BMI interacted with the association, with BRI being associated with decreased risk of CHF in a subgroup of normal weight subjects and increased risk of CHF in a subgroup of obese subjects. The multiple imputation further confirmed the robustness of these results. Additionally, the ROC curve

indicated that BRI, BMI and WC had predictive power for CVD and CHF (AUC > 0.05). BRI has similar predictive power to WC but better than BMI.

Conclusions: An elevated BRI is associated with a heightened risk of CVD in patients with CMS. BRI has similar ability to predict CVD and CHF as WC, but superior to BMI.

KEYWORDS

cardiometabolic syndrome, cardiovascular disease, body roundness index, NHANES, obesity

Introduction

Cardiovascular disease (CVD) is recognized as a significant public health concern due to its high prevalence, morbidity, and mortality rates globally (1, 2). The global burden of CVD is expected to increase, primarily driven by an aging population (3). A study examining the global burden of disease from 1990 to 2019 noted a rise in CVD cases from 271 million to 523 million, along with a marked increase in mortality rates (4). Cardiometabolic factors make one of the major contributors to the risk of CVD. Hypertension, hyperlipidemia, diabetes and obesity are modifiable metabolic risk factors for CVD (5, 6). Hence, it is important to identify and screen people at risk for CVD at an early stage, especially those with metabolic risk factors, and to implement timely interventions.

Cardiometabolic syndrome (CMS) serves as a significant risk factor for CVD. It contributes to heightened cardiovascular and all-cause mortality rates (7). CMS is defined by abdominal obesity, hypertension, increased triglycerides, reduced levels of high-density lipoprotein cholesterol (HDL-C), and glucose intolerance (8, 9). Typically, the diagnosis of CMS demands the existence of at least three of these risk factors. As the population ages, the global metabolic risk is rising, leading to an increased prevalence of CMS between 1999 and 2018 (10), the prevalence of CMS among American adults rose from 28.23% to 37.09%, suggesting a deterioration in cardiometabolic health status (11). Alarmingly, merely 6.8% of adults preserve optimal cardiometabolic well-being (12). It is widely recognized that excessive obesity, particularly centripetal obesity, independently intensifies a multitude of metabolic risk factors for CVD, including the induction of dyslipidemia, increased blood pressure, hyperglycemia, insulin resistance (IR), and systemic inflammation (5, 13). Obesity may also lead to an increased risk of cardio-metabolic disease in children and adolescents (14).

Obesity is identified as a primary contributor to the burden of CMS (11, 15, 16). Moreover, the incidence of CVD is significantly higher in obese people, and the excessive accumulation of body fat leads to the development of CVD by inducing an inflammatory response and increasing oxidative stress (17). Obesity is increasingly being used to identify people at risk for cardiovascular risk factors, and notably abdominal obesity is a strong risk factor for CVD. Thomas proposed a novel body roundness index (BRI) that estimates the rate of visceral fat to total body fat by combining waist circumference (WC) and height data (18). Traditional research methods frequently depend on indicators like body mass index (BMI) and WC for the identification and management of obesity (19, 20). However, they all have certain limitations. Compared with BMI and WC, BRI seems to reflect abdominal obesity more accurately and effectively predict obesity-related metabolic chronic diseases (21). The study by Lucas et al. confirmed that metabolically unhealthy/obese individuals present a higher risk of developing CVD compared to metabolically healthy/obese individuals (22). BRI can significantly identify the presence of CMS (23). At the same time, BRI is a valid predictor of the risk of CVD (24). A cohort study in China found that individuals with intermediate and high BRI levels had a 22% and 55% higher risk of experiencing cardiovascular events, respectively, compared to those with low BRI (25). However, the relationship between BRI and the risk of CVD in patients with CMS in the United States (U.S.) remains underexplored. The above suggests that it would be positive to further explore the relationship between BRI and the occurrence of CVD among CMS patients.

Therefore, this study intends to investigate the association of BRI with the risk of CVD and its components including congestive heart failure (CHF), coronary heart disease (CHD), angina, heart attack, and stroke in patients with CMS in the U.S. In addition, we assessed the ability of the BRI to identify CVD and its components in the U.S. population. We hypothesized that the BRI would identify CVD better than BMI or WC.

Materials and methods

Study design

This cross-sectional investigation employed data from the NHANES implemented in the U.S. NHANES is a research initiative of the Centers for Disease Control and Prevention (CDC). It is designed to evaluate the health and nutritional status of the American population by means of comprehensive interviews and physical examinations. This survey protocol was approved by

the Review Board of the National Center for Health Statistics (NCHS). All participants provided written informed consent. A detailed synopsis of the NHANES study and associated data can be found at https://www.cdc.gov/nchs/nhanes/.

Study population

The study encompassed subjects from the NHANES database covering the period from 2009 to 2018. These surveys offered extensive data on the BRI and multiple CVD, such as CHF, CHD, heart attack, angina, and stroke. Initially, 49,693 participants were included. After specific inclusion criteria were applied to filter the data, resulting in the exclusion of participants who met any of the following criteria: (1) age < 20 years; (2) missing data on height and WC data; (3) not diagnosed with CMS; (4) missing questionnaire data related to CVD; (5) missing data of covariates. Ultimately, a total of 6,640 subjects were included in the analysis (Figure 1).

Measurement of the body roundness index

The BRI was utilized as an exposure factor and calculated using the following equation (18): BRI = 364.2 - 365.5 × (1- [WC (m)/ $2\pi]^2$/[0.5 × height (m)]^2)^{½}. Waist circumference and height can be found in the body measurements of the examination data.

Measurement of cardiovascular disease

Data on cardiovascular conditions were obtained from the medical conditions section identified by the variable name prefix MCQ. This variable includes both self-reported and proxy-reported information that is collected through personal interviews regarding various health issues and histories for both children and adults. This section includes questions about whether a physician has diagnosed the participant with specific conditions, such as angina, congestive heart failure (CHF), coronary heart disease (CHD), heart attack, and stroke. Participants who responded 'yes' to these inquiries were categorized as having a history of CVD. We defined a composite endpoint for CVD. This endpoint included angina, congestive heart failure (CHF), coronary heart disease (CHD), heart attack, and stroke as primary outcomes. Meanwhile, the events related to these diseases were analyzed separately as secondary outcomes.

Measurement of cardiometabolic syndrome

The diagnostic criteria for CMS were founded on the guidelines of the National Cholesterol Education Project (NCEP) Adult Treatment Panel III (ATP III) (9). CMS is characterized by the occurrence of three or more of the following conditions: (1) WC ≥ 102 cm for men and ≥ 88 cm for women; (2) Elevated serum TG ≥ 150 mg/dL; (3) HDL-C < 40 mg/dL for men and < 50 mg/dL for women; (4) Elevated fasting blood glucose ≥ 110 mg/dL; (5) Elevated blood pressure is defined as having a systolic blood pressure (SBP) of at least 130 mmHg or a diastolic blood pressure (DBP) of at least 85 mmHg, or for individuals who are currently taking oral antihypertensive medications. WC was collected using standard procedures during the physical examination. SBP and DBP were calculated as the arithmetic mean of up to four repeated measurements for each participant. TG and HDL-C were measured in serum, while fasting glucose was measured in plasma.

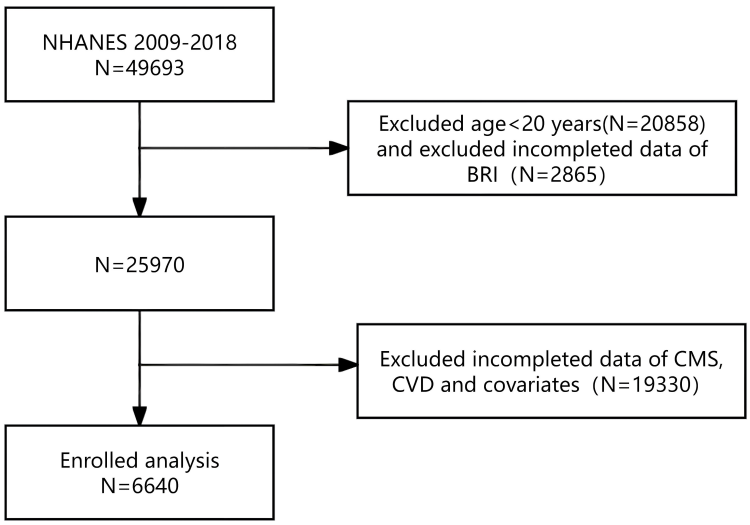

FIGURE 1
Screening flow of respondents.

Covariates

The covariates included in the analyses were age, sex, ethnicity, educational level, smoking status, diabetes, hypertension, BMI, SBP, and DBP. Laboratory test data comprised serum creatinine (SCR), serum uric acid (SUA), total cholesterol (TC), and HDL-C. Participants' age were categorized as < 60 years and ≥ 60 years. Ethnicity classifications included Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Others. Educational attainment was categorized into three groups: below high school, high school or general educational development (GED), and above high school. Smoking status was classified as never smoked, previously smoked, and currently smoking; BMI was further categorized into normal, overweight, and obese groups. Hypertension was defined as a medical diagnosis of hypertension, intake of blood pressure-lowering drugs, or a sequence of three or more readings with systolic pressure at least 130 mmHg or diastolic pressure at least 80 mmHg (26). Diabetes mellitus defined as medically diagnosed or oral hypoglycemic drugs or insulin use. Each participant in the study received 3-4 blood pressure readings, and the blood pressure recordings represent the average of the readings.

Statistical analysis

Participants were divided into quartiles (Q1 - Q4) according to their BRI values for analysis. Categorical variables were expressed as frequencies (percentages). Comparisons among groups were conducted using the chi-square test. Continuous variables were presented as mean ± standard deviation (SD). Evaluation was carried out using the t-test.

Multivariate logistic regression models were utilized to assess the connection between BRI and the primary outcome of CVD, as well as secondary outcomes including angina, CHF, CHD, heart attack, and stroke. Odds ratios (ORs) were calculated through three models. Model 1 had no adjustments made. Model 2 was adjusted for age, gender, and race. Model 3 included adjustments for age, gender, and race, education level, smoking status, diabetes, hypertension, BMI, SBP, and DBP. A generalized additive model (GAM) was employed for smooth curve fitting to examine potential non-linear associations between BRI and CVD. If the relationship was nonlinear, we estimated the threshold value and selected the infection point with the highest likelihood. Additionally, stratified logistic regression models were conducted to analyze subgroups based on age, sex, race, hypertension, diabetes, and BMI, with interaction tests employed to assess any variations in subgroup relationships. We reassessed the robustness of the results by multiple imputation for missing covariates mainly including HDL-C, TC, SCR, SUA, and BMI. Receiver operating characteristic (ROC) curves were used to assess the ability of BRI, WC and BMI in predicting CVD. Statistical analyses were carried out using R (version 4.4.1) and EmpowerStats (version 2.0). Statistical significance was defined as $P < 0.05$.

Results

Baseline characteristics of study participants

The study included 6,640 participants diagnosed with CMS, categorized according to BRI quartiles, as detailed in Table 1. The participants had a mean age of 56.72 ± 15.09 years, with females comprising 53.57% of the sample. The average BRI was 7.17± 2.27. The overall prevalence of CVD was 18.09%. This prevalence increased significantly as one moved across higher quartiles of BRI. Quartiles of higher BRI were linked with an elevated incidence of CHF, heart attack and stroke.

Obvious differences were detected among quartiles of BRI in terms of age, gender, race, education level, BMI, DBP, SCR, SUA, TC, smoking status, hypertension, diabetes, CHD, angina, and heart attack ($P < 0.05$). Participants in the highest quartile of BRI were more likely to have hypertension, diabetes, a higher obesity rate, and elevated SUA levels compared to those in the lowest quartile of BRI. No significant difference were found regarding SBP, HDL-C, or stroke among the quartiles.

Association between BRI and the risk of CVD

Logistic regression analysis

Logistic regression analysis was carried out to assess the connection between BRI and both the primary outcome of CVD as well as secondary outcomes such as CHF, CHD, angina, heart attack, and stroke. The results from the three multivariate logistic regression models are presented in Table 2.

A consistent positive association was observed between elevated BRI levels and the heightened likelihood of CVD. In Model 1, without any adjustments, each 1-unit increase in BRI was associated with a 8% increase in the prevalence of CVD among participants with CMS (OR = 1.08, 95% CI 1.05 - 1.11, $P < 0.0001$). This relationship remained significant after adjustments for age, sex, and race in Model 2 (OR = 1.14, 95% CI 1.11 - 1.18, $P < 0.0001$), and further adjustments in Model 3, which accounted for age, gender, race, education level, BMI, SBP, DBP, smoking status, hypertension, diabetes (OR = 1.11, 95% CI 1.07 - 1.15, $P < 0.0001$). In the fully adjusted model 3, participants in the highest BRI quartile showed a 75% greater risk of CVD (OR = 1.75, 95% CI 1.31 - 2.33, $P = 0.0001$) compared to those in the lowest quartile of BRI.

No significant correlations were found for CHD, angina, heart attack, and stroke. (Table 2). Our investigation revealed a positive association between the BRI and an increased probability of the prevalence CHF among participants with CMS. In our unadjusted model 1, each 1-unit increase in BRI was associated with a 13% increase in the risk of CHF (OR = 1.13, 95% CI 1.09 - 1.17, $P < 0.0001$). This relationship remained significant after adjustments for age, sex, and race in Model 2 (OR = 1.19, 95%CI 1.14 - 1.25, $P < 0.0001$), and further

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TABLE 1 Baseline characteristics of the study population.

Characteristics	BRI Index					
	Total	Q1	Q2	Q3	Q4	*P*-value
	n=6640	n=1660	n=1660	n=1659	n=1661	
Age (years)	56.72 ± 15.09	55.80 ± 15.21	58.01 ± 14.87	57.87 ± 15.25	55.21 ± 14.84	<0.001
Age group (years,%)						**<0.001**
<60	3414 (51.42)	913 (55.00)	804 (48.43)	779 (46.96)	918 (55.27)	
>=60	3226 (48.58)	747 (45.00)	856 (51.57)	880 (53.04)	743 (44.73)	
Gender (%)						**<0.001**
Male	3083 (46.43)	909 (54.76)	872 (52.53)	736 (44.36)	566 (34.08)	
Female	3557 (53.57)	751 (45.24)	788 (47.47)	923 (55.64)	1095 (65.92)	
Race (%)						**<0.001**
Mexican American	1104 (16.63)	201 (12.11)	324 (19.52)	294 (17.72)	285 (17.16)	
Other Hispanic	752 (11.33)	156 (9.40)	214 (12.89)	209 (12.60)	173 (10.42)	
Non-Hispanic White	2736 (41.20)	697 (41.99)	641 (38.61)	686 (41.35)	712 (42.87)	
Non-Hispanic Black	1397 (21.04)	322 (19.40)	316 (19.04)	351 (21.16)	408 (24.56)	
Other Race	651 (9.80)	284 (17.11)	165 (9.94)	119 (7.17)	83 (5.00)	
Education level (%)						**<0.001**
Less than high school	1881 (28.33)	412 (24.82)	501 (30.18)	526 (31.71)	442 (26.61)	
high school/GED	1589 (23.93)	395 (23.80)	394 (23.73)	380 (22.91)	420 (25.29)	
More than high school	3170 (47.74)	853 (51.39)	765 (46.08)	753 (45.39)	799 (48.10)	
BMI	33.27 ± 6.78	27.11 ± 2.94	30.45 ± 2.78	33.95 ± 3.30	41.58 ± 6.43	<0.001
BMI (%)						**<0.001**
Normal weight(<25)	417 (6.28)	384 (23.13)	32 (1.93%)	1 (0.06)	0 (0.00)	
Overweight (25~30)	1879 (28.30)	1001 (60.30)	706 (42.53)	165 (9.95)	7 (0.42)	
Obesity (>30)	4344 (65.42)	275 (16.57)	922 (55.54)	1493 (89.99)	1654 (99.58)	
SBP (mmHg)	131.90 ± 18.47	131.66 ± 17.98	132.42 ± 18.86	131.49 ± 18.38	132.02 ± 18.66	0.654
DBP (mmHg)	72.66 ± 12.80	73.50 ± 12.59	72.66 ± 12.43	72.51 ± 12.49	71.97 ± 13.62	0.002
SCR (mg/dL)	0.94 ± 0.49	0.94 ± 0.40	0.96 ± 0.65	0.94 ± 0.50	0.90 ± 0.37	0.005
SUA (umol/L)	351.03 ± 89.54	340.83 ± 88.59	345.55 ± 86.19	351.82 ± 87.30	365.92 ± 93.94	<0.001
TC (mg/dL)	192.10 ± 44.90	198.54 ± 49.00	192.35 ± 43.43	191.39 ± 44.15	186.13 ± 41.89	<0.001
HDL-C (mg/dL)	44.95 ± 13.24	45.28 ± 15.11	45.27 ± 12.92	44.84 ± 12.79	44.41 ± 11.94	0.486
Smoking status (%)						**<0.001**
Never	3436 (51.75)	850 (51.20)	861 (51.87)	861 (51.90)	864 (52.02)	
Former	1938 (29.19)	432 (26.02)	507 (30.54)	495 (29.84)	504 (30.34)	
now	1266 (19.07)	378 (22.77)	292 (17.59)	303 (18.26)	293 (17.64)	

(Continued)

10.3389/fendo.2025.1524352

TABLE 1 Continued

Characteristics	BRI Index					
	Total	Q1	Q2	Q3	Q4	*P*-value
Hypertension (%)						<0.001
Yes	4296 (64.70)	953 (57.41)	1078 (64.94)	1096 (66.06)	1169 (70.38)	
No	2344 (35.30)	707 (42.59)	582 (35.06)	563 (33.94)	492 (29.62)	
Diabetes (%)						<0.001
Yes	2169 (32.67)	390 (23.49)	519 (31.27)	592 (35.68)	668 (40.22)	
No	4471 (67.33)	1270 (76.51)	1141 (68.73)	1067 (64.32)	993 (59.78)	
CVD (%)						<0.001
Yes	1201 (18.09)	236 (14.22)	268 (16.14)	324 (19.53)	373 (22.46)	
No	5439 (81.91)	1424 (85.78)	1392 (83.86)	1335 (80.47)	1288 (77.54)	
CHF (%)						<0.001
Yes	403 (6.07)	69 (4.16)	78 (4.70)	106 (6.39)	150 (9.03)	
No	6237 (93.93)	1591 (95.84)	1582 (95.30)	1553 (93.61)	1511 (90.97)	
CHD (%)						0.001
Yes	475 (7.15)	85 (5.12)	117 (7.05)	137 (8.26)	136 (8.19)	
No	6165 (92.85)	1575 (94.88)	1543 (92.95)	1522 (91.74)	1525 (91.81)	
Angina (%)						<0.001
Yes	299 (4.50)	53 (3.19)	62 (3.73)	93 (5.61)	91 (5.48)	
No	6341 (95.50)	1607 (96.81)	1598 (96.27)	1566 (94.39)	1570 (94.52)	
Heart attack (%)						0.003
Yes	479 (7.21)	94 (5.66)	107 (6.45)	137 (8.26)	141 (8.49)	
No	6161 (92.79)	1566 (94.34)	1553 (93.55)	1522 (91.74)	1520 (91.51)	
Stroke (%)						0.072
Yes	394 (5.93)	77 (4.64)	102 (6.14)	105 (6.33)	110 (6.62)	
No	6246 (94.07)	1583 (95.36)	1558 (93.86)	1554 (93.67)	1551 (93.38)	

BRI, Body roundness index; GED, General educational Development; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; SCR, Serum creatinine; SUA, Serum uric acid; TC, Total cholesterol; HDL-C, High-density lipoprotein cholesterol; CVD, Cardiovascular disease; CHF, Congestive heart failure; CHD, Congestive heart disease.

adjustments in Model 3, which accounted for age, gender, race, education level, BMI, SBP, DBP, smoking status, hypertension, diabetes (OR = 1.15, 95% CI 1.08 - 1.21, $P < 0.0001$). After classifying the BRI into four quartiles, a significant statistical relationship was still observed. In comparison to individuals in the lowest quartile of BRI, those in the highest BRI quartile showed a 82% greater risk of CHF (Model 3: OR = 1.82, 95% CI 1.15 - 2.87, $P = 0.0102$).

Multiple imputation indicated that BRI remained positively associated with the risk of CVD and CHF in CMS patients, demonstrating robust results (Supplementary Tables S1).

Smooth curve analysis

We conducted a smoothed curve-fitting analysis using GAM, which indicated that the BRI was linearly associated with the risk of CVD in CMS patients (Figure 2). However, the association between BRI and CHF were revealed to be a U-shaped association (Figure 3). And then, the threshold effects analysis showed a BRI cut-off of 4.53 units, and showed that when the BRI level was lower than 4.53, the prevalence of CHF decreased by 58% for every 1-unit decrease in BRI (OR = 0.42, 95% CI 0.22 - 0.79, $P = 0.0072$), but after this inflection point, the prevalence of CHF increased by 16% for every 1-unit increase in BRI (OR = 1.16, 95% CI 1.09 - 1.22, $P < 0.0001$) (Table 3).

Subgroup analysis

Stratification and interaction analysis were conducted for age, gender, race, hypertension, diabetes and BMI to further investigate the association between BRI and the risk of CVD and CHF among CMS patients. Table 4 and Table 5 demonstrated that the relationship between BRI and CVD was consistent across the

TABLE 2 The association between the BRI index and the risk of CVD.

Characteristic	Model 1		Model 2		Model 3	
	(OR95%CI)	*p*	(OR95%CI)	*p*	(OR95%CI)	*p*
CVD						
Continuous BRI	1.08 (1.05, 1.11)	**<0.0001**	1.14 (1.11, 1.18)	**<0.0001**	1.11 (1.07, 1.15)	**<0.0001**
BRI index quartile						
Q1	Reference		Reference		Reference	
Q2	1.16 (0.96, 1.40)	0.1219	1.08 (0.88, 1.32)	0.4682	1.02 (0.81, 1.29)	0.8781
Q3	1.46 (1.22, 1.76)	<0.0001	1.42 (1.17, 1.73)	0.0004	1.27 (0.97, 1.67)	0.0862
Q4	1.75 (1.46, 2.09)	<0.0001	2.13 (1.76, 2.59)	<0.0001	1.75 (1.31, 2.33)	**0.0001**
P for trend		<0.0001		<0.0001		**<0.0001**
CHF						
Continuous BRI	1.13 (1.09, 1.17)	**<0.0001**	1.19 (1.14, 1.25)	**<0.0001**	1.15 (1.08, 1.21)	**<0.0001**
BRI index quartile						
Q1	Reference		Reference		Reference	
Q2	1.14 (0.82, 1.58)	0.4479	1.04 (0.74, 1.46)	0.8110	0.93 (0.63, 1.38)	0.7311
Q3	1.57 (1.15, 2.15)	0.0043	1.48 (1.07, 2.03)	0.0166	1.15 (0.74, 1.79)	0.5293
Q4	2.29 (1.71, 3.07)	<0.0001	2.62 (1.93, 3.55)	<0.0001	1.82 (1.15, 2.87)	**0.0102**
P for trend		<0.0001		<0.0001		**<0.0001**
CHD						
Continuous BRI	1.05 (1.01, 1.09)	0.0113	1.13 (1.08, 1.18)	<0.0001	1.06 (1.00, 1.12)	0.0694
BRI index quartile						
Q1	Reference		Reference		Reference	
Q2	1.41 (1.05, 1.87)	0.0207	1.28 (0.95, 1.72)	0.1109	1.14 (0.81, 1.61)	0.4537
Q3	1.67 (1.26, 2.21)	0.0003	1.60 (1.19, 2.14)	0.0017	1.30 (0.87, 1.93)	0.1970
Q4	1.65 (1.25, 2.19)	0.0004	2.07 (1.54, 2.79)	<0.0001	1.46 (0.96, 2.23)	0.0797
P for trend		0.0008		<0.0001		0.0755
Angina						
Continuous BRI	1.08 (1.03, 1.13)	0.0011	1.12 (1.06, 1.18)	<0.0001	1.03 (0.97, 1.11)	0.3457
BRI index quartile						
Q1	Reference		Reference		Reference	
Q2	1.18 (0.81, 1.71)	0.3935	1.11 (0.76, 1.62)	0.5981	0.86 (0.56, 1.31)	0.4752
Q3	1.80 (1.28, 2.54)	0.0008	1.71 (1.21, 2.43)	0.0027	1.11 (0.69, 1.78)	0.6771
Q4	1.76 (1.24, 2.48)	0.0014	1.92 (1.35, 2.73)	0.0003	1.08 (0.65, 1.79)	0.7708
P for trend		0.0004		<0.0001		0.5331
Heart attack						
Continuous BRI	1.05 (1.01, 1.09)	0.0141	1.11 (1.07, 1.16)	<0.0001	1.05 (0.99, 1.11)	0.1101
BRI index quartile						
Q1	Reference		Reference		Reference	
Q2	1.15 (0.86, 1.53)	0.3444	1.05 (0.79, 1.42)	0.7215	0.96 (0.68, 1.35)	0.8052

(Continued)

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TABLE 2 Continued

Characteristic	Model 1		Model 2		Model 3	
	(OR95%CI)	*p*	(OR95%CI)	*p*	(OR95%CI)	*p*
BRI index quartile						
Q3	1.50 (1.14, 1.97)	0.0035	1.48 (1.12, 1.96)	0.0065	1.16 (0.78, 1.71)	0.4678
Q4	1.55 (1.18, 2.03)	0.0016	1.92 (1.44, 2.54)	<0.0001	1.32 (0.88, 2.00)	0.1799
P for trend		0.0006		<0.0001		0.0657
Stroke						
Continuous BRI	1.03 (0.99, 1.08)	0.1574	1.05 (1.00, 1.10)	0.0526	1.02 (0.96, 1.09)	0.4412
BRI index quartile						
Q1	Reference		Reference		Reference	
Q2	1.35 (0.99, 1.82)	0.0555	1.29 (0.95, 1.76)	0.1037	1.48 (1.02, 2.15)	0.0379
Q3	1.39 (1.03, 1.88)	0.0331	1.30 (0.95, 1.77)	0.0966	1.44 (0.93, 2.23)	0.0987
Q4	1.46 (1.08, 1.97)	0.0136	1.49 (1.10, 2.03)	0.0111	1.54 (0.97, 2.44)	0.0647
P for trend		0.0278		0.0190		0.2428

Model 1: No adjustment.
Model 2: Adjusted for age, gender, race.
Model 3: Adjusted for age, gender, race, education level, BMI, SBP, DBP, smoking status, hypertension, diabetes.
OR, odds ratio; 95%CI, 95% Confidence interval.
Bold value indicates the statistical significance.

various subgroups. There was no significant interaction effect between BRI and stratified variables (*P* for interaction > 0.05). Notably, BMI interacted with the association (*P* for interaction = 0.0118), with BRI being associated with decreased risk of CHF in a subgroup of normal weight subjects (OR = 0.45, 95% CI 0.24 - 0.86, *P* = 0.0154) and increased risk of CHF in a subgroup of obese subjects (OR = 1.16, 95% CI 1.10 - 1.23, *P* = 0.0154). Age, gender, race, hypertension, and diabetes did not influence the association (*P* for interaction > 0.05).

BRI as a predictor for CVD and CHF

Figures 4 and 5 showed the area under the curve (AUC) of diagnostic capability in the CVD and CHF. These results revealed that both BRI, WC and BRI had statistically significant diagnostic capability for the detection of CVD and CHF (AUC > 0.5). BRI has diagnostic capability in detecting CVD and CHF Superior to BMI (for CVD: AUC = 0.563, for CHF: AUC = 0.594), but not better than WC (for CVD: AUC = 0.564, for CHF: AUC = 0.599).

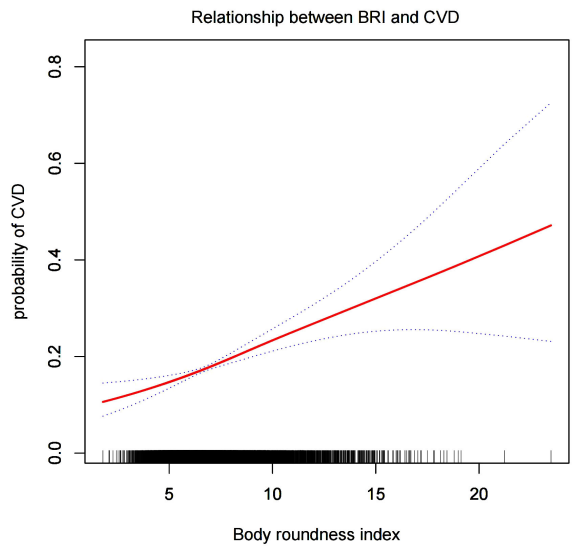

FIGURE 2
The smooth curve analysis between the BRI and the risk of CVD.

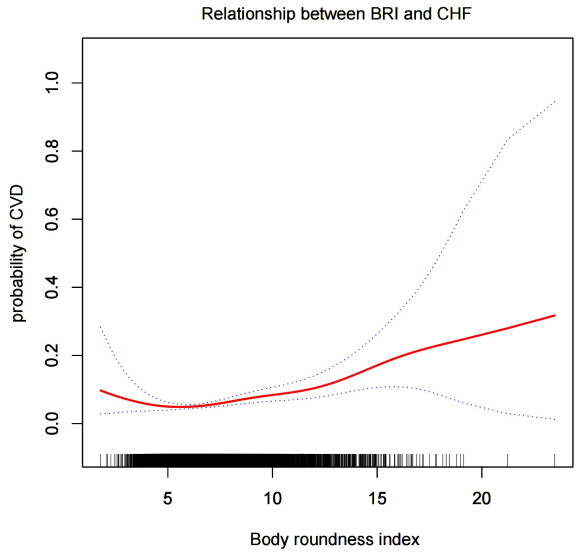

FIGURE 3
The smooth curve analysis between the BRI and the risk of CHF.

Discussion

This study, which encompassed 6,640 participants, detected a positive correlation between a high BRI and an elevated risk of CVD among adults with CMS in the U.S.

Additionally, our results reveal a nonlinear relationship between BRI and CVD risk, whereas a u-shaped correlation was observed with the risk of CHF. When the BRI level was lower than 4.53, the risk of CHF decreased by 58% for every 1-unit decrease in BRI, but after this inflection point, the risk increased by 16% for every 1-unit increase in BRI. The association between BRI and CVD was consistent across subgroups and there was no significant interaction. However, BMI interacted with the association, with BRI being associated with decreased risk of CHF in a subgroup of normal weight subjects and increased risk of CHF in a subgroup of obese subjects. Multiple imputation suggests proof of the robustness of the findings. More importantly, BRI has similar ability to predict CVD and CHF as WC, and better than BMI.

Previous studies have focused on the potential role of BRI in cardiovascular disease morbidity and mortality or cardiometabolic risk factors (23, 25, 27). BRI has been shown to be a valid predictor of cardiometabolic risk and is significantly associated with cumulative cardiometabolic risk factors (23, 27, 28). Cohort studies in China have shown that a long-term increase in BRI is associated with an increased risk of CVD, stroke, or cardiac events (25, 29). Moreover, Li et al. demonstrated that the BRI was superior to other anthropometric measures, including waist circumference, in predicting the risk of cardiovascular disease in a Chinese population (24). However, Maessen et al. showed that the BRI was not superior as a novel body metric for identifying CVD compared to established anthropometric measures such as BMI and WC (30). Higher WC is associated with an increased risk of CVD, and the positive association between WC and new myocardial infarction and stroke has been shown to be higher in individuals <60 years of age (31). Our conclusions are consistent with previous studies that a higher BRI is associated with an increased risk of CVD. Also, BRI predicted CVD similarly to WC but better than BMI. Unusually, we also found a U-shaped association between BRI and CHF in participants evaluated for CMS, which has not been found in previous studies. This may be since previous studies focused on cardiovascular diseases such as stroke and myocardial infarction. However, the low prevalence of CHF in this study encourages future studies to further explore the potential nonlinear association between BRI and CHF. In addition, our study found that BRI was associated with a reduced risk of CHF in a subgroup of normal-weight subjects and an increased risk of CHF in a subgroup of obese subjects. There is a complex link between BMI and CHF that may involve multiple aspects. Higher BMI may increase the risk of CHF through melatonin secretion and metabolism, reduced sleep quality, and reduced activity (32). In the Belgian cohort, patients in the high inositol level group (highest tertile) also had a higher BMI, predicting poor clinical outcomes in heart failure patients with preserved ejection fraction (HFpEF) (33). This may be related to IR or other metabolic disorders due to obesity, which in turn affects inositol metabolism. This suggests that weight control may help reduce the risk of heart failure and improve prognosis. Another study suggested that machine learning algorithms may help to address the heterogeneity of HFpEF patients and provide new directions for precision therapy (34). This deserves further exploration.

Traditional indicators like BMI and WC have limitations in clinical scenarios. BMI does not distinguish between fat, muscle, and bone mass. Meanwhile, WC measures abdominal fat without taking height into consideration, resulting in potential misclassification of obesity in individuals with different heights (35). In contrast, the BRI uses an ellipsoid model to assess body size by integrating waist circumference and height independent of body

TABLE 3 Analysis of the threshold effect between BRI and the risk of CHF.

Threshold effect analysis	CHF (OR95%CI) *P*-value
BRI	
Inflection point of BRI (K)	4.53
<K slope	0.42 (0.22, 0.79) 0.0072
>K slope	1.16 (1.09, 1.22) <0.0001
Log-likelihood ratio test	0.004

TABLE 4 Subgroup analysis for the association between BRI and CVD.

Subgroup	OR (95%CI)	*P*-value	*P* for interaction
Age			0.2933
<60	1.07 (1.02, 1.13)	0.0103	
≥60	1.12 (1.06, 1.18)	<0.0001	
Gender			0.4572
Male	1.13 (1.07, 1.19)	<0.0001	
Female	1.10 (1.05, 1.15)	<0.0001	
Race			0.6111
Mexican American	1.09 (0.97, 1.22)	0.1471	
Other Hispanic	1.19 (1.04, 1.35)	0.0114	
Non-Hispanic White	1.12 (1.06, 1.19)	0.0002	
Non-Hispanic Black	1.07 (1.00, 1.15)	0.0666	
Other Race	1.18 (0.99, 1.40)	0.0601	
Hypertension			0.8028
Yes	1.11 (1.06, 1.15)	<0.0001	
No	1.12 (1.02, 1.23)	0.0196	
Diabetes			0.7735
Yes	1.10 (1.05, 1.16)	0.0004	
No	1.12 (1.06, 1.18)	<0.0001	
BMI			0.6305
Normal weight	0.98 (0.67, 1.45)	0.9350	
Overweight	1.18 (1.00, 1.40)	0.0495	
Obesity	1.11 (1.07, 1.16)	<0.0001	

This analysis was adjusted for age, gender, race, education level, BMI, SBP, DBP, smoking status, hypertension, and diabetes.

10.3389/fendo.2025.1524352

weight, allowing for a more accurate representation of body fat as a proportion of total body weight (18). And it is critical for identifying health risks in individuals with an abnormal distribution of body fat (36). BRI effectively quantifies central obesity and is significantly associated with metabolic dysregulation, inflammatory response, vascular dysfunction, and oxidative stress, all of which can accelerate the progression of CVD (37). A study showed that the BRI performed similarly or better than BMI and WC in predicting CMS and CMS components in Peruvian adults, and showed the best ability to identify IR in obese and overweight populations (38). The mechanisms linking elevated BRI levels to increased CVD risk are not fully understood in patients with CMS. We will elaborate on the following aspects. First, previous cross-sectional studies have demonstrated a role for branched-chain amino acids (BCAAs) and lipid metabolism in the pathogenesis of type 2 diabetes mellitus (T2D) and coronary atherosclerotic heart disease (CAD), suggesting that obesity has an important role in the development of CVD (39). Secondly, the accumulation of excess body fat contributes to an inflammatory response in the blood and leads to oxidative stress, which increases the risk of CVD (17). This suggests that by calculating the BRI, we can identify the risk of metabolism in overweight and obese people at an early stage and reduce the risk of CVD by controlling weight and reducing fat accumulation. In recent years, an increasing number of studies have focused on the association between gut fungi and metabolism (40). This suggests that the relationship between gut fungi and other metabolic diseases, such as diabetes and cardiovascular disease, deserves further investigation. Kun et al. showed that gut fungi may affect CAD through mechanisms such as influencing immunity, metabolic processes, or systemic inflammation (41). Therefore, it is promising to develop interventional strategies based on gut fungi in

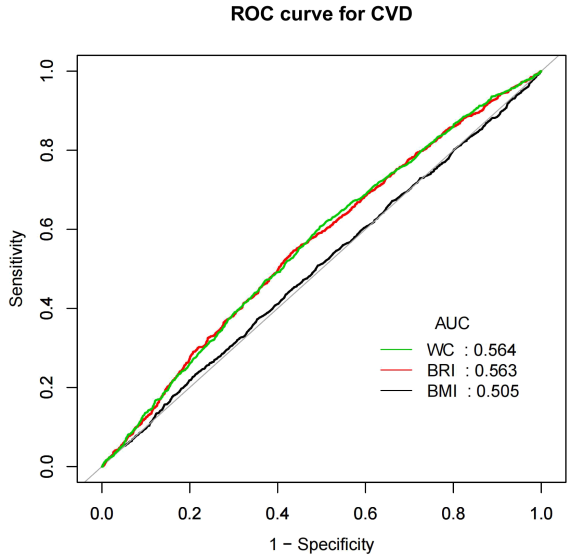

FIGURE 4
CVD, Cardiovascular disease; WC, Waist; BRI, Body roundness index; BMI, Body mass index; AUC, Area under the curve; ROC, Receiver operating characteristic.

TABLE 5 Subgroup analysis for the association between BRI and CHF.

Subgroup	OR (95%CI)	*P*-value	*P* for interaction
Age			0.6294
<60	1.12 (1.03, 1.21)	0.0098	
≥60	1.15 (1.07, 1.23)	0.0002	
Gender			0.5115
Male	1.17 (1.08, 1.26)	<0.0001	
Female	1.13 (1.06, 1.21)	0.0003	
Race			0.4228
Mexican American	1.09 (0.90, 1.32)	0.3599	
Other Hispanic	1.06 (0.88, 1.29)	0.5468	
Non-Hispanic White	1.17 (1.08, 1.26)	0.0002	
Non-Hispanic Black	1.12 (1.01, 1.24)	0.0303	
Other Race	1.40 (1.10, 1.78)	0.0060	
Hypertension			0.5639
Yes	1.15 (1.09, 1.22)	<0.0001	
No	1.08 (0.89, 1.32)	0.4400	
Diabetes			0.8127
Yes	1.14 (1.06, 1.22)	0.0004	
No	1.15 (1.06, 1.25)	0.0008	
BMI			0.0118
Normal weight	0.45 (0.24, 0.86)	0.0154	
Overweight	1.12 (0.85, 1.47)	0.4189	
Obesity	1.16 (1.10, 1.23)	<0.0001	

This analysis was adjusted for age, gender, race, education level, BMI, SBP, DBP, smoking status, hypertension, and diabetes.

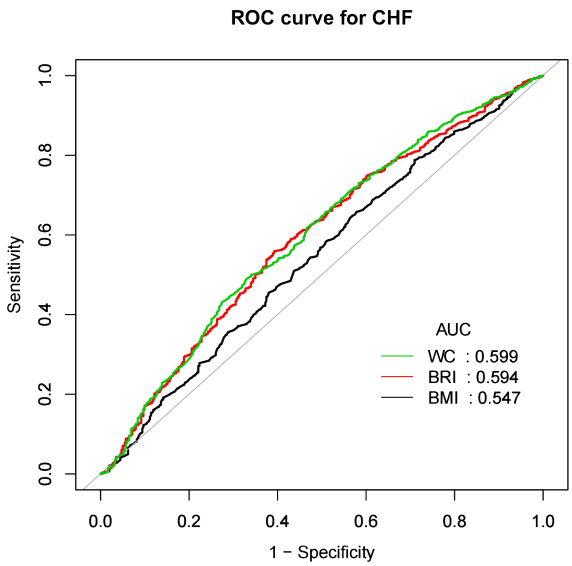

FIGURE 5
CHF, Congestive heart failure; WC, Waist; BRI, Body roundness index; BMI, Body mass index; AUC, Area under the curve; ROC, Receiver operating characteristic.

the future, e.g., by modulating the intestinal fungal community for the prevention and treatment of metabolic diseases.

Limitation

There are several limitations of our study. Firstly, being a cross-sectional study, it cannot establish a causal connection between BRI and the risk of CVD in patients with CMS. This design is unable to track changes in variables over time or recognize trends and dynamic patterns in time-series data, thus limiting its ability to assess long-term impacts and changes in time dynamics. In future studies, prospective cohort studies could be used to validate our findings. Secondly, diagnosis of CVD relied on participant self-reporting, but participants' lack of knowledge about cardiovascular disease could affect the accuracy of subsequent analyses. Thus, the BRI's ability to recognize CVD may be somewhat higher. In addition, the research sample is largely composed of subjects originating from the US., which limits the applicability of the findings to a worldwide context. Although we have strived to control for potential complicating variables, the likelihood of remaining confounding factors cannot be entirely ruled out (such as dietary habits and physical activity levels). Undocumented eating habits may affect body weight and fat distribution, which in turn affects BRI. Physical activity not only affects body weight and shape, but also directly affects cardiovascular health. Physical inactivity may lead to a higher risk of BRI and CVD, but this confounder may not be adequately captured in the NHANES data. Future studies should consider a more comprehensive assessment and adjustment of these potential confounders. Furthermore, we did not account for the influence of pharmacological treatments. Patients with CMS often experience multiple coexisting chronic diseases that necessitate antihypertensive, hypoglycemic, and lipid-lowering therapies. This could lead to a decrease in the number of patients we have diagnosed with CMS. Despite these limitations, this study highlights the association between BRI and the risk of cardiovascular disease in patients with CMS and paves the way for future longitudinal studies.

Conclusion

This study demonstrated the positive relationship between the BRI and CVD in individuals diagnosed with CMS. Notably, a U-shaped correlation was observed between BRI and the risk of CHF. Increased assessment of BRI would facilitate easier and more effective screening of individuals at risk for CHF. In addition, this threshold could be used as a target for interventions to reduce CHF risk. Future studies should further explore whether interventions targeting the BRI may improve the clinical prognosis of CMS patients with CVD.

Author contributions

XH: Conceptualization, Software, Validation, Visualization, Writing – original draft. JZ: Formal analysis, Software, Writing – original draft. WL: Data curation, Formal analysis, Writing – original draft. XY: Data curation, Visualization, Writing – original draft. WN: Methodology, Supervision, Writing – review & editing. ZZ: Supervision, Writing – review & editing. JC: Project administration, Supervision, Writing – review & editing. QH: Project administration, Resources, 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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1524352/full#supplementary-material

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Advancing early detection of organ damage and cardiovascular risk prevention: the Suzhou cardiometabolic health study protocol - exploring the role of oral microbiome and metabolic profiling in risk stratification

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Background: Cardiovascular Disease (CVD) is the leading cause of global mortality, with its incidence rate rising year by year due to the prevalence of metabolic diseases. Existing primary and secondary prevention strategies for cardiovascular disease have limitations in identifying some high-risk groups, and 1.5-level prevention aims to achieve more precise intervention by early identification of subclinical target organ damage. This study introduces oral (tongue coating) microbiota as metabolic markers for the first time, in combination with multiple metabolic factors, to explore their potential in assessing subclinical target organ damage and optimizing cardiovascular risk stratification, in order to provide a new path for the early identification and intervention of CVD.

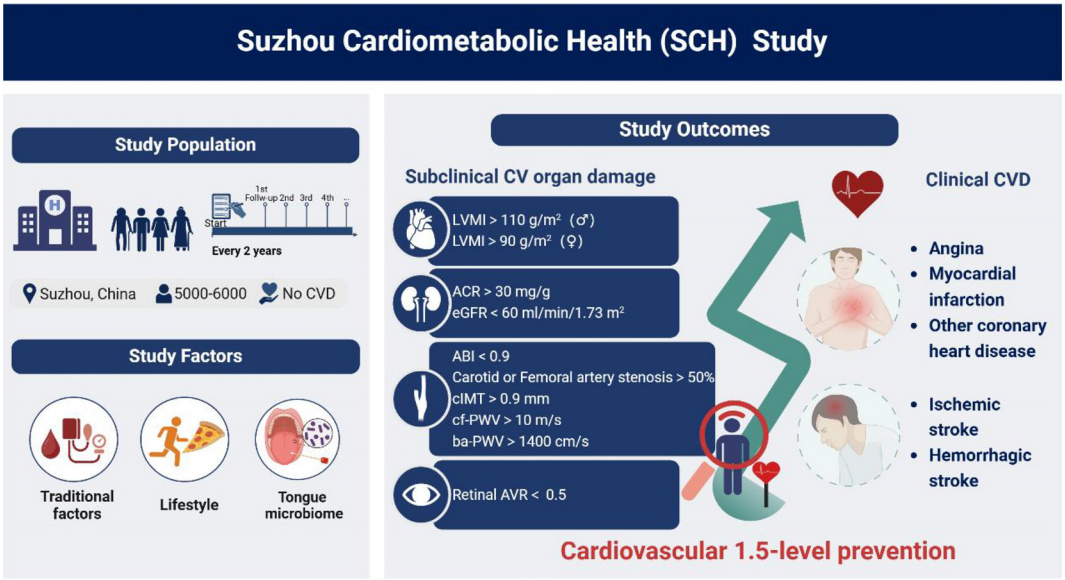
Methods: This study is a prospective cohort study aimed at assessing the association between tongue coating microbiota characteristics and multiple metabolic factors with subclinical target organ damage, and identifying high-risk groups suitable for cardiovascular 1.5-level prevention. The study will be conducted in Suzhou City, Jiangsu Province, China, planning to include 5000-6000 eligible subjects, with inclusion criteria of age ≥18 years, excluding individuals with a history of CVD and other serious diseases. Baseline assessment includes demographic information, lifestyle (including dietary patterns), medical history, physical examination, and collection of tongue coating microbiota samples. Subjects will be followed up every 2 years, with the primary outcome being the first occurrence of coronary heart disease and stroke, and the secondary outcome being subclinical target organ damage.

Discussion: This study focuses on cardiovascular 1.5-level prevention strategy, combining metabolic factors with tongue coating microbiota characteristics, aiming to optimize the risk assessment system for subclinical target organ damage. This approach can not only fill the gap in traditional risk assessment but also provide new ideas for the early identification and intervention of CVD. In the future, the feasibility and effectiveness of this strategy will be verified through multicenter studies, and it is expected to be promoted to a wider medical system, significantly improving the health management level of high-risk groups for CVD.

Trial registration number: http://itmctr.ccebtcm.org.cn, identifier ITMCTR2024000616.

KEYWORDS

cardiovascular disease, metabolic risk factors, subclinical target organ damage, oral microbiota, risk stratification



GRAPHICAL ABSTRACT

Introduction

Cardiovascular Disease (CVD) is the leading cause of death and disease burden worldwide (1). With the prevalence of metabolic diseases (such as diabetes, obesity, etc.) (2), the high incidence rate of CVD has become increasingly severe, and the relationship between the two has become closer (3, 4). Although primary and secondary prevention strategies for CVD have been widely applied in clinical practice, they still have significant deficiencies in comprehensively reducing the incidence of CVD (5). The current primary prevention has limited effectiveness in identifying high-risk and elderly populations, leading to many potential beneficiaries not receiving timely intervention, which is difficult to meet the needs of large-scale prevention (6, 7). In terms of secondary prevention, a large number of patients do not receive continuous and comprehensive management support after the first cardiovascular event, resulting in a high recurrence rate of myocardial infarction and stroke (8–10). This indicates that relying solely on existing prevention strategies is difficult to achieve comprehensive management of CVD, and new assessment and management methods are urgently needed to more accurately identify and intervene in potential cardiovascular risks.

Abbreviations: ASCVD, Atherosclerotic Cardiovascular Disease; CVD, Cardiovascular Disease; CKD, Chronic Kidney Disease; LVH, Left Ventricular Hypertrophy; PAD, Peripheral Arterial Disease.

In the progression of CVD, many patients have subclinical target organ damage at an early stage, such as left ventricular hypertrophy (LVH), microalbuminuria (MAU), and arteriosclerosis, which usually exist before clinical symptoms appear (11). Early organ damage not only significantly increases the risk of cardiovascular events but also has a profound impact on the long-term prognosis of patients (12, 13). However, the traditional CVD risk assessment system is difficult to effectively capture this period of damage, leading to inaccurate screening of high-risk individuals. Therefore, to fill the gap between primary and secondary prevention, the concept of cardiovascular 1.5-level prevention has emerged. The core of cardiovascular 1.5-level prevention is to identify and manage subclinical target organ damage, and reduce the risk of future cardiovascular events through earlier and more personalized intervention measures (14).

In recent years, with the increase of people with unhealthy lifestyles and the expansion of the base of metabolic abnormal patients, the potential risk factors for CVD have also become more complex (15, 16). Even if some individuals do not show typical metabolic risk factors, they may still face a higher risk of cardiovascular events (17). Therefore, we hope to establish a more comprehensive cardiovascular risk stratification system by integrating the assessment of multiple metabolic factors and subclinical target organ damage, providing a scientific basis for the identification of hidden high-risk groups.

This study innovatively introduces the tongue coating microbiota as a new type of metabolic marker, emphasizing its potential value in cardiovascular risk assessment. In recent years, the connection between the microbiota and systemic metabolic disorders has gradually attracted attention (18), and the composition, microbiota age, and metabolic state of the microbiota are closely related to various metabolic diseases and cardiovascular events (19). Among them, the oral microbiota can affect cardiovascular risk through multiple pathways such as inflammation, immune regulation, and endothelial dysfunction (20, 21), among which the tongue coating microbiota is conveniently sampled, and the characteristics of the tongue coating microbiota can distinguish and even predict the disease status of the human body (22, 23). Based on the above background, this study aims to investigate the novel concept of the oral microbiota, by measuring the diversity, abundance, relative proportion of specific microbiota, and their metabolic functions of the tongue coating microbiota, revealing the characteristics of the tongue coating microbiota in different age groups and metabolic states, and assessing its feasibility as a predictive biomarker for CVD risk.

To address the above challenges, we have launched the "Suzhou Cardiometabolic Health (SCH) Study" in the Suzhou area of China. This study is a large-scale prospective observational cohort study aimed at integrating tongue coating microbiota characteristics with multiple metabolic factors, systematically assessing their relationship with subclinical target organ damage, and constructing a multi-dimensional risk assessment model to optimize cardiovascular risk stratification. This model is expected to play a key role in the early identification and intervention of high-risk individuals, providing a scientific basis for the implementation of cardiovascular 1.5-level prevention and the formulation of individualized intervention strategies, promoting precise prevention and intervention of CVD (Figure 1).

Methods

Objectives

To explore the relationship between tongue coating microbiota characteristics and multiple metabolic factors and subclinical target organ damage, to optimize the risk stratification of CVD, and to provide a basis for the selection of 1.5-level prevention targets.

Study population

Inclusion criteria include (1): age ≥18 years; (2) voluntarily signing an informed consent form (3); capable of long-term follow-up.

Exclusion criteria include: (1) history of CVD, including coronary heart disease, heart failure, stroke, peripheral arterial disease; (2) severe liver and kidney dysfunction; (3) cancer or life expectancy <5 years; (4) pregnant or lactating women; (5) mental or cognitive disorders and other individuals who cannot cooperate; (6) those who have already participated in other clinical studies.

Recruitment

Recruitment is carried out in Suzhou City, Jiangsu Province, China, by full-time project personnel from Xiyuan Hospital Suzhou Hospital (Suzhou Hospital of Traditional Chinese Medicine). A combination of online and offline recruitment methods will be used to ensure the recruitment of participants in the widest range: (1) promote the study information and recruitment notices through social media platforms; (2) post recruitment posters at Xiyuan Hospital Suzhou Hospital (Suzhou Hospital of Traditional Chinese Medicine) and related community hospitals, detailing the purpose of the study, participation requirements, and contact information; (3) distribute recruitment flyers at resident committees and community activity centers, communicate directly with potential participants, and answer related questions.

Baseline assessment

Baseline assessment includes general data collection, physical examination, laboratory tests, imaging examinations, and collection of tongue coating microbiota samples (Figure 2). To standardize research methods and procedures, all researchers received training before the start of the study. The specific items are described below.

General data collection:

General data is collected using standardized questionnaires and face-to-face interviews, including socio-demographic information, lifestyle, medical history, and medication use.

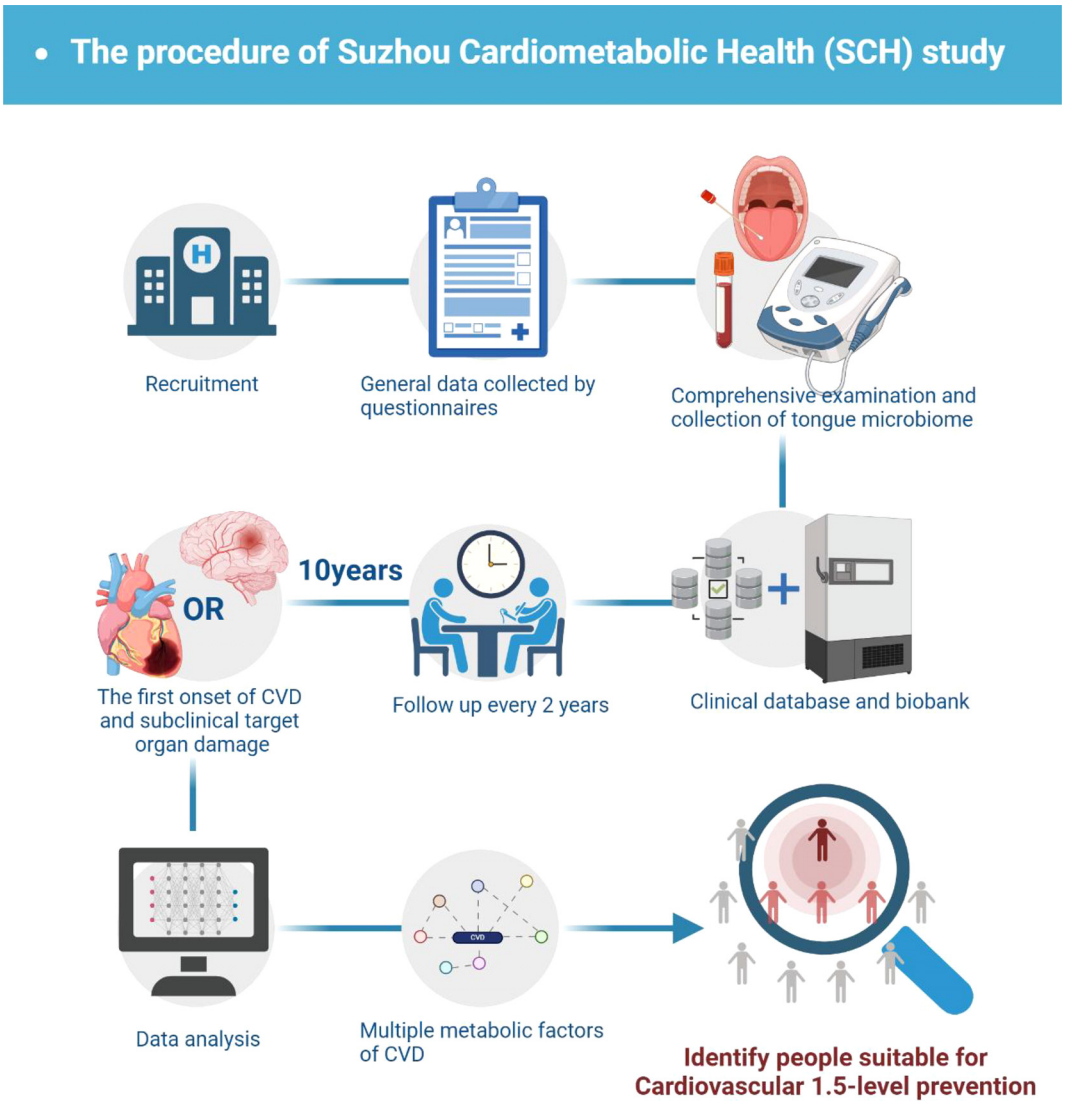


FIGURE 1
Study flowchart.

Socio-demographic information: including gender, age, race, marital status, education level, occupation, place of residence.

Lifestyle: collecting information on smoking, drinking, physical activity, sleep, and dietary patterns of subjects.

Smoking: divided into never smokers, former smokers, occasional smokers, and current regular smokers, with never smokers referring to those who do not smoke at the time of the baseline interview and have smoked less than 100 cigarettes in their lifetime; former smokers refer to those who have smoked at least 100 cigarettes but have quit smoking for at least 6 months at the time of the baseline interview; occasional smokers refer to those who do not meet the standard of never smokers and have not completely quit smoking for at least 6 months at the time of the baseline interview. Current regular smokers are those who smoke at least one cigarette a day for at least 6 months.

Drinking: divided into never drinkers, former drinkers, occasional drinkers, and current regular drinkers, with never drinkers referring to those who do not drink at the time of the baseline interview and have never had a continuous 6 months of weekly drinking in their lifetime; former drinking history refers to those who have had at least 6 months of weekly drinking of alcoholic beverages in the past but have abstained from alcohol for at least 6 months at the time of the baseline interview; occasional drinking history refers to those who do not meet the standard of never drinkers and have not completely quit drinking for at least 6 months at the time of the baseline interview; current regular drinkers are those who drink at least once a week for at least 6 months. Current regular drinkers are divided into excessive drinkers and non-excessive drinkers, with excessive drinking defined as at least 20g of alcohol per day for women and at least 40g for men.

Physical activity: the International Physical Activity Questionnaire Short Form (IPAQ-SF) is used to survey (24), asking individuals about their physical activities related to work, transportation, housework, and leisure in the past 7 days, as well as the frequency and daily cumulative time of physical activities of

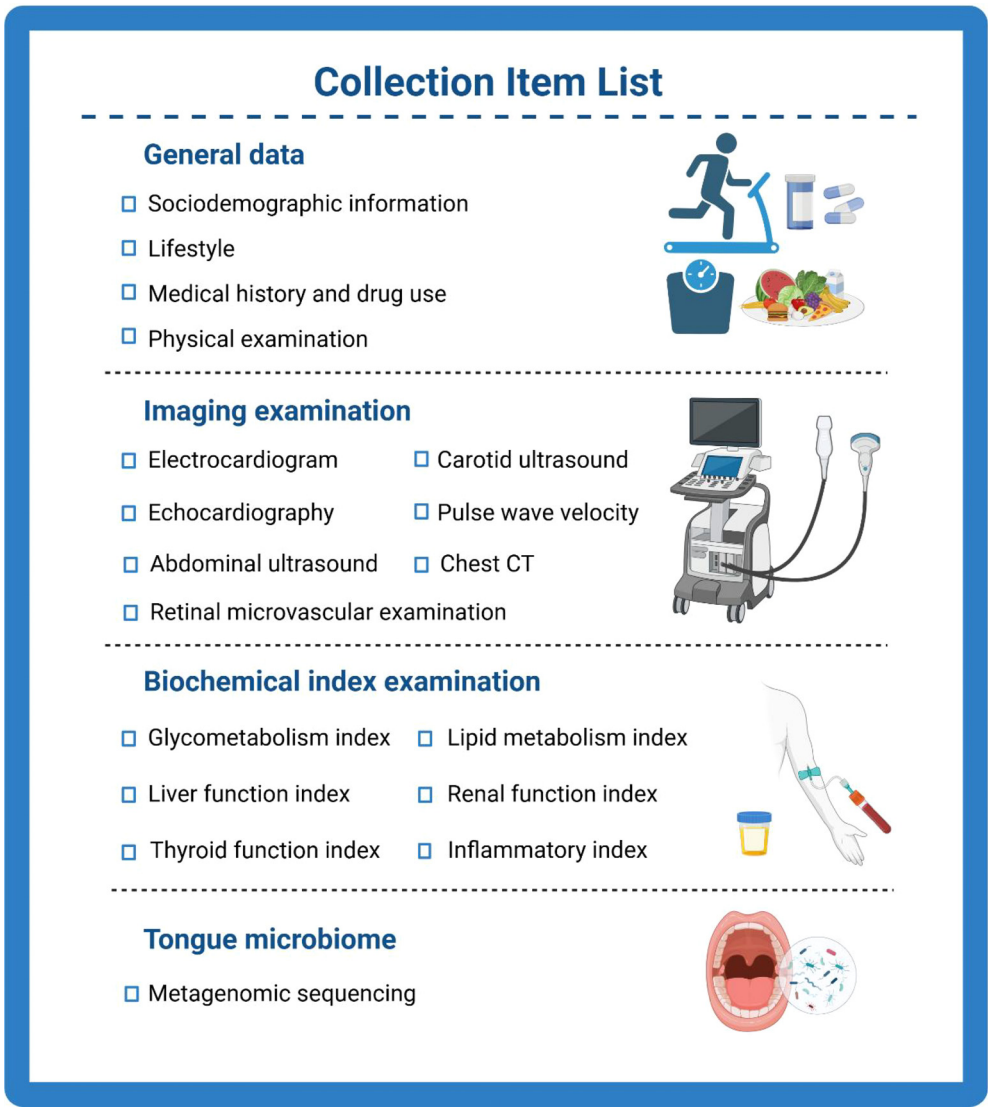


FIGURE 2
Overview of information collection.

different intensities (Supplementary Table S1). Sleep is divided into short sleep, moderate sleep, and excessive sleep, corresponding to less than 6 hours per day, 6 to 8 hours per day, and more than 8 hours per day, respectively.

Dietary patterns: a food frequency questionnaire (FFQ) designed according to the dietary characteristics of southern China is used to assess the dietary intake of patients in the past 12 months(Supplementary Table S2). The design of this questionnaire refers to the internationally common FFQ content (25, 26) and combines the dietary characteristics of the Jiangnan area in China (27, 28), covering various typical Jiangnan food categories, such as rice, noodles, bean products, freshwater fish, etc., combining the frequency, portion, and cooking methods of food intake to fully capture the daily dietary patterns of the Suzhou area population. In addition, for subjects receiving nutritional treatment guidance, their dietary intervention plans and actual intake will be recorded separately.

Medical history and medication use: investigate the medical history of diabetes, hypertension, etc., and verify through medical or hospital records. Investigate the family history of CVD among patients and their age of onset, and those with CVD in first-degree relatives (men <55 years, women <65 years) are determined to have a family history of early-onset CVD. Collect the self-reported medication status of patients within 30 days before follow-up, including hypoglycemic or lipid-lowering drugs.

Physical examination:

Measure the weight, height, body mass index (BMI), body fat, waist circumference, hip circumference, and upper arm circumference of all subjects. Before measuring height and weight, and visceral fat, subjects remove heavy clothing and shoes and stand. Use V-body HBF-371 (OMRON, Kyoto, Japan) to measure body fat and visceral fat. The calculation method for BMI is weight (kg) divided by the square of height (m^2). When measuring waist circumference, hip circumference, and upper arm circumference, subjects stand with

their arms naturally hanging down. The waist circumference is measured at the midpoint circumference of the line connecting the lower rib edge and the anterior iliac spine, the hip circumference is measured at the maximum circumference of the buttocks, and the upper arm circumference is measured at the midpoint circumference of the line connecting the acromion and the olecranon. Use a soft tape to measure closely to the corresponding position on the skin, accurate to 0.1cm.

Blood pressure and ankle-brachial index: Before measuring blood pressure, subjects are asked to urinate and rest for at least 30 minutes. Sit and use a professional portable blood pressure monitor (OMRON, Kyoto, Japan) to measure blood pressure and pulse of the right arm three times, with an interval of 30 seconds. Lie on your back and use VP-1000 (OMRON, Kyoto, Japan) to measure blood pressure of the four limbs three times, with an interval of 30 seconds. Calculate the average value of the three measurements for analysis. The calculation method for ankle-brachial index (ABI) is the systolic pressure of the ankle joint divided by the systolic pressure of the brachial artery.

Auxiliary examination:

Electrocardiogram examination: Electrocardiogram examination is operated by experienced cardiovascular physicians from Suzhou Hospital of Traditional Chinese Medicine. Before the electrocardiogram examination, subjects are asked to urinate and rest for at least 5 minutes. Lie on your back, and record the 12-lead electrocardiogram at a speed of 25mm/s and 1mv/cm with standard equipment. If the depth of the S wave in V1 + the highest R wave height in V5 or V6 > 3.5mv, it suggests LVH.

Ultrasonic examination: Echocardiography is performed according to the guidelines recommended by the American Society of Echocardiography (29). Obtain parasternal long-axis and short-axis, apical four-chamber, subcostal four-chamber, and other sections, measure cardiac ultrasound data, including left atrial internal diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPW), the ratio of mitral valve flow E peak velocity to the average of the lateral and septal early diastolic velocities at the mitral annulus (E/e'), etc., and measure left ventricular ejection fraction (LVEF) by the biplane Simpson method.

Abdominal ultrasound: After fasting for 12 hours, lie on your back and record the parameters of liver ultrasound according to the guidelines of the Hepatology Branch of the Chinese Medical Association, to assess the condition of liver fat metamorphosis (30).

Carotid ultrasound: Lie on your back with the neck elevated to recline the head, and slightly turn the head to one side to fully expose the neck, continuously obtain the cross-section and longitudinal section of the common carotid artery, internal and external carotid artery bifurcation, internal carotid artery, and external carotid artery branches, and measure the intima-media thickness (IMT) of the carotid artery. IMT is defined as the distance between the inner lumen and the interface between the inner and outer membranes of the vascular wall. IMT≥1.5mm or a local change that is thicker than the adjacent IMT by >0.5mm or 50% and protrudes into the lumen is considered a carotid plaque. If a plaque is detected, the location, number, size, shape, and echo characteristics of the carotid plaque need to be measured.

Pulse wave velocity examination: Pulse wave velocity examination (PWV) is performed by experienced cardiovascular physicians from Suzhou Hospital of Traditional Chinese Medicine. Subjects need to rest for at least 5 minutes before the examination, maintain a calm state, and lie on their back with the neck elevated to recline the head, and slightly turn the head to one side. Place pressure sensors at the most obvious places of carotid and femoral artery pulsation, obtain arterial pulse waveforms, record pulse wave transmission time, and calculate the carotid-femoral pulse wave velocity (cfPWV) of the subjects. Place sensors at the measurement sites of the ankle artery and brachial artery, and calculate the brachial-ankle pulse wave velocity (baPWV). Record the pulse wave transmission time, waveform characteristics, and heart rate and blood pressure of the subjects during the measurement to comprehensively assess arterial elasticity and its changes.

Chest CT examination: Use 64-slice spiral CT to scan the heart, performed by experienced radiology professionals. Score the coronary artery calcification by Agatston scoring (31), that is, the total calcium score = ∑(calcification density score) × calcification area; the total coronary artery calcification score is the sum of the calcification scores of the left main trunk, anterior descending branch, circumflex branch, and right coronary artery branches.

Retinal microvascular assessment:

Retinal microvascular assessment was conducted by experienced ophthalmologists at Suzhou Hospital of Traditional Chinese Medicine. Using a 45°color fundus camera, color fundus photographs of both eyes were taken with the optic disc and macula as the centers, and data from the right eye were selected for analysis. The IVAN computer-assisted program (University of Wisconsin, USA) was used to measure the diameters of 6 major branches of retinal arterioles and venules within a range of 0.5 to 1.0 disc diameters from the optic disc margin. The central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) were calculated using the Parr-Hubbard formula (32). The arteriole-to-venule ratio (AVR) was then determined as AVR = CRAE/CRVE.

Biochemical indicators examination:

Subjects fast for >8 hours and collect elbow venous blood and urine samples the next morning. Detect fasting biochemical indicators: blood glucose (GLU), glycated hemoglobin (HbA1c), fasting insulin (fast insulin, FIN) level, and calculate the insulin secretion index and insulin resistance index. The calculation method for the insulin secretion index is fasting insulin divided by fasting blood glucose concentration. The calculation method for insulin resistance index (Homeostatic Model Assessment of Insulin Resistance, HOMA-IR) is fasting blood glucose multiplied by fasting insulin divided by 22.5. The following indicators were also measured: aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), γ-glutamyl transferase (γ-GGT), total bilirubin (TBi), direct bilirubin (DBi), indirect bilirubin (IBi), blood creatinine (SCr), uric acid (UA), glomerular filtration rate (eGFR), triglycerides (TG), cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B

(ApoB), lipoprotein (a) [LP(a)], thyroid-stimulating hormone, free thyroxine (FT4), free triiodothyronine (FT3), homocysteine (Hcy), C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and lipopolysaccharide (LPS).

Tongue coating microbiota collection:

Subjects fast for >8 hours and collect tongue coating samples the next morning. Roll the swab from the root to the tip of the tongue for 1 time, place the swab into an EP tube containing 1 mL of phosphate-buffered saline (PBS), gently stir the swab to wash off the tongue coating microbiota. Repeat the above steps with a new swab twice to ensure sufficient collection of tongue coating samples. After collection, centrifuge (10000×g, 4°C, 15 min), gently absorb and discard the supernatant, take the sediment as the sample, freeze with liquid nitrogen, and store at -80°C for analysis.

Outcome and follow-up

The primary outcome of this study is the first occurrence of coronary heart disease and stroke, with the earlier occurrence as the standard, and the secondary outcome is subclinical target organ damage. Coronary heart disease includes other coronary heart diseases (ICD-10 codes I23-I25), angina pectoris (I20), myocardial infarction (I21, I22). Cerebral stroke includes hemorrhagic stroke (I60-I62) and ischemic stroke (I63). Other unspecified strokes are classified as I64. Secondary outcomes are the first occurrence of subclinical target organ damage. All subjects will be followed up once every 2 years after the completion of the baseline survey. During the follow-up period, the occurrence of events will be confirmed with the same diagnostic criteria as the baseline assessment to ensure the reliability of the data. In the case of death, the death of the subject will be confirmed by the death certificate issued by the local civil registry office or community health center.

Definition of subclinical target organ damage

Subclinical target organ damage includes cardiac, renal, vascular, and microvascular damage (33). Among them, cardiac damage includes LVH (left ventricular mass index (LVMI) > 110g/m^2 for men and LVMI > 90g/m^2 for women); renal damage includes MAU (ACR >30mg/g) and chronic kidney disease (CKD, eGFR <60ml/min/1.73 m^2); vascular damage includes peripheral arterial disease (PAD, ABI <0.9), vascular stenosis (carotid or femoral artery stenosis >50%), increased carotid intima-media thickness (carotid IMT >0.9mm), arterial stiffness (AS, cf-PWV>10 m/s or ba-PWV>1400cm/s); microvascular damage includes retinopathy (retinal AVR<0.5).

Statistics

The sample size of this study is based on the primary endpoint, which is the time to the first occurrence of coronary heart disease or stroke. Previous studies have shown that patients with cardiovascular metabolic risk factors have an increased risk of CVD compared to those without risk factors, with a hazard ratio (HR) of 1.82 (34). We set the alpha value to 0.05 and the statistical power to 80% (β= 0.20). According to the sample size calculation formula, approximately 4340 participants are needed. We expect that 10% to 15% of participants will be lost to follow-up during the follow-up process, so the final study will recruit 5000 to 6000 participants.

In prospective cohort studies, data missing and follow-up loss are common problems. We will first conduct a descriptive analysis of data missing to determine whether it is randomly missing or partially randomly missing. For randomly missing cases, only samples with complete data will be analyzed. For non-completely random missing data, multiple imputation techniques will be used to generate multiple alternative datasets to ensure the robustness of the analysis.

Random effects models will be used to deal with repeated measurement data iterated through Markov Chain Monte Carlo methods, and model the long-term trajectories of individuals and groups. Elastic net regression, random forests, tree-based methods, and support vector machines, and other machine learning methods will be used to explore the relationship between variables and outcomes, to deal with high-dimensional data and complex interactions between variables, and to find variables highly related to the risk of CVD occurrence. These models will be evaluated through cross-validation to ensure reasonable allocation of validation and training sets and to avoid overfitting and other issues. Standard random effects models combined with structural equation models will be used to explore potential causal pathways. Structural equation models can comprehensively analyze the impact of multiple variables on predictive variables, providing more comprehensive model validation. For the main outcome, we will further explore the potential mediating effect of tongue coating microbiota in the occurrence and development of CVD through structural equation models. To evaluate the predictive performance of the model, standardized indicators such as accuracy, precision, recall, F1 value, and area under the ROC curve will be used for assessment.

All statistical analyses will be completed in R software, using its related packages such as lme4 for random effects models, glmnet for elastic net regression, randomForest for random forest analysis, lavaan for structural equation model analysis. Machine learning analysis will also be implemented in R.

Discussion

The pathogenesis of CVD is complex, involving the combined action of demographic, environmental, lifestyle, genetic, and immune factors (35, 36). This study is based on the concept of cardiovascular 1.5-level prevention proposed by us, focusing on subclinical target organ damage, which makes up for the shortcomings of traditional risk assessment tools in the early pathological changes. As a prospective cohort study conducted in Suzhou, China, the “Suzhou Cardiometabolic Health (SCH) Study” is committed to revealing the unique role of oral (tongue coating)

microbiota and multiple metabolic factors in cardiovascular risk assessment, promoting the implementation of more precise 1.5-level prevention strategies. Suzhou is located in the Yangtze River Delta economic zone, with a unique population composition and dietary pattern, providing an important background for the study of cardiovascular metabolic health. Through systematic follow-up of individuals of different age groups and metabolic states in this region, the SCH study will provide a scientific basis for future multi-dimensional CVD risk assessment tools and personalized health management. 1.5-level prevention reflects the concept of "prevention before disease", aiming to reduce the occurrence of CVD and subclinical target organ damage through earlier identification and intervention, and promoting personalized precision medicine.

This study introduces tongue coating microbiota characteristics as metabolic markers for the first time, exploring their potential role in CVD risk assessment. In recent years, more and more evidence has shown that oral microbiota plays an important role in metabolic cardiovascular diseases, especially its complex interactions with inflammation, immune regulation, and endothelial dysfunction (21, 37, 38). Our team's previous cohort study discovered and validated that the increased abundance of *Fusobacterium nucleatum* in the oral cavity is one of the notable characteristics of patients with diabetic coronary heart disease. Moreover, the oral-gut microbial transmission serves as a crucial intermediary mechanism through which diabetes affects myocardial ischemia-reperfusion injury, laying the groundwork for further exploration of the regulatory role of oral microbiota in cardiovascular and metabolic health (37). However, high-throughput sequencing data is insufficient, the field lacks large-scale, long-term clinical cohorts that integrate diverse metabolic factors and oral microbiota. Our research should focus on the diversity, composition, functional potential of tongue coating microbiota, coupled with advanced approaches such as machine learning model construction (39, 40). Species such as *Fusobacterium nucleatum* and members of the "red complex" (*Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*) have been implicated in systemic inflammation and atherosclerosis, underscoring their potential role as biomarkers or therapeutic targets in cardiovascular health (41, 42).

At the same time, this study adopts a prospective, large-scale cohort design, covering comprehensive data collection from lifestyle to metabolic indicators, including subjects' diet, exercise, sleep, smoking, and drinking factors. By detailed recording and analysis of these lifestyle factors, this study can comprehensively assess the risk of cardiovascular diseases from multiple dimensions, providing lifestyle suggestions for clinicians and patients, promoting interdisciplinary cooperation between cardiovascular science and endocrinology, nutrition, and other fields, to meet global health challenges.

The main advantages of this study are the diversity of the study population, the application of high-throughput tongue coating microbiota sequencing technology, and advanced statistical schemes. The study not only includes laboratory indicators such as sugar and lipid metabolism but also pays special attention to young people with unhealthy lifestyles, providing a broader perspective for the identification of cardiovascular disease risk. The introduction of tongue coating microbiota as a new metabolic marker not only helps in the early identification of cardiovascular risk but also provides a modern scientific basis for traditional Chinese medicine tongue diagnosis theory. Traditional Chinese medicine theory believes that tongue coating reflects the internal state of the human body and is closely related to metabolic disorders such as phlegm and dampness. Research shows that this macro concept may have specific scientific connotations. For example, tongue coating is highly related to microbiota, and the disorder of tongue coating microbiota can promote the progression of coronary heart disease (43, 44). This study explores this concept and provides modern scientific evidence for the traditional Chinese medicine theory of tongue diagnosis.

This study also has some limitations. First, this study is a single-center cohort study, which may affect the generalizability of the results. Second, the sequencing and analysis of tongue coating microbiota depend on highly specialized equipment and technology, which may limit its promotion in a larger population. Finally, the longer follow-up period may lead to some participants being lost to follow-up, thereby affecting the completeness and robustness of the final data and results.

In the future, we will focus on conducting multi-center studies and aim to expand the applicability of tongue coating microbiota characteristics across different regions and populations. Second, exploring how to incorporate the strategy of cardiovascular 1.5-level prevention into daily clinical practice, especially in health management and risk assessment, to ensure that high-risk individuals can receive intervention as early as possible is also an important topic for the future. In addition, future research will explore the potential mechanisms of tongue coating microbiota in the occurrence of CVD, especially its interactions with other metabolic markers. By early identification and intervention of pre-disease damage in cardiovascular diseases, this study hopes to provide high-quality evidence for reducing the incidence of CVD and improving the overall health level of the population.

Conclusion

In summary, this study proposes an integrated multi-dimensional factor CVD risk assessment strategy by combining oral (tongue coating) microbiota, a new type of metabolic marker, with traditional metabolic factors. This study aims to verify the feasibility and effectiveness of this new method in identifying subclinical target organ damage and CVD risk stratification, striving to improve the early identification and precise prevention level of CVD, thereby providing a scientific basis for cardiovascular 1.5-level prevention.

Ethics statement

This study was approved by the Ethics Committee of Xiyuan Hospital Suzhou Hospital (Suzhou Hospital of Traditional Chinese Medicine, approval number: 2024-LYP-055). Participants were informed that they can refuse to participate or withdraw from the study at any time without any consequences.

Author contributions

MZ: Formal analysis, Methodology, Resources, Validation, Writing – original draft. YiL: Data curation, Formal analysis, Investigation, Validation, Writing – original draft. WW: Formal analysis, Investigation, Writing – original draft. LL: Formal analysis, Methodology, Writing – original draft. WL: Investigation, Methodology, Writing – original draft. JY: Resources, Validation, Writing – original draft. QX: Investigation, Methodology, Writing – original draft. JC: Investigation, Methodology, Resources, Writing – original draft. YaL: Investigation, Methodology, Project administration, Writing – original draft. KC: Investigation, Project administration, Writing – review & editing. YuL: Conceptualization, Funding acquisition, 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.

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.

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Comorbidity patterns and implications for disease control: a network analysis of medical records from Shanghai, China

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Background: The aging problem in Shanghai is rapidly increasing, leading to the development of chronic comorbidities in older adults. Studying the correlations within comorbidity patterns can assist in managing disease prevention and implicate early control.

Objectives: This study was a cross-sectional analysis based on a large sample size of 3,779,756 medical records. A network analysis and community classification were performed to illustrate disease networks and the internal relationships within comorbidity patterns among older adults in Shanghai.

Methods: The network analysis and community classification were performed using the IsingFit and Fast-greedy community functions. Datasets, including disease codes and disease prevalence, were collected from medical records.

Results: The top five prevalent diseases were hypertension (64.78%), chronic ischemic heart disease (39.06%), type 2 diabetes mellitus (24.97%), lipid metabolism disorders (21.79%), and gastritis (19.71%). The sampled population showed susceptibility to 11 comorbidities associated with hypertension, 9 with diabetes, 28 with ischemic heart disease, 26 with gastritis, and 2 with lipid metabolism disorders in male patients. Diseases such as lipid metabolism disorders, gastritis, fatty liver, polyps of the colon, osteoporosis, atherosclerosis, and heart failure exhibited strong centrality.

Conclusion: The most common comorbidity patterns were dominated by ischemic heart disease and gastritis, followed by a ternary pattern between hypertension, diabetes, and lipid metabolism disorders. Male patients were more likely to have comorbidities related to cardiovascular and sleep problems, while women were more likely to have comorbidities related to thyroid disease, inflammatory conditions, and hyperuricemia. It was suggested that healthcare professionals focus on monitoring relevant vital signs and mental health according to the specific comorbidity patterns in older adults with chronic diseases, to prevent the development of new or more severe comorbidities.

KEYWORDS

older adults, aging, chronic disease, comorbidity network, community classification, disease prevention

1 Introduction

The World Health Organization (WHO) defines comorbidity as the presence of two or more persistent health conditions in the same individual, requiring prolonged intervention for maintenance (1). By the middle of this century, it is projected that the population aged 60 years and above in China will reach 430 million (2). Chronic comorbidity has long been a significant health challenge among older adults. In Shanghai, one of the regions undergoing severe aging problems, the detection rate of chronic diseases among older adults has reached 70% (3). Compared to single-diagnosed diseases, comorbidity poses a more substantial threat to health, as the interplay of various diseases creates a complex network of risk factors, further increasing mortality risk among patients (4). The growing trend of comorbidity not only complicates diagnosis and treatment but also places a significant economic burden on families as well as society. Therefore, there is an urgent need for effective strategies to prevent and manage comorbidities, as well as to provide professional guidance for caregiving to older adults and their families.

Several domestic and international studies have conducted in-depth research on the prevalence of comorbidity and the associations between different chronic conditions among older adults in various regions, utilizing data collected from epidemiological surveys and medical records, combined with the practical application of various network theories. These studies also provided recommendations for control approaches of different comorbidity patterns. A study applied a self-organizing map (SOM) neural network to visually present the associations between various common chronic diseases among middle-aged and older adults in China. They explored the differences in comorbidity patterns affected by age, gender, urban–rural residence, and treatment outcomes through visual cluster analysis (5). A study used a network mapping strategy to explore comorbidity patterns among the Zhuang population in Guangxi, identifying nine patterns strongly associated with hypertension. These findings helped improve the health condition of the study population (6). Another study examined comorbidity networks in communities within Jiangsu Province based on large-scale network analysis tools to figure out comorbidity patterns, disease prevalence, clustering characteristics, risk factors, and preventive strategies (7). In addition, a South Korean study focused on comorbidity patterns among obese populations demonstrated the relationship between several chronic diseases and obesity across different genders (8). However, there were still some limitations to the current research progress. Previous studies had been limited to a few common diseases and had primarily focused on specific regions, lacking normality across the whole target population in China. Although some studies had collected data from whole areas within the country, the dataset required an update.

Currently, the situation regarding comorbidity among older adults in Shanghai remains unclear. This study applied visual network approaches to medical records from outpatient, emergency, and hospital visits among individuals aged 60 to 99 years in Shanghai, aiming to illustrate the coexistent diseases associated with the top five most prevalent conditions: hypertension, chronic ischaemic heart disease, type 2 diabetes mellitus, gastritis, and lipoprotein metabolism disorders. The study focused on analyzing potential comorbidities of these five diseases and aimed to provide insights into the prevention and management of chronic comorbidity among older adults in Shanghai. Additionally, it might lay a solid foundation for future exploration of potential associations and control of chronic disease incidence.

2 Materials and methods

2.1 Data processing and study population

The dataset was collected from the Shanghai Municipal Health Commission database (9). It was derived from a collection of medical records of outpatient visits, emergency visits, and hospitalized records from a total number of 520 public, private, and community hospitals, based on the enrollment of country's national basic medical insurance programs. Medical visits were traced by ID number enrolled in the insurance system during July 2022 and June 2023. The accuracy of the medical records uploaded was inspected under rigorous quality control. Repeat visits under one ID for the same disease were only counted once and combined into one record. In this case, each line of record represented the occurrence of all diseases for a single patient without duplication, no matter how many times patients repeat their visits for the same disease. In this study, we defined that the number of visiting records represented the prevalence of each disease.

All disease codes were referred to ICD-10 (International Classification of Diseases, 10th Revision). Only the records that met ICD-10 coding rules were selected (e.g., A01.001). Incomplete, inaccurate, inconsistent, duplicate, and garbled codes were also directly excluded from the database. Additionally, records that contained only one disease under the same ID were excluded since they were not meaningful for comorbidity analysis. Diseases that were unrelated to chronic diseases were excluded. Diseases with a prevalence below 1% of the total number of records were also excluded. The dataset originally contained 129,682,778 records from 4,847,895 patients aged 60 to 99 years. After processing, this study included 3,779,756 lines of records (1,734,188 for men and 2,045,568 for women) (Figure 1). Then, 150,000 records were randomly sampled by gender for further network analysis and community classification.

2.2 Re-coding of diseases

ICD-10 codes contain similar diseases under the same code level, some of which were disordered and included insufficient subjects for analysis. For statistical feasibility, diseases that occur in the same body part with similar pathogenesis were combined to generate a new code. For example, EE03 referred to a combination of E03.8 and E03.9, which represented a sum of hypothyroidism. II2520 referred to a combination of diseases under I25 (chronic ischaemic heart disease) and I20 (angina pectoris) since I20 might be an outcome of I25.

Based on the new coding rules, the top five prevalent diseases were determined first. They were hypertension, ischaemic heart disease (IHD), type 2 diabetes mellitus (T2DM), lipoprotein metabolism disorders (LMD), and gastritis. Then, the top 40 diseases with their respective comorbidity rate of these five diseases were determined. A total number of 38 chronic diseases were retained after deleting duplication (new codes were listed in Table 1). The 38 diseases were hypertension, IHD, T2DM, gastritis, LMD, hypothyroidism, non-toxic diffuse goiter, sleep disorders, sleep apnea, acute myocardial infarction, cardiac arrhythmia, cerebral infarction, cerebrovascular disease, chronic rhinitis, chronic pharyngitis, bronchitis, gastro-esophageal reflux disease with esophagitis (GERD with esophagitis), non-infective gastroenteritis and colitis, constipation, functional diarrhea, polyps of the colon, non-alcoholic fatty liver disease

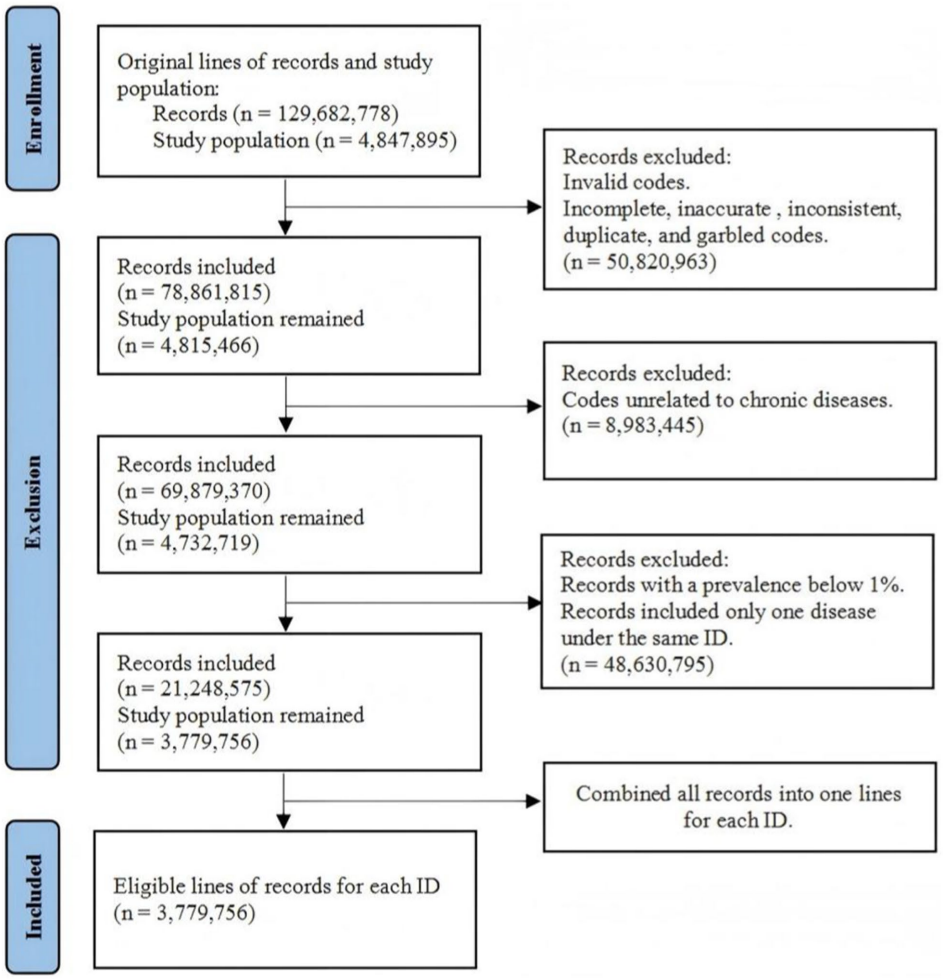

FIGURE 1
Flowchart of data processing and records exclusion.

(NAFLD), dermatitis, arthritis, osteoporosis, chronic kidney disease, dizziness and giddiness, anxiety disorders, neurotic disorders, atrial fibrillation and flutter, heart failure, atherosclerosis, chronic obstructive pulmonary disease (COPD), gastric ulcer, hyperuricemia, gonarthrosis, spondylosis, and (peri-)menopausal disorder.

2.3 Statistical analysis

The database was generated using Excel 2013. The characteristics of age were presented as weighted means with a standard deviation (SD). The number of medical visits of the study population by age group and the prevalence of the top five diseases were presented as weighted percentages.

2.4 Comorbidity network analysis

Network analysis was conducted using the IsingFit function ($\alpha = 0.05$) with R version 4.3.0. This network estimation employed eLasso, which combines l1-regularized logistic regression with model selection based on the Extended Bayesian Information Criterion (EBIC), enabling the identification of relevant relationships between diseases:

$$P_\theta\left(x_i = 1 | x_{\setminus i}\right) = \frac{\exp\left(\sum_{j \varepsilon V \setminus i} w_{ij} x_j + b_i\right)}{1 + \exp\left(\sum_{j \varepsilon V \setminus i} w_{ij} x_j + b_i\right)}$$

A coefficient w_{ij} greater than 0 indicates a higher frequency of two diseases occurring simultaneously, suggesting a higher likelihood of comorbidity. On the contrary, a coefficient smaller than 0 indicates a lower frequency of simultaneous occurrence. This is because the appearance of the two diseases in the 0/1 statistical matrix was decentralized, but the association still exists. In this study, positive and negative associations were used to describe the comorbidity frequency. The weight value of edges was used to describe this association in this study.

The network results included diseases as nodes and relevant associations as edges (10, 11). A node represents a single chronic disease. Edge connects two comorbid diseases. The thickness of the

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TABLE 1 Results of the centrality of each disease in the comorbidity network of male and female patients.

New code	Disease category	Male			Female		
		Strength	Closeness	Betweenness	Strength	Closeness	Betweenness
i10	Hypertension	2.617	0.005	0	3.882	0.006	14
ii2520*	**Chronic IHD****	**10.879**	**0.008**	**83**	**10.327**	**0.008**	**95**
ee1114	T2DM**	3.457	0.006	0	2.880	0.005	0
kk29*	**Gastritis**	**10.178**	**0.007**	**90**	**10.819**	**0.007**	**116**
e78	LMD**	1.285	0.006	0	0	-	0
ee03	Hypothyroidism	1.781	0.005	35	3.446	0.005	34
ee04	Non-toxic diffuse goiter	1.100	0.004	0	1.207	0.004	0
g47_0	Sleep disorders	4.167	0.005	7	3.697	0.005	6
g47_3	Sleep apnea	1.285	0.006	14	0	-	0
i21	Acute myocardial infarction	4.085	0.007	0	2.656	0.007	0
i49	Cardiac arrhythmia	6.842	0.007	23	6.842	0.007	23
i63	Cerebral infarction	4.752	0.007	9	4.606	0.006	9
ii67	Cerebrovascular disease	6.197	0.007	26	5.822	0.007	23
j31_0	Chronic rhinitis	4.494	0.007	39	4.620	0.006	23
j31_2	Chronic pharyngitis	5.495	0.006	21	6.009	0.006	8
jj4042	Bronchitis	5.937	0.007	36	6.442	0.007	42
k21	GERD**with esophagitis	5.219	0.006	0	5.370	0.006	0
k52_9	Non-infective gastroenteritis and colitis	3.423	0.006	11	3.793	0.006	2
k59_0	Constipation	5.219	0.007	13	4.657	0.006	4
k59_1	Functional diarrhea	5.794	0.006	16	5.665	0.006	10
k63_5*	**Polyps of the colon**	**5.846**	**0.007**	**64**	4.713	0.007	37
k76_0*	**NAFLD****	**5.918**	**0.007**	**87**	**5.991**	**0.007**	**55**
l30_9	Dermatitis	1.893	0.004	0	2.954	0.004	0
m13	Arthritis	6.480	0.007	24	6.480	0.007	24
m81*	**Osteoporosis**	**7.011**	**0.008**	**70**	6.674	0.007	47
nn18	Chronic kidney disease	7.011	0.007	47	7.146	0.007	37
r42	Dizziness and giddiness	4.238	0.006	19	4.606	0.006	22
f41	Anxiety disorders	4.512	0.006	17	4.449	0.006	18
f48	Neurotic disorders	4.466	0.006	11	3.833	0.005	5
i48	Atrial fibrillation and flutter	5.221	0.007	22	5.628	0.007	21
i50*	**Heart failure**	**9.612**	**0.008**	**97**	**9.671**	**0.008**	**110**
i70*	**Atherosclerosis**	**6.750**	**0.007**	**73**	5.207	0.007	19
j44	Chronic obstructive pulmonary disease	3.804	0.007	33	4.135	0.007	39
k25	Gastric ulcer	2.435	0.006	0	2.245	0.007	0
me1079	Hyperuricemia	3.828	0.007	8	5.000	0.007	10
m17	Gonarthrosis	3.423	0.006	4	3.330	0.006	1
m47	Spondylosis	4.431	0.007	23	4，431	0.006	23
n95	(peri-)Menopausal disorders	0	-	0	2.919	0.005	1

*Diseases represented in bold text have a strength greater than 5, a closeness equal to or greater than 0.007, and a betweenness greater than 50. These diseases have strong centrality and are easily susceptible to comorbidity. **IHD, ischaemic heart disease; T2DM, type 2 diabetes mellitus; LMD, lipoprotein metabolism disorders; GERD, gastro-esophageal reflux disease; NAFLD, non-alcoholic fatty liver disease.

edge is proportional to the intensity of comorbidity. A thicker edge indicates a stronger correlation of comorbidity. Strength is defined as the sum of the weights of all nodes. Closeness quantified the indirect distance between two diseases. A greater closeness indicates a shorter distance between two diseases, and they may co-occur more easily. Betweenness indicates the number of times a disease acts as a

connecting pathway to other pairs of comorbidity. A higher betweenness emphasizes the importance of the disease and its strong relationship with others (12).

2.5 Community classification

The comorbidity network conducted preliminary correlations among the studied diseases. Then, community classification was applied to further examine those positive correlations in depth to focus the results on comorbidity patterns. The analysis of clustering was based on the weights of the edges generated in the network, which introduced a concept of modularity, a quality index. The fast-greedy community function was applied to calculate modularity based on the weights of the edge. Modularity defined as

$$Q = \frac{1}{2m}\sum_{i,j}\left(A_{ij} - \gamma\frac{k_i k_j}{2m}\right)\delta\left(c_i, c_j\right)$$

where m is the number of edges, A_{ij} is the element of the A adjacency matrix in disease i and disease j. k_i is the sum of weights of adjacent edges for disease i. kj is the degree of disease j. ci and cj are the components of diseases i and j.γ is a resolution parameter to weight random null model and it is usually set to 1 (13).

2.6 Ethics statement

There was no personal information included in the dataset. The Shanghai Medical and Technology Information Institute Ethics Committee approved this study and the use of the dataset (No.2024004). All participants and procedures followed the required guidelines (14).

3 Results

3.1 Characteristics of the study population

This study initially analyzed the distribution of the study population based on their number of visits regarding single-diagnosed diseases across different age groups, stratified by gender. The overall percentage of medical visits of patients aged 60 to 69 years was 47.28% (men: 22.26%, women: 25.02%). The percentages for age groups 70–79, 80–89, and 90–99 were 33.99% (men: 16.04%, women: 17.95%), 14.37%, (men: 6.13%, women: 8.25%) and 4.36% (men: 1.46%, women: 2.90%), respectively. The average age for the study population was 72.87 (SD, 8.578) years. 72.52 (SD, 8.320) for men and 73.13 (SD, 8.758) for women (Table 2).

3.2 Top 10 most visiting diseases

Hypertension had the highest frequency of visits among all the study subjects, with a total of 11,422,288 visits for men and 1,306,260 visits for women. The top 10 diseases were hypertension, IHD, T2DM, LMD, gastritis, sleep disorders, conjunctivitis, intestinal disorders, bronchitis, and respiratory disorders (Table 3).

3.3 The comorbidity network of the top five diseases within all 38 analyzed diseases

Both comorbidity networks for men and women, as illustrated in Figure 2, indicated that hypertension positively correlated with 11 diseases. These included IHD, hyperuricemia, chronic kidney failure, cerebral infarction, T2DM, cerebrovascular disease, arthritis, cardiac arrhythmia, dizziness and giddiness, bronchitis, and NAFLD (weight of edges greater than 0, see Supplementary Tables 1, 2). Conversely, hypertension exhibited a negative correlation with chronic pharyngitis, gastritis, polyps of the colon, sleep disorders, and dermatitis (weight of edges lower than 0, see Supplementary Tables 1, 2). There was an additional negative association with neurotic disorder, chronic rhinitis, and COPD in men than in women. These diseases had a lower frequency of occurring simultaneously due to the decentralization of the records. Hypertension had an additional positive correlation between atrial fibrillation and flutter, constipation, and gonarthrosis, and an additional negative correlation with osteoporosis, spondylosis, hypothyroidism, and (peri-) menopausal disorders.

T2DM was found to be positively associated with nine diseases and negatively associated with three diseases. The nine diseases were chronic kidney failure, NAFLD, hypertension, atherosclerosis, heart failure, IHD, cerebral infarction, osteoporosis, and constipation. The three diseases were chronic pharyngitis, sleep disorders, and gastritis. Additionally, men were more likely than women to have acute myocardial infarction and less likely to have dizziness and giddiness, polyps of the colon, bronchitis, hyperuricemia, and COPD alongside T2DM. In women, T2DM additionally exhibited positive associations with hyperuricemia, arthritis, bronchitis, gastroenteritis and colitis, and dermatitis.

There were positive correlations between IHD and 28 diseases which included cardiovascular pathology (e.g., acute myocardial infarction, heart failure, cardiac arrhythmia, atrial fibrillation and flutter, cerebrovascular disease, hypertension, cerebral infarction, atherosclerosis, and LMD), chronic kidney failure, osteoporosis, arthritis, bronchitis, chronic pharyngitis, sleep disorders, T2DM, functional diarrhea, NAFLD, chronic rhinitis, gonarthrosis, and gastroenteritis and colitis. Women were additionally found to have hyperuricemia, gastric ulcer, spondylosis, and dermatitis with IHD.

Gastritis was positively associated with gastrointestinal (GI) disorders such as GERD with esophagitis, gastric ulcers, polyps of the colon, gastroenteritis and colitis, functional diarrhea, and constipation. It was also positively correlated with 26 other diseases, such as chronic pharyngitis, chronic rhinitis, NAFLD, anxiety disorders, bronchitis, osteoporosis, cardiac arrhythmia, IHD, sleep disorders, and COPD. Furthermore, it was negatively correlated with T2DM and hypertension. As mentioned above, the negative correlation indicated a lower frequency of existing simultaneously. The comorbidity pairs still existed. Women additionally had cerebral infarction, hyperuricemia, and (peri-) menopausal disorders positively associated with gastritis.

In men, LMD was positively associated with atherosclerosis, IHD, and hyperuricemia. It should be noted that women were not sampled for LMD and its associated diseases due to the low frequency of comorbidity (Figure 2).

TABLE 2 Basic characteristics of the study population.

Characteristics	Total		Male		Female	
Age (year)	No. of visits*	%	No. of visits	%	No. of visits	%
60–69	1,787,022	47.28	841,369	22.26	945,653	25.02
70–79	1,284,756	33.99	606,310	16.04	678,446	17.95
80–89	543,220	14.37	231,466	6.13	311,754	8.25
90–99	164,758	4.36	55,043	1.46	109,715	2.90
Age (year)	Average	SD	Average	SD	Average	SD
60–99	72.87	8.578	72.52	8.320	73.13	8.758

*The number of visits represents the prevalence of each disease. There was no duplication of diagnosis in this study.

TABLE 3 Top 10 single-diagnosed diseases based on the number of medical visits of the study population.

Top 10 single-diagnosed diseases	Total No. Visits (%*)	Male	Female
1. Hypertension	2,448,548 (64.78)	1,142,288	1,306,260
2. IHD**	1,476,396 (39.06)	637,315	839,081
3. T2DM**	943,812 (24.97)	465,184	478,628
4. LMD**	823,572 (21.79)	329,847	493,725
5. Gastritis	744,880 (19.71)	311,084	433,796
6. Sleep disorders	667,676 (17.66)	272,915	394,761
7. Conjunctivitis	518,629 (13.72)	195,735	322,894
8. Intestinal disorders	513,921 (13.60)	218,230	295,691
9. Bronchitis	458,076 (12.12)	199,803	258,273
10. Respiratory disorders	430,433 (11.39)	200,616	229,817

*Prevalence of each disease based on the total study population (3,779,756). **Explanation of abbreviation: IHD-ischaemic heart disease; T2DM-type 2 diabetes mellitus; LMD-lipoprotein metabolism disorders.

3.4 Network centrality of the 38 analyzed diseases

This study identified diseases with a strength greater than 5, a closeness equal to or greater than 0.007, and a betweenness greater than 50 as having strong centrality and were easily susceptible to comorbidity. Regarding the top five prevalent diseases, IHD (men: s = 10.879, c = 0.008, b = 83; women: s = 10.327, c = 0.008, b = 95) and gastritis (men: s = 10.178, c = 0.007, b = 90; women: s = 10.819, c = 0.007, b = 116) were the major two diseases that would easily be susceptible to comorbidity in both men and women. Among the 38 diseases, NAFLD (men: s = 5.918, c = 0.007, b = 87; women: s = 5.991, c = 0.007, b = 55), polyps of the colon (men: s = 5.846, c = 0.007, b = 64), osteoporosis (men: s = 7.011, c = 0.008, b = 70), and atherosclerosis (men: s = 6.750, c = 0.007, b = 73) were strongly associated with other diseases. Furthermore, the centrality of heart failure (men: s = 9.612, c = 0.008, b = 97; women: s = 9.671, c = 0.008, b = 110) was strong, indicating that this disease could commonly develop into outcome complications and thus correlated with the majority of the analyzed chronic diseases (Table 1).

3.5 Network-based community classification of the top five prevalent diseases

Modularities for clustering were both greater than 0.3 by gender (men: 0.34, women: 0.31), indicating that this method is effective in clearly categorizing the target diseases into smaller communities. In men, a cluster was observed among T2DM, hypertension, chronic kidney failure, hyperuricemia, NAFLD, atherosclerosis, LMD, and sleep apnea. A cluster was identified among IHD, cardiac arrhythmia, heart failure, acute myocardial infarction, and atrial fibrillation and flutter. Gastritis clustered with polyps of the colon, gastroenteritis and colitis, GERD with esophagitis, and gastric ulcers (Figure 3A). In women, a cluster was observed among T2DM, chronic kidney failure, hyperuricemia, hypothyroidism, NAFLD, atherosclerosis, non-toxic diffuse goiter, and hypertension. Gastritis clustered with polyps of the colon, gastritis, GERD with esophagitis, functional diarrhea, and gastric ulcers. IHD clustered with cardiac arrhythmias, atrial fibrillation flutter, heart failure, and acute myocardial infarction (Figure 3B).

Additional clusters were identified. In men, sleep disorders were clustered with cerebral infarction, cerebrovascular disease, dizziness and giddiness, neurotic disorders, constipation, and anxiety disorders. Bronchitis was associated with arthritis, dermatitis, COPD, chronic rhinitis and pharyngitis, osteoporosis, gonarthrosis, and spondylosis. Hypothyroidism was associated with non-toxic diffuse goiter. In women, sleep disorders were clustered with constipation, cerebral infarction, cerebrovascular disease, dizziness and giddiness, anxiety disorders, and neurotic disorders. Bronchitis was clustered with osteoporosis, arthritis, dermatitis, chronic rhinitis and pharyngitis, osteoarthrosis, gonarthrosis, spondylosis, (peri-)menopausal disorders, and COPD (Figure 3).

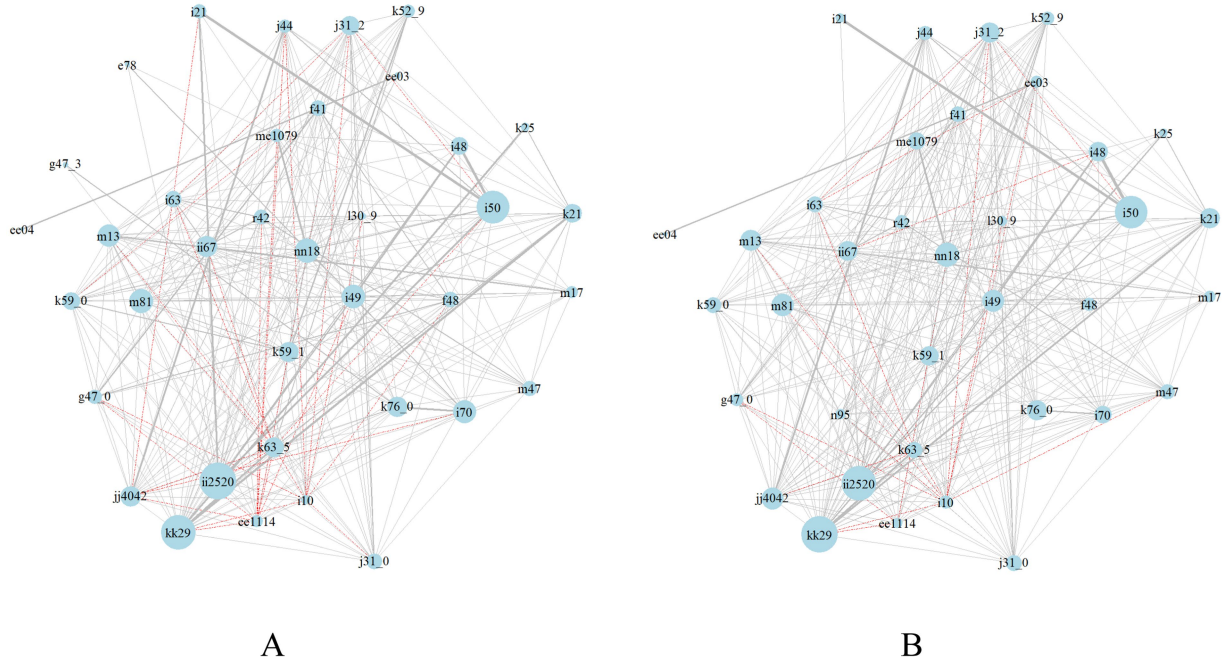

FIGURE 2
Comorbidity network in men **(A)** and women **(B)** aged 60 to 99 years. Nodes represent chronic diseases. Node size is proportional to the strength of diseases. Edges connect comorbid diseases. Black edges indicate positive correlations and red edge indicates negative correlations. Edge thickness indicates the intensity of the correlation.

4 Discussion

4.1 Chronic ischemic heart disease and its comorbidity patterns

IHD is associated with chronic diseases such as cardiovascular pathology, GI disorders, chronic kidney failure, osteoporosis, arthritis, bronchitis, chronic pharyngitis, sleep disorders, T2DM, NAFLD, chronic rhinitis, and gonarthrosis. IHD is one of the major types of cardiovascular disease (CVD) developing in China. Known studies have analyzed that IHD is closely associated with hypertension, T2DM, LMD, overweight or obesity, and unhealthy lifestyles. Risk factors are not significantly different between men and women (15). This study indicated that IHD is associated with not only commonly recognized CVD, cerebrovascular diseases, and T2DM but also abnormalities of hepatic and renal function, upper respiratory problems, lung diseases, bone and joint diseases, mental disorders, and GI disorders, which are susceptible to comorbidity in older patients with IHD. Deterioration of renal function is one of the most common comorbidities of IHD and CVD, which is often accompanied by heart failure as well (16, 17). NAFLD and CVD are manifestations of end-organ damage in the metabolic syndrome, and they are associated with each other through multiple mechanisms. Patients with IHD are likely to have atherosclerosis, cardiomyopathy, and arrhythmia, which contribute to CVD morbidity and mortality (18). CVD and IHD are also the most common comorbidities of COPD, accelerating disease progression, increasing risk factors, and resulting in the usage of therapeutic agents (19). Gastritis, gastric ulcers, osteoarthritis, and upper respiratory tract problems, such as chronic nasopharyngitis and bronchitis, induced by IHD are triggered by inflammatory mechanisms, a very common comorbidity pattern in older patients (20). Mental disorders such as sleep disorders, anxiety disorders, and vertigo are triggered by stress (21). This pattern is associated with a long duration of illness, high therapeutic difficulty, and high mortality of IHD. In addition, the comorbidity of hyperuricemia, dermatitis, and spondylosis in women with IHD was identified. Although asymptomatic hyperuricemia has long been considered to be a marker of metabolic disorders, several prospective large-scale clinical studies suggested that it may be an independent risk factor for CVD and IHD, and is strongly associated with poor outcomes of cardiac, vascular, and renal problems (22, 23).

4.2 Early detection and implications for disease control for chronic ischemic heart disease comorbidity patterns

Due to the complexity of IHD comorbidity patterns in older patients, it is necessary to apply a multidisciplinary diagnosis strategy to monitor these conditions in the early stage. It is crucial to regularly screen blood pressure, blood glucose, serum lipid level, hepatic and renal function, cardio-respiratory function, inflammatory response, and other physiological conditions for IHD patients (24–26). The intervention strategy should focus on preventing end-organ damages associated with metabolic syndrome, such as atherosclerosis, myocardial problems, and arrhythmias. Due to the strong association between IHD, heart failure, CVD, COPD, and decline in renal function, it is therefore recommended that monitoring cardiac, pulmonary, and renal functions plays an important role in preventing the potential morbidity of IHD (16). NAFLD and IHD interact

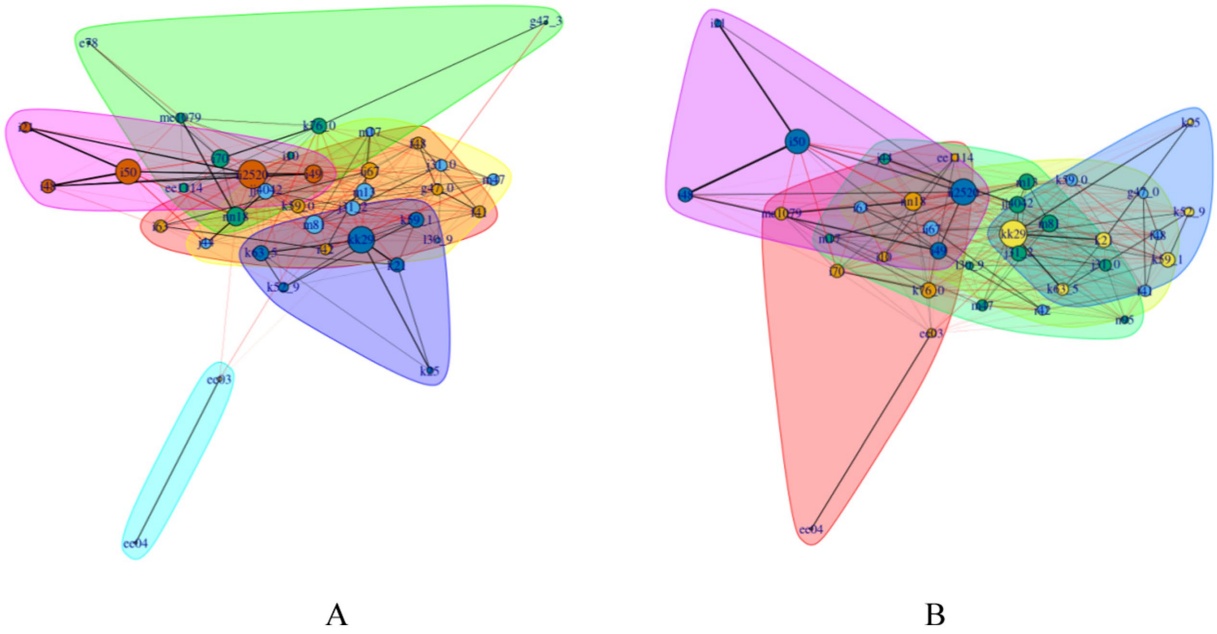

FIGURE 3
Network-based community clustering in men **(A)** and women **(B)** aged 60 to 99 years. Definitions of node, node size, and edge thickness remain constant, as described in Figure 2. Each cluster with a specific color refers to a disease community. Edges within the same cluster are in black. Edges across different clusters are in red. The color of nodes remains the same within the cluster.

through similar metabolic pathways. We recommended that IHD patients ease the double burden of the liver and cardiovascular system by weight management and glycaemic control. Women with IHD are more likely to have hyperuricemia, dermatitis, and spondylosis problems. It will be helpful to monitor inflammatory levels of the whole body to prevent adverse complications (27).

4.3 Chronic gastritis and its comorbidity patterns

Although the results of the community classification demonstrated that gastritis comorbidity patterns in older patients were predominantly associated with conventional GI diseases, network analysis provided a more general vision of all the potential diseases that are susceptible to gastritis. The comorbidity of gastritis with upper respiratory tract diseases may be attributed to acid reflux, which irritates the mucosa of the digestive system and ultimately exacerbates symptoms (28). A long-term diet high in fat and cholesterol may impact hepatic metabolism, potentially leading to the development of NAFLD. This is followed by the presentation of impaired endocrine function, which reduces the decomposition ability of greasy food, and then elevated GI burden (29). The prevalence of gastritis, ulcerative esophagitis, duodenitis, and other GI diseases is increased in patients with chronic kidney failure and hyperuricemia (30). Patients with gastritis are also susceptible to mental disorders, which result from the psychological burden due to long-term treatment (31). The comorbidity pattern between gastritis and hypothyroidism is also significant in older patients because hypothyroidism may lower appetite and slow down GI peristalsis. In this case, gastric disorders such as gastritis, dyspepsia, and constipation may happen (32, 33). Additionally, chronic gastritis may result in a systemic low-grade inflammatory response, thereby increasing the risk of vascular endothelial damage and CVD (34). It is important to highlight the increased prevalence of menopausal disorders, cerebral infarction, and hyperuricemia in women with gastritis compared to men. During the menopausal stage, as the decline of ovarian function lowers estrogen levels, it leads to endocrine disruption and results in changes in hormone levels, which may affect GI tract function, thereby increasing the risk of gastritis (35). Hormone fluctuation affects gut microbiota dysbiosis in the menopausal stage, which can also affect GI functions (36). In addition, cerebral infarction and hyperuricemia are risks resulting from the long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) and unhealthy diets.

4.4 Early detection and implications for disease control for gastritis comorbidity patterns

Most patients with chronic gastritis and its morbidity have been taking anti-inflammatory agents and other medications for a long period. Consequently, the primary objective of risk prevention should be protecting GI mucosa by selecting appropriate medications (37). It is recommended that patients should take medications with less irritation to GI mucosa, along with mucosal protectors and slow-released preparations, or take medicine after meals (38). The side effects of medications should be regularly assessed. It is recommended that older patients should intake low-fat, low-cholesterol diets to promote GI function. GI symptoms such as dyspepsia and constipation in gastritis patients with hypothyroidism need to be monitored frequently to facilitate timely intervention.

Additionally, chronic gastritis can also impose a systemic low-grade inflammatory response, thereby increasing the risk of CVD (34). In treating complications, the usage of medications with multi-target effects is a priority, along with appropriate adjustment of quantity, dosage, and frequency to reduce side effects. Furthermore, women with gastritis around 60 years should be particularly concerned about the potential comorbidities associated with menopausal diseases, such as cerebral infarction and hyperuricemia. Given the fluctuations in hormone levels during this phase of the disease, it is important to monitor endocrine function frequently, as it may impact GI conditions (39).

4.5 A ternary comorbidity pattern of type 2 diabetes mellitus, hypertension, and lipid metabolism disorders

T2DM, hypertension, and LMD were identified in the same community with some other chronic diseases such as hyperuricemia and hypothyroidism for women and sleep apnea for men, which indicated that these chronic diseases were closely related, and hypertension is prone to comorbid with metabolic syndromes (40). The major causes of this comorbidity pattern include insulin resistance, chronic inflammatory response, obesity, genetic factors, endothelial dysfunction, unhealthy lifestyle, and renal impairment. These factors interact to form a complex network of metabolic syndromes. The coexistence of chronic renal failure and hyperuricemia in this pattern may result from the fact that insulin resistance elevated uric acid levels (41, 42). Chronic inflammatory response exacerbates insulin resistance by triggering responses of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6), resulting in T2DM and renal impairment and increasing uric acid levels (43, 44). Meanwhile, elevated blood glucose in the liver activates glycogen synthase to accumulate hepatic fat, leading to LMD and NAFLD (45). In women, the decreasing insulin sensitivity is associated with the decreased metabolic rate of thyroid hormones, which triggers hypothyroidism and goiter (46). Both T2DM and hypothyroidism increase the risk of high cholesterol and hypertension, which are common cardiovascular risk factors in people with T2DM. Sleep apnea syndrome in male patients will lead to frequent apneic episodes and hypoxemia, which is associated with hypertension by activating and raising oxidation (47). Activating the sympathetic nervous system may contribute to insulin resistance, which can increase the risk of T2DM (48).

4.6 Early detection and implications for disease control for comorbidity pattern of type 2 diabetes mellitus, hypertension, and lipid metabolism disorders

The prevention of this ternary comorbidity pattern should focus on regulating blood glucose and insulin levels by pharmacological approaches such as in-taking metformin and insulin sensitizers. It is recommended that a healthy lifestyle, including weight management, frequent physical activity, and low-sugar, low-fat diets, can improve insulin sensitivity, overall metabolic status, and lower inflammation makers (49, 50). Regular detections of hepatic and renal function can help identify early impairment in older patients with T2DM and hyperuricemia.

It is also essential to consider gender factors in this comorbidity pattern. Female patients are recommended to regularly assess thyroid gland function and hormone levels due to the potential interaction between hypothyroidism and T2DM. Male patients undergoing sleep apnea syndrome should specifically screen their blood pressure and blood glucose. Using a respiratory assistant device and modifying sleeping posture to improve sleep quality. Taking less fats, sugar, salts, and alcohol will reduce the progression of comorbidity.

4.7 Mental health management and patient self-management

Neurotic disorders, sleep disorders, and other psychiatric factors were prevalent in the comorbidity pattern discussed above. It can be inferred that the long-term treatment of comorbidity in older adults is often accompanied by challenges on the psychological burden, such as anxiety and depression, which have a significant impact on patients' life quality and motivation for treatment. Comorbidities, such as insomnia and neurotic disorders, will develop into a chronic inflammatory response that affects cardiovascular, cerebral, respiratory, and GI health. Therefore, strengthening emotional support for older patients with comorbidity is an indispensable part of their treatment. This not only helps to reshape their confidence but also significantly improves their cooperation and ensures the effectiveness of treatment plans. For patients presenting with severe emotional disturbances, it is recommended that close collaboration with psychologists be established to implement psychological interventions and emotional relief strategies. Furthermore, self-management plays an active role in maintaining health conditions. Patients are encouraged to learn basic disease mechanisms and how to utilize medical tools to regularly monitor their health data, such as heart rate, blood pressure, blood glucose, and uric acid, to take immediate action to any potential health problems.

4.8 Implications and potential policy actions

Shanghai is a typical region in China facing comorbidity challenges. The network analysis is an effective approach for public health practitioners to quickly identify potential comorbidity patterns among the target population and then take action to reduce risk factors of disease development. This study discovered pre-existing comorbidity patterns and unusual ones, providing evidence to strengthen more effective management strategies. New-identified patterns may draw more attention from practitioners for the development of novel technology and strategies to monitor and prevent risk factors. Currently, China is implementing community-based primary medical services. It offers free screening for common chronic diseases such as T2DM, ICH, and GI diseases. Patients with T2DM could have additional screenings on thyroid function, uric acid levels, and sleeping quality. In addition, residents are encouraged to

enroll in the family doctor program. Family doctors are suggested to provide personalized medical consultations regarding the potential comorbidity patterns older adults may have, helping them strengthen comorbidity monitoring, arrange appropriate follow-up visits, and maintain good mental health. These actions aim to prevent and slow down the development of comorbidity and reduce any further medical burden for both patients and the public health system.

4.9 Limitations

The dataset was derived from cross-sectional medical records, so it is not appropriate to conclude causality. There were no covariates, such as educational level, smoking, and drinking alcohol, including for data analysis because medical records did not contain such information. In addition, some diseases were initially categorized vigorously in ICD-10. In this case, the final subjects included in some disease groups might be less than or more than expected, which leads to bias in the analysis. Moreover, the results only represented some general comorbidity patterns in the region of Shanghai, which lacked normality across the whole target population in China. Therefore, the implications for disease control could only be applied within the specific region.

5 Conclusion

The visualized analysis revealed that the most two prevalent comorbidity patterns among the study population were dominated by IHD and gastritis, followed by a ternary pattern of hypertension, T2DM, and LMD. Men are more likely to simultaneously have cardiovascular and sleep problems than women when they suffer from the top five prevalent diseases, whereas thyroid disease, chronic inflammatory diseases, and hyperuricemia are more commonly comorbid within women. By monitoring vital signs, such as heart rate, blood pressure, blood glucose, hepatic and renal function, and inflammatory markers, and their influencing factors within comorbidity patterns, healthcare professionals may take immediate actions toward the potential onset of comorbidity. Furthermore, it is vital to pay more attention to the mental health of patients who suffer from long-term chronic diseases and undergo complex treatment over a long period. Given the accelerating aging problem in Shanghai, it is insufficient to intervene after diseases occur. Early detection and prevention strategies are also necessary to control the onset, progression, and mortality rates. This study provided a general insight into the current comorbidity situation among older adults in Shanghai and suggestions on prevention strategies, which may help control the prevalence of chronic diseases.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Dataset is not available to the public due to ethical restrictions. Requests to access these datasets should be directed to niuyuhong@126.com.

Ethics statement

The studies involving humans were approved by the Shanghai Medical and Technology Information Institute Ethics Committee. 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

YS: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. WT: Data curation, Formal analysis, Visualization, Writing – review & editing. NL: Conceptualization, Writing – review & editing. YN: Conceptualization, Funding acquisition, 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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Healthcare providers' perspectives on the organization of health services to manage people with multiple long-term conditions in primary care settings in Kerala, India: a qualitative exploratory study

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Background: Multiple long-term conditions (MLTCs) are a major public health challenge globally. Complexity in managing MLTCs and their adverse consequences confronts the public healthcare systems in India. However, data from India to understand how to improve capacity to manage multiple chronic conditions are limited. We aimed to explore the challenges healthcare providers (HCPs) face in managing people with MLTCs in a south Indian primary care setting.

Methods: Semi-structured interviews were conducted with HCPs in four districts of Kerala, India. Key themes and sub-themes were identified using the Framework method for thematic analysis. We categorized the systemic drivers that influenced management of patients with MLTCs in the government primary care settings as health system, organizational and individual HCPs, and patient-levels.

Results: 33 in-depth, semi-structured interviews were conducted. Two main themes with sub-themes were found: multimorbidity preparedness (*program and human resource planning; treatment guidelines and protocols; combination medicines; and handover communication between HCPs*), multimorbidity care *competence* (*awareness, implementation, and practices; attitudes of HCPs; and multimorbidity patient characteristics*). Management of MLTCs at primary care was facilitated by the presence of programs for chronic respiratory conditions and depression, perceived value of electronic health records, awareness of HCPs regarding programs and patients' needs. However, several challenges at the health system level including lack of long-term planning, treatment guidelines and combination medicines, leading to fragmentation of care and poor program implementation and uptake by HCPs and patients.

Conclusion: Our study confirms sub-optimal health system preparedness and highlights the challenges for a transitioning primary care for managing people with MLTCs in one of India's states with a well-developed healthcare system. Our results suggest a need for improved planning and re-organization of primary health services with ongoing training support for HCPs.

KEYWORDS

multiple long-term conditions, healthcare providers experiences, primary care challenges, non-communicable diseases, India, multimorbidity, primary care, health care providers

Introduction

Globally, the prevalence of multiple long-term conditions (MLTCs) has increased substantially in the past two to three decades and has substantive healthcare needs, stressing most health systems (1, 2). MLTCs or multimorbidity, refers to the existence of two or more long-term conditions in a single individual, which may be chronic non-communicable diseases (NCDs), chronic infectious diseases, and mental health conditions of long duration (3). The prevalence of MLTCs increases with several socio-demographic variables such as age and economic deprivation (4, 5). In low and middle-income countries (LMICs) such as India, NCDs are the most significant contributors to mortality and morbidity (6, 7), including an increasing prevalence of mental health disorders (8).

There is a lack of consensus regarding the most effective approach to managing care for people with MLTCs (9, 10). Further, the existing care models often prioritize addressing individual diseases in silos, with specialists for each disease rather than considering the comprehensive requirements and contexts of individuals with complex care needs (11, 12). Generally, people with MLTCs utilize healthcare services more frequently than those with a single disease (1). The long-term nature of these conditions requires patients to undergo frequent examinations, take various medications, and attend numerous medical appointments with different healthcare providers (HCPs), leading to fragmentation of care, which increases the treatment burden (13–15). The enormity of the burden, the complexity of managing MLTCs, and the worldwide diversity in primary care systems calls for developing contextually relevant, resource-sensitive, and culturally appropriate primary care models. This is particularly the case in India which has a growing number of people with MLTCs (16, 17).

In response to the growing burden of NCDs in India, several policy actions, such as a National NCD program, have been taken by the government for effective management in the public health system (18). However, several studies highlighted the significant gaps in the public health system to manage chronic conditions effectively (19–22). The state of Kerala in India (the focus of this paper) has implemented health system reforms to enhance primary care services in the public health system. These reforms include the introduction of diabetes and hypertension screening and treatment, the adoption of electronic health records, and the establishment of a structured sequence of checkpoints for patients, leading to improved patient flow at the family health centers (FHCs), which are upgraded primary health centers (PHCs) (23–25). Additionally, the Directorate of Health services in Kerala expanded primary care services by including SWAAS (*Stepwise approach to airway diseases*) for Chronic Obstructive Pulmonary Disease (COPD) management and ASWASAM for depression screening and management (23–25). However, how these changes address (or not) the needs of individuals with MLTCs is unknown.

There is limited research from India on MLTCs, and none examines the challenges for HCPs in managing MLTCs at the primary care level. In our first paper of the series, we published the perspectives of patients with MLTCs, who reported care coordination difficulties such as traveling to multiple healthcare facilities, leading to fragmented and reduced continuity of care, struggles with medication procurement and management, and primary care not being sufficient to meet their healthcare needs (26). To obtain a complete picture of the issues needing to be addressed for a health system model, in this paper, we explored the perspectives of HCPs in Kerala's public health system in managing MLTCs in primary care, and identified facilitators and barriers to care within the context of primary care reforms.

Methods

Study design

We conducted a descriptive qualitative study as part of the project Systems Thinking Approach to developing an Integrated and patient-centered intervention model for multimorbidity care in primary care settings in India (27) between June 2022 and February 2023 using a thematic analysis (the Framework method) (28).

Settings

The study was conducted in eight FHCs in the Northern ($n = 3$), Central ($n = 3$), and Southern ($n = 2$) districts of Kerala. These settings were selected to represent different geographical regions of Kerala. As stated above, Kerala revitalized its primary health centers (PHCs), transforming them into patient-friendly FHCs as part of the "Aardram", a mission-based initiative in 2016 (23–25). The initiative introduced a series of reforms in the state's health sector at the FHC level with extended hours of operation and improved quality and range of NCD services with the support of local self-government (LSG) or panchayats (decentralized local bodies). As early as 1995, Kerala had taken steps to fulfill the constitutional mandate for decentralizing power, following which the state transferred funds, functions, and functionaries from various state government institutions, including health, to LSGs. LSGs consist

of a three-tier system of local government in Kerala, consisting of gram panchayats (village councils), block panchayats, and district panchayats (29, 30). Elected members of LSGs collaborate with FHCs' officials to assess community health needs and implement tailored strategies by using fiscal and administrative policies vested in the LSGs (31).

The upgraded FHCs are staffed by three medical officers (doctors), four staff nurses, two pharmacists, and one laboratory technician. The FHCs provide NCD preventative and curative health services including screening and management of diabetes, hypertension, chronic respiratory diseases, and depression (23–25).

Study participants and sampling

All primary health centers upgraded to FHCs in the north, central, and southern regions were eligible to participate in the study. We aimed to recruit at least two centers from each region and selected FHCs based on their availability to participate. The study participants were HCPs. HCPs were purposively (32) sampled to include doctors, nurses, and pharmacists, working in the FHCs and hospital specialists. Hospital specialists working in the public health system (secondary or tertiary) were eligible to participate in the study and were purposively sampled to include specialists in medicine, pulmonology and psychiatry based on the corresponding specialty clinic services available at the FHCs. Researchers visited the FHCs to conduct the interviews and recruited until theoretical saturation (33) was obtained. Researchers contacted hospital specialists by phone and agreed interviews at their preferred location or by telephone (34). Face-to-face interviews took place in private rooms within the healthcare facilities to maintain confidentiality. Telephone interviews took place based on the convenience of the HCPs.

Data collection

We collected qualitative data through in-depth semi-structured interviews with the study participants. Experienced qualitative researchers (LJ and LTR) led the data collection process, assisted by two research assistants (AK and NS). The interviews were conducted in English or Malayalam, the regional language, if preferred by participants, to ensure effective communication. Before conducting the interviews, the research assistants received specific training by conducting mock interviews using the topic guides. Topic guides (Supplementary Box S1) were piloted with three HCPs to ensure clarity. Topic guides were prepared based on an understanding of the literature on NCD management in India, MLTCs globally, and discussion with the research team. The topic guide was designed to explore the experiences and challenges HCPs face in managing MLTCs in primary care settings. The interviews were audio-recorded.

Data analysis

Interviews lasted between 20 and 120 min; there was no difference in length of interviews between face-to-face and telephone. Three researchers (LJ, AK, and NS) transcribed and translated the interviews in Malayalam to English, and one researcher (LTR) crosschecked the transcriptions against the audio recording for discrepancies. The Framework method (28) was used to identify and explore key themes and sub-themes related to the experiences of all interviewees in providing care for patients with MLTCs.

Two researchers (LJ and LTR) independently carried out the open coding of a sample of transcripts. These initial codes and areas from the topic guide were discussed among the two researchers (LJ and LTR) to develop a coding framework for the analysis of the remaining transcripts. This coding framework was subsequently used to code the complete interviews with ongoing discussions and revisions (PJ, LJ, LTR) as required. Taguette (35), qualitative data software, was used to facilitate coding. After coding all interviews, the codes and interview data were placed into a Microsoft Excel matrix, sorted by participant identifier and code name. An iterative process was followed to develop categories by regrouping codes for detailed review and interpretation of the recurrent themes and sub-themes. Themes and sub-themes were reviewed by the whole team. To determine barriers and facilitators, the interview data within the themes and sub-themes were deductively organized under three headings health system, organizational and individual HCPs, and patient-levels. We have reported the qualitative study using SRQR (Standards for Reporting Qualitative Research) checklist (see Supplementary Table S2; Supplementary Box S2).

Ethics

We obtained Institutional Ethical Committee approval for the study from the Sree Chitra Tirunal Institute for Medical Science and Technology, Thiruvananthapuram (IEC/1543). Written informed consent was obtained before data collection.

Findings

We interviewed 10 doctors, 8 nurses, 5 pharmacists working in 8 FHCs in Kerala, and 10 hospital specialists working in secondary or tertiary settings in the public health system in Kerala (Table 1). They were interviewed either face-to-face ($n = 27$) or by telephone ($n = 6$). HCPs were 7 male and 26 female participants with work experience ranging from 6 months to 17 years from north ($n = 8$), central ($n = 14$), and south ($n = 11$) regions in Kerala.

The findings were organized into two main themes and sub-themes (see Figure 1). HCP quotes supporting the themes and sub-themes are illustrated within the manuscript. Additional quotes are presented in the Supplementary Table S1.

Multimorbidity preparedness

Multimorbidity preparedness addresses the gaps and opportunities in managing people with MLTCs in the existing public health system. It is split into four sub-themes: program and human resource planning, treatment guidelines and protocols, combination medicines, and handover communication between HCPs.

TABLE 1 Demographic details of interviewees.

Participant ID	HCP category	Gender	Years of experience	Institution location
ID1	Doctor	F	13	South
ID2	Doctor	F	8	South
ID3	Doctor	F	0.5	North
ID4	Doctor	F	12	North
ID5	Doctor	F	5	North
ID6	Doctor	M	12	Central
ID7	Doctor	M	15	Central
ID8	Doctor	F	3	Central
ID9	Doctor	F	3	North
ID10	Doctor	F	4	South
ID11	Staff nurse	F	6	South
ID12	Staff nurse	F	6	South
ID13	Staff nurse	F	9	South
ID14	Staff nurse	F	4	Central
ID15	Staff nurse	F	15	North
ID16	Staff nurse	F	10	North
ID17	Staff nurse	F	4	Central
ID18	Staff nurse	F	15	Central
ID19	Pharmacist	F	10	South
ID20	Pharmacist	F	3	South
ID21	Pharmacist	M	17	Central
ID22	Pharmacist	F	4	North
ID23	Pharmacist	F	7	Central
ID24	Specialist-psychiatry	M	8	Central
ID25	Specialist-psychiatry	F	11	North
ID26	Specialist-psychiatry	M	10	Central
ID27	Specialist-psychiatry	F	7	Central
ID28	Specialist-medicine	F	8.5	South
ID29	Specialist-medicine	F	22	Central
ID30	Specialist-medicine	M	8.5	Central
ID31	Specialist-respiratory medicine	F	15	South
ID32	Specialist-respiratory medicine	M	26	South
ID 33	Specialist-respiratory medicine	F	6	Central

Programme and human resource planning

HCPs emphasized that there is a lack of long-term planning for programs and as a consequence patient-centeredness is not a key element in care delivery. They explained long-term planning issues related to deficiencies in fund allocation, several vertical programs leading to duplication of work and wastage of resources; and consequently, some stages of the program, such as screening, may function while others, such as treatment and follow-up often fail, leading to fragmentation of care.

> *"We screen and find out all those with issues, but do not have a provision to give them medications or the doctors to treat them. In such a situation, the system will not or cannot take responsibility. When we start it as a new programme such as initiatives for chronic respiratory conditions, initially it will run with a high intensity such as screening activities but later the administrator's concern will be that it is not sustainable." (ID32, Specialist, Respiratory medicine)*

> *"Many agencies and vertical programmes doing the same work, means multiple diabetes detection camps and comorbidities detection camp. They will do all those that are meant for screening and detecting new cases, but our patients who are used to taking treatment from secondary and tertiary care centers will go directly, and will again get screened." (ID29 Specialist, Medicine)*

Generally, doctors who have completed undergraduate training are posted at the primary care level. However, many doctors who have also completed specialty training work in FHCs. Some doctors working in FHCs with specialty training felt that their expertise could not be put into practice due to the hierarchical transfer of responsibility from primary care to higher centers for case management.

> *"Specialists should be rearranged and posted in taluk or district hospital to improve the quality; otherwise, we will not be able to manage the patients with the limited resources at the primary care level even if we can." (ID9, Doctor with specialty training in Medicine working at family health centre)*

Treatment guidelines and protocols

Most doctors at FHCs responded that they have several cases of patients with MLTCs. Doctors reported that common NCD MLTCs are diabetes, hypertension, dyslipidaemia, chronic obstructive pulmonary disease, cardiac diseases, and osteoarthritis. Staff nurses and pharmacists reported similar conditions for patients with MLTCs visiting the FHCs.

> *"Then I would say COPD cases and asthma along with diabetes and hypertension. Then joint pains, age-related all kinds of pain." (ID2, Doctor with specialty training in Paediatrics working at family health centre)*

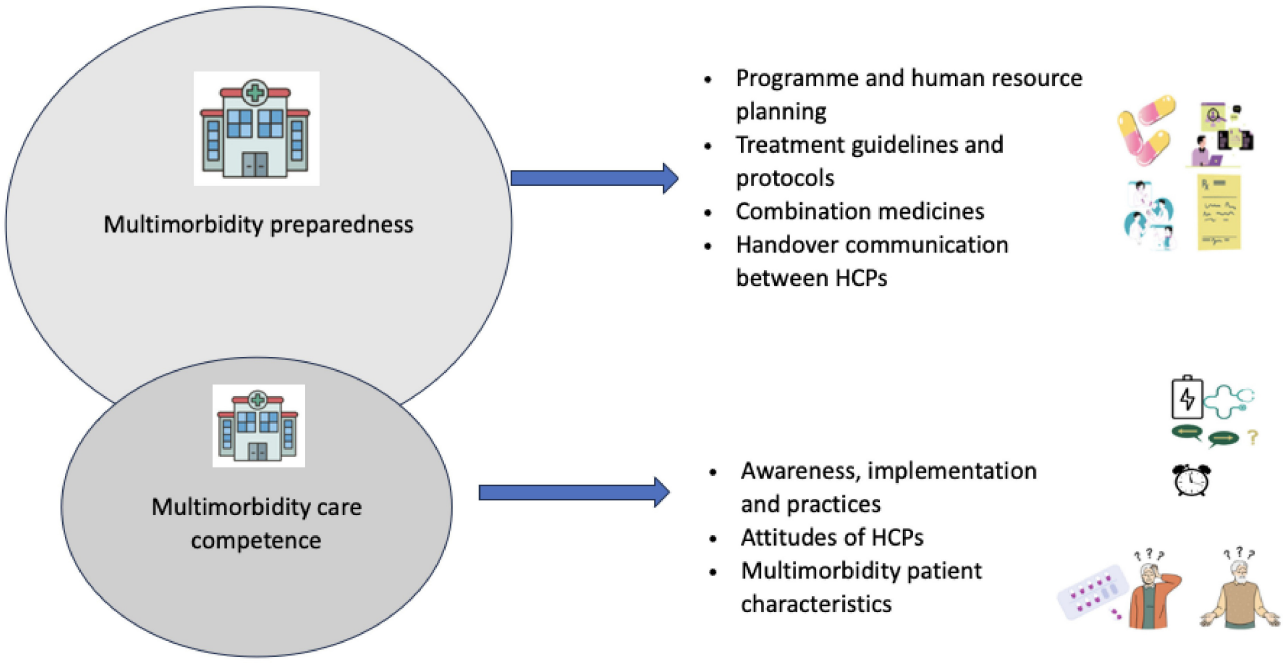

FIGURE 1
Themes and sub-themes illustrated.

HCPs at FHCs described their current approach to managing patients with MLTCs. They mentioned adhering to treatment protocols for single-disease management (where available) and attempting to manage multiple conditions together. They explained how patients with MLTCs have several NCDs, however HCPs may not be able to provide comprehensive care for patients due to lack of services available at the primary care. Several HCPs reported the need to focus on non-pharmacological interventions such as diet, physical activity and stress reduction for preventing and managing NCD MLTCs. They emphasized that currently they provide incidental health education for patients with NCDs, but they also recognize that behavior change is challenging and needs supportive mechanisms for patients to adhere to the recommended lifestyle modifications which are currently not available.

> *"So, for OA (osteoarthritis) knee, we can explain to them that painkillers are there. But they are only supportive management; physiotherapy and exercises are also part of it. We are not providing them at the primary care now. We do follow the STG (standard treatment guidelines)." (ID2, Doctor with specialty training in Paediatrics working at family health centre)*
>
> *"Whether patients make changes in diet or increase physical activity or not, we tell them about it without fail. We cannot tell them they will be free from all diseases or that their diabetes and hypertension will vanish forever. Moreover, most people want to know whether they can stop their medicines if they start to walk. A few would also ask if they could escape from getting affected by diabetes or hypertension… That's the only thing we can do." (ID4, Doctor working at family health centre)*

Most HCPs explained that having protocols and guidelines for managing patients with MLTCs particularly with emphasis on screening, early diagnosis and long-term care would be helpful. Both pulmonary and psychiatry specialists explained that they have developed guidelines for some specific conditions such as COPD, asthma, and depression. Two pulmonary specialists involved in the guideline development for COPD and asthma highlighted that they have included the common NCD comorbidities and their management. Specialists emphasized how the current system is highly single disease focused with several vertical programs running leading to missing comorbidities.

> *"Whether the screening for diabetes or hypertension is done or not done, when the patient reaches the medical officers' OP (outpatient consultation), they will focus on the primary concern for which the patient has come, so patient may get the treatment for that disease and may miss out on the additional comorbidities." (ID32, Specialist, Respiratory medicine)*

Combination medicines

Pharmacists and doctors at FHCs raised concerns about the limited availability of combination medicines within the public health system. They also highlighted that the public health system may have only specific fixed dosages for many common drugs, which increased the number of pills patients had to take, complicating medication adherence.

> *"The medicines prescribed for diabetic patients are single or fixed doses; they may need to take the same medicine twice or multiple pills to control their condition. Combination medicine is unavailable in cases like hypertension and diabetes in FHC." (ID5, Doctor working at family health centre).*

Further, HCPs at FHCs also highlighted the limited availability of medicines for several NCDs such as chronic kidney disease which affects many patients.

Handover communication between HCPs

HCPs reported that the implementation of electronic health records in the public health system would be beneficial for them to view patients' records and thus aid in information transfer between healthcare visits. However, many HCPs at FHCs reported difficulties in using electronic health records and need help to adapt to these changes, and specialists find documentation often incomplete.

> *"I think ehealth (electronic health records) is an advantage when it comes to old people, we will get their medical information once we check the health record. So even if they forget to bring all their past medical details in every visit, we will have some of the medical information in the system (electronic health records) because they come here regularly." (ID8, Doctor with specialty training in ENT working at family health centre)*
>
> *"…Along with screening for respiratory conditions, hypertension and diabetes were also supposed to be screened. When I open my patient's files, what I see is that BP is not recorded, and blood glucose is not recorded. When I view the records, these are not being measured nor documented and so it is not being implemented well at the primary care level." (ID32, Specialist, Respiratory medicine)*

Participants highlighted a prominent issue, the need for more effective communication among different HCPs across the health system. This problem was observed in the communication between specialty doctors and primary care doctors. HCPs from primary care reported that this lack of communication worsened when patients went to other HCPs; especially to HCPs from private healthcare settings.

> *"A problem here is that there is no proper system. They (patients) will go to any physician and get themselves treated. In such a situation, sometimes, we cannot give the medicines from here (FHC) that have been prescribed for them from elsewhere. Moreover, we will be unable to contact their doctor, and there will be a communication gap." (ID7, Doctor with specialty training in Community medicine working at family health centre)*

Multimorbidity care competence

Multimorbidity care competence describes the HCPs' reported knowledge, skills, and attitudes regarding managing people with MLTCs specifically with the changes implemented in primary care. It is split into three sub-themes: awareness, implementation, and practices; attitudes of HCPs and multimorbidity patient characteristics.

Awareness, implementation, and practices

Participants were asked to reflect on their experiences with the current programs in FHCs and how they fit or not with management of patients with MLTCs. Most doctors and nurses were aware of the need for screening patients with diabetes and hypertension for early diagnosis of long-term complications such as kidney diseases.

> *"The current rising epidemic is not infectious disease but non-communicable diseases. If kidney diseases are diagnosed earlier, we can delay the progression with medication rather than going to dialysis. Anyhow we may not be able to completely prevent the occurrence, but delay the onset of CKD, especially in diabetes patients. We can control and screen if they have CKD or liver diseases. There is no use once they reach the end stage." (ID9, Doctor with specialty training in Medicine working at family health centre)*

They also highlighted that currently most patients with MLTCs would be diagnosed elsewhere and would come to FHCs for repeat prescriptions. Most doctors and staff at FHCs reported how comprehensive services are not available for patients with MLTCs and hence it is often difficult to track or follow-up.

> *"What is happening now is that the patients come initially but after that they will not come for regular checkups correctly or may go to other centres (private) for treatment or they may not be taking treatment." (ID7, Doctor with specialty training in Community medicine working at family health centre)*

Both hospital specialists and HCPs at FHCs reported delays and inadequacies in the training for HCPs thus impacting the running of specialized clinics at FHCs. Specialists noted inconsistencies in screening for respiratory and mental health issues at FHCs. These inconsistencies ranged from missing screening to over diagnosing or inappropriately diagnosing respiratory conditions. Additionally, they felt that bidirectional screening for patients with known diabetes or other long-term conditions are not routinely screened for associated comorbidities, leading to missed opportunities for early intervention.

> *"Here, the first thing needed is to identify that the patient is anxious or is having depression. And how much of this is identified in the primary care setting, I do not know." (ID31, Specialist, Respiratory medicine)*

Most HCPs from FHCs in this study reported having received training for running specialized clinics. However, most felt they were not sufficiently equipped to carry out the screening.

> *"Two of our staff nurses have received training for the fundus test. But they are not confident enough to handle it themselves." (ID7, Doctor with specialty training in Community medicine working at family health centre)*

Nurses also reported varying practices in screening patients referred for sleep or emotional difficulties, or mental health conditions.

> *"No, we don't use any [assessment] scales to measure or the questionnaire; we just talk to them, and if we feel like they need assistance, we will provide that." (ID16, Staff nurse working at family health centre)*

Even with additional HCPs at FHCs, HCPs reported limited time for interactions with patients at the primary care level, hindering effective management of patients with MLTCs.

> *"Usually, screening time is significantly less in the periphery. We can detect multimorbidity in the first instance itself but the amount of time available to a primary care physician for screening is less. There is a mismatch in the patient load and time available." (ID 28, Specialist, Medicine)*

Attitudes of HCPs

Within the background of HCPs reporting no protocols or guidelines or provisions for managing patients with MLTCs in Kerala, when asked how to improve care for patients with MLTCs in primary care, they articulated organizational boundaries for responsibilities and tasks at the FHC level which suggests that primary care may not be suitable for managing patients with MLTCs. As a result, they believed that providing care for individuals with MLTCs at the primary care level is not feasible. They asserted that implementing additional services at the FHC is necessary if they must manage MLTCs, which would, in turn, require increased staff. Some HCPs felt that managing complex MLTCs should not be the responsibility of primary care.

> *"If we added an ECG setup but did not have enough staff to manage it, we can refer them to a centre where the facility is available. Therefore, there will be an unnecessary delay, or we will need to have more and more necessary support factors related to it (screening or support activities), like more staff, facilities, admits, observation, etc. The patients may feel comfortable with this, but by starting one service at the FHC level, we will need to arrange more related facilities. Honestly, I am not convinced we need to arrange more facilities like that." (ID4, Doctor working at family health centre)*

Doctors at FHCs emphasized a prevailing organizational culture encouraging patient referrals to specialists or higher centers with better facilities. They cited past experiences and saw it as a risk to treat these patients, especially in emergencies. Furthermore, doctors pointed out that patients with MLTCs often prefer consulting their specialists when deciding on medications or titrating the doses or further treatment plans.

> *"After any cardiac intervention, it is unlikely that patients will continue coming here; they will most likely revert to their previous specialists. Besides those who need regular medication or BP/sugar check-ups, very few patients rely on us. Additionally, post-intervention, some patients may experience further symptoms, and as a primary care facility, we cannot afford to take unnecessary risks. That is why we often refer them to a cardiology specialist. It is worth mentioning that even the general hospital lacks a cardiologist. When higher-level facilities are hesitant to take risks, it becomes challenging for us at the primary care level to do so." (ID9, Doctor with specialty training in Medicine working at family health centre)*

Particularly with respect to mental health conditions, specialists reported that doctors in primary care were not inclined to screen for them in patients with MLTCs even with the guidelines. Hospital specialists and doctors at FHCs reported that they try to refer patients with MLTCs, especially when the patient has had a history of previous cardiovascular intervention or when the patient has psychiatric conditions, as they do not feel obliged to manage them.

> *"I have completed MD in ENT surgery. Many people with psychiatric-related symptoms come to our FHC. It can be difficult to handle people with mental health problems; we cannot change the dosage of their medicines or anything like that. We can give them the little help they need by repeating the medicines. Those who require counselling are usually referred for a psychiatric consultation." (ID8, Doctor with specialty training in ENT surgery working at family health centre)*

Several doctors at FHCs reported actively liaising with the local self-governments for adding services for patients with NCDs including screening for thyroid conditions, medication support for patients on dialysis and secured provisions for gym equipment. However, they pointed out that these additional services are not sustainable without regular funding and therefore they often feel demotivated to work within primary care.

> *"This time we have organised a diabetic neuropathy follow-up project at a panchayat level which includes screening camps for neuropathic complications but only if it is at government level, there is consistency in funding and we can provide services that patients need, or else it is certainly disappointing that we cannot continue the work we started." (ID6, Doctor working at family health centre)*

Multimorbidity patient characteristics

HCPs at FHCs pointed out that managing most patients with MLTCs is difficult because these patients often have many symptoms and are usually older, which brings additional challenges. Both doctors and nurses have emphasized that many patients, particularly older individuals with MLTCs, encounter challenges being alone at home. These difficulties mainly revolve

around their ability to manage medications and adhere to prescribed diets. Being alone at home may lead to forgetfulness, confusion, or lack of support. Their medical conditions may restrict their ability to travel, leaving them with limited activities.

> *"Mostly older adults, all they need is emotional support. And they are sad when it comes to having to deal all their different conditions." (ID16, Staff nurse working at family health centre)*

Most HCPs noted that there is poor awareness regarding complications of diabetes and hypertension. They felt that if people are being guided and supported to manage lifestyle, medicines with adequate monitoring and follow-up, MLTCs may be delayed.

> *"The problem with the younger age group is that they are not aware of complications. Actually, we should make them comprehend the consequences. See, life is not what we see or enjoy in the next 5, 6 or 7 years it is something which lasts longer. If a person loses his ability to see or has erection issues, then what will be his quality of life after that? or any kidney issues and then life-long dialysis. What will happen to his family?" (ID7, Doctor with specialty training in Community medicine working at family health centre)*

HCPs noted that the role of primary care could have been better understood by patients; especially their role in monitoring for complications, delaying progression to multiple conditions and ongoing management of MLTCs. Most HCPs reported that follow-up and monitoring for further complications was poor among younger patients and that younger patients stop medicines when the blood reports are normal. However, they felt that older patients were aware of the facilities available in the FHCs and sub-center level and would visit the facilities for monitoring their blood glucose and blood pressure.

> *"Once they (patients) test and if their BP is normal, they decide to stop taking the medicine. For cholesterol, the same thing happens. If the value is less than 200, they will stop taking the medicine." (ID23, Pharmacist working at family health centre)*

HCPs were aware that patients with MLTCs have a lot of issues that lead to non-adherence to medications. They pointed out that there were many gaps in the care system and felt that there is a need for improving the support systems for patients with MLTCs. HCPs pointed out financial difficulties as a reason for non-adherence, noting that medications for patients with MLTCs may not always be accessible even within the public healthcare system. Further, HCPs suggested that the patients often perceive the quality of medications provided by the public health system as inferior, further contributing to non-adherence to prescribed treatment regimens. Additionally, most doctors responded that the medication adherence issue is more when the patients are younger as they may have difficulty accepting that they are sick.

HCPs felt that younger and older people with MLTCs have difficulty adhering to recommended lifestyle modifications. Many HCPs recognized and felt that most people with MLTCs are under immense stress and need better support for managing lifestyle. They highlighted how younger adults are more stressed due to their work environments, while young and older patients are stressed regarding financial difficulties in daily life. They also noticed that most stress in people with multiple conditions is not managed well, leading to long-term health issues.

> *"Younger age group would show reluctance in taking medicines and not only that they will not have any diet control and suffer from excessive stress and no lifestyle modification. What we can do is provide some advice. We tell them what we think they can do at home. For example, to walk at least 30 minutes, but right now we can only tell them.... they may need more individual support to plan and perform these self-care activities." (ID5, Doctor working at family health centre)*

Barriers and facilitators for managing MLTCs in primary care

The barriers and facilitators for managing MLTCS in primary care were organized under three levels; health system, organizational (at the primary care level) and HCP, and patient (see Figure 2). Overall, most barriers were classified at the health system level. The presence of a program for chronic respiratory conditions and mental health conditions at the primary care level and the ongoing implementation of electronic health records were facilitators for management of patients with MLTCs in primary care. Barriers at the health system level include poor planning, lack of treatment guidelines and protocols, lack of combination medicines and little or no protocols for communication between HCPs at the primary care and district/medical colleges. At the organizational and individual HCP level, HCPs' awareness regarding the need for monitoring for complications and liaison with local self-governments to organize screening and medications for long-term conditions such as thyroid, chronic kidney disease were identified as facilitators. Inconsistent implementation of specialty clinics, perceived confidence issues in implementing the screening due to insufficient training, attitudes toward screening and managing mental health conditions and reluctance to manage medications for patients with MLTCs indicated barriers to care. At the patient level, HCPs' awareness of the reasons for patient non-adherence and difficulties in management of lifestyle particularly due to financial difficulties and stress was a facilitator in managing care. HCPs identified the barriers of managing patients with several symptoms, patients' reliance on specialists and poor medication and lifestyle management.

Discussion

Our study represents one of the first qualitative reflections of the perspectives of HCPs in India in managing patients living with MLTCs in primary care settings in Kerala, India. The study included the perspectives of specialists, doctors, nurses, and pharmacists regarding the management of patients living with MLTCs at primary care and can assist in informing development of this evolving healthcare system. The emergent findings were grouped into two main themes; multimorbidity preparedness, and multimorbidity care competence and the barriers and facilitators

Barriers	Levels	Facilitators
• Lack of long-term planning (non-systematic fund allocation, competing vertical programmes, reduced priority for patient centredness); lack of comprehensive services • Lack of treatment guidelines and protocols • Poor human resource distribution • Lack of combination medicines; lack of medicine availability for chronic conditions such as thyroid insufficiency • No protocols for handover communication between HCPs and specialists • Difficulties in consistently utilising electronic health records • Insufficient training for HCPs to run specialty clinics • Limited time per patient for HCPs during consultations	**Health system**	• Presence of programme for chronic respiratory and mental health programme at primary care • Electronic health records; perceived value-if implemented may improve documented information transfer between specialists and HCPs at FHCs • Medicine availability for diabetes, hypertension, chronic respiratory conditions such as asthma
• Inconsistent implementation and differing practices of clinics for respiratory and mental health due to inadequate training, reluctance in taking responsibilities and risks • Viewing the changes in FHCs such as specialty clinics as burden, additional tasks • Organisational culture encouraging patient referrals to specialists	**Organisational and individual HCPs**	• Awareness of the need for monitoring patients with diabetes and/hypertension for early signs of complications to prevent MLTCs • Awareness of protocols for single conditions such as diabetes, hypertension • Motivated HCPs liaising with local self-governments for adding services for patients with chronic conditions
• Poor understanding of role of primary care in monitoring and follow-up of MLTCs • Poor understanding of patients regarding complications • Poor medication and lifestyle management adherence • Illness burden, factors such as financial difficulties, poor stress management for patients with MLTCs, perceived poor quality of medicines may lead to non-adherence to medicines and life-style modifications	**Patient-level**	• HCPs' awareness of factors affecting adherence to medicine and lifestyle management in patients' living with MLTCs

FIGURE 2
Barriers and facilitators for managing patients with MLTCs in Kerala.

were organized under health system, organizational and individual HCPs, and patient-levels. Overall, most barriers were identified at the health systems level which hindered subsequent management of patients with MLTCs at the organizational and HCP level.

The HCPs highlighted several barriers at the health system level, including poor planning, lack of treatment guidelines, inadequate communication with other HCPs, and human resources, which collectively hinder the comprehensive and patient-centered management of patients with MLTCs. Our study acknowledges initiatives like the National Non-Communicable Disease (NCD) program in 2012 (36) and subsequent health sector reforms like Aardram in 2017 (23) in Kerala which aimed to enhance primary care services. However, our findings suggest that as well as control of conditions remaining a challenge, that health systems and HCPs continue to focus on achieving control for individual conditions, particularly (CVD, diabetes, respiratory illnesses) rather than addressing the broader challenges faced by patients with MLTCs. Further, our study shows that the exclusion of several chronic conditions such as musculoskeletal, neurological conditions and chronic kidney diseases have failed to address much of the NCD MLTCs' burden among the poor. This has been acknowledged as a limitation to global NCD strategies with the focus on prevention and management of selective NCDs (37, 38), our study shows how HCPs struggle in providing patient-centered and comprehensive care.

Previous research has highlighted a need for treatment guidelines for managing MLTCs globally (39, 40). Our study results suggest that health systems in Kerala and similar environments need to evolve to respond to the needs of HCPs to equip them to manage care for patients with MLTCs. Other studies have clearly stated that health service delivery should be guided by treatment protocols considering the potential interplay of multiple chronic conditions throughout the entire process, from diagnosis to management (41, 42). Along with an environment that enables the delivery of quality health care, our results also suggest the need for prioritization of the needs of individuals with MLTCs in the existing primary care guidelines and policy documents. The average consultation length in primary care settings is an essential determinant of quality of care as reported by Kruk et al. (43). Substantial evidence from clinical trials also supports longer consultations to improve the quality of life in individuals with MLTCs (44). While prioritizing care delivery for individuals with MLTCs in primary care, policy documents and guidelines should recommend reasonable consultation length.

Electronic medical records systems are considered a key facilitator for managing MLTCs. Available evidence supports the use of electronic medical records in care coordination (45). It promotes the quality and safety of patient care and improves the efficiency of HCPs' time and resource use, especially in managing chronic conditions. However, the introduction of electronic

medical records in the primary care system needed to be better received by some HCPs in our study. Frequent disruptions in internet availability, lack of familiarity, the longer learning curve to use electronic medical records, and high patient load were cited as the main reasons for reluctance to use electronic medical records which are similar to previous findings (46, 47). Investments in improving the infrastructure and sufficient training may help the HCPs to adopt the electronic medical records system for efficient use of their time while managing chronic conditions.

Globally, failure to successfully implement and sustain change over the long term remains a major problem in primary care. Modifications made to routine clinical practice are known to be complex, and for them to be sustained over time, HCPs' behavior needs to change accordingly (48). Programmes such as ASWASAM trains doctors and staff nurses to provide psychosocial counseling and clinical guidelines for screening and management of depression. However, as found in this study, these are not easy to be adopted by HCPs. Interventions that aim to reorganize and strengthen new behavioral norms and connect them with the actions of peers and reference groups, such as opinion leaders, educational meetings with guidelines, and reminders for HCPs, are more likely to result in changes in behavior (49). However, these changes in clinical practice guidelines such as those envisioned in the ASWASAM and SWAAS, need to be well-supported with training, reminder systems and collaboration with specialists.

Our study revealed that the HCPs at FHCs interviewed relied on hospital specialists to manage patients with MLTCs. Lack of confidence in managing complex cases, training deficiencies and patients' preferences for specialist care were the primary reasons for referral to specialists. Findings from our qualitative study with patients with MLTCs also confirm that patients prefer hospital specialists to manage their multiple conditions (26). Globally, there have been difficulties for primary care providers regarding clarity in their role in screening and managing medications for patients with MLTCs (50, 51). In Kerala, where private and public specialists (52, 53) are available for providing care, our study emphasizes the need for a shift in the mindset of primary care providers, specialists and patients in managing MLTCs given that Kerala is one of the states with highest out-of-pocket expenditures for healthcare (54). Along with preventing chronic NCDs, primary care should ideally play a prominent role in monitoring and managing the complexities of patients with MLTCs (42). Collaborative interventions (9) that enhance communication between primary care providers and specialists for deciding management plans for patients with MLTCs must be explored and implemented. Generalists, medical officers (non-specialists), nurses, and pharmacists with adequate training can increase the coverage and ensure the quality of primary care delivery for individuals with MLTCs in LMIC settings.

Healthcare providers in this study identified challenges related to patient behaviors, such as lack of medication adherence, loss of follow-up, and difficulties in lifestyle management. From the HCPs' point of view, having combination medicines could help patients in adherence to medications. This is in line with the World Health Organization's recommendation of adding a polypill or fixed-dose combinations of multiple drugs for prevention and management of cardiovascular diseases to the World Health Organization Model List of Essential Medicines (EML) (55).

Strengths and limitations

Our study provides critical insights into the LMIC perspectives on challenges faced by HCPs in primary care for managing MLTCs. Furthermore, the Kerala context adds value to the literature by exploring the health system challenges of managing MLTCs in a transitioning primary care system. Despite introducing health sector reforms recently in Kerala to manage NCDs in primary care effectively, the HCPs' perceptions indicate sub-optimal health system preparedness in managing MLTCs. Our study stands out as one of the few qualitative studies (56, 57) that have delved into HCP perspectives on the care they provide to patients with MLTCs within such a setting. We have selected HCPs from three different Kerala zones, improving the findings' possible transferability. A potential limitation is that while we have managed to gather perspectives of HCPs from primary care centers upgraded to FHCs, the FHCs could be in separate phases of upgrading. Therefore, HCPs' views on resources would have reflected the transition stage of upgrading primary health centers to FHCs. However, this is an actual representation of changes happening within the health system.

Conclusion

Our study findings highlight substantial barriers at the health system level, including the need for treatment guidelines, inadequate communication among HCPs, and limited resources, which hinder the comprehensive management of patients with MLTCs in primary care in Kerala. These barriers highlight the need for further research that considers the interconnected relationships and dependencies within the health system. Addressing the systemic issues, rather than focusing on isolated components, can help avoid unintended consequences and achieve a more effective and integrated management of MLTCs. Group model building could be used to develop a shared understanding of interconnected factors influencing health system performance and access a wider range of potential leverage points for intervention. Hence, by developing an understanding on how positive outcomes are consistently achieved, we can design and implement intervention models that enhance overall system performance and ensure better care for patients with MLTCs.

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 Sree Chitra Tirunal Institute for Medical Science and Technology, Thiruvananthapuram. 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

TL: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – review & editing. LJ: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing – review & editing, Validation, Visualization, Writing – original draft. NS: Data curation, Investigation, Project administration, Writing – review & editing. AK: Data curation, Formal analysis, Investigation, Resources, Writing – review & editing. JD: Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. PG: Conceptualization, Funding acquisition, Supervision, Validation, Writing – review & editing. SG: Conceptualization, Formal analysis, Funding acquisition, Supervision, Validation, Writing – review & editing. SH: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. JT: Conceptualization, Funding acquisition, Supervision, Writing – review & editing. MV: Conceptualization, Funding acquisition, Resources, Writing – review & editing. SM-H: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. PJ: Conceptualization, Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, 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/fpubh.2025.1480710/full#supplementary-material

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Cardiometabolic multimorbidity and frailty in middle-aged and older adults: a cross-nationally harmonized study

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Background: Cardiometabolic diseases are prevalent among ageing populations and have a close association with frailty. However, the cumulative impact multiple cardiometabolic diseases have on frailty remains underexplored.

Methods: This study used data from four international cohorts – HRS, CHARLS, ELSA and SHARE – to examine the correlation between frailty and cardiometabolic diseases (CMD). The frailty index was used for assessing frailty and statistical analyses were performed as a means of analysing the correlation between the number of cardiometabolic conditions and frailty severity. Linear regression models were employed to evaluate the associations between CMD and frailty severity.

Results: The study found that as the number of cardiometabolic diseases increased, the frailty index rose significantly [one disease, $\beta = 7.80$ (95% CI: 7.70 to 7.90) $p < 0.05$; two diseases, $\beta = 17.92$ (95% CI: 17.76 to 18.08) $p < 0.05$; three diseases, $\beta = 28.79$ (95% CI: 28.41 to 29.17) $p < 0.05$]. Stroke was found to have the most pronounced impact on frailty ($\beta = 12.34$ [95%CI 12.20 to 12.48] $p < 0.05$) and the coexistence of multiple conditions served to amplify the symptoms of frailty.

Conclusion: This study highlights the compounded impact multiple cardiometabolic diseases have on frailty and also emphasizes the necessity for early intervention.

KEYWORDS

multicohort cardiometabolic diseases, frailty index, diabetes, heart disease, stroke, middle-aged and older people

Introduction

Cardiometabolic diseases (CMD), including stroke, diabetes and heart disease, have become increasingly prevalent among the ageing population (1). As people age, their risk of developing these chronic conditions increases significantly as a result of a combination of genetic, lifestyle and environmental factors (2–4). Diabetes, which is characterized by impaired glucose regulation, is particularly common in older adults and is often compounded by obesity and physical inactivity (5). CMDs, which involve heart failure, hypertension and coronary artery diseases are prevalent in ageing populations and contribute to increased morbidity and mortality (6). Similarly, stroke incidence increases with age and is driven by factors including hypertension, atherosclerosis and atrial fibrillation (7). These diseases are highly prevalent and

also frequently coexist, which compounds the health burden of older adults, increasing the risk of disability and frailty and lowering their quality of life (8, 9).

In older people, frailty is a prevalent and debilitating condition that is marked by an increased susceptibility to unfavourable health problems and reduced physiological reserves (10). The key factors that contribute to frailty include ageing, chronic diseases, physical inactivity, malnutrition and psychological stress (11). These factors serve to create a vicious cycle, with frailty negatively impacting multiple health domains, including functional impairment, reduced mobility and a loss of independence (12, 13). As frailty progresses, life quality is significantly diminished by impaired mental health, physical capacities and social interaction (14, 15). In addition, frailty has a close association with higher risks of hospitalization, disability and mortality (16, 17).

Cardiometabolic diseases such as stroke, diabetes and heart disease make a significant contribution to this decline in physical function by impairing critical physiological processes (18, 19). These conditions lead to vascular damage, insulin resistance, muscle wasting and neurodegeneration, which all undermine physical capacity and increase frailty risk (20–22). Frailty becomes more pronounced as the number of cardiometabolic diseases increases, with a progressive decline in physical strength and overall resilience (23).

Cardiometabolic diseases are highly prevalent among older populations and have been shown to be strongly associated with frailty (24–26). However, existing research has predominantly focused on the impact of single cardiometabolic conditions on frailty, with limited exploration of the cumulative effects of comorbid cardiometabolic diseases (27). Moreover, most studies to date are based on data from a single region, lacking cross-national validation. This study leverages four international longitudinal cohorts (HRS, CHARLS, ELSA, and SHARE) to systematically examine how multiple cardiometabolic diseases interact to influence frailty, while also investigating the moderating effects of gender and age in this relationship.

Although previous studies have examined the associations between CMD or cardiometabolic multimorbidity (CMM) and outcomes such as depression, cognitive decline, and disability (28–30), these studies primarily focus on individual health outcomes rather than the broader construct of frailty. The uniqueness of our study lies in its comprehensive approach to assessing how the cumulative impact of CMD exacerbates frailty. By constructing a Frailty Index, we evaluate an individual's health holistically, considering physiological, psychological, and functional domains. This approach moves beyond the limitations of studying isolated diseases or impairments and provides a more integrated understanding of health outcomes. Our research fills a significant gap in the current literature and offers critical insights that can inform the development of public health policies and targeted intervention strategies.

Methods

Study design and population

This integrated multicohort analysis used data from four international longitudinal cohorts targeting older and middle-aged people: the China Health and Retirement Longitudinal Study (CHARLS), the Health and Retirement Study (HRS), the Survey of Health, Ageing and Retirement in Europe (SHARE) and the English Longitudinal Study of Ageing (ELSA). The study used data from approximately overlapping time frames: HRS covers waves 10 to 15 (2010–2020), CHARLS includes waves 1 to 4 (2011–2018), ELSA encompasses waves 7 to 9 (2014–2018) and SHARE spans waves 4 to 7 (2011–2017) (Supplementary Table 2). Participants needed to be 50 years of age or older to be included and exclusions were applied to individuals with missing data relating to cardiometabolic diseases or frailty index. The study received ethical approval from the relevant committees for each study and participants were recruited after providing written informed consent.

Exposure assessment

In the context of cardiometabolic diseases, the study focused on diabetes, heart disease and stroke as these conditions all have the potential to exacerbate frailty. The presence of these diseases was determined by face-to-face interviews between researchers and participants and supplemented by self-reported medical histories that were obtained from structured questionnaires. The cardiometabolic disease status of participants was classified on the basis of the total number of conditions they had (i.e., diabetes, heart disease or stroke). Participants were then categorized into three groups: those without any cardiometabolic disease, those with a single cardiometabolic condition and those who exhibited cardiometabolic multimorbidity (with two or more coexisting conditions).

Outcome assessment

The frailty index, which quantifies the cumulative burden of age-related health deficits, was used to assess frailty (31). In accordance with previous studies, items that could be consistently applied across all four cohorts were selected (32, 33). After data screening, 30 items from the CHARLS, HRS, ELSA and SHARE surveys were included to construct the frailty index. These items encompassed self-reported health status, a range of chronic disorders, depression, functional limitations and cognitive impairment (Supplementary Table 3). Most of the items were dichotomised based on established cut-off values, with a score of 0 denoting the lack of a deficit and a score of 1 denoting its existence. Self-reported measures of general vision, hearing, health status and cognition were scored on a scale from 0 to 1, with higher scores indicating more serious deficits. The frailty index was computed by summing the deficits present in each individual, dividing by 30 and then multiplying by 100 for this study. Therefore, the frailty index was theoretically a continuous variable with a range from 0 to 100. Participants who missed any of the 30 items in the four databases were excluded from the process of frailty index calculation.

Data collection

The following information was collected for this study: (i) demographic information: this consisted of marital status, sex, age and educational attainment. Three groups were created based on educational attainment: lower secondary education or below, upper secondary and higher than upper secondary. Marital status was

divided into married and other marital statuses (such as separated, single, widowed and divorced). (ii) Lifestyle information: information was collected related to drinking and smoking patterns. Physical activity was defined as engaging in moderate or vigorous exercise at least once per week. (iii) Anthropometric measurements: body mass index (BMI). (iv) Medical history: information was gathered relating to the presence of hypertension, lung disease and cancer. For further details, please see Supplementary Table 4. In the data preprocessing of this study, we employed a complete case analysis method, including only samples with complete data for analysis. Variables or samples with a high proportion of missing values were subject to rigorous screening and exclusion to ensure data integrity.

Statistical analysis

For continuous variables with a normal distribution, the data was presented as mean ± standard deviation (SD) and group differences were assessed through the use of ANOVA. Categorical variables were expressed as numerical values (percentages) and intergroup differences were analysed using Pearson's chi-square test.

In the assessment of cardiometabolic diseases, we not only considered the classification based on the number of cardiometabolic diseases but also further analyzed the impact of different cardiometabolic diseases combinations on the frailty index. Specifically, we categorized the subjects into the following groups based on whether they had diabetes, heart disease, or stroke: (1) diabetes only, (2) heart disease only, (3) stroke only, (4) both diabetes and heart disease, (5) both diabetes and stroke, (6) both heart disease and stroke, and (7) all three diseases. Linear regression models were used to assess the relationship between cardiometabolic diseases and frailty index. Multiple models were constructed, each adjusting for a different set of covariates to provide a more detailed understanding of their impact on the observed association. Model 1 included no adjustments, Model 2 adjusted for age and gender, and Model 3 adjusted for age, gender, marital status, education, obesity, hypertension, cancer, lung disease, physical activity, and current smoking and drinking status.

Subgroup analyses were conducted to assess whether the association between CMD and the frailty index varies in strength across different populations. Participants were divided into different subgroups based on their gender, age (less than 65 years vs. more than 65 years), marital status, drinking and smoking habits and physical activity. MSTATA software[1] and R software (version 4.3.1) were used for all of the statistical analyses. A two-sided *p*-value of below 0.05 was considered to be statistically significant.

Results

The flowchart for the investigation population screening procedure in HRS, CHARLS, ELSA and SHARE can be seen in Supplementary Figures 1–4. There was a total of 403,609 participants and their mean age was 66.7 (SD 10.3) years. 224,867 (55.7%) of the participants in the final analytic cohort were female and 178,740 (44.3%) were male. Figure 1 shows the distribution of cardiometabolic diseases in HRS, CHARLS, ELSA and SHARE. 257,525 (63.8%) of the participants were free from any cardiometabolic diseases, while 146,084 (36.2%) exhibited at least one form of cardiometabolic disease. The frailty index for participants without cardiometabolic diseases was 14.2 (SD 11.2). In contrast, those with a single cardiometabolic disease had a higher frailty index of 25.1 (SD 14.4), while those with two or more cardiometabolic diseases exhibited an even further increase, with a frailty index of 37.5 (SD 17.6) (Table 1). The baseline table classified by diabetes, heart disease and stroke is shown in Supplementary Table 5. The distribution of the frailty index across the various databases can be seen in Supplementary Figure 5.

Participants without cardiometabolic diseases were used as the reference group in this study. Among those with a single cardiometabolic condition, a modest yet statistically significant increase in frailty index was observed [unadjusted $\beta = 7.80$ (95% CI: 7.70 to 7.90)]. In addition, a more rapid increase in the frailty index was observed with the increasing number of cardiometabolic conditions. More specifically, the frailty index increased significantly in individuals with two cardiometabolic diseases [unadjusted $\beta = 17.92$ (95% CI: 17.76 to 18.08)] and more markedly in those with three cardiometabolic diseases [unadjusted $\beta = 28.79$ (95% CI: 28.41 to 29.17)]. Model 2 made adjustments for both gender and age, while Model 1 was an unadjusted model. Several covariates, including obesity, cancer, lifestyle factors and educational attainment, were taken into consideration by Model 3 (Table 2). These patterns remained significant even after adjustments for covariates were made.

Analysis of the relationships between specific combinations of individual cardiometabolic diseases and frailty indicated that stroke had the most significant effect on the frailty index of all the single cardiometabolic conditions (Figure 2). Among combinations of two coexisting cardiometabolic diseases, the pair of diabetes and stroke was found to be most strongly associated with a more rapid increase in the frailty index. Furthermore, in comparison to the presence of one or two cardiometabolic diseases, the coexistence of three cardiometabolic diseases was found to have a significant association with a more substantial increase in the frailty index (Supplementary Tables 6–9).

In addition to the overall analysis, the association between the prevalence of cardiometabolic diseases and frailty across the four datasets was examined. A dose–response correlation between the number of cardiometabolic diseases and the frailty index was found in the HRS, with β values increasing progressively as the number of comorbidities increased [single cardiometabolic disease: $\beta = 3.72$ (95% CI: 3.55 to 3.89), two cardiometabolic diseases: $\beta = 10.15$ (95% CI: 9.91 to 10.38), three cardiometabolic diseases: $\beta = 17.61$ (95% CI: 17.10 to 18.13)]. The CHARLS, ELSA and SHARE datasets all exhibited a similar trend (Figure 3).

In the subgroup analysis, we employed interaction tests (P for interaction) to assess the differences in the strength of the association between CMD and the frailty index across different subgroups. The results showed that the interaction effects of age (P for interaction <0.01) and gender (P for interaction <0.01) were statistically significant, while the interaction effects of current drinking (P for interaction = 0.912), current smoking (P for interaction = 0.993), and physical activity (P for interaction = 0.134) were not significant. Specifically, in the older

1 www.mstata.com

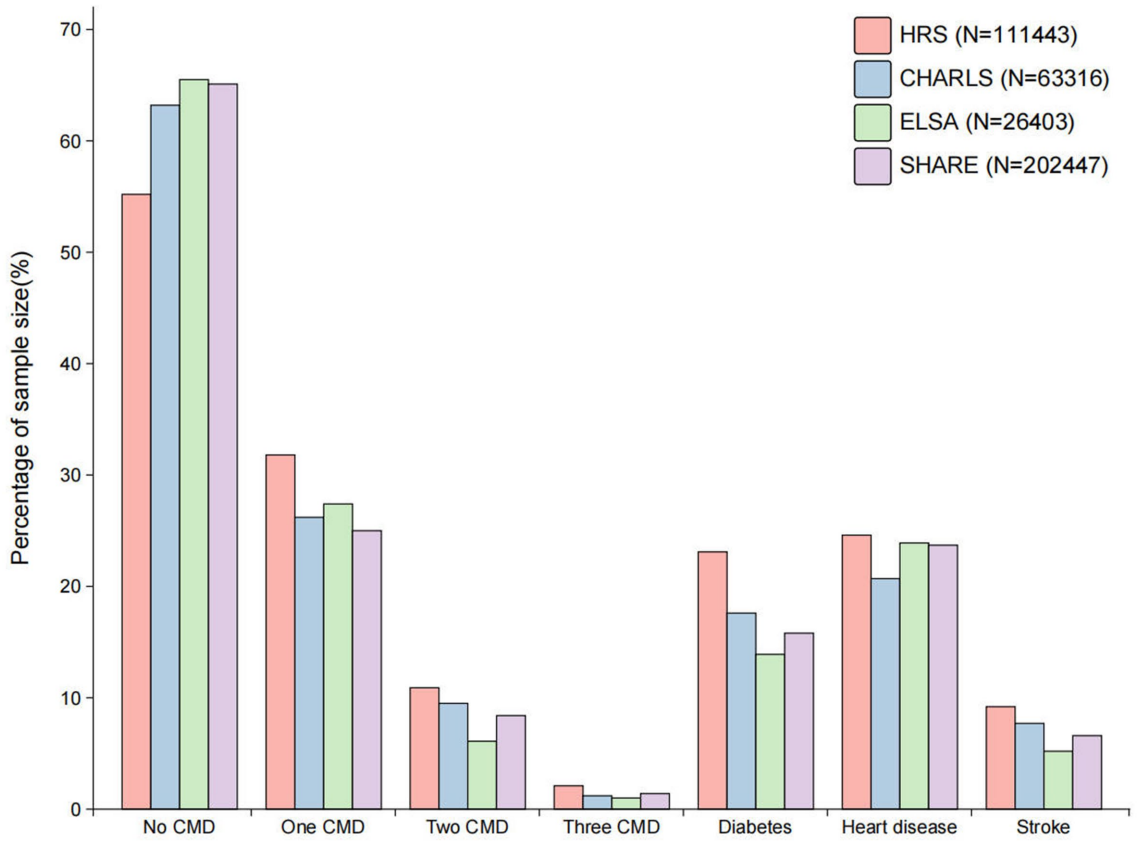

FIGURE 1
The distribution of cardiometabolic diseases across the various databases. CMD, cardiometabolic diseases; HRS, Health and Retirement Study; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; SHARE, Survey of Health, Ageing and Retirement in Europe.

population (age ≥ 65), the association between CMD and the frailty index was stronger (β = 6.74, 95% CI: 6.62–6.86, $p < 0.01$), whereas in the younger population (age < 65), the association was weaker (β = 5.00, 95% CI: 4.87–5.14, $p < 0.01$). Similarly, in the female subgroup, the association was more pronounced (β = 7.37, 95% CI: 7.24–7.51, $p < 0.01$), while in the male subgroup, the association was weaker (β = 5.76, 95% CI: 5.63–5.88, $p < 0.01$). These results suggest that gender and age may be important moderating factors in the relationship between CMD and the frailty index, while drinking, smoking, and physical activity do not significantly impact this relationship (Supplementary Figure 6).

Discussion

This study has summarized the prevalence of cardiometabolic diseases across four international cohorts (HRS, CHARLS, ELSA and SHARE) and explored the relationship between cardiometabolic multimorbidity and frailty. The findings revealed a significant increase in frailty index as the number of cardiometabolic conditions increased, with greater multimorbidity having a significant correlation with more severe frailty. More specifically, those with a single cardiometabolic disease already had a higher frailty index, while those with two or more conditions had a more pronounced increase in frailty. Further analysis served to demonstrate a distinct dose–response correlation between the frequency of cardiometabolic diseases and the frailty index, particularly in individuals with stroke, where the increase in frailty was particularly marked. The coexistence of diabetes and stroke was found to have the most significant impact on frailty, potentially due to the compounded effect these conditions have on physical decline and overall health burden. These findings serve to highlight the substantial impact cardiometabolic multimorbidity has on frailty in older populations, which shows that there is a need for clinical interventions to address multiple comorbidities in older adult patients.

Cardiometabolic diseases, which include diabetes, heart disease and stroke, share several overlapping pathophysiological processes that make a collective contribution to the exacerbation of frailty (34). One of the primary mechanisms is chronic inflammation, which is a common feature with all of these conditions (35, 36). In diabetes, insulin resistance promotes a pro-inflammatory state (37), while heart disease is associated with systemic inflammation that is driven by endothelial dysfunction and atherosclerosis (38, 39). Stroke leads to neuroinflammation as a result of cerebral ischemia and neuronal injury, particularly in its chronic phase (40, 41). The systemic elevation of inflammatory markers, such as tumour necrosis factor-α (TNF-α) and C-reactive protein (CRP) (42), is important in the pathogenesis of frailty as it contributes to vascular damage (43),

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TABLE 1 Characteristics of participants by cardiometabolic disease status.

	No cardiometabolic diseases (*n* = 257,525)	One cardiometabolic disease (*n* = 106,822)	Cardiometabolic disease multimorbidity (*n* = 39,262)
Frailty	14.23 ± 11.23	25.11 ± 14.44	37.54 ± 17.57
Age	64.56 ± 9.66	69.65 ± 10.32	72.29 ± 10.04
Missing	207	54	13
Gender			
Female	147,173 (57.1%)	57,569 (53.89%)	20,125 (51.3%)
Male	110,350 (42.9%)	49,253 (46.11%)	19,137 (48.7%)
Missing	2	0	0
Educational attainment			
Lower secondary education or below	103,142 (40.3%)	45,186 (42.56%)	17,720 (45.3%)
Upper secondary	100,074 (39.1%)	43,229 (40.71%)	15,957 (40.8%)
Higher than upper secondary	52,626 (20.6%)	17,765 (16.73%)	5,436 (13.9%)
Missing	1,683	642	149
Marital status			
Other	81,658 (31.7%)	40,097 (37.54%)	16,584 (42.2%)
Married	175,867 (68.3%)	66,725 (62.46%)	22,678 (57.8%)
Obesity			
Underweight or normal (<25 kg/m^2)	100,340 (39.7%)	30,684 (29.35%)	9,440 (24.7%)
Overweight (25–29.9 kg/m^2)	100,935 (39.9%)	42,118 (40.29%)	14,477 (37.9%)
Obesity (≥30 kg/m^2)	51,466 (20.4%)	31,731 (30.36%)	14,308 (37.4%)
Missing	4,784	2,289	1,037
Hypertension	96,560 (37.9%)	69,284 (64.90%)	31,676 (80.7%)
Missing	2,750	67	18
Cancer	20,524 (8.1%)	12,897 (12.08%)	6,059 (15.4%)
Missing	2,924	31	9
Lung disease	18,585 (7.3%)	14,042 (13.15%)	7,787 (19.8%)
Missing	2,875	39	9
Current drinking	42,032 (16.3%)	12,250 (11.47%)	3,004 (7.7%)
Missing	219	18	5
Current smoking	62,898 (24.6%)	21,655 (20.36%)	7,890 (20.2%)
Missing	1,420	481	251
Physical activity	211,229 (82.0%)	75,079 (70.28%)	21,712 (55.3%)
Missing	5	0	1

TABLE 2 Associations between cardiometabolic multimorbidity status and frailty.

	Model 1	Model 2	Model 3
	Beta (95% CI)	Beta (95% CI)	Beta (95% CI)
No cardiometabolic diseases	Ref	Ref	Ref
One cardiometabolic disease	7.80 (7.70, 7.90)	5.89 (5.79, 5.99)	3.50 (3.42, 3.58)
Two cardiometabolic diseases	17.92 (17.76, 18.08)	15.29 (15.15, 15.44)	10.46 (10.31, 10.57)
Three cardiometabolic diseases	28.79 (28.41, 29.17)	25.51 (25.15, 25.86)	17.96 (17.65, 18.26)

Model 1: no covariates were adjusted. Model 2: adjusted for Age and Gender. Model 3: adjusted for Age, Gender, Marital status, Educational attainment, Obesity, Hypertension, Cancer, Lung disease, Current drinking, Current smoking, and Physical activity.

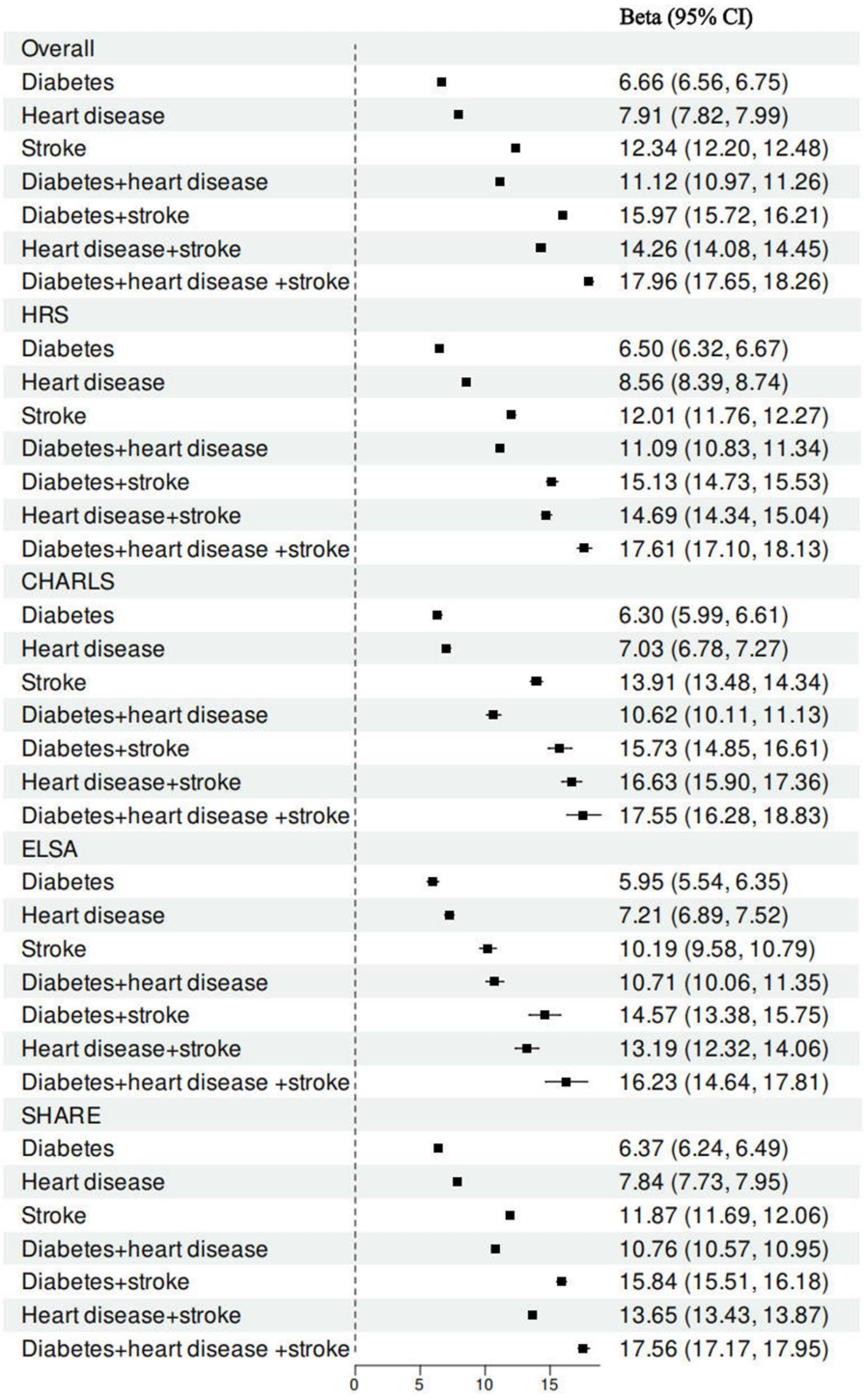

FIGURE 2
Associations between cardiometabolic disease status and frailty index by specific combination of individual cardiometabolic diseases. All models were adjusted for age gender, marital status, educational attainment, obesity, hypertension, cancer, lung disease, current drinking, current smoking, and physical activity.

muscle atrophy (44) and diminished functional capacity (45), thereby accelerating frailty progression.

Oxidative stress is another shared pathological process that plays a significant role in the cellular damage that is observed in these diseases (46). In diabetes, hyperglycaemia leads to an excess of ROS, which causes damage to cellular structures, including endothelial cells, thereby exacerbating cardiovascular complications (47). Similarly, in heart disease, persistent heart failure contributes to impaired tissue oxygenation, which further amplifies oxidative stress (48). After a stroke, cerebral ischemia induces mitochondrial dysfunction, increasing ROS production and damaging both neuronal and muscle tissues (49, 50). The

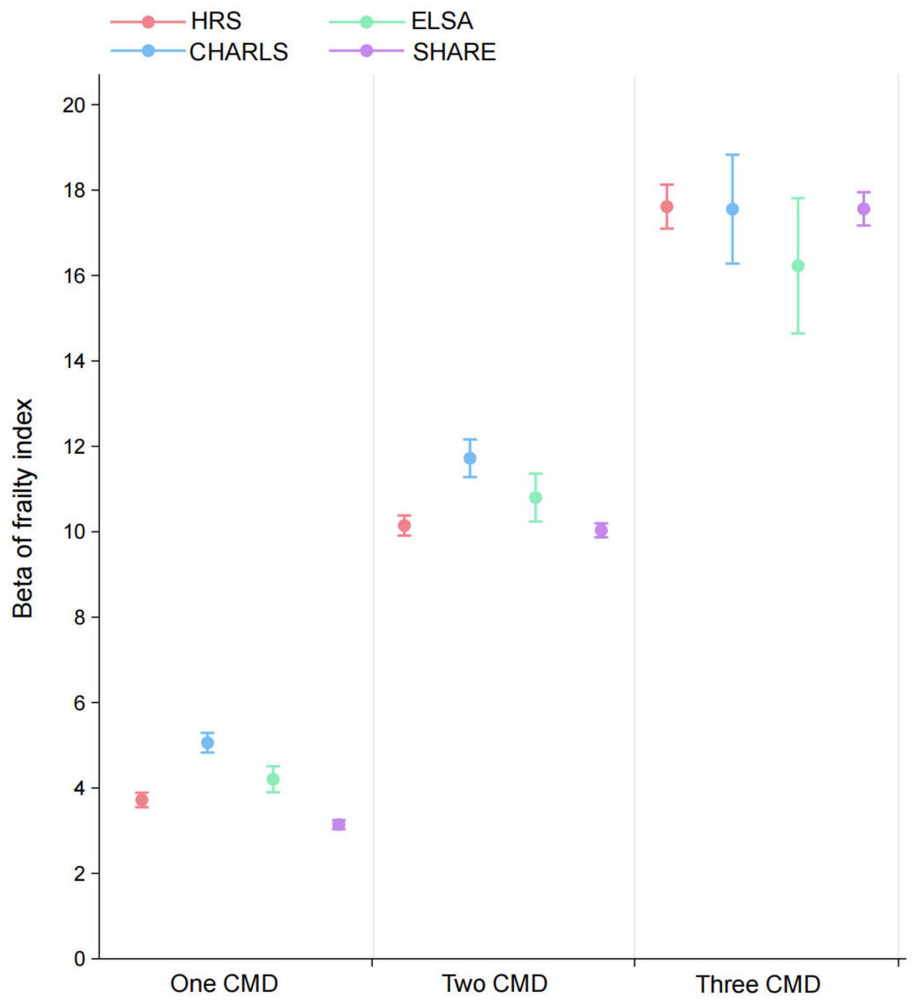

FIGURE 3
Associations between cardiometabolic multimorbidity status and frailty index in HRS, CHARLS, ELSA, and SHARE. All models were adjusted for age gender, marital status, educational attainment, obesity, hypertension, cancer, lung disease, current drinking, current smoking, and physical activity. CMD, cardiometabolic diseases; HRS, Health and Retirement Study; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; SHARE, Survey of Health, Ageing and Retirement in Europe.

cumulative oxidative damage in skeletal muscles results in muscle wasting and weakness, which are key components of frailty (51, 52).

Autonomic dysfunction is a critical common pathway in cardiometabolic diseases, which affects the neuro-muscular coordination that is necessary for maintaining physical strength and stability (53). Diabetic neuropathy and the disruption of central nervous system control following a stroke impair motor coordination, which leads to reduced physical performance and mobility (54, 55). These mechanisms act synergistically and this results in more severe frailty in those with multiple cardiometabolic comorbidities.

In comparison to previous studies, the results of this study are largely consistent and demonstrate broader applicability. Gao et al. identified a significant association between cardiometabolic multimorbidity, frailty and healthcare utilization and highlighted that the presence of multiple cardiometabolic diseases increases the incidence of frailty and healthcare expenditure (23). In this study, the findings from datasets from the United States, England and Europe similarly indicate a clear dose–response relationship between cardiometabolic multimorbidity and frailty. More specifically, as the number of cardiometabolic conditions increases, the severity of frailty and the corresponding healthcare demands both exhibit a substantial increase.

There is a notable alignment when comparing the findings of Tang et al. with the results from the subgroup analysis of this study, particularly regarding gender differences. Tang et al. found women to have a higher frailty index than men, particularly in the presence of cardiometabolic diseases, such as stroke (56). The subgroup analysis in this study found that the association between CMD and the frailty index was significantly stronger in females than in males. Several factors may have contributed to these differences, such as hormonal variations, particularly the decline in oestrogen post-menopause, which accelerates muscle loss and increases frailty risk in women (57). In addition, it is typical for women to experience a higher burden of chronic

illnesses, including CVD and osteoporosis, which further exacerbates frailty (58).

Furthermore, our study was compared with the study by Luo et al. (59), which explored the relationship between multimorbidity and frailty transitions in USA, finding that multimorbidity significantly increased the risk of frailty deterioration, with distinct patterns affecting frailty transitions. In contrast, our research utilized data from four international cohorts and focused on cardiometabolic diseases, revealing that stroke had the most pronounced impact on frailty. This study not only corroborates previous findings but also provides novel insights, emphasizing the cumulative impact of multiple cardiometabolic conditions on frailty, thus offering a new perspective for clinical intervention strategies.

Our findings suggest that CMD significantly increases the risk of frailty, particularly among older adults and women. Therefore, public health policies should place greater emphasis on high-risk populations, such as through regular health screenings and personalized health management, to identify and intervene in potential frailty risks at an early stage (15, 60). From a disease prevention perspective, promoting healthy lifestyles should be incorporated into national and regional public health programs. For example, optimizing nutritional guidance, encouraging regular physical activity, and managing chronic disease risk factors can effectively reduce the incidence of frailty.

From a healthcare policy standpoint, our study provides a foundation for optimizing chronic disease management. As CMD patients often require long-term, multidisciplinary medical support, healthcare systems should strengthen the capacity of primary healthcare institutions in managing chronic diseases, such as by offering integrated health management services, reducing repeated hospitalizations, and minimizing medical resource waste. These measures will not only improve patient health outcomes but also reduce the burden on the healthcare system and enhance resource utilization efficiency.

The strengths of this study include the use of multinational data, its large sample size and the use of harmonized standards across four international cohorts, which served to significantly enhance the generalisability and representativeness of the findings. By including diverse populations from different geographical regions, the study provided a robust analysis of cardiometabolic multimorbidity and frailty, which allowed for more accurate comparisons in a variety of healthcare systems and cultural contexts.

However, the study also has a number of limitations that must be noted. Firstly, some health conditions and lifestyle factors were based on self-reported data, which may present biases such as social desirability bias and recall bias, thereby potentially compromising the accuracy of the information that was supplied. Although our study employed complete case analysis to ensure the robustness of the data, we recognize that methods such as multiple imputation could further enhance data utilization and reduce potential selection bias. Secondly, although this study utilized multiple international cohorts (HRS, CHARLS, ELSA, SHARE), offering a broad sample representation, we acknowledge that there are methodological differences in the data collection processes across these cohorts. For instance, variations in disease diagnosis, health indicator measurements, and survey design may introduce certain biases during data integration. While we employed linear regression models to examine the relationship between cardiometabolic diseases and frailty, the statistical analysis may still be influenced by unmeasured variables, such as dietary habits and socioeconomic factors, which could potentially confound the results. Future research could consider employing more rigorous standardization methods or statistical strategies like propensity score matching to reduce inter-cohort biases and enhance the robustness of the findings. In addition, cross-sectional data was used in this investigation, which served to restrict the capacity to draw clear causal inferences between cardiometabolic multimorbidity and frailty. Furthermore, although this study has employed multilevel regression models and subgroup analyses to ensure the accuracy and robustness of the analyses, we acknowledge that further statistical techniques, such as more advanced Bayesian methods or machine learning approaches, could offer a more comprehensive assessment of the relationship between cardiometabolic diseases and the frailty index. However, due to constraints in time and resources, we have not yet conducted more extensive statistical expansions. In future research, we intend to incorporate additional statistical methodologies to further enhance the depth and precision of the study.

Conclusion

This study demonstrates a significant dose–response relationship between cardiometabolic multimorbidity and frailty, with stroke having the most pronounced impact. Older adults and women, in particular, are more susceptible to the exacerbation of frailty due to the influence of multiple cardiometabolic conditions. These findings underscore the importance of implementing early intervention strategies targeting the aging population to mitigate the risk of frailty.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: CHARLS (https://charls.pku.edu.cn/en), ELSA (https://www.elsa-project.ac.uk/), SHARE (https://share-eric.eu/), and HRS (https://hrs.isr.umich.edu/). The original contributions presented in the study are included in the article/Supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

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

Author contributions

KZ: Data curation, Methodology, Software, Writing – original draft. AW: Data curation, Software, Writing – original draft. KY:

Formal analysis, Methodology, 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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2025.1565682/full#supplementary-material

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Cardiometabolic multimorbidity and the risk of sudden cardiac death among geriatric community dwellers using longitudinal EHR-derived data

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Background: Cardiometabolic multimorbidity (CMM) has increased globally in recent years, especially among geriatric community dwellers. However, it is currently unclear how SCD risk is impacted by CMM in older adults. This study aimed to examine the associations between CMM and SCD among geriatric community dwellers in a province of China.

Methods: This study was a retrospective, population-based cohort design based on electronic health records (EHRs) of geriatric community dwellers (≥65 years old) in four towns of Tianjin, China. 55,130 older adults were included in our study. Older adults were categorized into different CMM patterns according to the cardiometabolic disease (CMD) status at baseline. The count of CMDs was also entered as a continuous variable to examine the potential additive effect of CMM on SCD. Cox proportional hazard models were used to evaluate associations between CMM and SCD. The results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: The prevalence of CMM was approximately 25.3% in geriatric community dwellers. Among participants with CMM, hypertension and diabetes was the most prevalent combination (9,379, 17.0%). The highest crude mortality rates for SCD were 7.5 (2.9, 19.1) per 1000 person-years in older adults with hypertension, coronary heart disease, diabetes and stroke (HR, 4.496; 95% CI, 1.696, 11.917), followed by those with hypertension, coronary heart disease, and stroke (HR, 3.290; 95% CI, 1.056, 10.255). The risks of SCD were significantly increased with increasing numbers of CMDs (HR, 1.787; 95% CI, 1.606, 1.987). The demographic, risk factors, serum measures and ECG-adjusted HR for SCD was

1.488 (1.327, 1.668) for geriatric community dwellers with an increasing number of CMDs.

Conclusion: The risk of SCD varied by the pattern of CMM, and increased with increasing number of CMM among geriatric community dwellers.

KEYWORDS

cardiometabolic multimorbidity, sudden cardiac death, mortality, older adult, electronic health records

1 Introduction

1.1 Background

Multimorbidity has become more prevalent across the globe in recent years, mainly for cardiometabolic conditions (1, 2). Cardiometabolic multimorbidity (CMM), the coexistence of two or more cardiometabolic diseases (CMDs), is related to higher disability, lower quality of life and increased health care costs (3, 4). A recent increase in life expectancy has resulted in a higher likelihood of individuals with single CMDs developing other CMDs, which has led to an increase in the prevalence of CMM (5). It is an emerging research area for public health, to understand the impact of CMM on the community (6). There is substantial evidence that CMM affects an estimated 30% of older adults (7). Over the past few years, the proportion of older adults in China has increased in China (8). The risk of cardiovascular death in older adults with CMM increases significantly with CMM (9) and CMM has become an increasingly challenging issue.

It is estimated that approximately half of all cardiovascular deaths are caused by sudden cardiac death (SCD), resulting in over 4-5 million deaths worldwide each year (10). SCD refers to an unexpected death or arrest from a cardiovascular cause (11). SCD is often fatal due to the short time available for effective medical intervention. Considering the poor prognosis of SCD, risk factors for progression to SCD in geriatric community dwellers are of concern. Several studies have demonstrated that any one of these CMDs alone may increase the risk of SCD (12, 13). However, previous studies on the association between CMDs and SCD have focused primarily on the association between a single disease and SCD, with little attention being given to the association between specific CMD combinations and SCD (14–16). Currently, it is unknown how much CMM impacts SCD risk.

1.2 Goals of investigation

To bridge these research gaps, this study aimed to evaluate the associations between CMM and SCD, using longitudinal EHR-derived data from older adults in the community. By examining the relationships between CMM and SCD, we hope to optimize the prevention of SCD, planning and the delivery of healthcare services for older adults with CMDs.

2 Methods

This report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

2.1 Study population

Data for this study was derived from the Data Library of Jinnan study. The Jinnan study was designed as a retrospective, population-based cohort study based on EHRs. The anonymized and encrypted EHRs of four towns including physical examinations and cause-of-death surveillance data were provided by the Tianjin Jinnan District Health Commission. These four towns were located in Jinnan District, Tianjin (117.41 N, 38.92 E). There were 290 thousand people, including about 20% of older adults in four towns.

In line with the *Tianjin Code for Basic Public Health Services*, a standardized national physical examination was recorded by township health centers based on the Community Health Service information system, mainly for the older adults. This was done by substrate medical and health institutions. Approximately 68% of people over the age of 65 had a physical examination and were enrolled into the system every year. The data was collected by community medical and health institutions. To obtain accurate outcomes for all older adults, the study linked physical examination data to cause-of-death surveillance data from the China national cause-of-death surveillance system. All deaths in the national cause-of-death surveillance system are reported online through the cause-of-death registration and reporting information system of the Chinese Center For Disease Control and Prevention, which reviews and verifies data reported by provinces and corrects any errors found (17).

The geriatric community dwellers who attended a physical examination from 2017 to 2022 were included in the study. We excluded patients with missing data on outcomes, exposures, or

primary covariates. In this study, the first physical examination data of geriatric community dwellers was taken as the baseline data.

2.2 Ascertainment of cardiometabolic multimorbidity

In this study, CMM in the baseline data was exposure. CMM was defined as the presence of ≥1 of the following CMDs based on hypertension: coronary heart disease (CHD), stroke, or diabetes (4). Ascertainment of HT, CHD, DM and stroke was by reported physician diagnosis, medication history, via verbal interview.

2.3 Ascertainment of outcomes

The primary outcome was SCD. Based on the Framingham study criteria, SCD was defined as death caused by coronary heart disease (definite myocardial infarction, coronary insufficiency, or angina pectoris) within one hour of the onset of symptoms with no other probable cause of death indicated from cause-of-death surveillance data (18). Suspected SCD events were adjudicated by a panel of three trained physicians who applied SCD criteria, using physical examination and cause-of-death surveillance data. Inter-rater reliability values were calculated using Cohen's Kappa. The Cohen's kappa was above 0.7. We reviewed SCD events that occurred after January 2017 (baseline) and before December 2022. All-cause mortality was a secondary outcome.

2.4 Covariates

Based on existing prior literature and guidelines, the research team's prior foundational studies, and expert opinions from clinicians and health management professionals, candidate variables were enrolled in this study based on demographics (including gender and age), risk factors (including heart rate, body mass index (BMI), waist, systolic blood pressure (SBP), diastolic blood pressure (DBP), physical activity, current smoking status, serum measures (fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), serum creatinine (Scr), blood urea nitrogen (BUN) and total bilirubin (TBIL)), and Electrocardiograph (ECG) (including QTc prolongation and ST wave abnormality) (13, 14). The candidate predictors were listed in the Supplementary Materials.

2.5 Sensitivity analyses

We performed several sensitivity analyses to test how the results depended on the disease definition, study population, and confounding factors. First, we tested an alternative definition of CMM, which was the presence of ≥1 of the following CMDs: CHD, stroke, or DM. Second, we excluded deaths occurring in the first 2-years of follow-up. Third, we estimated the associations between the different CMDs combinations and SCD, additionally adjusting for ECG at baseline.

2.6 Statistical analyses

Continuous variables were expressed as the mean ± standard deviation (SD) or the median (interquartile range). Categorical variables were sorted by frequency (percentages). Baseline characteristics of geriatric community dwellers are presented by baseline CMM status using the χ^2 test for categorical variables, analysis of variance for parametric continuous variables, and Kruskal-Wallis test for nonparametric continuous variables.

Cox proportional hazard models were used to evaluate the associations of CMM with SCD and all-cause mortality by CMDs combination and count. The results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was assessed using Schoenfeld residuals, and no significant violations were noted. First, we assessed the associations between single CMDs and SCD and all-cause mortality. Subsequently, we estimated the associations between the different CMDs combinations and SCD, with no CMDs as the reference category. Third, we assessed the associations between CMDs count (categorized as 0, 1, 2, and ≥3) and SCD, using geriatric community dwellers without CMDs as the reference group. CMDs count was entered as a continuous variable to examine its potential additive dose effect on SCD. Based on prior analyses, covariates were selected *a priori* (13), and multivariable modeling was performed with sequential adjustment as follows: model 1 unadjusted; model 2 adjusted for age and gender; model 3: model 2 plus BMI, physical activity, current smoking status, SBP, and DBP; model 4: model 3 plus FBG, TC, TG, BUN, TBIL, and Scr; model 5: model 4 plus QTc prolongation and ST wave abnormality. Finally, the survival curves and subgroup analysis (model 1) were plotted by the number of CMM. Statistical significance was defined as 2-sided $\alpha < 0.05$ in the main analysis. Analyses were performed using R version 4.3.2.

3 Results

A total of 55,184 geriatric community dwellers attended a physical examination from 2017 to 2022. 54 geriatric community dwellers were excluded for missing data on outcomes, exposures, or primary covariates. After these exclusions, 55,130 geriatric community dwellers were included in the analysis (Supplementary Figure S1).

Table 1 shows the characteristics of geriatric community dwellers and prevalence of CMM at baseline. The median (IQR) age was 71 (68, 77) years, and 46.8% of geriatric community dwellers were male. The prevalence of CMM was 25.4%, in which 3.6% had ≥3 CMDs. In geriatric community dwellers with CMM, the combination of HT and DM was the most common (17.0%). Individuals with CMM were older, more likely to be female, and had a higher prevalence of cardiovascular risk factors (eg, higher heart

TABLE 1 Baseline characteristics of geriatric community dwellers classified by baselinecardiometabolic multimorbidity.

Characteristics	HT + CHD	HT + DM	HT + Stroke	HT + CHD + DM	HT + CHD+ Stroke	HT + DM + Stroke	HT + CHD + DM + Stroke
n (%)	944 (1.7)	9379 (17.0)	1659 (3.0)	677 (1.2)	122 (0.2)	1128 (2.0)	118 (0.2)
Male (%)	369 (39.1)	4115 (43.9)	992 (59.8)	266 (39.3)	65 (53.3)	616 (54.6)	65 (55.1)
Age, years (median (IQR))	77 (71, 82)	72 (68, 77)	74 (70, 80)	75 (70, 80)	77 (73, 81)	74 (70, 79)	76 (70, 82)
Heart rate, bpm (median (IQR))	70 (62, 78)	72 (65, 80)	70 (63, 79)	71 (64, 80)	73 (64, 81)	72 (66, 80)	72 (65, 82)
BMI, kg/m^2 (median (IQR))	25.6 (23.4, 28.0)	25.8 (23.5, 28.2)	25.9 (23.5, 28.1)	26.1 (23.8, 28.4)	26.3 (24.1, 28.2)	25.8 (23.5, 28.2)	26.0 (24.1, 28.9)
Waist, cm (median (IQR))	90.0 (84.0, 97.0)	90.0 (83.0, 96.0)	89.0 (83.0, 96.0)	90.0 (84.0, 98.0)	92.0 (85.0, 98.0)	89.0 (83.0, 96.0)	91.5 (87.0, 99.8)
SBP (mmHg) (median (IQR))	130.0 (122.0, 138.0)	130.0 (120.0, 138.0)	130.0 (120.0, 138.0)	130.0 (122.0, 138.0)	130.0 (120.0, 138.0)	130.0 (120.0, 138.0)	130.0 (120.0, 138.0)
DBP (mmHg) (median (IQR))	80.0 (74.0, 84.0)	80.0 (74.0, 84.0)	80.0 (76.0, 84.0)	80.0 (74.0, 84.0)	80.0 (76.0, 84.0)	80.0 (74.0, 84.0)	80.0 (72.0, 84.0)
Physical activity (%)	610 (64.6)	6401 (68.2)	1019 (61.4)	416 (61.4)	66 (54.1)	667 (59.1)	58 (49.2)
Smoke (%)	339 (35.9)	3741 (39.9)	894 (53.9)	203 (23.0)	44 (36.1)	514 (45.6)	41 (34.7)
FBG, mmol/L (median (IQR))	5.4 (5.0, 5.9)	7.2 (6.1, 8.7)	5.4 (4.9, 5.8)	7.0 (6.0, 8.4)	5.4 (5.0, 6.0)	7.3 (6.0, 9.1)	7.1 (6.1, 8.8)
TBIL, μmol/L (median (IQR))	12.2 (9.1, 15.9)	12.4 (9.1, 16.6)	12.3 (9.2, 16.7)	11.3 (8.4, 15.3)	12.2 (9.4, 16.7)	11.9 (8.7, 15.9)	12.5 (8.9, 15.7)
Scr, μmol/L (median (IQR))	67.0 (56.5, 79.0)	64.0 (54.0, 77.0)	71.6 (60.6, 85.5)	65.9 (56.0, 80.0)	70.3 (59.0, 85.9)	69.0 (58.0, 84.3)	68.8 (58.0, 83.0)
BUN, mmol/L (median (IQR))	5.4 (4.6, 6.5)	5.4 (4.5, 6.5)	5.6 (4.5, 6.7)	5.6 (4.6, 7.0)	5.5 (4.2, 6.8)	5.6 (4.5, 6.8)	5.5 (4.5, 6.6)
TC, mmol/L (median (IQR))	5.1 (4.3, 5.9)	5.3 (4.6, 6.1)	5.1 (4.4, 5.9)	5.0 (4.3, 6.0)	4.8 (3.9, 5.8)	5.1 (4.2, 5.9)	4.9 (4.1, 5.7)
TG, mmol/L (median (IQR))	1.4 (1.1, 1.9)	1.6 (1.2, 2.3)	1.4 (1.0, 1.9)	1.6 (1.2, 2.2)	1.4 (1.1, 1.8)	1.6 (1.2, 2.3)	1.4 (1.1, 2.0)
QTc prolongation (%)	40 (4.2)	485 (5.2)	76 (4.6)	47 (6.9)	9 (7.4)	70 (6.2)	11 (9.3)
ST wave abnormality	51 (5.4)	302 (3.2)	77 (4.6)	51 (7.5)	9 (7.4)	43 (3.8)	5 (4.2)
SCD (%)	15 (1.6)	160 (1.7)	17 (1.0)	9 (1.3)	2 (1.6)	24 (2.1)	4 (3.4)
All-cause mortality (%)	100 (10.6)	1182 (12.6)	346 (20.9)	102 (15.1)	22 (18.0)	310 (27.5)	28 (23.7)

HT, hypertension; CHD, coronary heart disease; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TBIL, total bilirubin; Scr, serum creatinine; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglyceride.

10.3389/fendo.2025.1515495

rate, higher BMI, bigger waist size, greater proportion of smokers, higher FBG, TC and TG, lower TBIL and Scr, greater proportion of QTc prolongation and ST wave abnormality) compared to those without CMD. The median follow-up was 5.7 years. During the follow-up, 452 SCDs and 4,657 deaths were documented. Individuals with HT, DM, stroke, or CHD had a higher prevalence of SCD and all-cause mortality (Supplementary Tables S1, S2). Supplementary Tables S3, S4 shows the characteristics of geriatric community dwellers and the prevalence of single CMD at baseline.

The crude mortality rates for SCD were 1.9 (1.2, 3.1) per 1000 person-years in overall older adults with HT and stroke, 3.4 (2.1, 5.6) per 1000 person-years in older adults with HT and CHD, 3.3 (2.8, 3.9) per 1000 person-years in older adults with HT and DM. 2.9 (1.5, 5.5) per 1000 person-years in older adults with HT, CHD, and DM, 4.0 (2.7, 5.9) per 1000 person-years in older adults with HT, DM, and stroke, 3.7 (0.1, 13.4) per 1000 person-years in older adults with HT, CHD and stroke, 7.5 (2.9, 19.1) per 1000 person-years in older adults with HT, CHD, DM and stroke, respectively. Figure 1 shows the crude mortality rates for all-cause mortality.

CMDs combinations were associated with a higher risk of SCD, compared with the reference group (Figure 1). Geriatric community dwellers with HT, CHD, DM, and stroke were associated with the greatest risk of SCD (HR, 4.496; 95% CI, 1.696, 11.917), followed by those with HT, CHD, and stroke (HR, 3.290; 95% CI, 1.056, 10.255). Geriatric community dwellers with HT, CHD, stroke, and stroke were associated with the greatest risk of all-cause mortality (HR, 4.193; 95% CI, 3.043, 5.777), followed by those with HT, CHD, and stroke (HR, 3.345; 95% CI, 2.307, 4.850). A statistical model with more conservative covariate adjustment was also conducted and results are presented in Table 2.

The results of associations between CMDs and all-cause mortality, and CMDs count are shown in Figure 2; Supplementary Figure S2. There was an unadjusted additive dose effect of increasing CMDs numbers on SCD (HR, 1.787; 95% CI, 1.606, 1.987). The demographic, risk factors, serum measures and ECG-adjusted HR for SCD was 1.488 (1.327, 1.668) for geriatric community dwellers with an increasing number of CMDs. There was an unadjusted additive dose effect of increasing number of CMDs on all-cause mortality (HR, 1.628; 95% CI, 1.574, 1.683). The demographic, risk factors, serum measures and ECG-adjusted HR for all-cause mortality were 1.473 (1.420, 1.527) for geriatric community dwellers with an increasing number of CMDs. Our findings remained robust after sensitivity analyses (Supplementary Figures S3, S4).

In the stratified analysis, older adults with 65≤age<75 (HR, 2.114; 95% CI, 1.747, 2.559) and BMI<24 (HR, 1.921; 95% CI, 1.607, 2.297) showed increased CMM risk. In addition, positive associations between CMM and all-cause mortality were more pronounced in non-smokers (HR, 1.721; 95% CI, 1.640, 1.806) (Table 3).

4 Discussion

We found the prevalence of CMM was approximately 25% in geriatric community dwellers in our population. HT and DM was the most prevalent combination of CMM. For single CMDs, DM was associated with the greatest risk of SCD. For CMM, the risk of SCD varied by the pattern of CMM, and were significantly higher with increasing numbers of cardiometabolic conditions (DM, stroke, and CHD) among geriatric community dwellers, even after adjusting for established cardiovascular risk factors. Given

Cardiometabolic disease combinations				Crude incidence rate*	HR (95%CI)
Sudden cardiac death					
HT	CHD	DM	Stroke	1.9 (1.2, 3.1)	1.122 (0.692, 1.819)
HT	CHD	DM	Stroke	3.4 (2.1, 5.6)	2.002 (1.197, 3.349)
HT	CHD	DM	Stroke	3.3 (2.8, 3.9)	2.440 (2.012, 2.959)
HT	CHD	DM	Stroke	2.9 (1.5, 5.5)	1.701 (0.882, 3.279)
HT	CHD	DM	Stroke	4.0 (2.7, 5.9)	2.358 (1.564, 3.556)
HT	CHD	DM	Stroke	3.7 (0.1, 13.4)	3.290 (1.056, 10.255)
HT	CHD	DM	Stroke	7.5 (2.9, 19.1)	4.496 (1.696, 11.917)
All-cause mortality					
HT	CHD	DM	Stroke	25.9 (24.5, 27.4)	2.438 (2.185, 2.720)
HT	CHD	DM	Stroke	43.2 (39.0, 47.9)	1.343 (1.105, 1.632)
HT	CHD	DM	Stroke	23.5 (19.4, 28.5)	1.524 (1.427, 1.628)
HT	CHD	DM	Stroke	34.5 (28.5, 41.7)	1.977 (1.629, 2.399)
HT	CHD	DM	Stroke	57.4 (51.5, 63.9)	3.264 (2.909, 3.662)
HT	CHD	DM	Stroke	43.8 (29.1, 65.4)	4.193 (3.043, 5.777)
HT	CHD	DM	Stroke	59.3 (41.3, 84.4)	3.345 (2.307, 4.850)

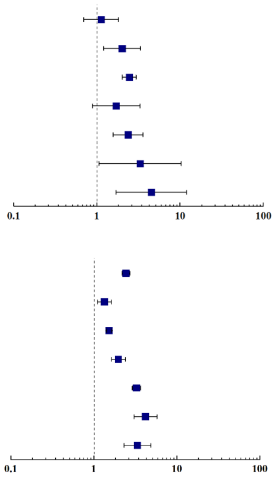

FIGURE 1
Forest plots of the association of the pattern of cardiometabolic multimorbidity with sudden cardiac death and all-cause mortality. *: No. per 1000 person-years (95% CI).

TABLE 2 The association of the pattern of cardiometabolic multimorbidity with sudden cardiac death and all-cause mortality.

Outcome	Non-CMD	HT+CHD	HT+DM	HT+Stroke	HT+CHD+DM	HT+CHD+Stroke	HT+DM+Stroke	HT+CHD+DM+Stroke
SCD								
Model, HR (95% CI)								
1	Reference	2.002 (1.197, 3.349)	2.440 (2.012, 2.959)	1.122 (0.692, 1.819)	1.701 (0.882, 3.279)	3.290 (1.056, 10.255)	2.358 (1.564, 3.556)	4.496 (1.696, 11.917)
2	Reference	1.419 (0.847, 2.379)	2.542 (2.096, 3.084)	0.862 (0.530, 1.401)	1.431 (0.739, 2.769)	1.650 (0.411, 6.621)	2.031 (1.346, 3.064)	3.434 (1.315, 8.964)
3	Reference	1.454 (0.867, 2.437)	2.572 (2.120, 3.121)	0.811 (0.499, 1.319)	1.416 (0.731, 2.743)	1.635 (0.407, 6.566)	1.901 (1.259, 2.869)	3.098 (1.188, 8.075)
4	Reference	1.574 (0.937, 2.645)	2.163 (1.747, 2.678)	0.890 (0.546, 1.450)	1.088 (0.559, 2.116)	1.824 (0.454, 7.327)	1.363 (0.892, 2.083)	2.200 (0.822, 5.892)
5	Reference	1.544 (0.919, 2.594)	2.178 (1.760, 2.694)	0.880 (0.540, 1.433)	1.014 (0.521, 1.974)	1.771 (0.441, 7.117)	1.311 (0.855, 2.012)	2.218 (0.824, 5.970)
All-cause mortality								
Model, HR (95% CI)								
1	Reference	1.343 (1.105, 1.632)	1.524 (1.427, 1.628)	2.438 (2.185, 2.720)	1.977 (1.629, 2.399)	4.193 (3.043, 5.777)	3.264 (2.909, 3.662)	3.345 (2.307, 4.850)
2	Reference	0.848 (0.695, 1.034)	1.636 (1.531, 1.747)	1.839 (1.648, 2.052)	1.569 (1.289, 1.909)	1.692 (1.113, 2.573)	2.845 (2.535, 3.192)	2.578 (1.797, 3.698)
3	Reference	0.880 (0.721, 1.073)	1.662 (1.555, 1.776)	1.714 (1.536, 1.914)	1.574 (1.293, 1.917)	1.668 (1.097, 2.536)	2.700 (2.406, 3.031)	2.262 (1.560, 3.281)
4	Reference	0.901 (0.739, 1.100)	1.485 (1.379, 1.599)	1.816 (1.626, 2.029)	1.345 (1.103, 1.640)	1.750 (1.151, 2.663)	2.312 (2.052, 2.606)	1.894 (1.305, 2.750)
5	Reference	0.897 (0.735, 1.095)	1.490 (1.384, 1.604)	1.800 (1.611, 2.011)	1.014 (0.521, 1.974)	1.735 (1.141, 2.640)	2.305 (2.045, 2.599)	1.885 (1.298, 2.736)

HT, hypertension; CHD, coronary heart disease; DM, diabetes mellitus; HR, hazard ratio.
Model 1 unadjusted; model 2 adjusted for age and gender; model 3: model 2 plus BMI, physical activity, current smoking status, SBP and DBP; model 4: model 3 plus FBG, T, TG, BUN, TBIL and Scr; model 5: model 4 plus QTc prolongation and ST wave abnormality.

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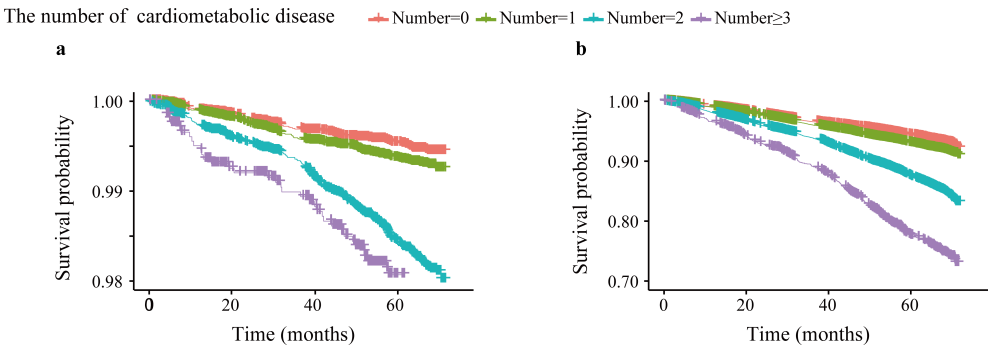

FIGURE 2
Survival curves for sudden cardiac death and all-cause mortality by the number of cardiometabolic multimorbidity. **(a)**: sudden cardiac death; **(b)**: all-cause mortality.

the growing challenges of multimorbidity among older adults living in the community, our study holds important implications for public health.

Although, CMM studies have been conducted in Western countries, health concern remains poorly explored in China. With a dense population and an aging society, CMM is notably prevalent among its older population, substantially contributing to the burden on the Chinese public health system. Our study revealed that one in five older adults had CMM. A systematic review of nine published studies in China reported the prevalence of multimorbidity among those aged ≥ 60 years ranging from 6.4% (95% CI: 5.1 to 8.0) to 76.5% (95% CI: 73.6 to 79.2) (19). However, most of the included studies considered morbidities in addition to CMDs and only reported prevalence based on the number of diseases, which prevented us from making direct comparisons. Previous studies have examined that the overall crude prevalence of CMM was 11.5% in Chinese adults aged 35-75 based on a population-based screening project in Southern China (20), and 6.3% of Chinese adults aged 35-75 in China Kadoorie Biobank had CMM (21). The findings may not be generalizable to the wider population. Our study provided additional evidence for CMM studies in Chinese older adults and the urgency for CMD prevention, considering population ageing (22).

Our results indicate that the associations between cardiovascular disease and DM, and mortality are multiplicative. HT is the principal cause of stroke, a major risk factor for DM, CHD, and SCD. It is estimated that HT prevalence was about 40%, which was broadly consistent with estimates from previous studies (23). Previous studies have indicated that older adults with multimorbidity are most likely to have HT and at least one other chronic illness (4). Further, one study found that the risk of all-cause mortality increased significantly (from 7% to 30%) after the progression of CMM in patients with HT (9). SCD resulting from ventricular tachycardia and fibrillation (VT/VF) is closely linked to HT. Left ventricular hypertrophy, a common consequence of HT, increases the risk of ventricular arrhythmias, which in turn elevates the likelihood of SCD.

The estimated prevalence of DM in our study was 4.4%, which was broadly consistent with estimates from national surveillance (24). In addition, we found DM, as a kind of CMD, was associated with the greatest risk of SCD (25). A number of epidemiologic studies have shown that the risk of SCD is higher among patients with DM compared with those without this condition (26). In a meta-analysis of individuals over 50 years of age, people with DM have a higher risk of SCD than people without DM (risk ratio, 2.02; 95% CI, 1.81-2.25) (27). Consequently, our findings highlight the importance of preventing cardiovascular disease in people with DM, as well as preventing DM in people with cardiovascular disease. DM contributes to SCD through a combination of structural, electrical, and inflammatory changes in the heart, as well as through its effects on coronary and autonomic function.

With the higher prevalence of risk factors, the incidence of CAD and associated mortality is increasing in China. The results of published literature indicate that CAD accounts for approximately 80% of all SCD cases, and that the incidence of CAD increases with increasing age (28). This demonstrates the importance of cardiovascular disease risk factor control to prevent SCD.

According to recent publications, risk for all-cause mortality was the highest for people with stroke (HR, 1.74; 95% CI, 1.24-2.42) for people with only 1 CMD (29). In our study, stroke was more associated with all-cause mortality than SCD. It is unclear why stroke mortality is higher, but it may be attributed to a higher stroke incidence and mortality after strokes (30).

The estimated prevalence of CMM in our study was broadly consistent with estimates from previous studies. For example, about 1.3% of participants aged ≥ 60 years had multimorbidity for DM and CHD, and the prevalence of HT, DM and stroke was 2.0% in our study (31). Moreover, our study indicated a positive association between CMDs, and SCD and all-cause mortality risks. The Emerging Risk Factors Collaboration (ERFC) pooled 91 prospective cohorts conducted in North America, Europe, and Australia. Compared with no CMDs, the HR (95% CIs) for concurrent three CMDs at baseline was 6.0 (5.0, 7.1) (2). Compared with those without CMDs at baseline, the HR (95% CIs) for concurrent three CMDs was 3.22 (3.15, 3.30) in the Clinical Practice Research Datalink (CPRD) study (32). CHD, DM and stroke were associated with the highest mortality rates among Black adults in the Jackson Heart Study (JHS)

TABLE 3 The association of the number of cardiometabolic multimorbidity with sudden cardiac death and all-cause mortality stratified by potential risk factors.

	Sudden cardiac death	all-cause mortality
Model, HR (95% CI)		
Gender		
Male	1.771 (1.532, 2.047)	1.608 (1.537, 1.682)
Female	1.801 (1.541, 2.106)	1.652 (1.571, 1.737)
Age, years		
65 ≤ Age < 75	2.114 (1.747, 2.559)	1.692 (1.589, 1.803)
75 ≤ Age < 85	1.591 (1.358, 1.864)	1.564 (1.486, 1.645)
Age≥85	1.306 (1.044, 1.633)	1.302 (1.222, 1.389)
BMI		
BMI < 24	1.921 (1.607, 2.297)	1.614 (1.525, 1.710)
BMI ≥ 24	1.730 (1.515, 1.976)	1.645 (1.579, 1.715)
Physical activity		
No	1.866 (1.607, 2.167)	1.747 (1.667, 1.832)
Yes	1.676 (1.443, 1.946)	1.502 (1.434, 1.574)
Smoke		
No	1.958 (1.690, 2.268)	1.721 (1.640, 1.806)
Yes	1.627 (1.394, 1.899)	1.563 (1.492, 1.638)
TC, mmol/L		
<5.20	1.667 (1.440, 1.930)	1.591 (1.520, 1.665)
≥5.20	1.912 (1.638, 2.232)	1.652 (1.572, 1.736)
TG, mmol/L		
<1.7	1.718 (1.506, 1.961)	1.631 (1.568, 1.698)
≥1.7	1.956 (1.627, 2.351)	1.752 (1.646, 1.866)
QTc prolongation		
No	1.773 (1.587, 1.981)	1.629 (1.574, 1.687)
Yes	1.712 (1.153, 2.543)	1.431 (1.249, 1.639)
ST wave abnormality		
No	1.773 (1.586, 1.982)	1.613 (1.559, 1.670)
Yes	1.670 (1.045, 2.202)	1.591 (1.376, 1.840)

HR, hazard ratio; BMI, body mass index; TC, total cholesterol; TG, triglyceride.

(HR, 3.68; 95% CI, 1.96-6.93) (29). Based on the China Kadoorie Biobank study, participants with three CMDs at baseline had an adjusted HR between CMM and all-cause mortality and circulatory system diseases of 2.93 (2.80, 3.07) and 5.05 (4.74, 5.37) respectively (21). The HRs might be explained by differences in race, healthcare services, and economic levels. This suggests that it is important to consider differences when developing strategies to improve public health. For health professionals, a holistic assessment of this information has the potential to improve disease management. The multiplicative increased risk of SCD is a call to action to prevent the development of cardiometabolic disease and advance the treatment of care of those with known cardiometabolic morbidities. Additionally, a lifestyle intervention program and effective treatment for prevalent CMDs should be implemented to prevent the occurrence of CMM and reduce the risk of SCD and mortality among patients with CMDs. Future studies should explain why certain cardiometabolic diseases (CMDs) combinations may have synergistic effects leading to higher SCD risk.

The strength of this study was that it was a large-scale, comprehensive study under real-world circumstances using EHR data. To the best of our knowledge, this is the first comprehensive population-based cohort investigating the association of CMM and SCD among general older adults. Moreover, sensitivity analysis was conducted in our study to confirm the robustness of our results. We were able to comprehensively analyze the associations between single CMDs and different CMM patterns, and SCD risk.

Despite these strengths, our study remains limited due to several shortcomings. First, self-reported disease diagnoses could underestimate the disease prevalence. Second, multimorbidity might be affected by detection biases (ie, one disease is detected and then others are tested because of it). Third, CMDs commonly have an insidious onset. Therefore, the registration date recorded in our study may be later than actual onset, and the accurate time of disease onset was not available. We could only approximate this information using the first registration time for these diseases. The short follow-up period could potentially bias the results, particularly for diseases with a longer progression period. Information on medication use and risk control was also not available. Fourth, this study had a relatively short follow-up period and the long-term effect of CMM needs to be further evaluated. Fifth, unknown or unmeasured factors may induce residual confounding, and these factors may affect our results (such as medication use, lifestyle interventions, healthcare systems, socioeconomic factors and genetic predispositions). Sixthly, The study design is observational, so causality cannot be established. Finally, it should be acknowledged that the study's findings are based on research conducted solely on older Chinese adults and, therefore, may not be generalizable to other cultural or ethnic populations.

5 Conclusion

In this cohort study, an increasing number of CMM was associated with a multiplicative increase in risk of SCD and all-cause mortality among geriatric community dwellers, with a greater magnitude of association for SCD.

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

This study was approved by the Tianjin University Institutional Review Board (TJUE-2024-003). 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

YL: Conceptualization, Methodology, Writing – original draft. ZM: Formal analysis, Visualization, Writing – original draft. ZL: Methodology, Software, Writing – original draft. JL: Data curation, Writing – original draft. GS: Data curation, Resources, Writing – original draft. MO: Writing – review & editing. JC: Data curation, Funding acquisition, Writing – review & editing. HF: Funding acquisition, Supervision, Writing – review & editing. CC: Funding acquisition, 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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1515495/full#supplementary-material

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Association between hemoglobin glycation index and the risk of cardiovascular disease in early-stage cardiovascular-kidney-metabolic syndrome: evidence from the China health and retirement longitudinal study

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Background: Cardiovascular-kidney-metabolic (CKM) syndrome reflects the interplay among metabolic risk factors, chronic kidney disease, and cardiovascular disease (CVD). While the hemoglobin glycation index (HGI) has demonstrated prognostic value for cardiovascular events, its clinical utility remains unexplored in early-stage CKM syndrome.

Methods: Participants with early-stage CKM syndrome (stage 0-3) were recruited from the China Health and Retirement Longitudinal Study (CHARLS) database. Using k-means clustering analysis, the participants were classified according to the values of HGI measured at baseline and 3 years later, respectively. The primary outcome was self-reported CVD during the follow-up of at least 3 years. Extreme gradient boosting (XGBoost) algorithm was applied, with the Shapley additive explanation (SHAP) method used to determine feature importance. Multivariable logistics proportional regression analysis the association between HGI and CVD, and restricted cubic spline (RCS) regression assessed potential nonlinear relationships.

Results: A total of 4676 eligible participants were included in the final analysis, with 944 (20.19%) progressed to CVD within 10 years. Among the baseline clinical features, HGI ranked the second for the impact on the occurrence of CVD. According to the changes of HGI values, the participants were clustered into 4 classes. Compared to the class 1 with lower level of HGI, higher risk of CVD was observed in class 3 (adjusted OR: 1.34, 95% CI: 1.06-1.69, P = 0.013) and class 4 (adjusted OR: 1.65, 95% CI: 1.01-2.45, P = 0.025) with higher and rapidly increasing level of HGI. RCS analysis showed cumulative HGI and the risk of CVD were linearly related (P for nonlinearity = 0.967). Subgroup analyses confirmed the stability of the association. Additionally, the SHAP plot revealed that HGI were the more important features than traditional risk factors such as FBG for predicting CVD.

Conclusion: HGI is associated with an elevated risk of CVD in participants with early-stage CKM syndrome. HGI can serve as an independent biomarker for guiding clinical decision-making and managing patient outcomes.

KEYWORDS

HGI, glycemic variability, cardiovascular kidney metabolic syndrome, CVD, CHARLS

1 Introduction

Cardiovascular disease (CVD), chronic kidney disease (CKD), diabetes, and obesity are pathophysiologically interrelated that concurrently affect adult population with the prevalence of 5% in the United States (1), and 15% in China (2). In 2023, the American Heart Association defined this systemic condition as Cardiovascular-Kidney-Metabolic (CKM) syndrome, which may lead to premature mortality and increased morbidity (3). As reported, the combination of CKD and diabetes escalated the 10-year mortality rate markedly to 31.1% (4). The risk of CVD determines the staging and prognosis of CKM syndromes. Central to the CKM framework is the emphasis on risk-based primary prevention of CVD for individuals in CKM stages 0 to 3 (5). However, the prediction of the risk of CVD in the early stages of CKM syndromes is by far a challenge (6).

For patients with CKM syndromes, it is crucial to effectively control blood sugar levels and use reliable indicators to minimize diabetes-related complications and mortality (7). Glycosylated hemoglobin A1c (HbA1c) is strongly associated with the development of both microvascular and macrovascular diseases, likely due to its involvement in protein glycation (8). Despite standardized assays, discrepancies between HbA1c and other glycemic measures are well-documented and can affect the accuracy of glycemic control and management (9, 10). The mean erythrocyte lifespan, differences in cell membrane glucose transmembrane gradients and enzyme abnormalities can independently impact the reliability of HbA1c (11–13). Other genetic factors like genetic variation in hemoglobin can also affect the association of HbA1c with "true" average glucose exposure, particularly in the low (no diabetic) range (14). For most patients with metabolic disorders, a more tailored and individualized approach should be implemented to prevent vascular complications (10).

To solve these problems, the hemoglobin glycation index (HGI) was developed to directly reflect the individual glycemic variability by quantifying the difference between HbA1c and plasma glucose concentration (15). HGI could predict the risk of diabetic complications, including CVD, microvascular diseases, and mortality in patients with diabetes mellitus (16, 17). Presently, there have been few research that examined the correlation in patients with complex metabolic abnormalities. Prior research has shown that HGI was positively associated with the incidence of obesity, increased levels of low-density lipoprotein, triglyceride, and postprandial glycemic excursion, respectively (18). Therefore, in this study, we aimed to examine the association between HGI and the risk of CVD in the early stages of CKM syndromes.

2 Methods

2.1 Data source and study population

This prospective study used data from the China Health and Retirement Longitudinal Study (CHARLS), which includes clinical information from participants aged 45 years in China from 2011 to 2012 were considered as baseline (Wave 1), and follow-up each two years. Up to now, CHARLS has released three waves of follow-up data (Wave 2 in 2013, Wave 3 in 2015 and Wave 4 in 2018). The protocol of CHARLS study was approved by the Ethical Review Committee of Peking University (IRB00001052-11015). Informed consent was obtained in writing from all participants prior to their inclusion.

In the study, 17,635 individuals who completed the baseline survey were included in the analysis. We excluded 12,959 individuals for the following reasons: (1) lack of information on age and gender, (2) participants younger than 45 years, (3) absence of information on cardiovascular disease and chronic kidney disease, (4) participants with CKM stage 4 at baseline, already diagnosed with CVD, (5) participants with less than 3 years of follow-up, (6) lack of data on FBG or HbA1c. Ultimately, a total of 4,676 individuals were included in the analysis (Figure 1).

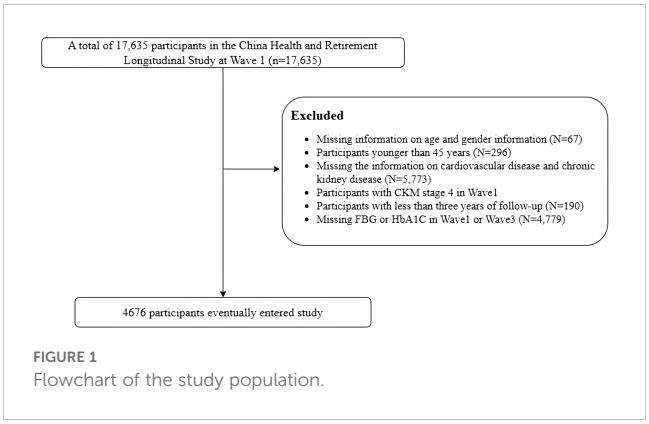

FIGURE 1
Flowchart of the study population.

2.2 Deriving HGI from the HbA1c versus FBG regression equation

HGI was calculated following the methodology established by Hempe et al. (19). To estimate the inter-individual variance in HbA1c levels, we utilized baseline FBG and HbA1c data for our calculations. The predicted HbA1c level was calculated for each participant through linear regression analysis (HbA1c = 0.017 × FBG + 3.41). HGI was then defined as the difference between the measured HbA1c and the predicted HbA1c (HGI = measured HbA1c – predicted HbA1c). Cumulative HGI was calculated using hematological data from Waves 1 and 3, derived with the formula: $(HGI_{2012} + HGI_{2015})/2 \times$ time.

2.3 Determination of endpoints

The primary outcome was the incidence of CVD, adhering to the previous protocols established with the CHARLS dataset. It was ascertained by the question "Did your doctor tell you that you have been diagnosed with a heart attack, angina pectoris, coronary heart disease, heart failure, or other heart problem?" (6).

2.4 Data collection and definitions

Baseline data regarding socio-demographic status and disease-related information were collected through in-person interviews conducted by trained interviewers using a structured questionnaire. The socio-demographic information gathered included age, gender, education, and marital status. Disease-related factors encompassed body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension, dyslipidemia, diabetes, lifestyle factors (such as smoking and alcohol consumption). Participants were required to fast for at least 12 hours prior to the measurement of FBG, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). BMI was calculated as weight (kg) divided by height squared (m^2). Participants were categorized into three groups based on their BMI: as normal weight (< 25 kg/m^2), overweight (25–29.9 kg/m^2), and obesity (≥ 30 kg/m^2) (20).

Hypertension was defined as a history of diagnosis, the use of antihypertensive medication, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥ 90 mmHg (21). Diabetes was defined as self-reported diagnosis history, use of any insulin or oral hypoglycemic agents, and fasting glucose ≥ 7.0 mmol/L or an HbA1c of ≥ 6.5% at baseline (22). Dyslipidemia was defined by lipid abnormalities, including TC ≥ 240 mmol/L, LDL-C >160 mmol/L, TG>150 mmol/L, or HDL-C < 40 mmol/L or use of any lipid-lowering treatment (23).

The classification of CKM syndrome, as outlined in the AHA Statement, provides a comprehensive framework for the early assessment of risk factors and disease progression. Stage 0 is defined as the absence of CKM syndrome risk factors in healthy subjects. Stage 1 is characterized by overweight, abdominal obesity (waist circumference ≥ 80 cm in women and ≥ 90 cm in men), or prediabetes. Stage 2 involves the presence of at least one metabolic risk factor (such as hypertriglyceridemia, dyslipidemia, hypertension, metabolic syndrome, diabetes) or CKD. Stage 3 encompasses subclinical cardiovascular disease with a high predicted CVD risk calculated using the Framingham risk score. The estimated glomerular filtration rate (eGFR) was calculated using the Chinese Modification of Diet in Renal Disease (C-MDRD) equation to classify renal function according to the Kidney Disease Improving Global Outcomes (KDIGO) (3).

2.5 Statistical analysis

This study investigated HGI changes participants from Wave 1 and Wave 3 using k-means clustering within a logistic regression equation. K-means clustering, an unsupervised machine learning technique, groups data by minimizing distances within clusters, thereby partitioning the dataset into K distinct classes (24, 25). Each cluster was represented by a clustering center, defined as the mean value of all points within that cluster. The inflection point on the curve is considered the optimal number of clusters, representing the best division of the dataset. In our analysis, when K = 4, the curve tends to be steady (Supplementary Figure S1), so a four-cluster solution provided the optimal fit compared to other cluster counts (Figure 2). Data were presented as means ± standard deviation (SD) or median and interquartile range for continuous variables and percentages for categorical variables. Based on the result, we classified the participants into four groups: sustained low level (Class1); sustained medium level (Class2); high level and stable increasing (Class3); high level and fasting increasing (Class4). In Class 1 (n = 1305), the HGI ranged from -0.53 ± 0.39 in 2012 to 0.43 ± 0.46 in 2015, and the cumulative HGI was -0.10 ± 0.49, representing a consistently low and stable HGI; for Class 2 (n = 2334), the HGI ranged from 0.03 ± 0.25 in 2012 to 0.79 ± 0.31 in 2015, and the cumulative HGI was 0.82 ± 0.29, representing a sustained moderate HGI; for Class 3 (n = 902), the HGI ranged from 0.46 ± 0.44 in 2012 to 1.38 ± 0.49 in 2015, and the cumulative HGI was 1.83 ± 0.47, representing a high HGI with a slowly increasing trend (Figure 2). For Class 4 (n = 135), the HGI ranged from 1.51 ± 1.11 in 2012 to 3.46 ± 1.26 in 2015, and the cumulative HGI was 4.97 ± 1.36, representing a consistently high and fast increasing trend HGI.

Before investigating the association between HGI and incident CVD, we first employed machine learning algorithms for feature selection to determine their importance in the prognostic model (26). To improve the accuracy of feature selection, the eXtreme Gradient Boosting (XGBoost) model combined with SHapley Additive extension (SHAP) values was employed for feature screening and dimensionality reduction through Python package (version 3.11.10), identifying key features associated with CVD incident. The importance and the contribution of each feature can be directly observed by plotting the SHAP summary plot. Multiple

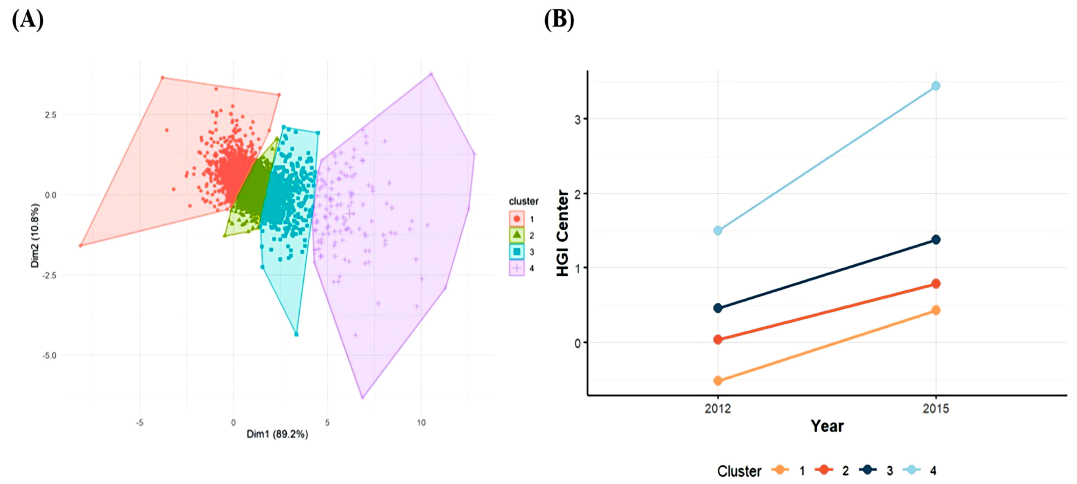

FIGURE 2
(A) The HGI clustering by k-means; **(B)** The trend of HGI changes in different clusters.

imputations were used to fill in missing data to maximize statistical power and mitigate any bias that may result from missing data (27). Two logistic regression models were used to estimate the association between changes and cumulative measures in HGI with CVD, quantified through odds ratio (ORs) and 95% confidence intervals (CIs).

To investigate potential nonlinear associations between cumulative HGI and CVD events, we employed a RCS regression model with four knots. Interaction analyses were conducted to determine whether the association between cumulative HGI and CVD varied across covariates.

Mediation analysis was conducted to determine whether this association was mediated by risk factors, such as BMI and triglyceride glucose (TyG) index (28). Mediation analysis was performed using the 'mediation' package.

All statistical analyses were performed using R version 4.3.3 software (http://www.R-project.org/). Statistical significance was set as a two-sided p value < 0.05.

3 Result

3.1 Baseline characteristics of participants

In this study, a total of 4,676 participants were included for analysis. The mean age at baseline was 58.62 ± 8.65 years, with 2,170 participants (46.41%) identifying as men. The mean HGI was 0.00 ± 0.58 in 2012 and 0.88 ± 0.71 in 2015. Table 1 presents the baseline characteristics of participants in each group based on the cluster analysis.

Participants with higher and rapidly increasing levels of HGI were more likely to be female, older, and obese. Those also exhibited a greater prevalence of metabolic disorders, with significantly elevated levels of serum creatinine (Scr), serum uric acid (UA), TC, LDL-C, FBG, and HbA1c compared to participants in the lower-level clusters.

3.2 Association between the changes of HGI and CVD risk

The incidence of 944 CVD during the follow-up period was presented in Table 2. The regression models were developed based on clinical expertise and feature importance selection results from the XGBoost algorithms, as shown in Figure 3. After adjusting for age, gender, smoking status, drink status, education, SBP, TG, TC, UA, platelet (PLT), Scr, blood urea nitrogen(BUN), FBG, and C-reactive protein (CRP) in Model 2, the multivariate-adjusted OR and 95% CI from lowest stable group to highest rapid increasing group were1.00 (reference), 0.97 (0.80, 1.18), 1.32 (1.05, 1.67), and 1.63 (1.01, 2.64), respectively.

3.3 Association between the value of cumulative HGI and CVD risk

Multivariable logistic regression analyses also indicated a positive relationship between the cumulative HGI and CVD risk, with an adjusted OR of 1.08 (95% CI: 1.04, 1.13) (Table 2). RCS regression analysis further confirmed the linear increase in CVD risk associated with higher values of the cumulative HGI (P for nonlinearity = 0.967, Supplementary Figure S2).

Subgroup analyses and interaction tests were conducted to evaluate the consistency of the association between cumulative HGI and the risk of CVD across various individual subgroups, including age, gender, smoking status, hypertension, diabetes, dyslipidemia, and stage of CKM. Interaction terms were utilized to assess heterogeneity within each subgroup. No statistically significant interactions were identified regarding the association between cumulative HGI and CVD (Figure 4 and Supplementary Table S1).

Overall, our results indicated that the positive association between cumulative HGI and CVD risk remains consistent across different population subgroups and is applicable in various settings.

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TABLE 1 Baseline characteristics of participants classified according to the changes of HGI.

Variables	Total (n = 4676)	Class 1 (n = 1305)	Class 2 (n = 2334)	Class 3 (n =902)	Class 4 (n = 135)	*P* value
Age, years	58.62 ± 8.65	57.84 ± 8.63	58.59 ± 8.77	59.82 ± 8.31	58.80 ± 7.97	<0.001
Gender, n (%)						<0.001
Male	2170 (46.41)	658 (50.42)	1096 (46.96)	363 (40.24)	53 (39.26)	
Female	2506 (53.59)	647 (49.58)	1238 (53.04)	539 (59.76)	82 (60.74)	
Education, n (%)						0.005
Middle school and above	1409 (30.13)	428 (32.80)	711 (30.46)	235 (26.05)	35 (25.93)	
No completion of middle school	3267 (69.87)	877 (67.20)	1623 (69.54)	667 (73.95)	100 (74.07)	
Smoking status, n (%)						0.051
Yes	1802 (38.54)	532 (40.77)	905 (38.77)	316 (35.03)	49 (36.30)	
No	2874 (61.46)	773 (59.23)	1429 (61.23)	586 (64.97)	86 (63.70)	
Drinking status, n (%)						<0.001
More than monthly	1211 (25.90)	383 (29.35)	619 (26.52)	187 (20.73)	22 (16.30)	
Less than monthly	393 (8.40)	127 (9.73)	186 (7.97)	66 (7.32)	14 (10.37)	
Never	3072 (65.70)	795 (60.92)	1529 (65.51)	649 (71.95)	99 (73.33)	
Hypertension, n (%)						<0.001
Yes	1700 (36.35)	493 (37.78)	781 (33.46)	347 (38.47)	79 (58.52)	
No	2976 (63.65)	812 (62.22)	1553 (66.54)	555 (61.53)	56 (41.48)	
Dyslipidemia, n (%)						<0.001
Yes	2214 (47.35)	630 (48.28)	1014 (43.44)	474 (52.55)	96 (71.11)	
No	2462 (52.65)	675 (51.72)	1320 (56.56)	428 (47.45)	39 (28.89)	
Diabetes, n (%)						<0.001
Yes	709 (15.16)	244 (18.70)	149 (6.38)	201 (22.28)	115 (85.19)	
No	3967 (84.84)	1061 (81.30)	2185 (93.62)	701 (77.72)	20 (14.81)	
BMI, kg/m^2	23.55 ± 3.79	23.35 ± 3.61	23.40 ± 3.81	23.95 ± 3.86	25.71 ± 3.69	<0.001
SBP, mmHg	128.16 ± 41.18	129.84 ± 46.12	126.74 ± 37.18	126.46 ± 19.58	147.92 ± 106.47	<0.001
DBP, mmHg	75.83 ± 12.89	74.68 ± 12.39	75.98 ± 13.15	76.49 ± 12.95	79.98 ± 11.39	<0.001
TC, mg/dl	193.81 ± 38.27	189.95 ± 38.71	193.34 ± 37.57	198.72 ± 38.65	206.52 ± 37.85	<0.001
HDL-C, mg/dl	51.37 ± 15.44	50.65 ± 16.23	52.26 ± 14.95	50.96 ± 15.39	45.63 ± 14.57	<0.001
LDL-C, mg/dl	116.83 ± 34.89	110.31 ± 35.52	118.04 ± 33.98	121.46 ± 34.16	127.90 ± 38.95	<0.001
TG, mg/dl	130.62 ± 106.18	145.28 ± 146.64	119.29 ± 77.71	134.24 ± 95.96	160.64 ± 108.10	<0.001
BUN, mg/dl	15.59 ± 4.36	15.82 ± 4.38	15.52 ± 4.33	15.51 ± 4.35	15.17 ± 4.57	0.126
Scr, mg/dl	0.76 ± 0.17	0.77 ± 0.17	0.77 ± 0.17	0.76 ± 0.18	0.75 ± 0.19	0.253
Uric acid, mg/dl	4.38 ± 1.22	4.44 ± 1.25	4.37 ± 1.20	4.36 ± 1.21	4.11 ± 1.25	0.019
CRP, mg/dl	2.55 ± 6.86	2.20 ± 5.95	2.57 ± 6.71	3.01 ± 8.45	2.68 ± 5.44	0.056
WBC, $\times10^9/L$	6.21 ± 1.88	6.02 ± 1.78	6.21 ± 1.88	6.41 ± 2.01	6.87 ± 1.74	<0.001
PLT, $\times10^9/L$	212.68 ± 73.90	207.33 ± 72.44	210.87 ± 73.74	224.81 ± 75.94	214.77 ± 68.42	<0.001
HGI_{2012}, %	0.00 ± 0.58	-0.53 ± 0.39	0.03 ± 0.25	0.46 ± 0.44	1.51 ± 1.11	<0.001

(Continued)

TABLE 1 Continued

Variables	Total (n = 4676)	Class 1 (n = 1305)	Class 2 (n = 2334)	Class 3 (n =902)	Class 4 (n = 135)	*P* value
HGI_{2015}, %	0.88 ± 0.71	0.43 ± 0.46	0.79 ± 0.31	1.38 ± 0.49	3.46 ± 1.26	<0.001
Cumulative HGI, %	0.88 ± 1.06	-0.10 ± 0.49	0.82 ± 0.29	1.83 ± 0.47	4.97 ± 1.36	<0.001
CVD, n (%)	716 (15.31)	184 (14.10)	331 (14.18)	171 (18.96)	30 (22.22)	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; BUN: blood urea nitrogen; FBG: fasting blood glucose; TC: total cholesterol ; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; CRP: C-reactive protein; HbA1c: hemoglobin A1C; UA: uric acid; Scr: serum creatinine; WBC: white blood cell count; PLT: platelet count; HGI: hemoglobin glycation index; CVD: cardiovascular disease
Notes: Continuous variables were expressed as mean ± standard deviation (SD) in case of normal distribution and compared between two groups by Kruskal-Wallis rank sum test. If the count variable had a theoretical number < 10, Fisher's exact probability test was used. Categorical variables are presented as counts (percentages) and compared by Chi-square test.

3.4 Mediation analysis

In mediation analysis, it was suggested that BMI partially mediates the relationship between the cumulative HGI index and CVD, accounting for approximately 18.6% of the effect. The mediating role of the TyG index in the association was 6.9%. Dyslipidemia also played a significant role in mediating the association between the HGI index and new-onset CVD, contributing approximately 11.0% to the effect. However, diabetes, hypertension, and the chronic inflammation biomarker CRP did not demonstrate a significant mediating effect (Table 3).

These findings emphasize the necessity of considering BMI and insulin resistance (IR) as an important risk factors in the development of strategies for preventing CVD in individuals with early-stage CKM syndrome, in conjunction with lipid control.

4 Discussion

This large prospective cohort study, based on data from CHARLS, is the first to investigate the association between HGI and the risk of CVD in early-stage CKM syndrome. Patients with CKM stages 0–3 who have not yet developed cardiovascular disease exhibit significant differences in clinical and metabolic characteristics across various groups. Individuals with high and rapidly increasing HGI levels demonstrate a greater prevalence of cardiovascular risk factors, leading to more complex comorbidities. HGI were the more important features than traditional risk factors such as FBG for predicting CVD. Additionally, we enhanced the understanding of the linear relationship between cumulative HGI and the incidence of CVD. TyG index, BMI and dyslipidemia showed potential mediating roles in the association between cumulative HGI and CVD. These findings further emphasize the crucial role of longitudinal monitoring of HGI in predicting CVD.

TABLE 2 Association between HGI and the risk of CVD in patients with early-stage CKM syndrome.

Cluster of HGI	Crude	Model 1	Model 2
	OR (95% CI) *P* value	OR (95% CI) *P* value	OR (95% CI) *P* value
Class 1	Reference	Reference	Reference
Class 2	1.01 (0.83,1.22) 0.946	0.98 (0.81,1.20) 0.877	1.00 (0.82,1.22) 0.992
Class 3	1.43 (1.13,1.79) 0.002	1.34 (1.06,1.69) 0.013	1.35 (1.07,1.70) 0.012
Class 4	1.74 (1.13,2.69) 0.012	1.65 (1.06,2.55) 0.025	1.57 (1.01,2.45) 0.045

Model I, adjusted for age, gender.
Model II, adjusted for important feature calculated by XGBoost algorithm including: gender, age, education, smoking status, drink status, SBP, UA, Scr, TC, TG, BUN, PLT, FBG, CRP.
OR, odd ratio; CI, confidence interval.

For patients with metabolic disorders, blood glucose levels are closely associated with the incidence and progression of vascular diseases. Hyperglycemia accelerates the non-enzymatic glycation of crucial proteins, causing the formation of glycated proteins. In addition to hemoglobin, other structural proteins are also susceptible to non-enzymatic glycation, leading to the formation of advanced glycation end products (AGEs) (29). AGEs trigger inflammatory signaling, enhance oxidative stress, and ultimately contribute to the development of atherosclerosis by damaging arterial endothelial cells and accelerating lipid oxidation (30). Although HbA1c remains a crucial tool for managing metabolic disorders, its limitations must be acknowledged. HGI could minimize clinical errors and optimize patient treatment, as a more personalized approach (19). Enhancing the management of HGI may not only help confirm the role of glycemic variability in the prevention and management of CKM syndrome, but also help make early lifestyle adjustments such as controlling glucose and cholesterol level.

This study is the first to investigate the association between cumulative HGI and CVD in a CKM syndrome population. Our results show that high cumulative level and rapidly growth of HGI is positively linked to the risk of CVD, consistent with previous research on single-measure HGI (31). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, individual with high HGI values had a higher incidence of CVD (15). The ACCORD trial suggested that HGI could serve as a reference for adjusting treatment options to achieve improved CVD outcomes. Another study from Korea suggested that the development of CVD was significantly associated with baseline HGI in patients with type 2 diabetes (HR, 1.74; 95% CI, 1.08-2.81) (32). Due to the inter-individual variability of HGI, the large-scale studies are required to determine whether HGI can serve as a universality marker to assess CVD risk.

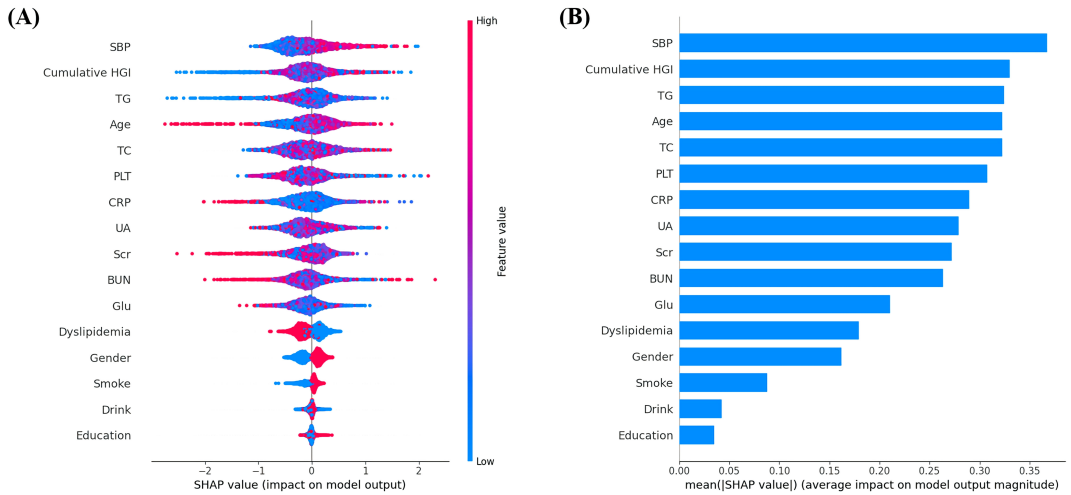

FIGURE 3
(A) Featured clinical variables screened by SHAP calculated by XGBoost model. Distribution of the impact of each feature on the model output. Each dot represents a patient in a row. The colors of the dots represent the feature values: red represents larger values and blue represents lower values. **(B)** The vertical axis shows the name of each variable, whereas the horizontal axis represents the feature value of each variable.

Asian populations bear a disproportionately high burden of diabetes and cardiovascular diseases. Due to genetic, dietary, and lifestyle factors, the relationship between HbA1c and blood glucose levels may exhibit unique characteristics in these populations (33). Longitudinal monitoring of the HGI can more accurately reflect glycemic variability and reduce the errors associated with relying solely on HbA1c. Our analysis also revealed this critical finding that the cumulative HGI demonstrated superior predictive capacity for

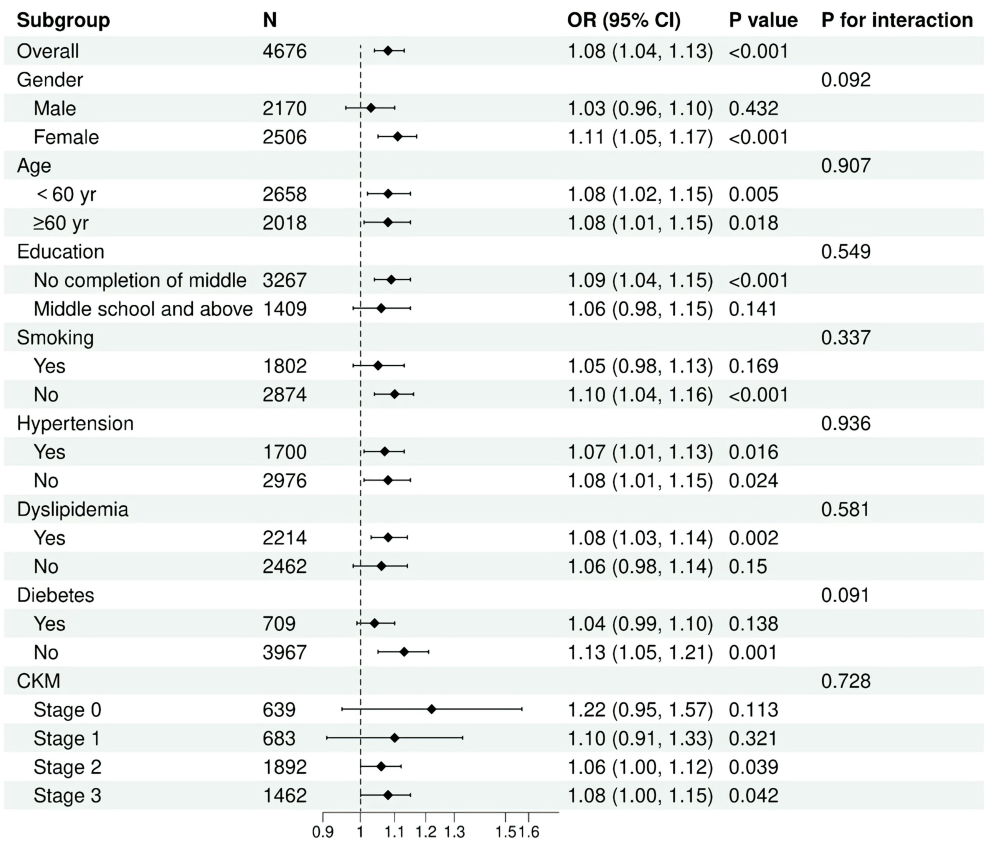

FIGURE 4
Forest plot of association between HGI and CVD in different subgroups.

TABLE 3 Mediation analysis for the associations between Cumulative HGI and CVD in patients with early-stage CKM syndrome.

Independent variable	Mediator	Total effect		Indirect effect		Direct effect		Proportion mediated, % (95% CI)
		Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value	
Cumulative HGI	BMI	0.009 (0.003, 0.015)	0.016	0.002 (0.001, 0.003)	<0.001	0.007 (0.001, 0.013)	0.020	18.6 (8.0, 54.6)
Cumulative HGI	TyG	0.010 (0.004, 0.015)	<0.001	0.001 (0.000, 0.001)	0.036	0.009 (0.004, 0.015)	<0.001	6.9 (0.4, 19.8)
Cumulative HGI	Dyslipidemia	0.010 (0.004, 0.016)	<0.001	0.001 (0.000, 0.002)	0.032	0.009 (0.004, 0.015)	<0.001	7.8 (0.6, 26.7)
Cumulative HGI	CRP	-0.011 (-0.017, -0.006)	<0.001	0.001 (-0.001, 0.001)	0.380	-0.011 (-0.017, -0.006)	<0.001	5.0 (-0.7, 2.9)
Cumulative HGI	Hypertension	0.010 (0.004, 0.016)	<0.001	0.001 (-0.000, 0.002)	0.128	0.009 (0.003, 0.015)	<0.001	10.7 (-3.0, 28.1)
Cumulative HGI	Diabetes	0.010 (0.004, 0.016)	<0.001	0.000 (-0.001, 0.001)	0.608	0.010 (0.004, 0.016)	<0.001	2.4 (-8.0, 22.1)

Adjusted for gender, age, education, smoking status, drink status, SBP, UA, Scr, TC, TG, BUN, PLT, FBG, CRP. The stratified variable was not included in the model when stratifying by itself.

CVD risk stratification in patients with CKM syndrome compared to conventional glucose metrics, including FBG. Some patients with diabetes exhibit higher postprandial glucose fluctuations and lower HbA1c levels, which may lead to an increased risk of inadequate glycemic control. By promoting the use of HGI monitoring, more precise glycemic assessment and personalized treatment strategies can be provided for Asian populations, thereby reducing the risk of cardiovascular diseases associated with CKM syndrome and minimizing potential harm caused by inaccurate glycemic evaluation and inappropriate therapeutic interventions.

Our findings revealed no statistical association between the HGI and CVD incidence during the ultra-early stages of CKM syndrome (stages 0 to 1). In individuals at stages 2 and 3 with elevated metabolic risk factors, the association between cumulative HGI and CVD incidence was more pronounced. This may be attributed to the fact that, metabolic disturbances in individuals may not yet reach the threshold level required to trigger cardiovascular risk in the early stages of CKM. Specifically, studies have shown that metabolic abnormalities, such as insulin resistance and chronic inflammation, need to accumulate to a certain extent before they can significantly impact vascular function and tissue damage (34). As an indicator reflecting long-term glycemic variability and hemoglobin glycation heterogeneity, HGI may lack sufficient sensitivity in the early stages when metabolic disturbances are relatively mild. This hypothesis is consistent with previous research, which indicates that the predictive ability of HbA1c and HGI is weaker in the prediabetic or early metabolic syndrome stages but becomes significantly enhanced as the disease progresses (35). During CKM stages 0-1, individuals may partially offset the vascular damage caused by glycemic fluctuations through compensatory mechanisms, such as enhanced insulin secretion or antioxidant capacity, thereby masking the predictive value of HGI. As the disease progresses to CKM stages 2-3, the decline in metabolic compensatory capacity allows the association between HGI and CVD risk to become more apparent. The latter stages of CKM are often accompanied by more pronounced chronic inflammation and oxidative stress, which may amplify the predictive role of HGI in CVD risk.

Reduced insulin sensitivity is considered as a significant risk factor for atherosclerotic disease (36), and serves as a central contributor to cardiovascular risk factors such as visceral obesity, atherogenic dyslipidemia, and hypertension, which frequently co-occur in individuals with metabolic disorders (37). In our study, an essential finding is that IR related indicators (TyG), BMI and dyslipidemia partially mediated the relationship between cumulative HGI and CVD. There is evidence that elevated HGI relate to the IR and increased risk of vascular atherosclerosis (38). The promotion of AGEs may alter insulin receptor signaling and impair glucose-uptake. In animal models, oral advanced AGEs have been shown to induce insulin resistance, contributing to metabolic disorders and lipid toxicity (39, 40).

IR can affect glucose metabolism through inflammatory factors, macrophage and adipocyte activation, and the renin–angiotensin–aldosterone system, can contribute to cardiac dysfunction and myocardial injury, ultimately leading to various cardiovascular diseases. Previous research has established that individuals with a metabolically healthy obesity phenotype face a higher risk of CVD compared to those with a metabolically healthy normal-weight profile (41). Marini et al. reported that elevated HGI may reflect the risk of metabolic disease associated with obesity (38). Our research further corroborates this finding. A study involving patients in American showed that BMI interacts with HGI, such that lower levels are associated with cardiovascular benefits (42). Regarding blood pressure, previous studies confirmed that BP status significantly modified the associations between cardiometabolic risk factors and CVD (43). HGI was found to be linked to arterial stiffening, independent of diabetes status (44).

With the progression of population aging, declining metabolic function and heightened chronic inflammatory states may amplify the impact of glycemic variability on CVD risk (45). Age is a non-

modifiable risk factor for vascular diseases such as coronary heart disease and stroke, but metabolic abnormalities may represent critical modifiable targets for risk reduction (46). In age-stratified analyses, although the interaction P-value did not reach statistical significance, it is noteworthy that the strength of the association between HGI levels and CVD risk was more pronounced in the older age group compared to the middle-aged group. Based on the CHARLS database of older adults, this study demonstrates that HGI serves as a robust independent predictor of coronary heart disease risk. Given the accelerating global aging population, HGI is expected to play an increasingly significant role in risk stratification, offering valuable insights for early identification of high-risk individuals and the development of personalized intervention strategies.

To our knowledge, this is the first study to explore the mediating effects of these risk factors in the relationship between the HGI and adverse health outcomes. Although CRP was not identified as mediators in this association, this does not negate their potential relationship with HGI and CVD.

The potential limitations of this study should not be overlooked. First, the exclusion of individuals without FBG and HbA1c measurements led to the omission of a significant portion of the diabetic metabolic population, which may affect the findings. Second, CVD diagnoses in CHARLS were self-reported, and no further adjudication of CVD events was conducted. Third, HbA1c measurements in CHARLS were only taken at two time points (2012 and 2015), which may not adequately capture short-term fluctuations or the complete metabolic trajectory, potentially influencing the observed relationship. Fourthly, due to the limited variables available in the database, residual confounding from unmeasured inflammatory mediators or adipose-derived hormones might partially mediate the observed HGI-CVD association. Lastly, since HGI may have ethnic variability, multinational multicenter validation studies are necessary to establish its broader clinical applicability.

5 Conclusion

This study found that a rapidly increasing and high cumulative level of HGI was associated with an elevated risk of CVD progression in individuals with early-stage CKM syndrome. This association was partially mediated by BMI, TyG and dyslipidemia. HGI can serve as an independent predictor for assessing cardiovascular risk in patients with CKM syndrome. Our findings offer new insights into the potential relationship between blood glucose control, insulin resistance, lipid metabolism, and CVD in individuals with CKM syndrome. Clinicians should consider regular HGI monitoring to facilitate timely lifestyle interventions or therapy adjustments.

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

HL: Conceptualization, Data curation, Methodology, Writing – original draft. SM: Conceptualization, Writing – original draft. YZ: Conceptualization, Writing – original draft. LD: Data curation, Writing – original draft. YW: Data curation, Writing – original draft. CL: Writing – review & editing. TY: Conceptualization, 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1554032/full#supplementary-material

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An unsupervised cluster analysis of multimorbidity patterns in older adults in Shenzhen, China

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Background: Population aging challenges health care systems due to the high prevalence and impact of multimorbidity in older adults. Studies on multimorbidity in Shenzhen have primarily focused on the quantity of multimorbidity, lacking in-depth exploration of multimorbidity patterns.

Methods: Based on baseline data from the Shenzhen aging-related disease cohort, this study analyzed information from 8,911 people aged 60 and above after excluding missing and abnormal values from interview results. Using self-organizing map combined with weighted k-means, the distribution of diseases in the population was visualized, dividing the overall population into four clusters. The study also analyzed comorbidity and association rules for each cluster.

Result: This study found a high prevalence of cardiometabolic comorbidities among the older adult in Shenzhen, reaching 15.83%, and detailed the distribution of specific comorbidity combinations. Hypertension had a high prevalence and was the most common factor in comorbidities among Shenzhen's older adult. Additionally, hyperuricemia was included as a disease to explore its multimorbidity patterns with other chronic conditions.

Conclusion: The study found that multimorbidity is prevalent among the older adult in Shenzhen and explored their patterns, suggesting that Shenzhen should enhance screening and integrated management of high-risk groups and implement public health interventions to alleviate the multimorbidity burden.

KEYWORDS

multimorbidity, multimorbidity pattern, unsupervised learning, older adults, Shenzhen city

1 Introduction

With increased life expectancy and declining fertility rates, the global population is rapidly aging (1). Concurrently, as populations age and lifestyles change, multimorbidity has become increasingly prevalent. Multimorbidity, typically referring to the coexistence of two or more chronic diseases in an individual, has garnered significant attention in recent years. Globally, approximately one-third of adults including a substantial proportion in low- and middle-income countries and more than half of all adults with any chronic disease suffer from multimorbidity (2). Among the global adult population aged 60 and above, over half are afflicted with multimorbidity (51.0, 95% CI: 44.1–58.0%) (3).

Multimorbidity is associated with numerous adverse health outcomes, such as increased mortality, disability, reduced quality of life, and elevated hospitalization rates, thereby posing significant public health challenges globally. In high-income countries, multimorbidity accounts for 78% of primary care consultations (4), and individuals with multimorbidity are hospitalized more frequently and for longer durations than those with one or no diseases (5). Moreover, there is an almost exponential relationship between the number of chronic diseases and the associated healthcare costs. Notably, the COVID-19 pandemic has also exposed vulnerabilities in global public health systems (6–10). During the pandemic, individuals with multimorbidity were at higher risk of infection and adverse outcomes, including hospitalization (10, 11).

In China, the management of chronic diseases, particularly multimorbidity, has received considerable attention from the government and health departments. Several studies have explored multimorbidity, including large-scale research such as analyses among two million Chinese adults and studies on the relationship between multimorbidity patterns and mortality involving 500,000 Chinese adults (12, 13). A recent systematic review indicated that nearly one-quarter of Chinese adults suffer from multimorbidity, with prevalence increasing rapidly with age (14). However, most studies on multimorbidity in China are based on medical data from a single city or province (14–18). Due to differences in economic levels, healthcare services, and population health quality among different regions in China, variations in the prevalence and patterns of diseases and multimorbidity exist, necessitating more specific analyses.

Shenzhen is one of the fastest-growing cities in China and is widely regarded as the "City of Innovation," with technology, finance, and manufacturing as its pillar industries. It has transformed from a fishing village into a modern metropolis within just a few decades. As one of China's first Special Economic Zones, Shenzhen has attracted talent from across the country and around the world, resulting in a highly diverse population. Although youthfulness has long been considered a defining characteristic of the city, projections suggest that Shenzhen will officially enter an aging society by 2029. As a representative southern Chinese city, several studies on multimorbidity have been conducted in Shenzhen to date (19–22). A large-scale cross-sectional study published in 2023 investigated the prevalence of multimorbidity among the older adult population in Shenzhen. The study demonstrated that the prevalence rates of obesity, hypertension, diabetes, anemia, chronic kidney disease, hyperuricemia, dyslipidemia, and fatty liver disease were 10.41, 62.09, 24.21, 12.78, 6.14, 20.52, 44.32, and 33.25%, respectively. The prevalence of multimorbidity was 63%, with an average of 2.14 chronic diseases per participant (22). The study also analyzed predictors of multiple diseases. However, most studies on multimorbidity in Shenzhen have primarily focused on the quantity of multimorbidity, lacking in-depth exploration of multimorbidity patterns.

Machine learning, particularly unsupervised clustering techniques, has been utilized to investigate patterns of multimorbidity within specific populations. Various methods have been employed, including Principal Component Analysis (PCA), Apriori algorithms, hierarchical clustering, and k-means clustering (23–26). In recent years, Self-Organizing Maps (SOM), a visualization-oriented unsupervised learning method, have also been applied to multimorbidity analysis, often in conjunction with hierarchical clustering and k-means clustering (27–29). This study proposes a novel unsupervised learning approach that combines SOM with Weighted k-means (W-k-means) to identify multimorbidity patterns among the older adult in Shenzhen. The primary objective is to identify disease groupings or clusters within Shenzhen's older adult population and to further characterize and describe patient profiles observed both in the overall population and within these clusters. This involves exploring common comorbidity combinations and the most common causes of multimorbidity among the older adult, aiming to provide valuable information for health policy formulation and the allocation of health services.

2 Methods

The data for this cross-sectional study were derived from the baseline data of the Shenzhen aging-related disease cohort established between 2017 and 2018 (30). This dataset includes 9,411 older adult participants aged 60 to 92 years from 51 community health service centers in Luohu District, Shenzhen. The inclusion and exclusion criteria have been previously published (30). All participants agreed to join in the cohort and provide informed written consent. The study has been approved by the Review Board of Shenzhen Center for Disease Control and Prevention (approval numbers: R2017001 and R2018020).

Data collected included demographic and socioeconomic information, lifestyle factors, medical history, family history of major non-communicable chronic diseases, environmental exposures, clinical analyses of blood and urine, imaging measurements, anthropometric measurements, and neurological and mental health assessments. Demographic data (e.g., name, ID number, gender, date of birth, education level) and chronic disease history (including hypertension, dyslipidemia, coronary heart disease, stroke, diabetes, cancer, neurological and psychiatric diseases) were collected using semi-structured questionnaires. The age range was calculated based on birth year reported in 5-year intervals, and the data was divided into four groups. Older adult individuals aged over 76 were classified as older seniors, and since the data volume was not suitable for division into 5-year intervals, they were grouped together. Body mass index (BMI) was categorized as underweight (BMI < 18.5), normal weight (BMI ≥ 18.5 and <25), overweight (BMI ≥ 25 and <30), and obese (BMI ≥ 30).

In this study, multimorbidity was defined as the simultaneous presence of two or more chronic diseases. A total of 21 chronic diseases were used to assess multimorbidity, including hyperuricemia, chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, pulmonary tuberculosis, hypertension, hyperlipidemia, angina pectoris, myocardial infarction, coronary heart disease, chronic hepatitis, nephritis, diabetes, migraine, stroke, Alzheimer's disease, Parkinson's disease, depression, osteoporosis, arthritis, and tumors. These 21 diseases encompass the majority of non-communicable chronic conditions associated with aging, including neurological disorders, mental illnesses, chronic respiratory diseases, cardiovascular diseases, metabolic disorders, cancers, injuries, and other non-communicable diseases. They can be used to describe the patterns of morbidity and multimorbidity among the older adult population in Shenzhen. Based on blood analysis results, males with uric acid levels exceeding 420 μmol/L and females exceeding 360 μmol/L were considered to have hyperuricemia (31–34). Each disease is derived from the patient's medical history report, based

on which a wide-format high-dimensional binary matrix is created for unsupervised clustering analysis. Each column corresponds to a diagnostic category, with "1" indicating the presence of the condition and "0" indicating its absence. Based on these disease characteristics and demographic features, patients with multiple missing values and subjects with incorrectly coded features were excluded, resulting in a final sample of 8,911 subjects.

Cardiometabolic multimorbidity refers to the coexistence of two or more cardiometabolic diseases, including hypertension, diabetes, coronary heart disease, stroke, and dyslipidemia. Additionally, multimorbidity focuses on the overall coexistence of multiple diseases, while comorbidity refers to more specific combinations of diseases, emphasizing the relationships and interactions between them.

The primary goal of this research was to identify disease groupings or clusters among older adult patients in Shenzhen and to characterize patient profiles within these clusters. Previous studies on multimorbidity have often employed hierarchical clustering and k-means clustering methods. In this study, we adopted a novel clustering approach to better delineate disease groups. We described the prevalence rates in the overall older adult population and within clusters, identified common comorbidity combinations and performed association rule mining. Social factors and demographic characteristics across clusters were also analyzed. Machine learning and statistical analyses were conducted using R statistical software (v. 4.4.1).

As shown in Figure 1, this study employs a two-stage self-organizing clustering method to determine whether multimorbidity conditions group together. The first stage provides the topological coordinates of prototypes, allowing for clustering in the second stage using classical methods. The Self-Organizing Map (SOM), proposed by Kohonen, is an unsupervised artificial neural network that transforms and visualizes high-dimensional input data onto a low-dimensional map (27, 35–37). SOM preserves the topological structure of the original data, forming a two-dimensional space composed of nodes that cluster relevant data. Input data are connected to a selected lattice of nodes, distributing the dataset across these nodes. The SOM process begins by initializing the grid with random samples from the dataset, then iteratively compares node distances and assigns individuals to nodes.

SOM + K-means is a commonly used method for exploring patterns of multimorbidity. Considering that the traditional K-means algorithm used in the SOM + K-means approach cannot effectively adjust for the distribution of sample sizes across SOM nodes, this study replaces K-means with the Weighted K-means algorithm. In addition to W-K-means, we conducted comparative analyses using SOM + K-means, conventional K-means, Latent Class Analysis (LCA), and Multiple Correspondence Analysis combined with K-means (MCA + K-means). As this study is based on real-world data, there are no ground-truth labels for patient clusters to directly assess clustering performance. Nevertheless, several internal metrics can provide guidance and reference during the clustering process, although the final evaluation ultimately depends on clinical interpretability and practical relevance. Through comparison, the W-K-means approach demonstrated several advantages, including: clinically interpretable clusters; more stable and distinct multimorbidity patterns; a clear gradient in disease burden; and moderate, clinically meaningful cluster sizes. Therefore, we report the clustering results based on the W-K-means method. Regarding the selection of SOM network size N, we chose a network that is large enough to differentiate the data evenly without causing over-dispersion, and adopted a sufficient learning rate to ensure adequate iteration and convergence.

As shown in Figure 2, in the two-stage clustering method, the first stage involves constructing the SOM network, and the second stage applies W-k-means clustering. The weighted k-means algorithm considers the importance of different data points by assigning weights during clustering. In this study (38), the activation frequency of each node in the SOM network was used as the weight. A 30 × 30 node network with hexagonal topology was initialized to simulate positional relationships within the network. The SOM was trained using an initial learning rate of 0.05 and a final learning rate of 0.01 over 20,000 iterations to ensure stability and convergence. To determine the appropriate number of clusters, we evaluated within-cluster distances for different values and visualized the within sum of squares (WSS). Based on the WSS plot (Supplementary Figure 1), four clusters were selected as the optimal number.

The Apriori algorithm was employed to analyze common combinations of comorbidities among older adult individuals with multimorbidity in both the overall population and the four clusters. The algorithm extracts frequent itemsets from large datasets and generates association rules describing relationships among these items. Key metrics for association rules include support, confidence, and lift. In multimorbidity research, support represents the frequency of

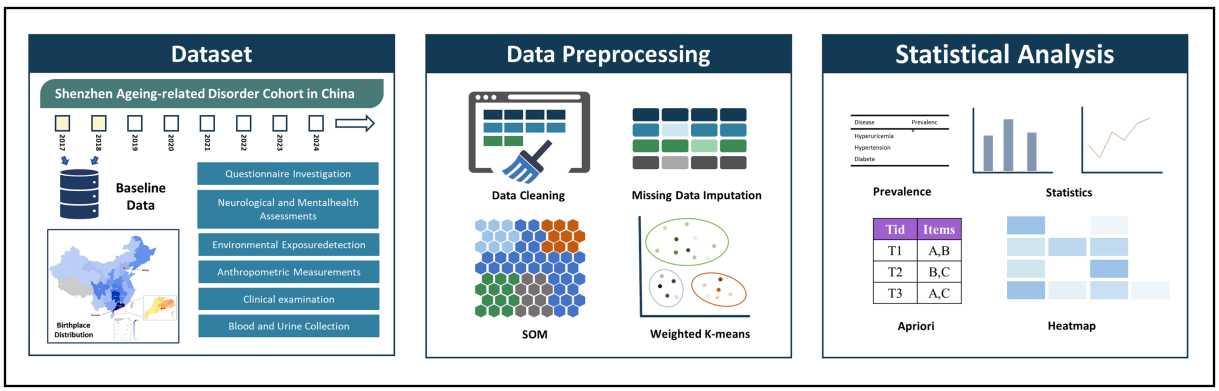

FIGURE 1
Overview of study approach (30). Map reproduced with permission from "The birthplace distribution of the studied individuals". By Liu L et al., licensed under CC BY-NC 4.0.

co-occurrence of diseases, confidence indicates the probability of one disease occurring given another, and lift measures the strength of the association beyond chance. In this study, the minimum support was set at 3.0%, the minimum confidence at 30%, and the maximum number of antecedent items at three, the parameter settings were adapted from another study on Multimorbidity among older adults in China.

3 Results

3.1 Overall population

Table 1 presents the disease characteristics among participants with different characteristics. The average age of all study participants

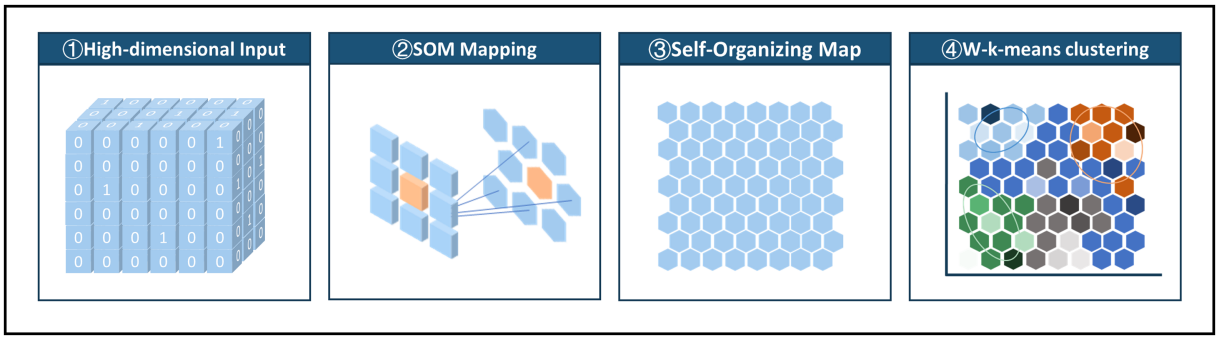

FIGURE 2
Two-level SOM clustering approach: mapping high-dimensional input data to a low-dimensional SOM network and using node activation frequencies as weights in a weighted K-means clustering.

TABLE 1 Multimorbidity prevalence in different features.

Features	Patients (*n*, %)	No disease (*n*, %)	Single disease (*n*, %)	Multimorbidity (*n*, %)
Woman	3,809 (42.74%)	1,090 (42.28%)	1,405 (43.63%)	1,314 (42.21%)
Man	5,102 (57.26%)	1,488 (57.72%)	1815 (56.37%)	1799 (57.79%)
Age				
60–65	2,987 (33.52%)	1,028 (39.88%)	1,122 (34.84%)	837 (26.89%)
66–70	3,086 (34.63%)	904 (35.07%)	1,102 (34.22%)	1,080 (34.69%)
71–75	1732 (19.44%)	423 (16.41%)	622 (19.32%)	687 (22.07%)
76-	1,106 (12.41%)	223 (8.65%)	374 (11.61%)	509 (16.35%)
BMI				
BMI < 18.5	208 (2.33%)	107 (4.15%)	75 (2.33%)	26 (0.84%)
18.5 ≤ BMI < 25	4,502 (50.52%)	1,584 (61.44%)	1,621 (50.34%)	1,297 (41.66%)
25 ≤ BMI < 30	3,668 (41.16%)	817 (31.69%)	1,344 (41.74%)	1,507 (48.41%)
BMI ≥ 30	533 (5.98%)	70 (2.72%)	180 (5.59%)	283 (9.09%)
Education				
Primary school and below	1,538 (17.26%)	417 (16.18%)	547 (16.99%)	574 (18.44%)
Junior high school	2,448 (27.47%)	710 (27.54%)	872 (27.08%)	866 (27.82%)
Senior high school	3,027 (33.97%)	891 (34.56%)	1,131 (35.12%)	1,005 (32.28%)
College or undergraduate	1875 (21.04%)	552 (21.41%)	664 (20.62%)	659 (21.17%)
Graduate and above	23 (0.26%)	8 (0.31%)	6 (0.19%)	9 (0.29%)
Smoke				
No	7,095 (79.62%)	2075 (80.49%)	2,556 (79.38%)	2,464 (79.15%)
Yes	1816 (20.38%)	503 (19.51%)	664 (20.62%)	649 (20.85%)
Drink				
No	7,625 (85.57%)	2,209 (85.69%)	2,747 (85.31%)	2,669 (85.74%)
Yes	1,286 (14.43%)	369 (14.31%)	473 (14.69%)	444 (14.26%)

was 67.72 ± 5.42 years, with 42.74% being male. A total of 7,373 individuals (82.74%) had an educational level of junior high school or above. There were 1,816 smokers (20.37%) and 1,286 alcohol drinkers (14.43%). Additionally, 47.14% of the participants were overweight or obese. There were 3,220 cases (36.14%) with only one disease, and 3,113 cases (34.93%) had multimorbidity.

We calculated the average number of diseases corresponding to different ages and BMI categories, and linear trend tests were performed, revealing a significant upward trend in the number of diseases with increasing age and BMI ($p < 0.0001$) (Supplementary Figure 2). Supplementary Figure 3 shows the prevalence of each disease across different characteristics.

As shown in Table 2, among the 21 diseases involved in the study, the top four diseases with prevalence rates greater than 10% are hyperuricemia (40.30%), hypertension (36.01%), diabetes (15.22%), and hyperlipidemia (11.32%). The top five diseases in terms of prevalence are all cardiometabolic diseases. In this table, two indicators are defined to assess comorbidity patterns. The Overall Comorbidity Rate refers to the proportion of individuals in the total population who have both the primary disease and at least one comorbid condition. This metric provides insight into the prevalence of comorbid cases within the general population. In contrast, the Internal Comorbidity Rate denotes the proportion of individuals with the primary disease who also present with one or more comorbidities. This measure reflects the burden of comorbidity within the subset of patients affected by the primary disease. Hypertension has the highest overall comorbidity rate (26.00%). The internal comorbidity rate for all 21 diseases are over 50%. Among them, depression (93.33%), Alzheimer's disease (92.86%), and stroke (90.32%) have the highest internal comorbidity rate. Additionally, among diseases with higher prevalence rates, hyperlipidemia (85.03%) and coronary heart disease (87.47%) also have high internal comorbidity rate, indicating that older adult individuals with these two diseases are more likely to have other comorbid conditions.

Table 3 presents the top 10 two-disease and three-disease comorbidity combinations in the overall population, where almost all combinations include cardiometabolic diseases. In addition, Supplementary Figure 4 shows the prevalence rates of all disease combinations in the overall population, with cardiometabolic multimorbidity accounting for a large proportion of the combinations. Specifically, among the top 10 two-disease multimorbidity combinations, hypertension and hyperuricemia appear in five combinations, and their comorbidity have the highest prevalence, reaching 17.26%, far higher than other disease combinations. The prevalence rates of combinations like hypertension and diabetes (8.21%) and hypertension and hyperlipidemia (6.81%) are also high. Additionally, combinations like diabetes and hyperuricemia (6.21%) and hyperlipidemia and hyperuricemia (5.29%) have relatively high prevalence rates. Among the three-disease multimorbidity

TABLE 2 Prevalence of each comorbid disease.

Diseases	Patients N = 9,811	Patients with other diseases	Prevalence	Overall comorbidity rate	Internal comorbidity rate
Hyperuricemia	3,591	2,120	40.30%	23.79%	59.04%
Hypertension	3,209	2,317	36.01%	26.00%	72.20%
Diabetes	1,356	1,041	15.22%	11.68%	76.77%
Hyperlipidemia	1,009	858	11.32%	9.63%	85.03%
Coronary heart disease	495	433	5.55%	4.86%	87.47%
Arthritis	453	353	5.08%	3.96%	77.92%
Osteoporosis	241	186	2.70%	2.09%	77.18%
Tumors	193	134	2.17%	1.50%	69.43%
Chronic bronchitis	130	97	1.46%	1.09%	74.62%
Stroke	93	84	1.04%	0.94%	90.32%
Migraine	54	44	0.61%	0.49%	81.48%
Myocardial infarction	48	40	0.54%	0.45%	83.33%
Chronic hepatitis	43	28	0.48%	0.31%	65.12%
Asthma	41	34	0.46%	0.38%	82.93%
Nephritis	34	27	0.38%	0.30%	79.41%
Tuberculosis	34	26	0.38%	0.29%	76.47%
Angina pectoris	32	28	0.36%	0.31%	87.50%
Parkinson's disease	21	12	0.24%	0.13%	57.14%
COPD	18	15	0.20%	0.17%	83.33%
Depression	15	14	0.17%	0.16%	93.33%
Alzheimer's disease	14	13	0.16%	0.15%	92.86%

Patients with other diseases refers to those who have the listed disease as well as additional comorbidities. Overall comorbidity rate: number of patients with both the disease and any comorbidities/overall population. Internal comorbidity rate: number of patients with both the disease and any comorbidities/patients with the disease.

TABLE 3 Top 10 multimorbidity combinations.

Comorbidity	Prevalence
Hypertension, Hyperuricemia	17.26%
Hypertension, Diabetes	8.21%
Hypertension, Hyperlipidemia	6.81%
Diabetes, Hyperuricemia	6.21%
Hyperlipidemia, Hyperuricemia	5.29%
Coronary heart disease, Hypertension	3.33%
Diabetes, Hyperlipidemia	3.25%
Coronary heart disease, Hyperuricemia	2.46%
Arthritis, Hypertension	2.08%
Arthritis, Hyperuricemia	2.00%
Hyperuricemia, Hypertension, Diabetes	3.83%
Hyperuricemia, Hypertension, Hyperlipidemia	3.41%
Hypertension, Hyperlipidemia, Diabetes	2.59%
Hyperuricemia, Hypertension, Coronary heart disease	1.63%
Hyperuricemia, Hyperlipidemia, Diabetes	1.41%
Hypertension, Coronary heart disease, Diabetes	1.23%
Hypertension, Hyperlipidemia, Coronary heart disease	0.95%
Hyperuricemia, Hypertension, Arthritis	0.90%
Hyperuricemia, Coronary heart disease, Diabetes	0.77%
Hyperuricemia, Hyperlipidemia, Coronary heart disease	0.63%

combinations, aside from the top four highest-ranking metabolic disease combinations, combinations involving coronary heart disease and arthritis along with metabolic diseases are also noteworthy.

Further association rule mining was performed on the overall population, as shown in Supplementary Table 1. The results indicate that hypertension has a strong comorbidity relationship with coronary heart disease (coronary artery disease), hyperlipidemia, and diabetes, with lift values all above 1.50. Hyperuricemia is strongly associated with hypertension and hyperlipidemia, with lift values of 1.19 and 1.16. Additionally, hyperuricemia occurs at a higher rate among patients who have both hypertension and hyperlipidemia (lift value of 1.79). The three-disease combinations of hypertension, diabetes, and hyperuricemia (lift value of 1.71), as well as hypertension, hyperlipidemia, and hyperuricemia (lift value of 1.79), indicate very strong associations among these diseases.

By describing the characteristics and comorbidity combinations in the overall population and performing association rule mining, we found that cardiometabolic multimorbidity accounts for the vast majority of comorbidity combinations, with 1,409 (15.81%) people having cardiometabolic multimorbidity. Hypertension and coronary heart disease, and diabetes and dyslipidemia, have strong comorbidity relationships. Hyperuricemia is shown to accompany the onset of metabolic diseases, with the comorbidity combination of hyperuricemia and hypertension appearing most frequently. In addition, hypertension demonstrates a strong comorbidity capability and may be the most common factor in multimorbidity among the older adult (Figure 2).

3.2 Clusters

Figures 3A, 4A shows the SOM network and the final output of the four clusters, Figure 3B shows how large each cluster is and each disease is visualized in Figures 4C–W. The count plot in Figure 4B depicts the count of observed individuals in each node; patients are evenly distributed across the map. The characteristics of each cluster are detailed in Table 4. Larger clusters are distributed on the left and top sides. Figures 4C–W respectively show the distribution of different diseases on the map. Due to the inclusion of multiple diseases (mental and physical), the complexity of the high-dimensional disease feature space may be retained in the low-dimensional SOM space, and after sufficient iterations, the data points are relatively scattered.

Supplementary Figure 5 includes radar charts for each of the four clusters; radar charts of the same color represent the disease conditions within the same cluster, where the radar chart on the left represents prevalence rates, and the one on the right represents positive rates. Supplementary Figure 6 presents the disease prevalence heatmaps of Clusters 1–4. Table 5 shows the top 10 two-disease and three-disease multimorbidity combinations for the four clusters. Additionally, Supplementary Table 1 contains the association rules for the four clusters.

Overall, unsupervised learning provides us with a new perspective to classify multimorbidity patterns at the population level. Older adult residents in Shenzhen can be divided into the Hypertension Group, Hypertension and Diabetes Comorbidity Group, Healthy Group, and Hyperuricemia Group. The description of the characteristics and comorbidity combinations of the four clusters, along with association rule mining, revealed a more specific distribution of comorbidity combinations, further confirming the prevalent comorbidity between hyperuricemia and cardiometabolic diseases (such as diabetes, hypertension, hyperlipidemia, and coronary heart disease).

Furthermore, this study examined inter-cluster differences in three fundamental demographic and health-related variables: gender, age, and BMI. Chi-square tests were used to assess differences in gender distribution across clusters, followed by pairwise Chi-square comparisons. For the continuous variables—age and BMI—one-way analysis of variance (ANOVA) was first performed to detect overall differences, and *post hoc* comparisons between clusters were conducted using the Tukey HSD test. The following section presents a descriptive summary of each cluster. Below is a descriptive summary of each cluster:

Cluster 1 (Hypertension Group): this group had a gender ratio similar to the overall population. The average age was 68.51 ± 5.68 years, which was significantly higher than that of Cluster 3 ($p < 0.001$), but significantly lower than Cluster 2 ($p < 0.05$); no significant difference was found compared to Cluster 4. The group exhibited a relatively high BMI, with significantly higher values than

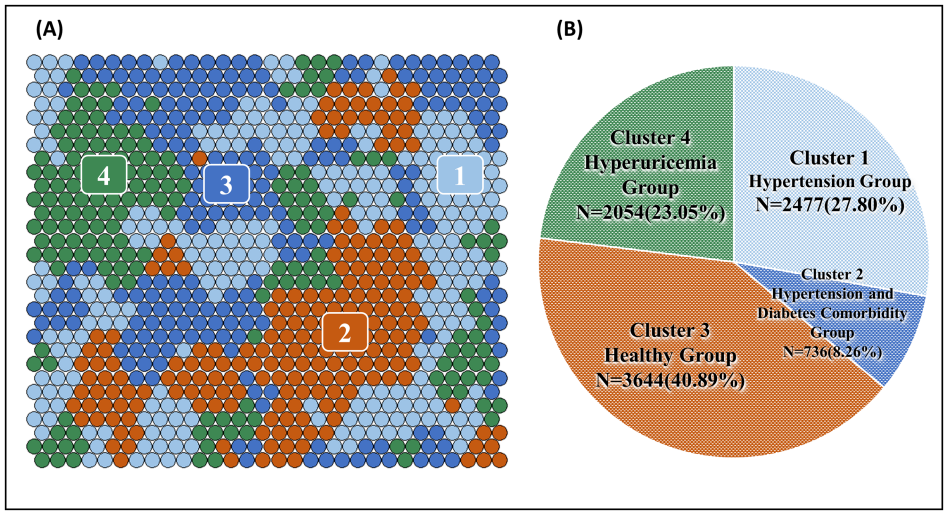

FIGURE 3
(A) Final SOM and **(B)** chart of the number and proportion of the four clusters.

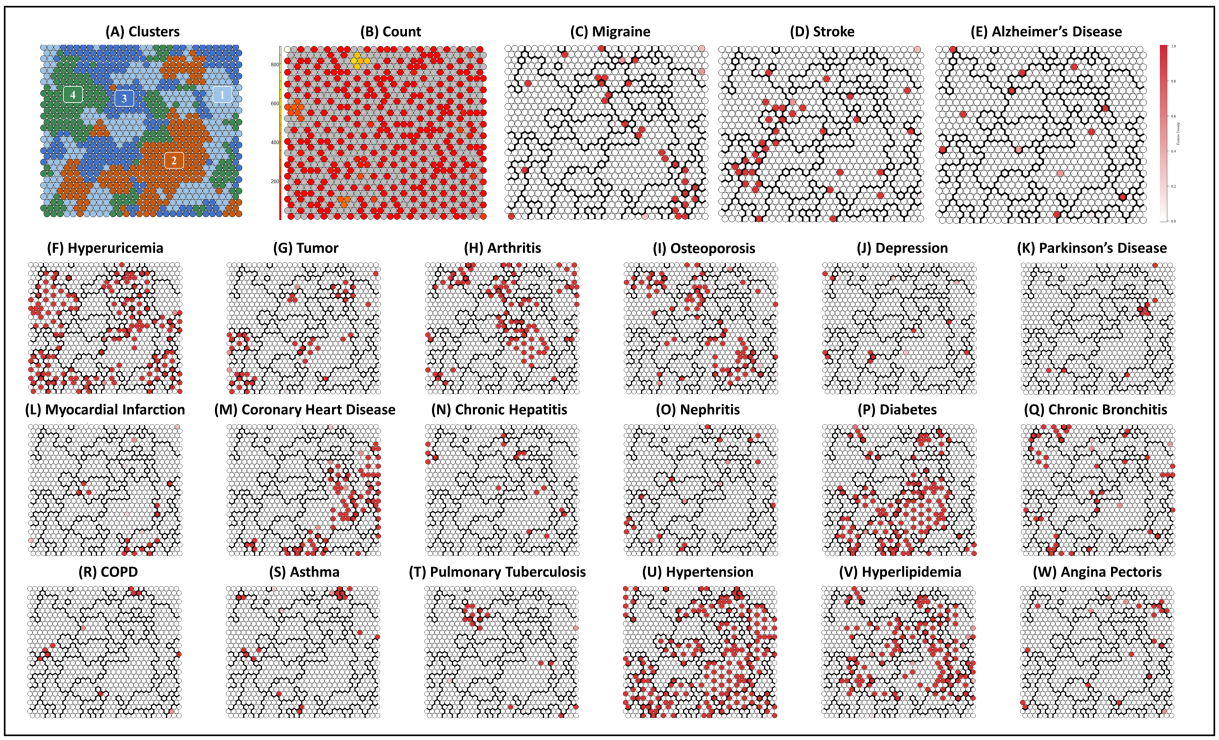

FIGURE 4
Final SOM and associated cluster boundaries. **(A)** Plot clusters: four clusters by two-level SOM clustering approach. **(B)** Plot count: count of individuals in each node. **(C–W)** Other plots: property heat maps of different diseases categories that show increased density on specific areas of the SOM.

Cluster 3 ($p < 0.001$), though similar to Cluster 2 ($p = 0.966$). The prevalence of overweight and obesity was relatively high. The age distribution was balanced. Educational attainment was higher compared to other clusters, and the proportions of smokers and drinkers were relatively low. All individuals in this group had hypertension; nearly half (48.32%) also had hyperuricemia, and a portion were diagnosed with hyperlipidemia.

Cluster 2 (Hypertension and Diabetes Comorbidity Group): this group also had a gender ratio similar to the overall population. The average age was 69.11 ± 5.63 years, the highest among all clusters, and was significantly greater than Clusters 1, 3, and 4 ($p < 0.001$). The BMI was relatively high, with most individuals falling into the overweight or normal categories. BMI in this group was significantly higher than in Cluster 3 ($p < 0.001$), similar to Cluster 1 ($p = 0.966$), and

TABLE 4 Features distribution in four clusters.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
	Count (prev%)	Count (prev%)	Count (prev%)	Count (prev%)
Sex				
Woman	1,033(41.70%)	315(42.80%)	1,523(41.79%)	938(45.67%)
Man	1,444(58.30%)	421(57.20%)	2,121(58.21%)	1,116(54.33%)
Age				
60–65	710(28.66%)	176(23.91%)	1,367(37.51%)	734(35.74%)
66–70	824(33.27%)	254(34.51%)	1,283(35.21%)	725(35.30%)
71–75	550(22.20%)	169(22.96%)	642(17.62%)	371(18.06%)
76-	393(15.87%)	137(18.61%)	352(9.66%)	224(10.91%)
BMI				
BMI < 18.5	19(0.77%)	6(0.82%)	149(4.09%)	34(1.66%)
18.5 ≤ BMI < 25	1,019(41.14%)	311(42.26%)	2,217(60.84%)	955(46.49%)
25 ≤ BMI < 30	1,216(49.09%)	342(46.47%)	1,172(32.16%)	938(45.67%)
BMI ≥ 30	223(9.00%)	77(10.46%)	106(2.91%)	127(6.18%)
Education				
Primary school and below	437(17.64%)	143(19.43%)	602(16.52%)	356(17.33%)
Junior high school	721(29.11%)	202(27.45%)	962(26.40%)	563(27.41%)
Senior high school	803(32.42%)	235(31.93%)	1,267(34.77%)	722(35.15%)
College or undergraduate	511(20.63%)	155(21.06%)	799(21.93%)	410(19.96%)
Graduate and above	5(0.20%)	1(0.14%)	14(0.38%)	3(0.15%)
Smoke				
No	1,999(80.70%)	578(78.53%)	2,925(80.27%)	1,593(77.56%)
Yes	478(19.30%)	158(21.47%)	719(19.73%)	461(22.44%)
Drink				
No	2,148(86.72%)	640(86.96%)	3,127(85.81%)	1,710(83.25%)
Yes	329(13.28%)	96(13.04%)	517(14.19%)	344(16.75%)

significantly lower than Cluster 4 ($p < 0.05$). Educational level was relatively lower, and the proportions of smokers and drinkers were slightly higher than in Cluster 1. Nearly all individuals (99.32%) had comorbidity of hypertension and diabetes; 46.20% had co-occurrence of hyperuricemia, hypertension, and diabetes. More than one-quarter had hyperlipidemia.

Cluster 3 (Healthy Group): this was the largest cluster, with a gender ratio similar to the overall population. The average age was 67.07 ± 5.11 years, making it the youngest group. This value was significantly lower than in all other clusters ($p < 0.001$). BMI was predominantly within the normal range and was significantly lower than in Clusters 1, 2, and 4 (all $p < 0.001$), representing the lowest among the clusters. This group had a relatively high level of educational attainment. The proportions of smokers and drinkers were moderate. Compared to other clusters, this group exhibited the lowest prevalence of chronic diseases and the lowest rates of multimorbidity.

Cluster 4 (Hyperuricemia Group): this group had a slightly higher proportion of females than the overall population. According to chi-square tests, the gender distribution was significantly different from that of Clusters 1 and 3 ($p < 0.01$). The average age was 67.41 ± 5.34 years, significantly higher than Cluster 3 ($p < 0.001$), but lower than Clusters 1 ($p < 0.05$) and 2 ($p < 0.001$). BMI was mostly within the normal and overweight categories and was significantly higher than in all other clusters ($p < 0.05$). Educational attainment was relatively lower. The proportions of smokers and drinkers were lower than those of non-smokers and non-drinkers. All individuals in this group had hyperuricemia, and the most common comorbidities involved hyperuricemia combined with other chronic diseases.

4 Discussion

This study conducted a cross-sectional analysis based on the baseline data of the Shenzhen older adult cohort. Utilizing information on the prevalence and multimorbidity of 21 diseases among the older adult in Shenzhen, we employed the Kohonen method combined with weighted k-means clustering to visualize the distribution of diseases within the population. Based on this visualization, we divided the overall population into four representative disease clusters. Furthermore, we described the common comorbidity combinations in both the overall population and each cluster and performed association rule mining. The results revealed a high prevalence of cardiometabolic diseases and their

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TABLE 5 Top 10 multimorbidity combinations in four clusters.

Comorbidity	Prevalence
Cluster 1	
Hyperuricemia, Hypertension	48.32%
Hyperlipidemia, Hypertension	15.14%
Hyperlipidemia, Hyperuricemia	8.11%
Hypertension, Coronary heart disease	7.51%
Hypertension, Arthritis	5.93%
Hyperuricemia, Coronary heart disease	3.75%
Hyperuricemia, Arthritis	2.54%
Hypertension, Osteoporosis	2.30%
Hypertension, Tumor	1.98%
Hyperlipidemia, Coronary heart disease	1.86%
Hyperuricemia, Hypertension, Hyperlipidemia	8.11%
Hyperuricemia, Hypertension, Coronary heart disease	3.75%
Hyperuricemia, Hypertension, Arthritis	2.54%
Hypertension, Hyperlipidemia, Coronary heart disease	1.86%
Hypertension, Hyperlipidemia, Arthritis	1.29%
Hyperuricemia, Hyperlipidemia, Coronary heart disease	1.01%
Hyperuricemia, Hypertension, Tumor	0.97%
Hyperuricemia, Hypertension, Osteoporosis	0.93%
Hyperuricemia, Hypertension, Stroke	0.69%
Hypertension, Osteoporosis, Arthritis	0.69%
Cluster 2	
Diabetes, Hypertension	99.32%
Hypertension, Hyperuricemia	46.33%
Diabetes, Hyperuricemia	46.20%
Diabetes, Hyperlipidemia	31.93%
Hyperlipidemia, Hypertension	31.52%
Diabetes, Coronary heart disease	15.49%
Coronary heart disease, Hypertension	15.08%
Hyperlipidemia, Hyperuricemia	13.99%
Coronary heart disease, Hyperuricemia	7.07%
Coronary heart disease, Hyperlipidemia	5.84%
Hyperuricemia, Hypertension, Diabetes	46.20%
Hypertension, Hyperlipidemia, Diabetes	31.39%
Hypertension, Coronary heart disease, Diabetes	14.95%
Hyperuricemia, Hypertension, Hyperlipidemia	13.99%
Hyperuricemia, Hyperlipidemia, Diabetes	13.86%
Hyperuricemia, Hypertension, Coronary heart disease	7.07%
Hyperuricemia, Coronary heart disease, Diabetes	6.93%
Hyperlipidemia, Coronary heart disease, Diabetes	5.71%
Hypertension, Hyperlipidemia, Coronary heart disease	5.30%
Hypertension, Diabetes, Arthritis	5.16%
Cluster 3	
Diabetes, Hyperlipidemia	0.85%

(Continued)

TABLE 5 (Continued)

Comorbidity	Prevalence
Arthritis, Osteoporosis	0.60%
Coronary heart disease, Hyperlipidemia	0.52%
Diabetes, Coronary heart disease	0.49%
Osteoporosis, Hyperlipidemia	0.47%
Arthritis, Diabetes	0.47%
Arthritis, Hyperlipidemia	0.44%
Arthritis, Coronary heart disease	0.27%
Tumor, Diabetes	0.27%
Arthritis, Chronic bronchitis	0.25%
Hyperlipidemia, Osteoporosis, Arthritis	0.14%
Chronic bronchitis, Hyperlipidemia, Diabetes	0.11%
Diabetes, Osteoporosis, Arthritis	0.11%
Hyperlipidemia, Migraine, Osteoporosis	0.08%
Chronic bronchitis, Hyperlipidemia, Osteoporosis	0.05%
Chronic bronchitis, Hyperlipidemia, Arthritis	0.05%
Chronic bronchitis, Diabetes, Arthritis	0.05%
Hyperlipidemia, Coronary heart disease, Osteoporosis	0.05%
Hyperlipidemia, Diabetes, Stroke	0.05%
Hyperlipidemia, Diabetes, Osteoporosis	0.05%
Cluster 4	
Diabetes, Hyperuricemia	10.32%
Hyperlipidemia, Hyperuricemia	8.13%
Arthritis, Hyperuricemia	4.77%
Coronary heart disease, Hyperuricemia	3.60%
Osteoporosis, Hyperuricemia	2.24%
Tumor, Hyperuricemia	1.56%
Chronic bronchitis, Hyperuricemia	1.41%
Diabetes, Hyperlipidemia	1.17%
Diabetes, Coronary heart disease	0.88%
Coronary heart disease, Hyperlipidemia	0.78%
Hyperuricemia, Hyperlipidemia, Diabetes	1.17%
Hyperuricemia, Coronary heart disease, Diabetes	0.88%
Hyperuricemia, Hyperlipidemia, Coronary heart disease	0.78%
Hyperuricemia, Hyperlipidemia, Arthritis	0.73%
Hyperuricemia, Osteoporosis, Arthritis	0.73%
Hyperuricemia, Diabetes arthritis	0.49%
Hyperuricemia, Hyperlipidemia, Osteoporosis	0.44%
Hyperuricemia, Chronic bronchitis, Diabetes	0.24%
Hyperuricemia, Diabetes, Osteoporosis	0.24%
Hyperlipidemia, Osteoporosis, Arthritis	0.24%

comorbidities, as well as common combinations of these diseases. Hyperuricemia was found to occur alongside metabolic diseases. Hypertension exhibited the strongest comorbidity tendency and may be a common cause of multimorbidity.

Compared with previous studies on multimorbidity in Shenzhen, this paper places a greater emphasis on exploring multimorbidity patterns. We employed a two-stage clustering method using Self-Organizing Maps to investigate the distribution of different diseases

within the population. Innovatively, this study used the activation frequency of each node in the SOM network as weights in the weighted k-means algorithm, aiming to better partition the population. We obtained three representative clusters: the first cluster consists entirely of hypertensive patients; the second cluster predominantly comprises patients with both hypertension and diabetes; and the third cluster is the hyperuricemia group. From these disease clusters, we can observe the multimorbidity patterns among the older adult in Shenzhen. After partitioning the comorbidity clusters at the population level, we further described the combinations in the overall population and within each cluster, and conducted association rule mining to further analyze the multimorbidity patterns.

This study found a high prevalence of cardiometabolic multimorbidity among the older adult in Shenzhen, reaching 15.83%, and demonstrated a more detailed distribution of comorbidity combinations. In a study conducted in Chongqing, China, 11.2% of middle-aged and older adult individuals had CMM, with the most common cardiometabolic disease being hypertension (16.5%), followed by dyslipidemia (15.1%) and diabetes (6.4%) (16). In another study using CLHLS data, 7.0% of participants had cardiometabolic multimorbidity (39). Similar patterns of cardiometabolic multimorbidity have also been observed in some studies analyzing multimorbidity patterns. In a study on multimorbidity among the older adult in China, the dyslipidemia/diabetes/hypertension/coronary heart disease/kidney disease pattern was the most common, with a prevalence of 22.4% (40). Another study classified 18.60% of patients under vascular system diseases such as hypertension, dyslipidemia, diabetes, heart disease, and stroke (41). Research indicates that hypertensive patients with two or more cardiometabolic diseases have significantly increased risks of all-cause mortality and cardiovascular mortality. Cohort studies have shown that in China, the prevalence of cardiometabolic multimorbidity has been increasing annually, more than doubling within 5 years, suggesting that cardiometabolic diseases are rapidly developing (42). Shenzhen should implement further management for this high-risk patient population.

In this study, we found that the prevalence of hypertension is very high, having the highest comorbidity rate, and it is the most common factor in multimorbidity among the older adult in Shenzhen. A previous study in Shenzhen also found that hypertension had the top four comorbidity prevalence rates with chronic pain, diabetes, hyperlipidemia, and bone diseases. Hypertension often coexists with multiple comorbidities. A review of the prevalence and patterns of multimorbidity in China showed that hypertension paired with hearing impairment, dyslipidemia, diabetes, eye diseases, and obesity constituted the five major multimorbidity patterns; other disease pairs also included hypertension, suggesting it may be the most common component in multimorbidity (14). In another study exploring cardiometabolic comorbidities among hypertensive patients in China, it was found that three-quarters of hypertensive patients had cardiometabolic comorbidities (43). In the UK Biobank database, 70, 64, and 57% of patients with chronic kidney disease (CKD), diabetes mellitus (DM), and stroke were also diagnosed with hypertension (44). A clinical study indicated that maintaining blood pressure control might be an effective method to slow the progression of comorbidities and could potentially reduce the population burden of multimorbidity (45).

Hyperuricemia was included as a disease in this study to explore its multimorbidity patterns with various other chronic conditions. Hyperuricemia is a metabolic disorder associated with gout, cardiovascular diseases, kidney diseases, and other ailments, and its global prevalence has been rising in recent years (46). Gout, as a metabolic disorder characterized by hyperuricemia and marked by prominent symptoms such as painful inflammatory arthritis, has been the subject of extensive research due to its high prevalence and substantial burden of comorbidities (47–49). In contrast, although hyperuricemia has been widely studied for its associations with various cardiovascular and metabolic diseases (47), relatively few studies have investigated the comorbidity patterns of hyperuricemia with other diseases at the population level.

In this study, we found that hyperuricemia among the older adult in Shenzhen often co-occurs with metabolic diseases. Another study from Guangdong Province found that dyslipidemia and hyperuricemia, and hyperuricemia and hypertension ranked first and third, respectively, among binary multimorbidity combinations. Among ternary multimorbidity combinations, dyslipidemia, hyperuricemia, and hypertension were the most common disease combination among middle-aged and older adult populations (50). Elevated serum uric acid levels are associated with the development of metabolic diseases (51). Compared to subjects with normal uric acid levels, patients with hyperuricemia have a 2.10-fold increased risk of metabolic syndrome (MetS) (PR = 2.10, 95% CI: 1.68–2.63). Among these, the association between high triglycerides and hyperuricemia is the strongest (PR = 2.32, 95% CI: 1.84–2.91) (52). A cohort study showed that over a 7-year follow-up, participants who maintained or progressed to hyperuricemia had a 1.86 times higher chance (95% CI: 1.29, 2.68) of progressing to cardiometabolic multimorbidity compared to those who maintained or reduced to non-hyperuricemia status (53). Therefore, uric acid control should be included in the formulation of chronic disease prevention and control policies in Shenzhen.

In recent years, the Chinese government has released a series of policy documents emphasizing the implementation of integrated chronic disease prevention and control strategies, as well as the improvement of health management efficiency. In 2020, China launched the "Three Highs" co-management initiative, which focuses on hypertension, hyperglycemia, and hyperlipidemia as key entry points for exploring new models of chronic disease prevention and control. While several international guidelines on comorbidity management have been established, there is currently a lack of corresponding guidelines specifically tailored to comorbidities in China (54). Managing comorbid conditions presents numerous challenges, particularly the transition from traditional single-disease treatment approaches to care models that address multiple coexisting conditions. Comorbidity management requires patient-centered and family-centered care, along with a consideration of individual patients' care goals—indicating that there is no one-size-fits-all approach to the management of multiple chronic conditions. This study identifies representative subgroups among older adult individuals with comorbidities in Shenzhen, shedding light on the heterogeneity of chronic disease populations in the community (2). These findings provide both a theoretical foundation and practical direction for precision health management. Further attention to the healthcare needs and care practices of these representative subgroups

will help facilitate the development of more effective strategies for comorbidity management and nursing care.

Based on the identified four clusters, targeted stratified management and intervention strategies can be envisioned:

- Cluster 1 (Hypertension Group): individuals in this group may benefit from enhanced blood pressure monitoring, improved medication adherence, and weight reduction interventions, aiming to prevent progression toward more complex metabolic comorbidities.
- Cluster 2 (Hypertension and Diabetes Comorbidity Group): this group should be considered a key target for chronic disease management. A multidisciplinary team (MDT) approach is recommended, focusing on integrated control of blood pressure, blood glucose, body weight, and lipid levels. Concurrently, behavioral interventions such as smoking cessation, alcohol restriction, dietary modification, and physical activity prescriptions should be reinforced.
- Cluster 3 (Healthy Group): as a relatively healthy population, this group is suited for preventive management strategies. Regular health check-ups and digital health interventions (e.g., apps and tracking systems) are encouraged, with an emphasis on early identification and management of sub-health conditions.
- Cluster 4 (Hyperuricemia Group): greater attention should be paid to the identification and management of hyperuricemia, particularly among women. Nutritional guidance and lifestyle modifications are essential to prevent the development of other chronic conditions such as hypertension and diabetes.

In addition, cluster labels derived from unsupervised learning may serve as important markers for future personalized healthcare. These labels could be integrated into community-based electronic health records or chronic disease follow-up systems, helping healthcare providers quickly assess individual risk levels. Moreover, the clustering results can inform resource allocation strategies. For instance, public health resources might be prioritized for Cluster 2 and Cluster 4 populations to enhance the effectiveness and cost-efficiency of interventions.

This study has limitations. As a cross-sectional study, it cannot assess causal relationships. Data compilation for the Shenzhen older adult cohort is still ongoing, and we look forward to future cohort studies better illustrating the progression of multimorbidity among the older adult in Shenzhen. Nevertheless, the evidence from this study can still provide useful information for the formulation of health-related policies and the allocation of social health services. The findings may also serve as a reference for similar cities in other countries.

5 Conclusion

Multimorbidity is prevalent among the older adult population in Shenzhen. The use of the SOM method and weighted k-means clustering effectively characterizes the health status of individuals within this group. The results indicate that hyperuricemia, along with hypertension, diabetes, hyperlipidemia, coronary heart disease, and other cardiometabolic diseases, imposes a heavy burden. Hypertension may be a common cause of these comorbidities. Shenzhen should strengthen screening of high-risk populations and enhance comprehensive management of multimorbidity. Public health interventions should be implemented to alleviate the burden of multimorbidity.

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 study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Shenzhen Center for Disease Control and Prevention (R2007001). The studies were conducted in accordance with 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

XG: Conceptualization, Data curation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. PL: Investigation, Supervision, Writing – review & editing. JG: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. NZ: Conceptualization, Data curation, Writing – review & editing. HH: Investigation, Writing – review & editing. JL: Investigation, Writing – review & editing. ZT: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. GD: Formal analysis, Funding acquisition, Project administration, Resources, 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 FIGURE 1
Elbow plot of the total within-cluster sum of squares (WSS) for varying numbers of clusters.

SUPPLEMENTARY FIGURE 2
Prevalence of different features across diseases. Each cell represents the prevalence of the feature in the disease patients of the corresponding column, calculated as: (Number of patients with the feature in the disease / Total number of patients with the disease in the column) × 100%. Values below 0.1% are hidden.

SUPPLEMENTARY FIGURE 3
Prevalence of different features across diseases. Same as Figure 2.

SUPPLEMENTARY FIGURE 4
Multimorbidity prevalence between pairs of diseases. Each cell represents the comorbidity prevalence between the row and column diseases, calculated as: (Number of comorbid patients / Total study population) × 100%. Values below 0.1% are hidden.

SUPPLEMENTARY FIGURE 5
Radar plots for four clusters with diseases. Left radar charts: Disease prevalence within each cluster, calculated as: (Number of patients with the disease in the cluster / Total cluster population) × 100%. Right radar charts: Positive rate of the disease in the cluster relative to the overall population, calculated as: (Number of patients with the disease in the cluster / Total patients with the disease in the overall population) × 100%.

SUPPLEMENTARY FIGURE 6
Multimorbidity prevalence between diseases within four clusters. Each cell represents comorbidity prevalence within the cluster, calculated as: (Number of comorbid patients in the cluster / Total cluster population) × 100%. Values below 0.1% are hidden.

SUPPLEMENTARY TABLE 1
Overall association rule mining results.

SUPPLEMENTARY TABLE 2
Association rule mining results stratified by four clusters.

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Association between metabolic-associated fatty liver disease and risk of cardiometabolic multimorbidity: a disease trajectory analysis in UK Biobank

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Objective: While metabolic-associated fatty liver disease (MAFLD) has been associated with individual cardiometabolic diseases (CMDs), its role in the dynamic progression to cardiometabolic multimorbidity (CMM) remains unclear. We investigated the association of MAFLD, its severity and subtypes with CMM in individuals with no or one CMD at baseline.

Methods: This prospective cohort study involved 386,651 individuals (344,415 without and 42,236 with a single CMD at baseline) from the UK Biobank. MAFLD was defined as the presence of hepatic steatosis plus overweight/obesity, type 2 diabetes (T2D), or metabolic abnormalities. CMM was defined as the coexistence of two or more CMDs in the same person, including T2D, coronary heart disease (CHD) and stroke. Cox proportional hazard models and multistate models were performed to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs).

Results: During a median follow-up of 13.85 years, 4,622 new-onset CMM cases emerged among participants free of CMD at baseline. MAFLD was significantly associated with an increased risk of incident CMM (adjusted HR: 2.78, 95% CI: 2.60-2.96). Multistate models showed that MAFLD adversely affected most transitions from baseline to single CMDs and then to CMM. Among the single-CMD participants, the adjusted HRs of incident CMM in the MAFLD group were 1.21 (95% CI: 1.13-1.31) for T2D patients, 1.90 (1.75-2.05) for CHD patients, and 1.65 (1.45-1.87) for stroke patients, respectively.

Conclusion: MAFLD independently elevated the risk of incident CMM, regardless of the baseline CMD status. These findings emphasize the necessity of targeted MAFLD interventions for CMM prevention.

KEYWORDS

metabolic-associated fatty liver disease, cardiometabolic multimorbidity, disease trajectory, multistate model, UK Biobank

1 Introduction

Multimorbidity, commonly defined as the coexistence of two or more chronic diseases in the same person, is a prevalent phenomenon among middle-aged and older populations worldwide, along with rapid population ageing (1–4). The prevalence of multimorbidity is estimated to be 20-30% in the general population and rise to 55-98% in people aged 60 years and older (1). Due to the shared risk factors and similar pathobiological changes between cardiometabolic diseases (CMDs), cardiometabolic multimorbidity (CMM) was reported to be one of the replicable and harmful multimorbidity patterns (5–7). Generally, CMM was defined as the simultaneous presence of at least two of type 2 diabetes (T2D), coronary heart disease (CHD), and stroke (5). Mounting evidence demonstrated that CMM was significantly associated with a higher likelihood of premature mortality (5), depressive symptoms (8), cognitive impairment (9), and dementia (10). However, existing medical guides and treatments mainly focus on single CMDs and individuals with CMM are often excluded from the clinical trials (1, 7). Thus, deeply understanding the potential risk factors of CMM is substantially critical for the primary prevention of CMM and for alleviating the disease burden.

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide and affects about a quarter of the global adult population, yet there are no effective treatments (11, 12). The existing diagnostic criteria of NAFLD include the presence of liver steatosis and the exclusion of excess alcohol consumption and other causes of liver disease (12). However, such an exclusive definition over-emphasizes the absence of alcohol drinking and neglects the cardiometabolic dysfunction related to heterogeneous disease characterization and adverse endpoints (13, 14). In 2020, an international panel of experts proposed an updated definition for NAFLD, named metabolic-associated fatty liver disease (MAFLD) (15). The new criteria are inclusive and emphasize the role of metabolic abnormalities in the incidence and development of liver diseases. Few studies have demonstrated that participants with MAFLD had a significantly increased risk of occurring individual CMDs, such as atrial fibrillation, myocardial infarction, ischemic stroke and heart failure, and even cancer (14, 16–21). However, the association of MAFLD with the subsequent risk of CMM has not yet been examined. Moreover, prior disease trajectory analyses of CMM pointed out that cardiometabolic risk factors disproportionally impacted the whole disease progression to CMM (22–24). To our knowledge, no prior studies have investigated whether and to which extent MAFLD impacts different transitions from the healthy status to single CMDs, and subsequently to CMM, which may provide crucial evidence to develop and implement targeted interventions for the onset and progression of CMM. We hypothesized that MAFLD could affect the whole trajectories of CMM development.

To address above knowledge gaps, we used a two-stage analytic strategy to investigate the association between MAFLD and the risk of incident CMM based on a prospective cohort study in the UK Biobank: (1) estimate the effect of MAFLD on transitions from a relatively healthy status (free of any CMD) to single CMDs (i.e., T2D, CHD and stroke) and to CMM in individuals with no CMD at baseline (stage one); (2) estimate the risk of developing CMM associated with MAFLD in individuals with a single CMD at baseline (stage two).

2 Materials and methods

2.1 Study population

The UK Biobank study is a large-scale prospective cohort study, and detailed information on its design and methods has been described previously (25). In brief, UK Biobank recruited more than 500,000 community-dwelling participants aged 37–73 years at 22 assessment centers across England, Wales, and Scotland between 2006 and 2010. Comprehensive information on sociodemographic characteristics, early-life experiences, lifestyle behaviors, health-related status and medication were collected via questionnaires, physical measurements, and biological sample assessment. The UK Biobank study was approved by the North West Multicenter Research Ethical Committee, and all participants provided written informed consent. This research was conducted under UK Biobank application number 104283.

Figure 1 presented the flowchart of participants selection process. Of 502,366 participants in the UK Biobank, we excluded those without complete data on MAFLD components (n=97,983) and those with a diagnosis of CMM before the baseline survey (n=17,732). Finally, 386,651 participants, including 344,415

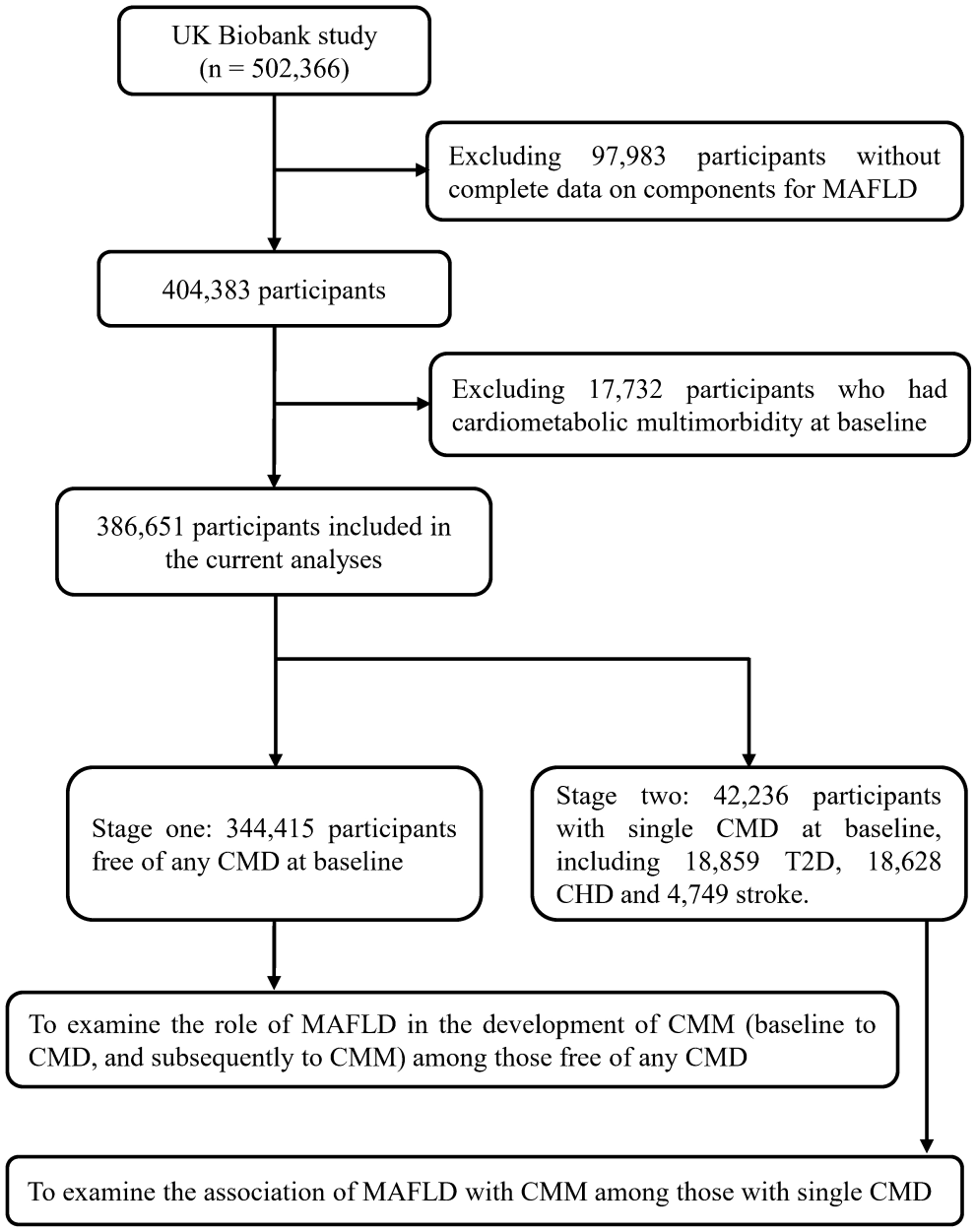

FIGURE 1
Flowchart of selecting study population. MAFLD, metabolic-associated fatty liver disease; T2D, type 2 diabetes; CHD, coronary heart disease; CMD, cardiometabolic disease; CMM, cardiometabolic multimorbidity.

participants free of any single CMD at baseline and 42,236 participants with a single CMD at baseline, were included to estimate the association of MAFLD with the risk of incident CMM.

2.2 Definition of MAFLD

According to international expert consensus and past studies based on UKB (15, 19, 26, 27), MAFLD was defined as the presence of hepatic steatosis in addition to one of the following three criteria: (1) overweight or obesity (overweight: body mass index [BMI] ≥25 kg/m^2; obesity: BMI ≥30 kg/m^2), (2) presence of T2D, or (3) two or more metabolic abnormalities including prediabetes (hemoglobin A1c [HbA1c] ≥39 mmol/mol), lower high-density lipoprotein (HDL) cholesterol (<1.03 mmol/L for men, <1.29 mmol/L for women), hypertriglyceridemia (≥1.7 mmol/L or taking lipid-lowering medication), hypertension (systolic/diastolic blood pressure [SBP/DBP] ≥130/85 mmHg or taking antihypertensive medication), subclinical inflammation (high-sensitivity C-reactive protein >2 mg/L), and increased waist circumference (WC, ≥102 cm for men, ≥88 cm for women). Due to the absence of liver imaging and histological data in the UK Biobank, the fatty liver index (FLI) (28) was calculated using WC, gamma-glutamyl transferase, triglycerides, and BMI to define the hepatic steatosis (FLI ≥60),

which had been widely used in prior UKB studies (19, 26, 27). The FLI had been verified to diagnose hepatic steatosis, with sensitivity and sensitivity of 87% and 86% (28). Notably, insulin resistance was not included in assessing metabolic abnormality due to the data availability in UK Biobank. The diagnosis of T2D was determined if participants met any of the following criteria: 1) had a self-reported diagnosis of T2D; 2) HbA1c > 47 mmol/mol; 3) took antidiabetic medication; 4) had International Classification Disease, version 10 (ICD-10) of E11 before the baseline assessment.

The severity of MAFLD was assessed via NAFLD fibrosis score calculated using the formula: −1.675+[0.037×age (years)] +[0.094×BMI (kg/m^2)]+[1.13×T2D (yes=1, no=0)]+[0.99×AST/ALT ratio]-[0.013×platelet count(10^9/L)]-[0.66×albumin(g/dL)] (29, 30). Participants were categorized into three groups according to this score: low (< -1.455), mild (-1.455 to 0.676), and severe (>0.676) liver fibrosis. Moreover, to assess the impact of different MAFLD subtypes, we further classified MAFLD into three subtypes: obese MAFLD (hepatic steatosis with only obesity), lean MAFLD (hepatic steatosis with only metabolic dysfunction), and obese and metabolic dysfunctional MAFLD (hepatic steatosis with obesity plus metabolic dysfunction). Because all individuals in stage one were free of T2D, we did not consider T2D in the MAFLD subtype.

2.3 Assessment of outcomes

The primary outcome was the incidence of cardiometabolic multimorbidity, which was defined as the simultaneous presence of two or three CMDs, including T2D, CHD and stroke (22, 23). In the UK Biobank study, disease incidence and diagnosis date were identified from the "first occurrence fields (Category ID: 1712)" based on the International Classification of Disease (ICD-10), which integrated information on self-reported disease history and linkage with electronic medical records and death registry records. Detailed information can be found at https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=1712. According to previous UKB studies on CMM (31–33), the corresponding ICD-10 codes were E11 for T2D, I20-I25 for CHD, and I60-I64 and I69 for stroke, respectively. For participants free of any CMD at baseline, the time of incident CMM was defined as the diagnosis date of occurring second CMD. For those with a single CMD at baseline, the time of incident CMM was the diagnosis date of another CMD.

2.4 Covariates

The potential covariates, including age, sex, ethnicity, educational levels, socioeconomic status, family income, employed status, lifestyle behaviors (smoking status, alcohol drinking, physical activity, sleep duration and diet), and family history of chronic disease, were collected through a self-reported questionnaire at baseline assessment. The Townsend deprivation index (TDI) is a measure of area-based socioeconomic status and derived from the residence postcode. Smoking and alcoholic drinking status were classified into never, previous, or current smoking/drinking. The levels of physical activity were estimated using the International Physical Activity Questionnaire short form, covering moderate and vigorous activities and walking over the last week. The total metabolic equivalent per week (METs, min/week) was then calculated to estimate the total volume of physical activity and categorized into three groups according to the tertiles. According to a previous study in UK Biobank (34), a healthy diet score was conducted by summing the following dietary factors: vegetables and fruits, fish, unprocessed red meat, and processed meat, and a higher score indicates a healthier diet. Sleeping duration was categorized into <7 h/day, 7–8 h/day, and >8 h/day, respectively. Family history of chronic disease included the occurrence of hypertension, diabetes, heart disease, and stroke in the participants' father, mother and siblings.

2.5 Statistical analysis

Baseline characteristics were described as mean and standard deviation (SD) for continue variables and frequency (%) for categorical variables according to baseline MAFLD status. The group differences in baseline characteristics were compared using *t* test or χ^2 test, as appropriate. For covariates with missing values or responses of "missing/unknown/prefer not to answer", we created an additional category for categorical variables to maximize sample size and reduce the potential for inferential bias.

The Kaplan-Meier curves with a log-rank test were adopted to compare the cumulative incidence rate of CMM between the non-MAFLD and MAFLD groups. Cox proportional hazard models were conducted to estimate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for associations of MAFLD, its severity and subtypes with the risk of incident CMM. The proportional hazards assumption of Cox regression model was verified by the Schoenfeld residuals method, and results showed no significant deviation of assumption (all *P* values>0.05). Follow-up time was calculated from the date of baseline assessment to the date of incident CMM, death, or censoring (Nov 30, 2022), whichever came first. Three models were conducted: model 1 adjusted for age and sex; model 2 additionally adjusted for ethnicity, educational levels, family income, socioeconomic status, employed status, smoking status, alcohol drinking, physical activity, sleep duration and healthy diet score; model 3 additionally adjusted for family history of diabetes, hypertension, heart disease and stroke.

Furthermore, we used the multi-state model to evaluate the role of MAFDL in the different transitions from baseline to single CMD and subsequently to CMM among individuals free of any CMD at baseline. As shown in Figure 2, we predefined a disease-developing framework with 6 transitions: 1) baseline status (free of any CMD) to T2D, 2) baseline status to CHD, 3) baseline status to stroke, 4) T2D to CMM, 5) T2D to CMM, and 6) stroke to CMM. The multi-state models were assumed to follow a Markov process, whereby the future state depends only on the current state and not on the prior history. This assumption is commonly applied in multistate models

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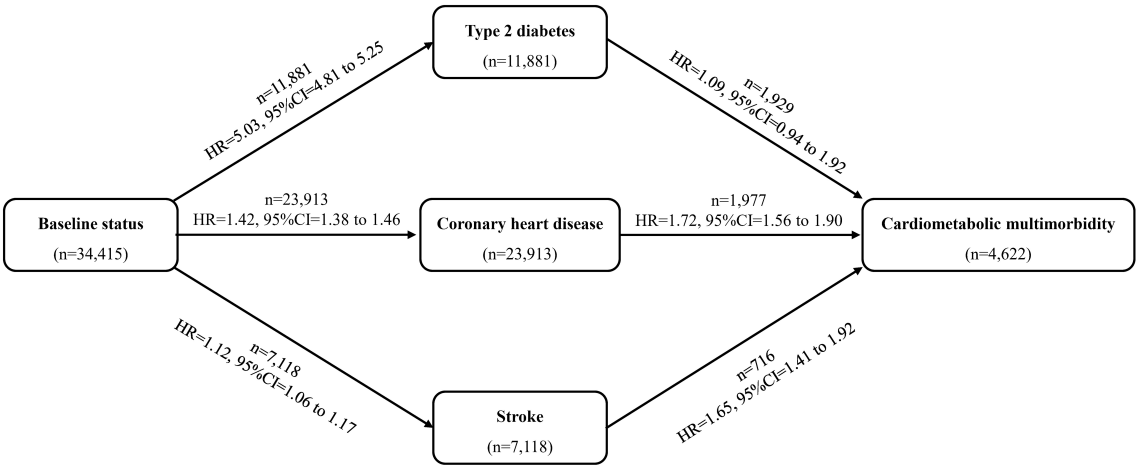

FIGURE 2
Role of metabolic-associated fatty liver disease (MAFLD) in the development of cardiometabolic multimorbidity. HR, hazard ratio; CI, confidence interval. Models adjusted for age, sex, ethnicity, educational levels, family income, socioeconomic status, employed status, smoking status, alcohol drinking, physical activity, sleep duration, healthy diet score, family history of diabetes, hypertension, heart disease and stroke.

of disease progression and was deemed appropriate based on the structure and objectives of our analysis. The multi-state models were performed using the R statistic software "*mstate*" package (35).

Subgroup analyses were performed by age, sex, ethnicity, employment status, education level, socioeconomic status, current smoking, current drinking, physical activity, healthy diet score, sleep duration, and obesity. In addition, a series of sensitivity analyses were conducted to confirm the robustness of the results. First, we imputed missing covariate data using multivariate imputations by chained equations (MICE) based on random forest models. Second, to minimize the potential reverse causality, we conducted a landmark analysis that excluded new-onset cases of cardiometabolic multimorbidity occurring in the first two years of follow-up. Third, to account for the competing risk of mortality from other causes, we applied the Fine-Gray subdistribution hazard model to assess the associations by taking mortality as a competing event.

All statistical analyses were performed using the R software (version 4.3.3), and a two-sided $P<0.005$ represented statistical significance.

3 Results

3.1 Stage one: individuals free of any CMD at baseline

Of 344,415 participants free of any CMD in stage one, 223,852 participants were non-MAFLD (mean age: 55.73 ± 8.19 years and 66.31% female), and 120,563 participants had MAFLD (mean age: 56.55 ± 7.89 years and 37.08% female) at baseline. Compared with the non-MAFLD group, participants with MAFLD tended to be older, men, White, not employed, more deprived, less educated, and have a lower income (Table 1). They also had a higher prevalence of smoking, alcohol drinking, physical inactivity, inappropriate sleep duration, unhealthy diet, family history of heart disease, stroke, and diabetes, higher levels of BMI, WC, SBP, DBP, HbA1c, C reactive protein, triglycerides, and Gamma-glutamyltransferase, and lower HDL cholesterol (Table 1).

During a median follow-up period of 13.85 years, we identified 4,622 new-onset CMM cases (1,536 in the non-MAFLD group and 3,086 in the MAFLD group). The incidence rates were 0.50 per 10,00 person-years in the non-MAFLD group and 1.86 per 10,00 person-years in the MAFLD group, respectively. As shown in Table 2, Supplementary Figure 1, individuals with MAFLD had a significantly increased risk of incident CMM, and the risk was raised with the increment in MAFLD severity. After fully adjusting for potential covariates (Model 3), Cox proportional hazard models revealed that the risk of incident CMM was 2.78 times (HR: 2.78, 95% CI: 2.60-2.96) higher in the MAFDL group than the non-MAFLD group. In terms of different severity of MAFLD, the fully adjusted HRs of incident CMM were 2.63 (95% CI: 2.46-2.81) for the MAFLD with no fibrosis group, 3.73 (95% CI: 3.38-4.12) for the MAFLD with mild fibrosis group, and 4.00 (95% CI: 1.66-9.64) for the MAFLD with severe fibrosis group, respectively (Table 2). For different subtypes of MAFLD, participants in the lean MAFLD group or the obese and metabolic dysfunctional MAFDL group had 1.96 (HR: 1.96, 95% CI: 1.49-2.58) and 2.87 times (HR: 2.87, 95% CI: 2.69-3.07) elevated risk of developing CMM than those in non-MAFLD group, but the risk was not statistically significant in the obese MAFLD group (HR: 1.12, 95% CI: 0.87-1.45) (Supplementary Table 1).

Results from the multi-state models showed that MAFLD was positively and significantly associated with all transitions from baseline to CMM, except the transition from T2D to CMM (Figures 2, 3, Supplementary Figure 2). After adjusting for potential covariates, compared with the non-MAFLD group, the fully adjusted HRs of MAFLD were 5.03 (95% CI: 4.81-5.25) for the transition from

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TABLE 1 Baseline characteristics of study population according to MAFLD.

Characteristic	Stage one individuals free of any CMD at baseline			Stage two individuals with single CMD at baseline		
	non-MAFLD group	MAFLD group	*P* value	non-MAFLD group	MAFLD group	*P* value
n	223852	120563		16716	25520	
Age, years	55.73 ± 8.19	56.55 ± 7.89	<0.001	60.45 ± 7.17	59.95 ± 6.95	<0.001
Gender			**<0.001**			**<0.001**
Female	148431 (66.31%)	44700 (37.08%)		8009 (47.91%)	8300 (32.52%)	
Male	75421 (33.69%)	75863 (62.92%)		8707 (52.09%)	17220 (67.48%)	
Ethnicity			**<0.001**			**<0.001**
White	203110 (90.73%)	110249 (91.45%)		14889 (89.07%)	23024 (90.22%)	
Non-white	20742 (9.27%)	10314 (8.55%)		1827 (10.93%)	2496 (9.78%)	
College degree			**<0.001**			**<0.001**
No	139799 (62.45%)	85509 (70.92%)		11814 (70.67%)	19510 (76.45%)	
Yes	81885 (36.58%)	33553 (27.83%)		4608 (27.57%)	5538 (21.70%)	
Missing	2168 (0.97%)	1501 (1.24%)		294 (1.76%)	472 (1.85%)	
Family income			**<0.001**			**<0.001**
<£18000	37172 (16.61%)	23973 (19.88%)		4602 (27.53%)	7792 (30.53%)	
£ 18000~51999	99790 (44.58%)	54206 (44.96%)		6697 (40.06%)	10372 (40.64%)	
>£ 51999	55017 (24.58%)	25946 (21.52%)		2309 (13.81%)	3134 (12.28%)	
Missing	31873 (14.24%)	16438 (13.63%)		3108 (18.59%)	4222 (16.54%)	
Employ status			**<0.001**			**<0.001**
Current employ	136039 (60.77%)	71405 (59.23%)		6322 (37.82%)	10135 (39.71%)	
Not employ	86804 (38.78%)	48553 (40.27%)		10285 (61.53%)	15233 (59.69%)	
Missing	1009 (0.45%)	605 (0.50%)		109 (0.65%)	152 (0.60%)	
TDI score	-1.55 ± 2.95	-1.21 ± 3.12	<0.001	-1.02 ± 3.25	-0.60 ± 3.35	<0.001
Smoking status			**<0.001**			**<0.001**
Never smoking	132375 (59.14%)	60135 (49.88%)		8316 (49.75%)	10437 (40.90%)	
Previous smoking	68743 (30.71%)	46050 (38.20%)		6313 (37.77%)	11909 (46.67%)	
Current smoking	21849 (9.76%)	13746 (11.40%)		1964 (11.75%)	2949 (11.56%)	
Missing	885 (0.40%)	632 (0.52%)		123 (0.74%)	225 (0.88%)	
Alcohol drinking			**<0.001**			**0.1**
Never drinking	8975 (4.01%)	4601 (3.82%)		1173 (7.02%)	1660 (6.50%)	
Previous drinking	6670 (2.98%)	4178 (3.47%)		961 (5.75%)	1540 (6.03%)	
Current drinking	207777 (92.82%)	111491 (92.48%)		14511 (86.81%)	22226 (87.09%)	
Missing	430 (0.19%)	293 (0.24%)		71 (0.42%)	94 (0.37%)	
Sleep duration			**<0.001**			**<0.001**
7–8 hours/day	157337 (70.29%)	77972 (64.67%)		10668 (63.82%)	14902 (58.39%)	
<7 hours/day	50828 (22.71%)	31987 (26.53%)		4249 (25.42%)	7176 (28.12%)	
>8 hours/day	14402 (6.43%)	9677 (8.03%)		1621 (9.70%)	3098 (12.14%)	

(Continued)

10.3389/fendo.2025.1585725

TABLE 1 Continued

Characteristic	Stage one individuals free of any CMD at baseline			Stage two individuals with single CMD at baseline		
	non-MAFLD group	MAFLD group	*P* value	non-MAFLD group	MAFLD group	*P* value
Sleep duration			<0.001			<0.001
Missing	1285 (0.57%)	927 (0.77%)		178 (1.06%)	344 (1.35%)	
Physical activity			<0.001			<0.001
Q1	51179 (22.86%)	35896 (29.77%)		3877 (23.19%)	7963 (31.20%)	
Q2	61460 (27.46%)	29207 (24.23%)		4147 (24.81%)	5515 (21.61%)	
Q3	63643 (28.43%)	27323 (22.66%)		4443 (26.58%)	5188 (20.33%)	
Missing	47570 (21.25%)	28137 (23.34%)		4249 (25.42%)	6854 (26.86%)	
Healthy diet score	3.46 ± 1.28	3.05 ± 1.33	<0.001	3.47 ± 1.33	3.12 ± 1.35	<0.001
BMI, kg/m^2	24.86 ± 2.83	31.18 ± 4.26	<0.001	25.49 ± 2.76	32.48 ± 4.99	<0.001
WC, cm	82.39 ± 8.87	101.60 ± 9.37	<0.001	86.47 ± 8.61	105.95 ± 11.08	<0.001
SBP, mmHg	134.81 ± 18.64	142.95 ± 17.49	<0.001	137.68 ± 18.70	141.78 ± 17.78	<0.001
DBP, mmHg	80.30 ± 9.74	86.46 ± 9.56	<0.001	78.94 ± 9.88	83.34 ± 10.00	<0.001
HDL cholesterol, mmol/L	1.58 ± 0.38	1.28 ± 0.29	<0.001	1.43 ± 0.37	1.18 ± 0.28	<0.001
HbA1c, mmol/mol	34.44 ± 3.52	35.74 ± 3.91	<0.001	40.74 ± 11.31	45.81 ± 13.64	<0.001
C reactive protein, mg/L	1.93 ± 3.78	3.55 ± 4.70	<0.001	2.27 ± 4.47	3.89 ± 5.36	<0.001
Triglycerides, mmol/L	1.34 ± 0.62	2.40 ± 1.17	<0.001	1.35 ± 0.62	2.36 ± 1.21	<0.001
Gamma-glutamyltransferase, U/L	26.02 ± 20.74	53.94 ± 54.94	<0.001	30.21 ± 26.44	59.91 ± 65.55	<0.001
Family history of disease						
Heart disease	91938 (41.07%)	51145 (42.42%)	<0.001	8708 (52.09%)	13216 (51.79%)	0.537
Stroke	57258 (25.58%)	31151 (25.84%)	0.096	5165 (30.90%)	7385 (28.94%)	<0.001
Diabetes	41670 (18.61%)	27629 (22.92%)	<0.001	4485 (26.83%)	8293 (32.50%)	<0.001
Hypertension	106914 (47.76%)	57084 (47.35%)	0.021	7781 (46.55%)	12336 (48.34%)	<0.001

MAFLD, metabolic-associated fatty liver disease; CMD, cardiometabolic disease; TDI, Townsend deprivation index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Analyses in stage one were conducted among individuals without any CMD at baseline; analyses in stage two were conducted among individuals with single CMD at baseline. Describe statistics were shown as mean ± standard deviation for continue variables and number (%) for categorized variables.

baseline to T2D, 1.42 (95% CI: 1.38-1.46) for the transition from baseline to CHD, 1.12 (95% CI: 1.06-1.17) for the transition from baseline to stroke, 1.09 (95% CI: 0.94-1.92) for the transition from T2D to CMM, 1.72 (95% CI: 1.56-1.90) for the transition from CHD to CMM, and 1.65 (95% CI: 1.41-1.92) for the transition from stroke to CMM, respectively. Moreover, as shown in Figure 3, Supplementary Table 2, different severities and subtypes of MAFLD showed various magnitudes for the associations with transitions from baseline to individual CMDs and subsequently to CMM.

3.2 Stage two: individuals with a single CMD at baseline

A total of 42,236 individuals with a single CMD at baseline (18,859 T2D, 18,628 CHD and 4,749 stroke) were included in stage two, and 25,520 had MAFLD (mean age: 59.95 ± 6.95 and 32.52% female). As shown in Table 1, participants with MAFLD were more likely to be younger, male, White, less educated, employed, more deprived, and have lower income than the non-MAFLD group. The prevalence of smoking, alcohol drinking, unrecommended sleep duration, physical inactivity, and unhealthy diet, the levels of BMI, WC, SBP, DBP, HbA1c, C reactive protein, triglycerides, and gamma-glutamyltransferase, lower level of HDL cholesterol were also observed in the MAFLD group (Table 1).

The Kaplan-Meier curves showed that the cumulative hazard of CMM was significantly higher in the MAFLD group than in the non-MAFLD group (all *P* values <0.001, Supplementary Figure 1). After full adjustment of covariates, compared with the non-MAFLD group, the HRs of incident CMM in the MAFLD group were 1.21 (95% CI: 1.13-1.31) for participants with T2D, 1.90 (1.75-2.05) for participants with CHD, and 1.65

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TABLE 2 Association between metabolic-associated fatty liver disease (MAFLD) and cardiometabolic multimorbidity.

Exposure	n	Cases/ person-years	Unadjusted	Model 1	Model 2	Model 3
Individuals free of cardiometabolic disease at baseline						
Non-MAFLD	223,852	1,536/3,092,787	Ref.	Ref.	Ref.	Ref.
MAFLD	120,563	3,086/1,657,654	3.76 (3.53-3.99)	3.19 (2.99-3.40)	2.86 (2.68-3.04)	2.78 (2.60-2.96)
MAFLD with low fibrosis	107,817	2,499/1485,362	3.39 (3.18-3.61)	3.00 (2.81-3.20)	2.70 (2.53-2.89)	2.63 (2.46-2.81)
MAFLD with mild fibrosis	12,644	582/170,898	6.97 (6.33-7.66)	4.42 (4.01-4.88)	3.85 (3.49-4.25)	3.73 (3.38-4.12)
MAFLD with severe fibrosis	102	5/1394	7.28 (3.03-17.51)	5.37 (2.23-12.92)	4.18 (1.74-10.08)	4.00 (1.66-9.64)
Individuals with type 2 diabetes at baseline						
Non-MAFLD	5,485	953/69,373	Ref.	Ref.	Ref.	Ref.
MAFLD	13,374	3,087/164,272	1.37 (1.28-1.47)	1.29 (1.20-1.39)	1.23 (1.14-1.32)	1.21 (1.13-1.31)
MAFLD with low fibrosis	4,821	964/60,444	1.16 (1.06-1.27)	1.25 (1.14-1.37)	1.19 (1.08-1.30)	1.17 (1.07-1.29)
MAFLD with mild fibrosis	8,015	1,953/97,590	1.46 (1.35-1.58)	1.29 (1.19-1.39)	1.23 (1.14-1.33)	1.21 (1.12-1.31)
MAFLD with severe fibrosis	538	170/6,237	2.00 (1.70-2.36)	1.69 (1.43-1.99)	1.58 (1.34-1.86)	1.55 (1.31-1.83)
Individuals with coronary heart disease at baseline						
Non-MAFLD	8,645	984/113,698	Ref.	Ref.	Ref.	Ref.
MAFLD	9,983	2,170/124,946	2.02 (1.88-2.18)	2.02 (1.88-2.19)	1.91 (1.77-2.07)	1.90 (1.75-2.05)
MAFLD with low fibrosis	7,720	1,583/97,507	1.89 (1.74-2.05)	1.91 (1.76-2.07)	1.81 (1.66-1.96)	1.79 (1.65-1.94)
MAFLD with mild fibrosis	2,234	574/27,156	2.48 (2.23-2.75)	2.39 (2.15-2.65)	2.26 (2.03-2.51)	2.23 (2.00-2.48)
MAFLD with severe fibrosis	29	13/283	5.56 (3.22-9.62)	5.46 (3.16-9.43)	5.25 (3.03-9.08)	5.32 (3.07-9.22)
Individuals with stroke at baseline						
Non-MAFLD	2,586	431/32,925	Ref.	Ref.	Ref.	Ref.
MAFLD	2,163	625/25,780	1.86 (1.65-2.10)	1.76 (1.56-2.00)	1.66 (1.46-1.88)	1.65 (1.45-1.87)
MAFLD with low fibrosis	1,857	509/22,376	1.75 (1.53-1.98)	1.69 (1.48-1.92)	1.58 (1.39-1.81)	1.57 (1.38-1.79)
MAFLD with mild fibrosis	304	116/3,377	2.64 (2.15-3.25)	2.26 (1.84-2.79)	2.15 (1.74-2.65)	2.16 (1.74-2.66)

MAFLD, metabolic-associated fatty liver disease.
Data were presented as hazard ratios (95% confidence intervals).
Model 1 adjusted for age and sex;
Model 2 adjusted for model 1 plus ethnicity, educational levels, family income, socioeconomic status, employed status, smoking status, alcohol drinking, physical activity, sleep duration and healthy diet score;
Model 3 adjusted for model 2 plus family history of diabetes, hypertension, heart disease and stroke.

(1.45-1.87) for participants with stroke, respectively (Table 2). Regard of different severity of MAFLD, the highest hazards of occurring CMM were found in the MAFLD with severe fibrosis group, with HRs of 1.55 (95% CI:1.31-1.83) in those with T2D, 5.32 (3.07-9.22) in those with CHD, and 2.16 (1.74-2.66) in those with stroke (in the mild fibrosis group). Among individuals with T2D at baseline, the subtypes of obese MAFLD and obese and metabolic dysfunction MAFLD had significant association with CMM (HR and 95% CI: 2.00, 1.10-3.63 and 1.22, 1.13-1.31), whereas the association was statistically significant in the obese and metabolic dysfunction MAFLD group among those with CHD (HR: 1.92, 95% CI: 1.78-2.08) or stroke (HR: 1.67, 95% CI: 1.47-1.90).

3.3 Additional analyses

Subgroup analyses showed that age (<60 *vs.* ≥60 years), gender (male *vs.* female) and current smoking status (no *vs.* yes) significantly modified the association of MAFLD with CMM risk among those with none CMD at baseline (all *P* values for interaction ≤0.001) (Supplementary Figure 3). The risk of incident CMM was significantly higher among those aged <60 years, females, and those who were not currently smoking than their corresponding counterparts. Among individuals with T2D at baseline, we found significant effect modification by current smoking status and physical activity, where increased risk of CMM was only significant in those who were not currently smoking and those

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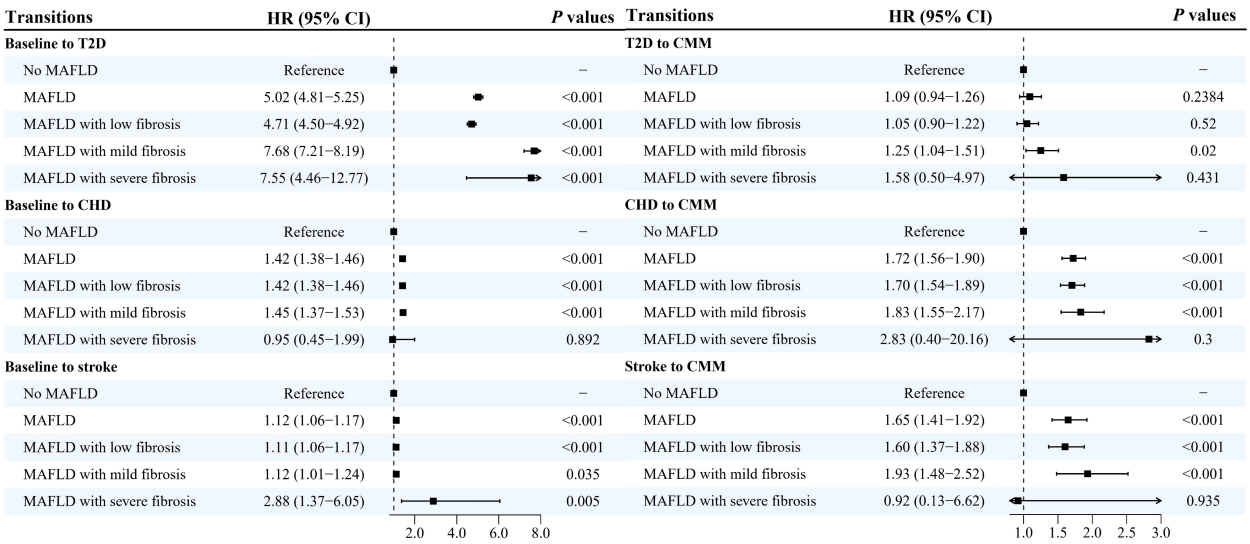

FIGURE 3
Hazard ratios and 95% confidence intervals for associations between severity of metabolic-associated fatty liver disease and the development of cardiometabolic multimorbidity HR, hazard ratio; CI, confidence intervals; MAFLD, metabolic-associated fatty liver disease; T2D, type 2 diabetes; CHD, coronary heart disease; CMM, cardiometabolic multimorbidity. Multi-state models were conducted to estimate the role of MAFLD in the development of cardiometabolic multimorbidity, and disease transitions were presented in Figure 2. Model adjusted for age, sex, ethnicity, educational levels, family income, socioeconomic status, employed status, smoking status, alcohol drinking, physical activity, sleep duration, healthy diet score, family history of diabetes, hypertension, heart disease and stroke.

with moderate or high physical activities (all *P* values for interaction <0.05, Supplementary Figure 4). Among individuals with CHD or stroke, the CMM risk was also more pronounced among those aged <60 years (all *P* values for interaction <0.05, Supplementary Figures 5, 6). Results from sensitivity analyses persisted robustly after excluding those experiencing CMM within the first 2 years of follow-up (Supplementary Table 3), multiple imputation for missing data on covariates (Supplementary Table 4), and when considering the competing risk of mortality from other causes (Supplementary Table 5).

4 Discussion

In this prospective cohort study in the UK Biobank, we found that MAFLD significantly increased the future risk of incident CMM, regardless of the CMD status at baseline. Importantly, MAFLD had detrimental influences on all transitions from the baseline status (free of any CMD) to T2D, CHD and stroke, and then from CHD or stroke to CMM. Besides, we also identified the subpopulation susceptible to the higher risk of CMM conferred by MAFLD.

As a novel concept updated from NAFLD, the clinical significance of MAFLD has attracted much interest from researchers, and limited studies evaluated its associations with several intrahepatic and extrahepatic diseases (including cardiovascular diseases, CVDs) in different national studies (13, 16, 18–21). A nationwide cohort study of about 9 million middle-aged Koreans showed that MAFLD was associated with a 1.52 times elevated risk of occurring the composite CVD outcome and a 1.20-1.89 times higher risk of incident specific CVD subtypes or CVD-related mortality (16). Based on a retrospective study in the JMDC Claims Database, Ohno and colleagues also found positive associations of MAFLD with heart failure, atrial fibrillation, myocardial infarction, and stroke, and risks varied between MAFLD subtypes (20). Moreover, including 24,772 pairs of new-onset MAFLD cases and age- and sex-matched controls from the Kailuan Study, Zheng and colleagues investigated whether the association of MAFLD with CVD differed across the onset-age of MAFLD (21). Their results indicated that the CVD risk gradually declined with the increases in MAFLD onset age, and MAFLD cases younger than 45 years had the highest hazard, whereas the risk in those older than 55 years was not statistically significant (21). In line with previous investigations, our results provided additional evidence that MAFLD also witnessed a stronger association with CMM among individuals with no or one single CMD, and the hazards raised with the severity of MAFLD. These findings suggested that targeted and regular screening and monitoring should be developed and implemented to target not only individual CMDs but also CMM among people with MAFLD.

In terms of the developing progression of CMM, multistate models have been widely applied in prior studies to assess the impacts of lifestyle behaviors (22–24), depressive symptoms (31), handgrips strength (36), pulmonary function (37), and air pollution (33, 38). Most studies found the influences of specific factors on CMM progression varied across the disease stages. For instance, an investigation of the Whitehall II cohort study indicated that all lifestyle behaviors (e.g., physical activity, diet, alcohol consumption and smoking) and clinical profiles (e.g., hypertension, obesity and hyperlipidemia) were significantly related to the transition from disease-free status to the first CMD, but only smoking and obesity

were associated with the transition from first CMD to CMM (23). Similarly, a study conducted in the China Kadoorie Biobank found that a composite lifestyle score consisting of heavy alcoholic drinking, tobacco smoking, poor diet, physical inactivity, and unhealthy body size had influences on each transition from healthy status to five CMDs, CMM and death, with a relatively greater risk in transitions to CMD than to CMM (22). Using the same data of the UK Biobank, previous researches have revealed the detrimental impacts of air pollutions (33, 38), depression symptoms (31), lower handgrip strength (36), low functional function (37), physical inactivity (39), frailty (40), and poor diet (32) on the different stages of CMM incidence, progress and prognosis. In the present study, our results further demonstrated that MAFLD affected the CMM progression and the influences depended on the disease stages and MAFLD subtypes. The results of multistate models were further confirmed in the analyses of participants with single CMDs at baseline (stage two). Differed from most previous studies using the first CMD stage in CMM progression (23, 32, 36, 40), we distinguished the individual CMDs into T2D, CHD and stroke, and conducted six disease transitions between healthy status, individual CMDs and CMM, which might provide evidence for the precise prevention of CMM and give an alternative analytic strategy for future studies. However, due to the relatively limited CMM cases and more complex disease transitions, we did not include death as an absorbing endpoint in our analyses. Future studies are warranted to investigate the association of MAFLD with cause-specific deaths.

Our subgroup analyses indicated that among people with no CMD at baseline, those younger than 60 years, females, and current non-smokers were more susceptible to the elevated risk of CMM incidence associated with MAFLD than their counterparts. Similarly, a greater risk was also observed in CHD and stroke cases younger than 60 years. Compared with the elderly, younger people with MAFLD may have a longer disease duration, a lower health literacy, and unhealthier lifestyles, which predisposes them to a greater CMM risk (21). Females were more prone to experiencing hepatic fibrosis than males, despite the relatively lower prevalence of NAFLD (41). Additionally, both hepatic nuclear receptors and estrogen play the critical roles in regulating liver lipid metabolic pathways, yet these nuclear receptors were found to be dysregulated in patients with fatty liver disease, which may diminish the anti-inflammation and anti-oxidative effect of estrogen (42). Beyond expectation that the risk of CMM was relative higher in current non-smoker than in current smoker, we speculated this difference may be explained by the higher rates of hypertension, hyperlipidemia, insulin resistant, and metabolic syndrome in smokers, which might mask the influence of MAFLD on the CMM to some extent (43). However, whether this association was a coincidence was needed confirmed in further studies.

Although biological mechanisms underlying the association between MAFLD and CMM remains poor understood, several pathways may be the major contributors. First, MAFLD may be the hepatic manifestation of metabolic syndrome, a pathological condition characterized by several metabolic dysfunctions. A large number of studies have documented the stronger associations of metabolic syndrome and individual CMDs (44). Second, inflammation and oxidative stress may two important contributors linking the MAFLD and CMM incidence. MAFLD is associated with the overexpression of pro-inflammation cytokines and the higher circulating levels of inflammation and oxidative stress factors (such as C-reactive protein, oxidized-LDL, plasma plasminogen activator inhibinor-1, and soluble NOX2-derived peptide), all of which can promote the development of atherosclerosis and CVD (45). Third, hepatic steatosis in MAFLD can damage mitochondrial function and hepatic peroxisomes, causing the reduced release of fibroblast growth factor 21 (Fgf21). Fgf21 is an important cardio-protected hepatokines in regulating the energy expenditure, glycemic control, and cardiovascular function, and its treatment promote lowers the blood pressure and protect heart against the oxidative stress (46, 47). Fetuin-A, another hepatokines, is found increased in MAFLD patients and may promote the insulin resistance to induce the development of T2D and CVDs (45).

To our knowledge, our study is the first to investigate the role of MAFLD in the CMM progression, and our results not only confirmed the clinical significance of MAFLD, but provided critical evidence for the early prevention of CMM. The major strengths of this study included the prospective cohort design, a large sample size, the longer follow-up period, the two-stage analytic strategy, and the application of multistate models. However, several limitations should be noted when interpreting our results. First, due to the unavailable data of liver imaging or biopsy in UK Biobank, we used the FLI to define the hepatic steatosis. However, guides recommended the utility of FLD to define the MAFLD and its accuracy was validated previously (15, 48). Second, we only used the single assessment of MAFLD at baseline, which may not comprehensively capture the metabolic characteristics of MAFLD patients. Future studies with longitudinally repeated measurements are needed to investigate the dynamic metabolic changes in MAFLD and its association with CMDs and CMM. Third, since the diagnosis of disease incidence relied on multiple sources, diagnostic date may delay, which may influence the observed disease trajectories. Forth, due to the UK Biobank is not a nationally representative study, our findings are not appropriate to generalize to other populations. Finally, there may exist several unmeasured residual confounders underlying the association between MAFLD and CMM, owing to the nature of observational study design.

5 Conclusions

In conclusion, this population-based cohort study revealed the detrimental influences of MAFLD on the whole CMM progression, including most transitions from baseline to individual CMDs, and subsequently to CMM. Given the higher prevalence and severe consequences of CMM, our findings suggest that developing and implementing the effective treatment measures for MAFLD may have profound implications for the primary prevention of CMM.

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.ukbiobank.ac.uk.

Ethics statement

The studies involving humans were approved by North West Multicenter Research Ethics Committee. 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

YG: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. JY: Conceptualization, Writing – original draft, Writing – review & editing. SL: Writing – original draft, Writing – review & editing, Formal analysis. SY: Writing – review & editing. ZJ: Conceptualization, Writing – review & editing. YH: Conceptualization, Formal analysis, Writing – review & editing, Funding acquisition, Resources, Supervision, Visualization. CZ: Conceptualization, Writing – review & editing, Formal analysis. DH: Conceptualization, 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.2025.1585725/full#supplementary-material

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The expression profiles and roles of microRNAs in cardiac glucose metabolism

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Background: MicroRNAs (miRNAs) are a class of endogenous, non-coding RNAs, that have been implicated in cardiovascular diseases. Recent studies have suggested that dysregulated miRNAs accumulate in the heart and may be associated with impaired cardiac glucose metabolism. However an inconsistent direction of expression was observed in the current available literature. The aim of this study was to characterize miRNA expression profiles associated with glucose metabolism, and to explore their potential as biomarkers for glucose metabolism disorders in diabetic cardiomyopathy (DCM).

Methods: A systematic search of electronic databases, including Embase, PubMed, and the Cochrane Library, was conducted until October 1, 2024. Studies reporting on miRNAs expression profiles that regulate glucose metabolism in the heart were selected for inclusion. Pooled results were presented as log10 odds ratios (logORs) with 95% confidence intervals (CIs), using random-effect models. Subgroup analyses were conducted based on species, region, and sample source. Analyses by species focused specifically on humans and mice. The quality of included articles was assessed using the modified Diagnostic Accuracy Study 2 (QUADAS-2) tool. All workflows, including abstract screening, full-text review, data extraction, and quality assessment, were independently performed by two reviewers.

Results: A total of 47 eligible articles were included in this study, identifying 70 dysregulated miRNAs. Further analysis revealed that compared with the non-DCM group, the DCM group exhibited differential miRNA expression, with 12 miRNAs consistently upregulated and 8 consistently downregulated. Among these miRNAs, miR-199a (logOR 4.59; 95% CI: 3.02-6.15) was the most upregulated and frequently reported (n=7 studies), while let-7 (logOR 4.48; 95% CI: 2.41-6.55) was the most downregulated (4 studies). Subgroup analysis indicated that miRNA-21 was the most upregulated in cardiac tissue, and miRNA-133 was the most downregulated in cardiomyocytes. Additionally, miRNA-21 was found to be the most upregulated across different species. In the region subgroups, miRNA-199a and miRNA-503 were the most upregulated and downregulated in Asian countries, whereas miRNA-378 was the most dysregulated in non-Asian countries.

Conclusion: In summary, this study identified 20 consistently dysregulated miRNAs assocaited with myocardial glucose metabolism. Six dysregulated miRNAs, including miRNA-199a, let-7, miRNA-21, miRNA-133, miRNA-503 and miRNA-378, have potential as candidate miRNA biomarkers of glycometabolism in the heart. These findings require further validation in future larger-scale studies.

KEYWORDS

miRNAs, heart, glucose metabolism, systematic review, biomarker

Introduction

The rising prevalence of diabetes mellitus (DM), including type 1, type 2, and other subtypes, poses a significant socioeconomic burden worldwide. Notably, type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by systemic and myocardial insulin resistance, thereby increasing the risk of cardiovascular complications (1). Diabetic cardiomyopathy, a common complication of diabetes, is marked by myocardial hypertrophy, myocardial fibrosis, and cardiac dysfunction (2–4). While the molecular mechanisms underlying insulin resistance have been extensively studied, the pathophysiology of myocardial insulin resistance remains poorly understood, necessitating further investigation. Abnormal glucose metabolism, observed in patients with diabetic cardiomyopathy, has been identified to be associated with cardiac dysfunction (5). Several key regulators, including GLUT-4, Pyruvate dehydrogenase complex (PDH), Glycogen synthase kinase 3β (GSK-3β), and Insulin-like growth factor 1 receptor (IGF-1R), are critical for cardiac glucose metabolism (6–8).

MicroRNAs (miRNAs), a class of small non-coding RNAs, have been recognized for their role in regulating gene expression through binding to the 3' untranslated region (3'-UTR) of target mRNAs (9). Previous studies have reported that miRNAs play a crucial role in glucose metabolism across various organs. MiR-146a has been shown to enhance hepatic glucose tolerance by targeting the oxidative metabolism of fatty acids (10). MiR-140-5p mitigates high glucose-induced apoptosis and inflammation in the kidney (11). Furthermore, it has been demonstrated that miRNAs are involved in the development of glucose metabolism in metabolic diseases (12, 13). For instance, miR-29 is dysregulated in muscle, fat, and liver tissues, where it regulates insulin-stimulated glucose uptake (14). Importantly, growing evidence demonstrates that miRNAs play a significant role in the development of various cardiac diseases, particularly in cardiac hypertrophy and glucose metabolism (15, 16). MiR-150 regulates glucose utilization through GLUT-4 in insulin-resistant heart muscle (17). GLUT-4, a key target gene, plays a critical role in myocardial insulin resistance (18).

Taken together, these findings in the current literature highlight the importance of miRNAs in glucose metabolism in the heart. However, the expression profiles of miRNAs across individual studies have yielded inconsistent results. This variability may stem from differences in miRNA sources. For example, miRNA-499 was found to be down-regulated in cardiomyocytes (19), yet up-regulated in myocardium (20). Moreover, even in the same tissue type, the direction of miRNA expression may vary across different studies. Wang et al. indicated a significant downregulation of miR-221 in myocardium (21), whereas another study observed upregulation of miR-221 (20). These conflicting findings underscore the critical impact of heterogeneity among individual studies in miRNA expression profiles. Therefore, this study aims to summarize dysregulated miRNAs in cardiac glucose metabolism, explores their pathological contributions to metabolic dysregulation, and identifies potential biomarkers for myocardial glucose metabolism monitoring.

Methods

Search strategy

A comprehensible search was performed across the PubMed, Embase, and Cochrane Library databases to identify relevant miRNA expression profiling articles from inception until October 1, 2024. The following items were used in the title/abstract: (microRNA or miR- or miRNA), (glucose metabolism or glycometabolism), (expression or profiling or profile). Detailed search queries are provided in Supplementary Table 1. Furthermore, a manual search was supplemented by screening the reference lists of retrieved studies. Two reviewers independently performed the literature search, and any discrepancies were resolved through discussion with a third reviewer to reach a consensus.

Literature selection

The retrieved articles were screened to identify eligible studies. After removing duplicates, an initial screening was performed to identify potentially eligible studies according to their titles and

abstracts. Afterwards, two investigators independently reviewed the full-text studies based on pre-defined criteria, and any discrepancies were resolved through consensus by a third researcher.

Inclusion and exclusion criteria

The eligibility criteria were as follows: (1) observational studies (including cohort,

cross-sectional, and case-control studies) that investigated miRNA expression patterns or the diagnostic value of miRNAs in myocardial glucose metabolism; (2) studies must report sample sizes for differentially expressed miRNAs between the normal and abnormal glycometabolism groups; (3) miRNA expression profiles were assessed using techniques such as qPCR, real-time PCR, and microarray; (4) only papers written in English were included. The exclusion criteria were as follows: (1) studies that examined glucose metabolism in organs other than heart (e.g., liver, kidney, adipose tissue, skeletal muscle, etc.); (2) various types of literature, including conference abstracts, case reports, meta-analyses, letters, comments, editorials, and reviews; (3) articles lacking essential data. In cases of duplicate studies from the same research, the study most closely aligned with the inclusion criteria was selected.

Data extraction and collection

Two reviewers independently extracted essential information from the included articles, with any discrepancies resolved through consensus after in-depth discussion involving a third researcher. The extracted data included the following details: first author, year of publication, country, ethnicity, species, detection methods, sample types, sample size, expressed direction, number of dysregulated miRNAs, and the regulatory mechanism of miRNAs.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) was utilized to assess quality of the included studies. This tool consists of eight questions, each of which is rated as "yes", "no" and "unclear". Two independent authors appraised the quality of all eligible articles, and any discrepancies were resolved through discussion with a third reviewer to reach a final consensus.

Data synthesis and statistical analysis

The extracted data were subjected to statistical analysis using Stata software version 13 (Statacorp, College Station, Texas, United States). Results were presented as log odds ratios (logORs) with corresponding 95% confidence interval (CI), refecting number and direction of dysregulation between the normal and abnormal glucose metabolism groups. Compared to the normal group, logOR values greater than 1 in the abnormal group indicate upregulation. Conversely, a logOR value greater than 1 in the normal group relative to the abnormal group indicates downregulation. A P-value<0.05 was considered statistically significant. Heterogeneity was assessed using the Q test and I^2 statistics by random-effects model, I^2< 50% suggests minimal heterogeneity among studies. The significance of dysregulated miRNAs in the abnormal group was ranked based on: (1) number of consistent sub-studies; (2) total sample size; (3) the magnitude of logOR values. Subgroup analysis were performed according to species, ethnicity and tissue type.

Results

Literature retrieval and search results

The literature search process and study selection were illustrated in Figure 1. The initial literature search yielded a total of 1,780 records (PubMed = 1,659, Embase = 92, and Cochrane = 29) according to the eligibility criteria (Supplementary Table 1). After removing 28 duplicates, the remaining 1,752 records were further screened based on their titles and abstracts. Subsequently, 76 full-text articles were assessed for eligibility. Ultimately, 47 studies were selected for the quantitative analysis. The specific reasons for excluding studies were displayed in Supplementary Table 2.

Study characteristics

All the included studies were published between 2009 and 2023, and quantitative real-time PCR (qRT-PCR) was used as the technique for evaluating miRNA expression in all studies. The number of differentially expressed miRNAs in individual studies ranged from 1 to 16, with the majority of miRNAs showing upregulation in studies of abnormal glucose metabolism. Sample sizes varied from 6 to 120 across the studies. Different specimen types were utilized, primarily including cardiomyocyte and myocardium. Detailed characteristics of the 47 eligible studies are provided in Table 1.

Quality assessment results

The quality of all included literature was assessed by The QUADAS-2 tool. Detailed information and results of quality assessment was presented in Supplementary Table 3. The validated and enhanced methodological standards were applicable to the eligible studies. The evaluation results indicated that the overall risk of bias was low, and the included studies met the majority of quality appraisal criteria.

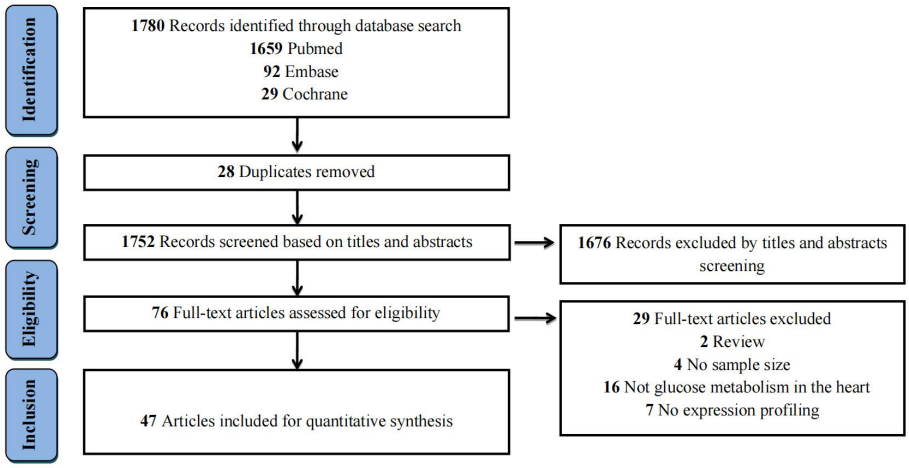

FIGURE 1
Flow chart of studies selection process for this systematic review.

TABLE 1 Main characteristics of miRNA expression from the included studies.

First Author	Country	Tissue	Method	Differentially expressed microRNAs			
				Sample size Case/Control	Total	Increased	Decreased
Zuo et al., 2016 (22)	China	cardiomyocyte	qRT-PCR	3/3	1	1	0
Zhu et al., 2017 (23)	China	cardiomyocyte	qRT-PCR	6/6	1	0	1
Zhang et al., 2017 (24)	China	cardiomyocyte	qRT-PCR	6/6	1	1	0
Zhang et al., 2013 (25)	China	cardiomyocyte/myocardium	qRT-PCR	8/8	1	0	1
Zhang et al., 2015 (26)	China	cardiomyocyte	qRT-PCR	5/5	1	1	0
Zhang et al., 2018 (7)	China	myocardium	qRT-PCR	11/5	1	1	0
Yu et al., 2021 (27)	China	myocardium	qRT-PCR	5/5	1	1	0
Yang T et al., 2019 (28)	China	cardiomyocyte	qRT-PCR	6/6	1	1	0
Yang Y et al., 2019 (29)	China	myocardium	qRT-PCR	9/9	1	1	0
Yan et al., 2015 (30)	China	myocardium	qRT-PCR	17/13	1	1	0
Xu et al., 2021 (31)	China	myocardium	qRT-PCR	3/3	2	1	1
Wu J et al., 2019 (32)	China	cardiomyocyte/myocardium	qRT-PCR	12/12	1	1	0
Wu N et al., 2019 (33)	China	cardiomyocyte	qRT-PCR	6/6	1	0	1
Wu et al., 2023 (34)	China	myocardium	qRT-PCR	10/10	1	0	1
Wei et al., 2014 (35)	China	myocardium	qRT-PCR	8/8	1	1	0
Wang et al., 2009 (6)	China	cardiomyocyte/myocardium	qRT-PCR	33/33	11	9	2
Wang et al., 2023 (36)	China	myocardium	qRT-PCR	30/30	10	5	5
Trotta et al., 2018 (37)	Romania	cardiomyocyte	qRT-PCR	9/9	1	0	1
Ruiz-Velasco et al., 2020 (38)	UK	myocardium	qRT-PCR	8/8	1	1	0
Park et al., 2018 (39)	Korea	cardiomyocyte	qRT-PCR	6/6	1	1	0
Nagalingam et al., 2013 (40)	USA	myocardium	qRT-PCR	6/6	1	0	1
Mallat et al., 2014 (41)	France	cardiomyocyte	qRT-PCR	3/3	1	0	1

(Continued)

TABLE 1 Continued

First Author	Country	Tissue	Method	Differentially expressed microRNAs			
				Sample size Case/Control	Total	Increased	Decreased
Lu et al., 2010 (42)	UK	myocardium	qRT-PCR	6/6	3	3	0
Lu et al., 2020 (43)	China	myocardium	qRT-PCR	12/12	1	1	0
Long et al., 2013 (44)	China	cardiomyocyte	qRT-PCR	4/4	1	0	1
Liu et al., 2019 (45)	China	cardiomyocyte	qRT-PCR	22/22	1	1	0
Liu et al., 2020 (46)	China	Pericardial fluid	qRT-PCR	60/60	3	0	3
Li et al., 2017 (47)	China	myocardium	qRT-PCR	3/3	1	1	0
Li et al., 2020 (10)	China	cardiomyocyte	qRT-PCR	3/3	2	1	1
Li et al., 2016 (48)	China	myocardium	qRT-PCR	7/6	1	0	1
Lei et al., 2020 (49)	China	cardiomyocyte	qRT-PCR	3/3	1	1	0
Kim et al., 2013 (50)	USA	myocardium	qRT-PCR	5/5	1	0	1
Ju et al., 2020 (17)	China	cardiomyocyte/myocardium	qRT-PCR	12/12	1	1	0
Horie et al., 2009 (51)	Japan	cardiomyocyte	qRT-PCR	6/6	1	0	1
He et al., 2014 (52)	China	cardiomyocyte	qRT-PCR	5/5	1	1	0
Guedes et al., 2016 (19)	Brazil	cardiomyocyte	qRT-PCR	5/5	9	5	4
Gong et al., 2019 (53)	China	myocardium	qRT-PCR	5/5	1	0	1
Fan et al., 2020 (54)	China	cardiomyocyte	qRT-PCR	5/5	1	0	1
Du et al., 2015 (55)	China	cardiomyocyte	qRT-PCR	5/5	1	0	1
Dong et al., 2019 (56)	China	cardiomyocyte	qRT-PCR	3/3	2	0	2
Dong et al., 2018 (57)	China	cardiomyocyte	qRT-PCR	12/12	1	1	0
Diao et al., 2011 (20)	China	myocardium	qRT-PCR	3/3	16	11	5
Das et al., 2012 (58)	USA	cardiomyocyte	qRT-PCR	5/5	1	0	1
Borden et al., 2019 (59)	USA	myocardium	qRT-PCR	3/3	1	1	0
Baseler et al., 2012 (60)	USA	myocardium	qRT-PCR	4/4	4	4	0
Bartman et al., 2017 (61)	USA	myocardium	qRT-PCR	3/3	1	1	0
Arnold et al., 2014 (62)	USA	cardiomyocyte	qRT-PCR	4/4	3	3	0

UK, United Kingdom; USA, United States of America; RT-PCR: reverse transcription- polymerase chain reaction.

Results of the dysregulated miRNAs in overall analysis

We conducted a comprehensive analysis of 47 articles encompassing 70 dysregulated miRNAs comparing the normal glycometabolism group with the abnormal glycometabolism group. Among these miRNAs, 20 (12 upregulated and 8 downregulated) were reported in two or more studies (Figures 2, 3). Detailed information for each miRNA is provided in Supplementary Figures 1-20. Additionally, 50 dysregulated miRNAs (34 upregulated and 16 downregulated) were reported only once (Supplementary Table 4). Based on the results from 7 sub-studies involving 82 samples, miRNA-199a (logOR 4.59; 95% CI: 3.02-6.15) was identified as the most significantly upregulated miRNA, followed by miRNA-21 (logOR 4.69; 95% CI: 2.63-6.75) due to myocardial glucose metabolism disorder. The most frequently reported downregulated miRNAs were let-7 (logOR 4.48; 95% CI: 2.41-6.55), followed by miRNA-378 (logOR 4.62; 95% CI: 2.24-7.00).

Results of subgroup analysis

Subgroup analysis was conducted according to sample source, which included tissue and cell samples. Six studies examined miRNAs in myocardial tissue, while four studies focused on miRNAs in myocardial cells. Overall, three consistently upregulated miRNAs (miRNA-21, miRNA-195, miRNA-208)

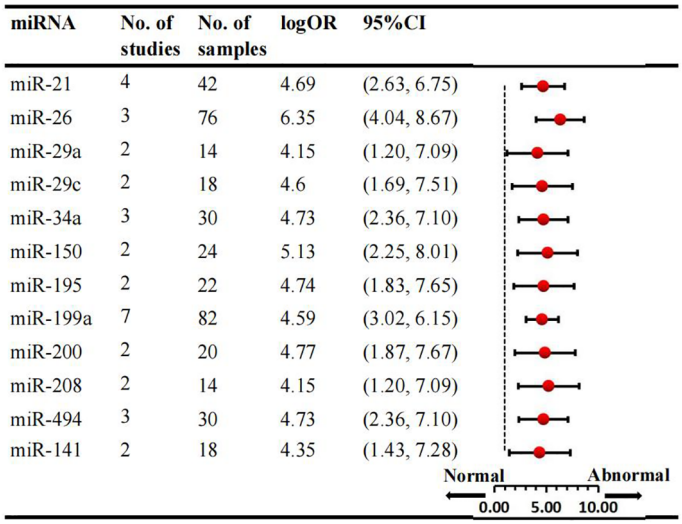

FIGURE 2
Consistently upregulated miRNAs in overall analysis. miR: microRNA; No.: number of included studies.

were identified as aberrantly expressed in myocardial tissue samples, with miRNA-21 being the most upregulated (logOR 4.69; 95% CI: 2.63-6.75). The summary results of the tissue source subgroup were presented in Supplementary Table 5. Sub-analyses based on species revealed that the number of studies in mice was the largest. Consequently, three consistantly upregulated miRNAs were identified, and the detailed results are provided in Supplementary Table 6. Among the animal studies, several miRNAs were consistently upregulated in two studies, including miRNA-21, miRNA-29a, miRNA-208, with the miRNA-21 being the most upregulated (logOR 4.69; 95% CI: 2.63-6.75). Subgroup analyses by ethnicity were conducted for Asian and non-Asian countries. When examining various species types, 8 dysregulated miRNAs were identified in Asian countries and 3 miRNAs in non-Asian studies. The expression signature of miRNAs is region-specific. In the Asian subgroup, 4 miRNAs were upregulated and 4 were downregulated, while in the non-Asian subgroup, 3 miRNAs were upregulated (Supplementary Table 7). Notably, miRNA-199a (logOR 4.59; 95% CI: 3.02-6.15) was consistently increased, and miRNA-26 (logOR 5.67; 95% CI: 2.81-8.52) was downregulated in Asian studies. In non-Asian countries, miRNA-29c was upregulated, and miRNA-378 was significantly downregulated.

Regulatory mechanisms of miRNAs in cardiac glucose metabolism

Dysregulated miRNAs have been identified to play critical roles by regulating glucose metabolism in the heart. The specific roles of miRNAs in cardiac glucose metabolism were summarized in Table 2.

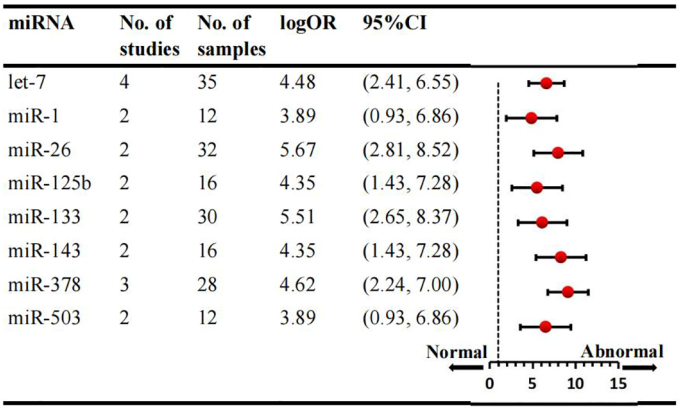

FIGURE 3
Consistently downregulated miRNAs in overall analysis. miR: microRNA; No.: number of included studies.

For instance, miRNA-200, miRNA-223, miRNA-150, and miRNA-141 regulate glucose transport via modulating myocardial GLUT4 expression. Additionally, multiple miRNAs, including miRNA-26, miRNA-99b-3p, miRNA-335, and miRNA-26a regulate glycogenesis by targeting Glycogen synthase kinase 3β (GSK-3β) in the heart. Furthermore, miRNA-34a has been reported to be involved in glycolysis process in the heart. Notably, miRNA-195 enhances the aerobic oxidation of glucose in the myocardium by increasing the acetylation of pyruvate dehydrogenase (PDH), which promotes the conversion of pyruvate and NAD+ into acetyl-CoA.

Discussion

miRNAs are a class of small non-coding RNAs that modulate gene expression by pairing with the 3'-untranslated region (3'UTR) of target mRNAs. Accumulating evidence suggests that miRNAs play pivotal roles in multiple facets of cardiac diseases, including myocardial injury, cardiac fibrosis, and heart failure (63, 64). Notably, prior studies have demonstrated that dysregulated miRNAs in the heart significantly influence cardiac glucose homeostasis (15, 65). However, a significant challenge remains the inconsistency in miRNA expression profiles across different

TABLE 2 Roles of microRNAs in the glucose metabolism in the heart.

Validated targets	miRNA(s)	Study	Key role	Down/Up
Pyruvate dehydrogenase kinase 1(PDK1)	miR-138	Zhu et al., 2017 (23)	Inhibit glycolysis and promotes mitochondrial respiration	down
Lactate dehydrogenase A (LDHA)	miR-34a	Zhang et al., 2017 (24)	Involved in glycolysis process	up
	miR-378	Kim et al., 2013/Mallat et al., 2014 (41)	Balance between oxidative phosphorylation and glycolysis	down
Glycogen synthase kinase 3β (GSK-3β)	miR-99b-3p	Yu et al., 2021 (27)	Involved in glycogen synthesis	up
	miR-26	Zhang et al., 2013/Lu et al., 2020 (25)/ (43)	Involved in glycogen synthesis	down
	miR-335	Wu N et al., 2019 (33)	Involved in glycogen synthesis	down
	miR-199a	Liu et al., 2019/Li et al., 2017/Zuo et al., 2016 (45)/ (47)/ (22)	Involved in glycogen synthesis	up
	let-7	Guedes et al., 2016 (19)	Involved in glycogen synthesis	down
	miR-26a	Park et al., 2018 (39)	Involved in glycogen synthesis	up
	miR-378	Nagalingam et al., 2013 (40)	Involved in process of myocardial fibrosis	down
	miR-29c	Guedes et al., 2016 (19)	Involved in glycogen synthesis	up
	miR-143	Guedes et al., 2016 (19)	Involved in glycogen synthesis	down
	miR-125b	Fan et al., 2020 (54)	Involved in glycogen synthesis	down
	miR-322	Dong et al., 2019 (56)	Involved in glycogen synthesis	down
	miR-503	Dong et al., 2019 (56)	Involved in glycogen synthesis	down
Pyruvate dehydrogenase complex (PDH)	miR-195	Zhang et al., 2018 (7)	Increase acetylation of PDH and ATP synthase	up
Stress-related selenoproteins	miR-200	Yang T et al., 2019 (28)	Lead to glucose metabolism disorder	up
Histone deacetylase 8 (HDAC8)	miR-21	Yan et al., 2015 (30)	Attenuate cardiac hypertrophy	up
Period circadian clock 2 (PER2)	miR-21	Bartman et al., 2017 (61)	Facilitates glycolysis and cardioprotection	up
Lactate dehydrogenase-A (LDHA)	miR-34a	Xu et al., 2021	Regulate glucose metabolic enzymes	up
Estrogen-related receptorβ (ERRβ)	miR-1	Wei et al., 2014 (35)	Lead to glycogen storage and cardiac dilation	up
Insulin-like growth factor 1 receptor (IGF-1R)	miR-503	Wang et al., 2009 (6)	Regulate insulin sensitivity	down
Insulin receptor substrate (IRS)	let-7	Li et al., 2016 (48)	Regulate glucose metabolism	down
	miR-128-3p	Ruiz-Velasco et al., 2020 (38)	Regulate insulin resistance	up
	miR-494	Wu J et al., 2019	Regulate insulin sensitivity	up

(Continued)

TABLE 2 Continued

Validated targets	miRNA(s)	Study	Key role	Down/Up
Glucose transporter 1/4 (GLUT1/GLUT4)	miR-223	Lu et al., 2010 (42)	Increase GLUT1/GLUT4 glucose transporters	up
	miR-133	Trotta et al., 2018/Horie et al., 2009 (37)/ (51)	Increase GLUT1/GLUT4 glucose transporters	down
	miR-34a	Lu et al., 2010 (42)	Increase GLUT1/GLUT4 glucose transporters	up
	miR-150	Ju et al., 2020 (17)	Regulate glucose metabolism	up
Solute carrier family 25 member 3(Slc25a3)	miR-141	Baseler et al., 2012 (60)	Regulate glucose metabolism	up
	miR-200	Baseler et al., 2012 (60)	Regulate glucose metabolism	down
Iron-sulfur cluster assembly proteins ISCU1/2	miR-210	He et al., 2014 (52)	Suppress proteins ISCU1/2	up

studies. To date, there is a paucity of research providing a comprehensive overview of dysregulated miRNAs involved in myocardial glucose metabolism regulation. Consequently, we undertook an integrative analysis to summarize the differentially expressed miRNAs implicated in myocardial glucose metabolism regulation, based on the available evidence.

In this study, we identified 20 consistently dysregulated miRNAs involved in cardiac glucose metabolism. Among theses, the expression levels of twelve miRNAs were elevated, whereas those of eight miRNAs was reduced. Further analysis revealed that six miRNAs, miRNA-199a, let-7, miRNA-21, miRNA-133, miRNA-503, and miRNA-378, were recognized as potential biomarkers and deemed crucial in the pathogenesis of myocardial glucose metabolism disorder. MiRNAs exhibit differential expression in the cardiovascular system, and play a regulatory role in the pathophysiology of cardiovascular diseases (66). Under normal physiological conditions, heart requires a continuous energy supply to support electrical and mechanical functions, primarily generated through mitochondrial oxidative phosphorylation (67). The involvement of miRNAs in cardiovascular diseases via the regulation of glucose metabolism has been extensively investigated. Previous studies have elucidated the mechanisms by which miRNAs influence various pathological processes, including glucose transport, glycolysis, aerobic oxidation of glucose, and glycogenesis in the heart (22–25).

It is well established that the enhanced glucose uptake primarily results from the translocation of glucose transporter 4 (GLUT-4) and GLUT-1 from intracellular compartments to the surface of cardiomyocytes (68, 69). Upon insulin stimulation, GLUT-4 translocates from the intracellular vesicles to the sarcolemma, thereby increasing glucose uptake and transport (70). Studies have shown that the expression and translocation of GLUT-4 in cardiac myocytes are regulated by miRNAs. Specifically, miRNA-133 and miRNA-223 modulate glucose uptake in cardiomyocytes by targeting GLUT-4 (42, 51). MiRNAs could affect glucose transport in cardiomyocyte hypertrophy. For instance, miRNA-133 has been found to reduce KLF15 expression, a direct upstream regulator of GLUT-4 (51), and decreased level of miR-133a lead to reduced GLUT-4 glucose transporters on the cell membranes in hypertrophic cells (37). Furthermore, cardiac glucose uptake is diminished due to decreased GLUT-4, contributing to impaired myocardial glucose utilization in diabetic cardiomyopathy (37). Additionally, the upregulation of let-7 family enhances glucose utilization via GLUT-4 pathways (48). In summary, dysredulated miRNAs play a crucial role in the regulation of glucose transport in cardiomyocytes.

Cardiomyocytes primarily produce ATP through the glycolysis of glucose, and myocardial glycolysis has been found to convert glucose to macromolecular precursors (71). Several studies have reported on the role of differentially expressed miRNAs in myocardial glycolysis. Mallet et al. discovered that miRNA-378 regulates cardiac energy metabolism by balancing oxidative phosphorylation and glycolysis (41). MiRNAs also influence glycolysis to regulate cardiac function under conditions of myocardial ischemia (59). Upregulated miRNA-21 facilitates increased glycolysis via Per2-dependent mechanisms in myocardial ischemia (61). It is noteworthy that upregulation of miRNA-195 modulates cardiac energy metabolism by directly targeting the pyruvate dehydrogenase complex (PDH) (7). Oxidative phosphorylation of glucose sustains energy necessary for cardiomyocyte function, and multiple miRNAs have been identified as regulators of mitochondrial function in the heart. For instance, miRNA-30 influences apoptosis by targeting the mitochondrial fission machinery (72), while overexpression of miRNA-761 suppresses mitochondrial fission and reduces cardiomyocyte apoptosis (44).

In addition to glucose consumption, excess glucose can be converted into glycogen to provide the high energy demands of the heart (73, 74). A study by Wei et al. demonstrated that the downregulation of miRNA-1 altered glycolysis and glycogenesis by upregulating the expression of related genes (35). Furthermore, miRNAs can target key enzymes in glycogenesis, such as glycogen synthase kinase-3α (GSK3α) and glycogen synthase kinase-3β (GSK3β) in various cardiac pathological processes involving glycogen synthesis. Several miRNAs, miRNA-21, miRNA-199a, miRNA-26, miRNA-378, and miRNA-29c have been shown to

regulate the development of pathological cardiac hypertrophy by targeting GSK3β (19, 25, 30, 40, 47). Additionally, other miRNAs, including miRNA-34a, miRNA-199a, and miRNA-26a, affect myocardial ischemia/reperfusion injury via the GSK3β pathway (33, 43, 45, 75). However, the explicit mechnism by which these miRNAs are involved in glucose metabolism in the heart remain to be elucidated.

According to the current inconsistency in miRNA expression profiles, it is crucial to summarize the role of miRNAs in cardiac glucose metabolism. This study evaluated miRNA expression signatures during the pathological process of myocardial glucose metabolism and identified six miRNAs that may serve as potential biomarkers in glycometabolism. Systematic evaluation serves as a robust framework for addressing complex clinical challenges, generating evidence-based solutions through rigorous synthesis of available data (36, 76–79). While a comprehensive analysis of miRNA levels based on available evidence is a significant strength, several limitations must be acknowledged. First, the limited number of individual studies included in the pooled analysis weakens the robustness of conclusions. To ensure statistical power and reliability, we integrated data from 47 articles. Second, due to the insufficient sample size, studies with small sample sizes were not excluded. Finally, the results presented in this article are preliminary, and there is a scarcity of research explicitly investigating the pathological roles of differentially expressed miRNAs in cardiac glucose metabolism. Further experimental validation is essential to ascertain the role of these miRNAs in glycometabolism. Overall, our findings suggest that these miRNAs have the potential to serve as reliable biomarkers for myocardial glycometabolism. Nevertheless, caution is advised in interpreting these results, and rigorous experimental verification remains essential in future investigations.

Conclusion

In conclusion, this study identified 20 significantly dysregulated miRNAs. Specifically, miRNA-199a, let-7, miRNA-21, miRNA-133, miRNA-503, and miRNA-378 may serve as potential biomarkers for myocardial glucose metabolism. However, their clinical feasibility and applicability remain to be validated, and further investigations is necessary to elucidate the underlying mechanism of these dysregulated miRNAs in cardiac glucose metabolism.

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

HQ: Methodology, Writing – review & editing. Y-FZ: Data curation, Methodology, Validation, Writing – review & editing. N-NS: Conceptualization, 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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1565385/full#supplementary-material.

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Association of pan-immune-inflammation value and atherogenic index of plasma with chronic coronary syndrome in non-alcoholic fatty liver disease patients

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Background: Non-alcoholic fatty liver disease (NAFLD) is linked to a higher risk of cardiovascular disease, particularly chronic coronary syndrome (CCS). However, reliable biomarkers for early CCS risk stratification in NAFLD patients remain lacking. This study aims to assess the pan-immune-inflammation value (PIV) and atherogenic index of plasma (AIP) for CCS in NAFLD patients and to construct a practical tool for personalized risk assessment.

Methods: This retrospective study included 459 NAFLD patients undergoing coronary angiography. Least absolute shrinkage and selection operator (LASSO) and multivariate logistic regression were used to discover independent risk variables for CCS. A nomogram was constructed to quantify CCS risk. Model performance was evaluated by calibration curves, concordance index, and decision curve analysis (DCA). Trend tests assessed the relationship between PIV, AIP quartiles, and CCS risk, while quantile regression analyzed their associations with coronary lesion severity (Gensini scores).

Results: Eight independent variables were identified. Elevated lnPIV (OR, 2.195; 95% CI, 1.564-3.125; P< 0.001) and AIP (OR, 4.147; 95% CI, 1.770-10.095; P< 0.001) were strongly associated with CCS. The nomogram demonstrated good discrimination (C-index = 0.782) and calibration. Trend tests revealed a significant positive correlation between lnPIV/AIP quartiles and CCS risk (P for trend< 0.05). Quantile regression further indicated that lnPIV and AIP positively correlated with higher Gensini scores.

Conclusions: lnPIV and AIP are independent biomarkers for CCS in NAFLD patients. The nomogram provides a valuable tool for CCS risk stratification and personalized management.

KEYWORDS

non-alcoholic fatty liver disease, chronic coronary syndrome, nomogram, atherogenic index of plasma, pan-immune-inflammation value

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most prevalent chronic liver condition globally, with an estimated prevalence of 32.4% and a continuing upward trend (1). NAFLD is not merely a hepatic disorder but a multisystemic disease that is associated with heightened risk of cardiovascular complications, diabetes mellitus (DM), and chronic kidney disease (2). Among the cardiovascular complications, coronary artery disease (CAD) stands out due to its considerable impact on morbidity and mortality (3). In China, the prevalence of CAD has been reported to be as high as 40.9% in NAFLD patients (4). CAD is a chronic and continuously progressive disease. Depending on the stages of disease progression, CAD is typically classified into acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) (5). CCS, characterized by stable but progressive accumulation of atherosclerotic plaques, accounts for a substantial proportion of CAD cases. Despite the therapeutic strategies having progressed in recent years, the clinical burden of CCS remains high (6). According to data from the American Heart Association, CCS is predicted to affect approximately 18% of adults by 2030 (7).

Coronary atherosclerosis is widely recognized as a chronic inflammatory disease of the arterial wall (8). NAFLD contributes to systemic chronic low-grade inflammation, endothelial dysfunction, and atherogenic dyslipidemia, providing a "breeding ground" for atherosclerosis progression and thereby accelerating the development of coronary artery lesions (9, 10). Consequently, identifying reliable inflammatory and lipid-related biomarkers is essential for the early detection and risk stratification of CAD, particularly CCS, in patients with NAFLD.

Given the critical role of inflammation in atherosclerosis, a range of novel biomarkers have been increasingly proposed to enhance the assessment of coronary atherosclerosis risk (11–13). The pan-immune-inflammation value (PIV), a composite index derived from peripheral blood counts, has emerged as a prognostic biomarker in several malignancies (14). Various studies have demonstrated that PIV exhibits superior predictive potential in cardiovascular disease risk assessment compared with traditional inflammatory biomarkers (15, 16). Similarly, the atherogenic index of plasma (AIP) has been recognized as a potential biomarker for adverse cardiovascular events in CAD patients (17). However, the clinical significance of PIV and AIP in assessing CCS risk among NAFLD patients has not been thoroughly investigated. Therefore, we sought to evaluate the associations of PIV and AIP with the presence and severity of CCS in individuals with NAFLD.

2 Materials and methods

2.1 Research study overview and participants

Between January 2021 and December 2022, 805 patients who had coronary angiography (CAG) at Shanxi Medical University's Second Hospital were included in our retrospective analysis. Following the implementation of specific inclusion and exclusion criteria, we included 459 patients with confirmed NAFLD in the final analysis (Figure 1). The protocol for this research project has been approved by a suitably constituted Ethics Committee of the Second Hospital of Shanxi Medical University and it conforms to the provisions of the Declaration of Helsinki. Due to the retrospective design of the study, the requirement for written informed consent was waived.

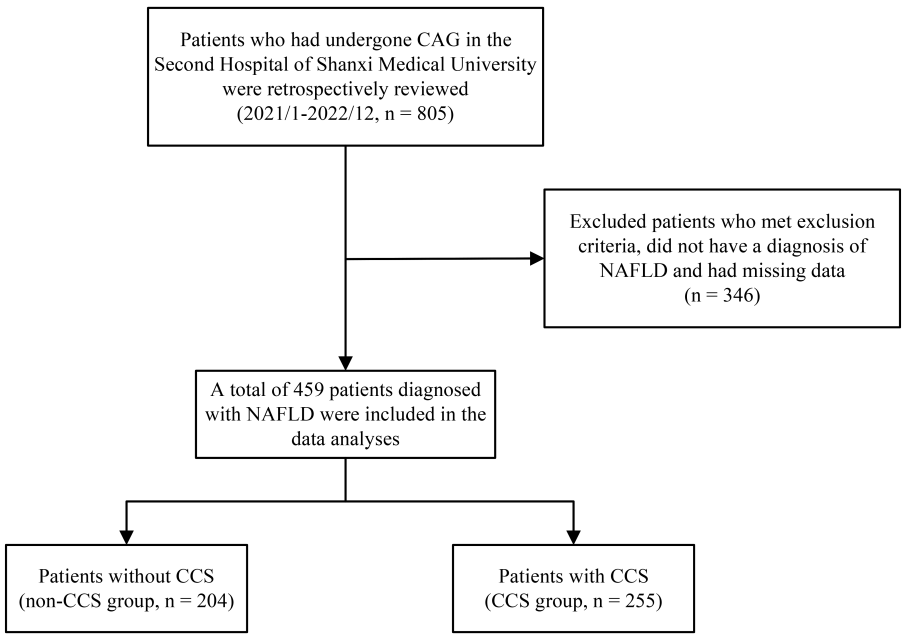

FIGURE 1
Flowchart of the subjects' screening and grouping process.

The NAFLD was diagnosed via abdominal ultrasonography following the 2017 Asia-Pacific Working Party group guidelines (18), requiring the exclusion of secondary hepatic steatosis (e.g., alcohol consumption >140 g/week for males or >70 g/week for females, viral hepatitis, or drug-induced liver injury).

Two experienced interventional cardiologists performed CAG following the Judkin's method (5, 19). Based on the angiographic findings, the diagnosis of CCS was independently assessed, and the Gensini score was subsequently calculated to quantify the degree of coronary stenosis (Supplementary Table 1).

Patients were excluded if they had any of the following conditions: incomplete patient data, recent use of lipid-lowering agents, heart failure, ACS, prior coronary revascularization, structural heart disease, severe hepatic or renal dysfunction, thyroid dysfunction, hematologic or autoimmune diseases, malignancies, familial hypercholesterolemia, or systemic infections.

2.2 Clinical information and lab measurements

Baseline clinical and demographic data were retrospectively obtained from electronic medical records, including gender, age, body mass index (BMI), smoking history, hypertension, and DM. All data were collected at the time of admission. Fasting venous blood samples were drawn in the morning following admission, after at least 12 hours of fasting, and prior to undergoing CAG. Laboratory parameters assessed include red blood cell count (RBC), hemoglobin concentration (HGB), red cell distribution width-coefficient of variation (RDW-CV), platelet count, lymphocyte count, monocyte count, neutrophil count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), serum albumin (ALB), serum creatinine (SCr), blood uric acid (URIC), blood urea nitrogen (UREA), fasting blood glucose (FBG), fibrinogen (FIB), D-dimer (D-Di), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C. The platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), pan-immune-inflammation value (PIV), atherogenic index (AI), remnant cholesterol (RC), and atherogenic index of plasma (AIP) were calculated using the following formulas:

$$PLR = \frac{\text{platelet count}}{\text{lymphocyte count}}$$

$$MLR = \frac{\text{monocyte count}}{\text{lymphocyte count}}$$

$$NLR = \frac{\text{neutrophil count}}{\text{lymphocyte count}}$$

$$SIRI = \frac{\text{monocyte count} \times \text{neutrophil count}}{\text{lymphocyte count}}$$

$$SII = \frac{\text{platelet count} \times \text{neutrophil count}}{\text{lymphocyte count}}$$

$$PIV = \frac{\text{neutrophil count} \times \text{platelet count} \times \text{monocyte count}}{\text{lymphocyte count}}$$

$$AI = \frac{TC - HDL - C}{HDL - C}$$

$$RC = TC - (HDL - C + LDL - C)$$

$$AIP = \log_{10}\left(\frac{TG}{HDL - C}\right)$$

2.3 Statistical analysis

Continuous variables were assessed for normality using the Shapiro-Wilk test. Data with normal distribution were presented as mean ± standard deviation ($\bar{x} \pm s$), and compared using the Student's t-test. Non-normally distributed variables were presented as median (Q1, Q3) and analyzed using the Mann-Whitney U test. Count data were expressed as frequencies (%) and compared by the chi-square test. Natural logarithmic transformation was done for PLR, MLR, NLR, SIRI, SII, and PIV to minimize skewness and stabilize variance.

Initially, variable selection was screened using the least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation to prevent overfitting. Next, we used multivariate logistic regression analysis to identify independent variables more closely. A nomogram was constructed using significant variables from the final logistic model. The model's discrimination was assessed using the concordance index (C-index) and receiver operating characteristic (ROC) curves. Moreover, to verify the model's robustness, ROC curves were generated by the bootstrap method (resampling 1,000 times). Calibration of the model was assessed via calibration plots based on the bootstrap method (resampling 1,000 times) to examine the agreement between predicted and observed outcomes. The clinical utility was evaluated using Decision Curve Analysis (DCA), and the net benefit at different thresholds was quantified using the Clinical Impact Curve (CIC). Additionally, quantile regression assessed the relationships between lnPIV and AIP levels and the 25th, 50th, and 75th percentiles of Gensini scores.

Analyses were conducted using R version 4.4.1. We used two-tailed P values, and a P value less than 0.05 was considered statistically significant.

3 Results

3.1 Comparison of baseline clinical characteristics and laboratory test parameters between the non-CCS and CCS groups

Table 1 summarizes the patients' baseline characteristics and laboratory test parameters. The CCS group had a much greater

TABLE 1 Baseline characteristics of non-CCS and CCS groups.

Characteristics	Non-CCS (N=204)	CCS (N=255)	*P*
Gender (Male)	106 (52.0%)	164 (64.3%)	.010*
Age	56.50 (50.50, 63.00)	59.00 (52.00, 66.00)	.004*
BMI (kg/m^2)	25.71 (24.22, 27.71)	26.12 (24.56, 28.01)	.146
Hypertension	94 (46.1%)	157 (61.6%)	.001*
DM	28 (13.7%)	91 (35.7%)	<.001*
Smoking	64 (31.4%)	128 (50.2%)	<.001*
RBC, 10^9/L	4.69 (4.35, 5.01)	4.71 (4.38, 4.98)	.727
Hemoglobin, g/dL	144.99 ± 14.39	145.23 ± 15.31	.863
RDW-CV (%)	12.45 (12.00, 12.90)	12.50 (12.10, 12.90)	.165
Platelet (10^9/L)	218.00 (184.50, 249.00)	221.00 (185.00, 253.00)	.347
Lymphocyte (10^9/L)	1.90 (1.51, 2.28)	1.91 (1.52, 2.38)	.673
Monocyte (10^9/L)	0.42 (0.34, 0.51)	0.48 (0.38, 0.58)	<.001*
Neutrophil (10^9/L)	3.43 (2.73, 4.63)	4.13 (3.21, 5.44)	<.001*
PLR	115.43 (91.40, 138.01)	116.26 (93.38, 142.98)	.566
MLR	0.22 (0.18, 0.27)	0.24 (0.19, 0.30)	.001*
NLR	1.89 (1.34, 2.56)	2.09 (1.59, 3.00)	<.001*
SIRI	0.77 (0.51, 1.12)	1.00 (0.66, 1.57)	<.001*
SII	402.25 (276.21, 558.34)	481.34 (338.27, 658.17)	<.001*
PIV	156.91 (110.75, 245.58)	236.20 (141.52, 326.81)	<.001*
lnPLR	4.73 ± 0.32	4.75 ± 0.35	.485
lnMLR	-1.51 ± 0.34	-1.39 ± 0.39	.001*
lnNLR	0.64 ± 0.43	0.79 ± 0.49	<.001*
lnSIRI	-0.25 ± 0.54	0.03 ± 0.63	<.001*
lnSII	5.99 ± 0.47	6.18 ± 0.52	<.001*
lnPIV	5.10 ± 0.58	5.42 ± 0.67	<.001*
ALT (U/L)	22.30 (16.00, 32.30)	22.80 (16.80, 33.90)	.478
AST (U/L)	21.95 (18.10, 25.95)	22.20 (17.50, 27.90)	.686
TBIL (umol/L)	14.15 (11.10, 17.85)	13.50 (10.70, 16.90)	.078
ALB (g/L)	41.70 (39.80, 43.55)	40.30 (38.70, 42.85)	<.001*
Urea nitrogen (mmol/L)	5.30 (4.40, 6.10)	5.30 (4.50, 6.40)	.398
Uric acid (umol/L)	362.55 ± 83.92	358.50 ± 81.42	.601
SCr (umol/L)	65.00 (56.00, 75.00)	66.00 (57.00, 74.50)	.322
TC (mmol/L)	4.29 (3.64, 5.04)	4.53 (3.91, 5.31)	.007*
TG (mmol/L)	1.67 (1.23, 2.22)	1.81 (1.35, 2.67)	.002*
HDL-C(mmol/L)	1.14 (0.97, 1.35)	1.08 (0.93, 1.28)	.006*
LDL-C(mmol/L)	2.27 (1.81, 2.66)	2.42 (2.04, 2.84)	.004*
AI	1.39 (1.27, 1.49)	1.40 (1.32, 1.50)	.176
RC	0.85 (0.59, 1.21)	0.95 (0.74, 1.30)	.001*
AIP	0.15 (0.00, 0.31)	0.25 (0.07, 0.41)	<.001*
FBG (mmol/L)	5.29 (4.94, 5.79)	5.56 (4.90, 6.99)	.008*
D-Dimer (ng/mL)	71.00 (49.50, 112.00)	79.00 (53.00, 128.00)	.055
Fibrinogen (g/L)	2.73 (2.35, 3.19)	2.85 (2.51, 3.21)	.051

Data are expressed as mean ± standard deviation, median (Q1, Q3), or n (%). lnPLR, lnMLR, lnNLR, lnSIRI, lnSII, and lnPIV are the natural logarithms of PLR, MLR, NLR, SIRI, SII, and PIV, respectively. *P value< 0.05.

proportion of males (64.3% vs. 52.0%; P = 0.010) and was older on average (59 [52, 66] vs. 56.5 [50.5, 63], P = 0.004) compared to the non-CCS group. Hypertension, DM, and smoking history were also more prevalent in the CCS group (61.6% vs. 46.1%; 35.7% vs. 13.7%; 50.2% vs. 31.4%; P = 0.001, P< 0.001, and P< 0.001, respectively). Additionally, laboratory findings showed levels of lnNLR, lnMLR, lnSII, lnSIRI, lnPIV, fasting glucose, TC, TG, LDL-C, AIP, and RC were significantly elevated in the CCS group (P< 0.05). In contrast, HDL-C level was lower in the CCS group (P = 0.006).

3.2 LASSO regression analysis for characteristics screening

The main variables of CCS were initially screened using LASSO regression analysis in combination with 10-fold cross-validation (Figure 2), and lambda.1se was selected as the optimal penalty coefficient. Nine non-zero coefficient variables were identified: age, hypertension, DM, smoking, neutrophil count, lnPIV, ALB, LDL-C, AIP, and RC. After testing the variance inflation factor (VIF) (Supplementary Table 2), we retained the lnPIV and excluded neutrophil count based on the principle of minimizing redundancy and enhancing model stability.

3.3 Multivariable logistic regression for characteristics selection

The variables preliminarily selected by LASSO regression were further analyzed by multivariate logistic regression (Table 2). Among these, the variable RC was initially included in Model I but was subsequently excluded from Model II due to its non-significance (P = 0.557). The multivariable logistic regression analysis results found that age (OR, 1.035; 95% CI, 1.010-1.061; P = 0.007), hypertension (OR, 1.869; 95% CI, 1.197-2.934; P = 0.006), DM (OR, 3.149; 95% CI, 1.876-5.414; P< 0.001), smoking (OR, 2.411; 95% CI, 1.526-3.849; P< 0.001), LDL-C (OR, 1.899; 95% CI, 1.357-2.698; P< 0.001), lnPIV (OR, 2.195; 95% CI, 1.564-3.125; P<

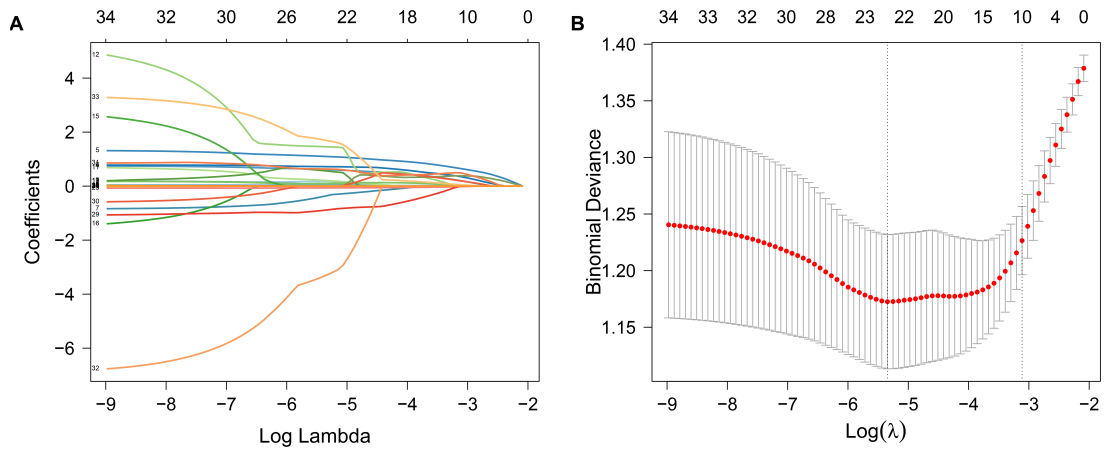

FIGURE 2
Variable selection was performed using LASSO regression analysis in combination with 10-fold cross-validation. **(A)** Path plot of LASSO regression coefficients for the independent variables constructed from log(λ); **(B)** Cross-validation error plot was used to determine the optimal penalty parameter λ. The vertical left dashed line represents λ (lambda.min) at minimum bias, while the right dashed line represents λ (lambda.1se) with one standard error to the right of lambda.min.

0.001), and AIP (OR, 4.147; 95% CI, 1.770-10.095; P = 0.001) were independent risk factors for CCS in patients with NAFLD. Conversely, ALB (OR, 0.923; 95% CI, 0.870-0.975; P = 0.005) was identified as an independent protective factor. We mapped the forest plot based on these independently correlated characteristics (Supplementary Figure 1).

3.4 Nomogram construction and validation

Multivariate logistic regression analyses revealed statistically significant independent variables. Based on these variables, a nomogram for CCS risk estimation in the NAFLD population was constructed (Figure 3A). The nomogram model's internal validation was performed using bootstrap (resampling = 1000), and the calibration curves demonstrated a strong match between the predicted and actual probabilities of CCS (Figure 3B). Furthermore, the nomogram's C-index was 0.782 (95% CI, 0.741-0.824), indicating high accuracy in predicting CCS risk.

3.5 Evaluation of the nomogram model's clinical utility

The DCA curves (Figure 4A) show that the nomogram model provides higher net benefits compared to lnPIV or AIP alone and outperforms both the "no intervention" and "intervention for all" strategies across a threshold probability range of approximately 0.1-0.9. Meanwhile, the CIC (Figure 4B) demonstrates the correspondence between predicted and actual case numbers at

TABLE 2 Multivariate logistic analyses of variables associated with CCS in NAFLD.

Characteristics	Model I				Model II			
	OR	95%CI		P	OR	95%CI		*P*
Age	1.034	1.009	1.060	0.009*	1.035	1.010	1.061	0.007*
Hypertension	1.871	1.199	2.938	0.006*	1.869	1.197	2.934	0.006*
DM	3.178	1.891	5.473	<0.001*	3.149	1.876	5.414	<0.001*
Smoking	2.425	1.535	3.873	<0.001*	2.411	1.526	3.849	<0.001*
ALB	0.924	0.870	0.976	0.006*	0.923	0.870	0.975	0.005*
LDL-C	1.813	1.254	2.66	0.002*	1.899	1.357	2.698	<0.001*
lnPIV	2.215	1.575	3.159	<0.001*	2.195	1.564	3.125	<0.001*
AIP	3.539	1.302	9.946	0.014*	4.141	1.770	10.095	0.001*
RC	1.173	0.685	2.006	0.557				

Model I was adjusted for variables screened by LASSO regression with 10-fold cross-validation; Model II adjusted for variables with a *P* value of less than 0.05 in Model I. **P* value< 0.05.

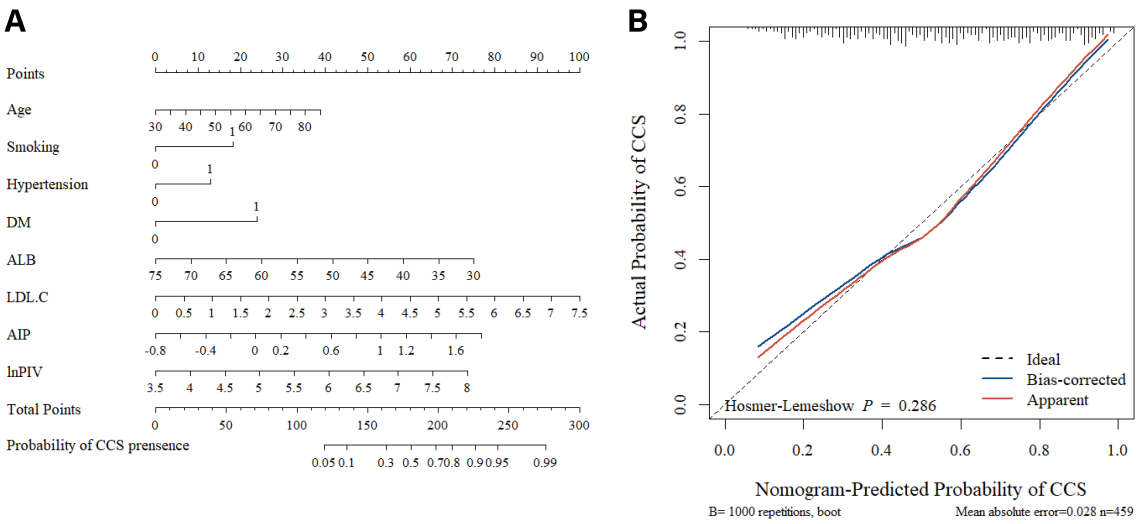

FIGURE 3
The nomogram and calibration curves. **(A)** Using the nomogram, each variable's location on its axis is identified to assign corresponding points. These points are then summed across all predictor variables to generate a total points score. Finally, the estimated probability of CCS occurrence is determined by referencing the bottom scale. **(B)** The nomogram calibration curves demonstrated the concordance between predicted and observed probabilities. The Hosmer-Lemeshow test yielded $P > 0.05$, indicating a good model fit.

different threshold probabilities. It reveals that the number of positive cases predicted by the nomogram model gradually approaches the number of actual positive cases as the risk threshold increases, indicating that the model has good predictive ability and clinical applicability.

3.6 ROC analysis of biomarkers and nomogram model

To evaluate the predictive value of each biomarker, their AUC values were calculated respectively. The results indicated that lnPIV had the highest AUC of 0.646 (95% CI, 0.595-0.696, P< 0.001), outperforming lnNLR (AUC = 0.590, 95% CI, 0.538-0.642, P = 0.001), lnPLR (AUC = 0.516, 95% CI, 0.463-0.596, P = 0.565), lnMLR (AUC = 0.587, 95% CI, 0.535-0.639, P = 0.001), lnSII (AUC = 0.607, 95% CI, 0.555-0.658, P< 0.001), and lnSIRI (AUC = 0.629, 95% CI, 0.578-0.679, P< 0.001). Additionally, the AUC of AIP (0.602, 95% CI, 0.550-0.653, P< 0.001) was significantly higher compared to AI (AUC = 0.537, 95% CI, 0.483-0.590, P = 0.176) and RC (AUC = 0.588, 95% CI, 0.536-0.640, P = 0.001). The ROC curves revealed that the AUC of the nomogram model was 0.782 (95% CI, 0.741-0.824, Figure 5A), which provided better discriminatory power than a single variable. After internal validation by the

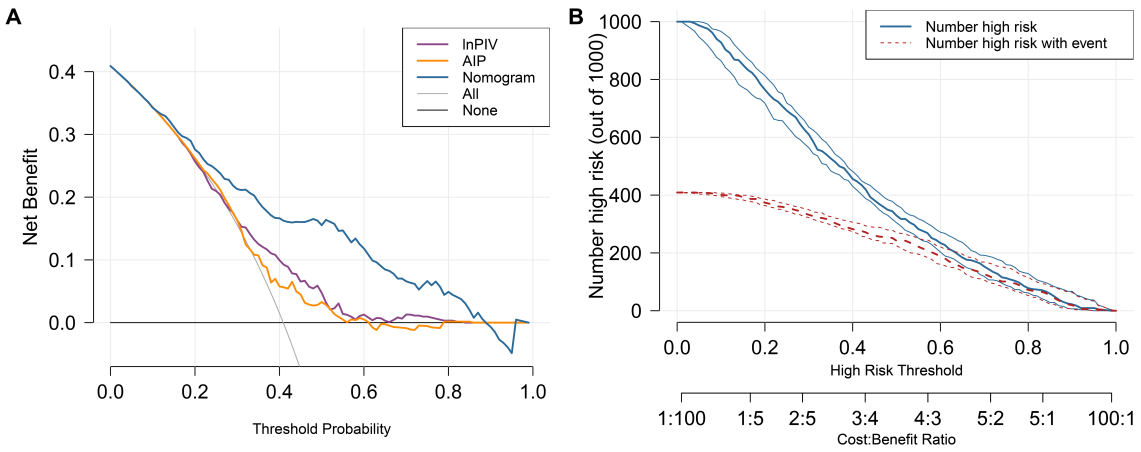

FIGURE 4
The DCA curves and CIC for the nomogram model. **(A)** DCA curves of lnPIV, AIP, and the nomogram. **(B)**The nomogram model's CIC displays two curves: the red curve represents the actual count of positives at each threshold, while the blue curve reflects the count of individuals identified as positive by the model at each threshold.

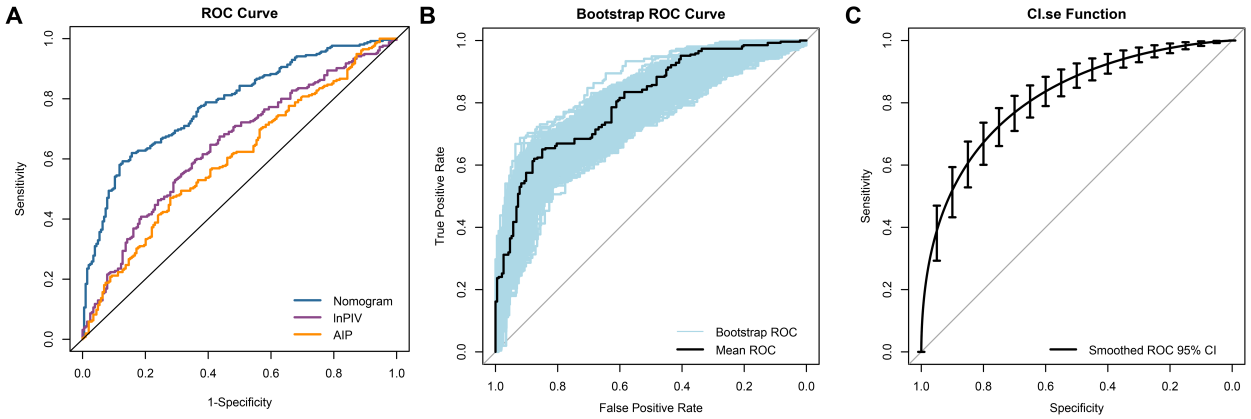

FIGURE 5
ROC curves analysis of the ability to predict CAD in NAFLD. **(A)** The ROC curves and AUC values for the nomogram model, lnPIV, and AIP are as follows: nomogram model: 0.782 (95% CI, 0.741 - 0.824); lnPIV: 0.646 (95% CI, 0.595 - 0.696); AIP: 0.602 (95% CI, 0.550 - 0.653); **(B)** The mean ROC curve displays the AUC from internal validation with the bootstrap method (resampling = 1000), yielding an AUC of 0.781 (95% CI, 0.735 - 0.823); **(C)** The dotted vertical lines indicate the 95% CI for the smoothed ROC curve, with a smoothed ROC AUC of 0.815 (95% CI, 0.775 - 0.850).

bootstrap method (resampling = 1000), the AUC of the mean ROC curve was 0.781 ± 0.022 (Figure 5B). Moreover, we fitted a smoothed ROC curve using the resampled data, estimated 95% confidence intervals for sensitivity, and presented them as error bars on the ROC plot. The smoothed ROC curve's AUC was 0.815 (95% CI, 0.775 - 0.850) (Figure 5C).

3.7 Association of lnPIV and AIP quartiles with CCS risk in NAFLD patients

To investigate the relationship between the levels of lnPIV, AIP, and the risk of CCS in NAFLD patients, we regrouped them according to quartiles of lnPIV or AIP and analyzed them separately using trend tests (Table 3). Specifically, the ORs of lnPIV increased gradually across quartiles, indicating a significant positive trend (Multivariate model, P for trend< 0.001). AIP showed a similar trend, significantly associated with increased risk of CCS across quartiles (Multivariate model, P for trend = 0.004).

3.8 Distributional effects of lnPIV and AIP on Gensini scores observed through quantile regression

Quantile regression analysis assessed the effects of lnPIV and AIP at different percentiles of Gensini scores and their statistical significance (Figure 6). The results indicated that the regression coefficients of lnPIV were 5.90 (P = 0.045) at the 50th percentile and 14.97 (P = 0.017) at the 75th percentile. In contrast, the coefficient at the 25th percentile was 1.661 (P = 0.153), which was not statistically significant (Supplementary Table 3). These findings suggest that lnPIV has a more pronounced positive effect on patients with higher Gensini scores (≥50th percentile), which indicates worse coronary stenosis. Similarly, the regression coefficient of AIP at the 75th tertile was 20.97 (P = 0.017) (Supplementary Table 3), highlighting its significant predictive value in patients with higher Gensini scores.

4 Discussion

In our study, we systematically assessed the combined predictive value of lnPIV and AIP for CCS in patients with NAFLD. Both lnPIV and AIP demonstrated independent associations with CCS risk and exerted a greater influence in moderate-to-severe coronary atherosclerosis, as reflected by Gensini scores. These findings suggest that systemic immune-inflammation burden and atherogenic dyslipidemia contribute to the progression of CCS in NAFLD-related cardiovascular disease. Additionally, the nomogram integrating these biomarkers exhibited robust discriminatory ability and calibration, providing a practical tool for CCS risk stratification in clinical settings.

CCS refers to a series of clinical manifestations caused by structural and/or functional abnormalities in the coronary arteries and/or microcirculation, excluding acute coronary thrombosis as the predominant cause (6). Its pathogenesis is primarily driven by maladaptive inflammatory responses and dysregulated lipid metabolism (20). NAFLD, as a metabolic disease, can induce immune signaling disturbances and maintain the body in a persistent low-grade inflammatory state (21). Besides the hepatic fat accumulation-induced inflammatory response, the enrichment of myeloid derived suppressor cells (MDSC) and natural killer T cells (NKT) in the spleen has been shown to exacerbate the hepatic inflammatory response (22). This spleen-hepatic crosstalk aggravates the systemic inflammatory response and is a key feature of NAFLD (23, 24). These inflammatory mechanisms likely serve as critical intermediaries linking NAFLD to CCS. Previous studies have shown that the atherosclerosis progression involves complex regulation of cytokines and immune cells across all stages (25). Consistent with this, our findings revealed

TABLE 3 Logistic analysis of CCS in NAFLD by lnPIV, AIP, and Nomogram points quartile.

Variable		CCS	Non-CCS	Non-adjusted		Multivariate model	
				OR (95%CI)	P	OR (95%CI)	*P*
lnPIV							
Q1	<4.802	46	69	Ref.		Ref.	
Q2	4.802-5.254	56	58	1.448 (0.859,2.452)	0.166	1.066 (0.590,1.924)	0.831
Q3	5.254-5.689	68	47	2.170 (1.286,3.694)	0.004*	2.044 (1.140,3.699)	0.017*
Q4	≥5.689	85	30	4.250 (2.451,7.514)	<0.001*	3.584 (1.944, 6.738)	<0.001*
P for trend				<0.001*		<0.001*	
AIP							
Q1	<0.0428	52	63	Ref.		Ref.	
Q2	0.0428-0.2023	58	56	1.255 (0.747,2.113)	0.392	1.320 (0.731, 2.393)	0.359
Q3	0.2023-0.3709	67	48	1.691 (1.006,2.860)	0.048*	1.580 (0.876, 2.864)	0.130
Q4	≥0.3709	78	37	2.554 (1.501,4.397)	0.001*	2.490 (1.346, 4.673)	0.004*
P for trend				<0.001*		0.004*	

Trend tests are based on the variable with a median value for each quintile. The multivariate model was adjusted for age, hypertension, smoking, DM, albumin, LDL-C, and lnPIV or AIP.
*P value< 0.05.

significantly higher levels of neutrophils, monocytes, and platelets in NAFLD patients with CCS compared to those without. Monocytes are the earliest immune cells recruited to sites of endothelial dysfunction. They secrete pro-inflammatory cytokines and reactive oxygen species (ROS), differentiate into macrophages, and contribute to early atherosclerotic lesion formation by uptaking lipoproteins and becoming foam cells that secrete additional inflammatory mediators (26). Neutrophils aggravate vascular injury by secreting ROS and pro-inflammatory molecules, which in turn recruit additional immune cells and amplify inflammatory cascades (27). Moreover, lymphocytes are also actively involved in various stages of atherosclerosis. In general, T cells promote disease progression by regulating cellular interactions and releasing inflammatory cytokines, whereas B cells may exert protective effects by dampening inflammation (28). Platelets, although anucleated, can secrete many chemokines upon activation,

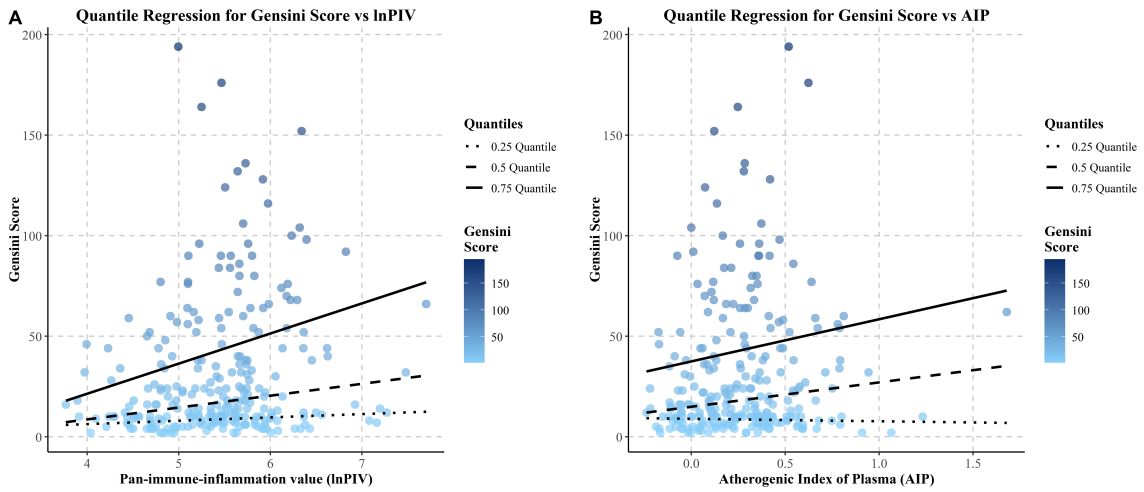

FIGURE 6
Quantile regression lines of gensini score on lnPIV and AIP across quantiles.

initiating and sustaining local inflammatory processes at the site of vascular injury (29). These cellular and molecular events drive the chronic inflammatory course of atherosclerosis together, ultimately leading to the pathologic progression of CCS. The PIV, which integrates neutrophils, monocytes, lymphocytes, and platelets, serves as a composite indicator of systemic inflammation (16). In our study, the ROC curves revealed that the PIV had the highest AUC value, indicating its predictive strength and clinical relevance.

In parallel, AIP reflects the atherogenic potential of lipid metabolism and is calculated by the logarithm of the TG/HDL-C ratio. The liver plays a central role in lipid homeostasis, but NAFLD-related hepatic disorder leads to elevated TG levels, reduced HDL-C levels, and increased production of small dense LDL particles (sdLDL), which are highly atherogenic (30–32). Despite adequate control of LDL levels in some patients, a "residual risk" of cardiovascular events may still exist, which may be attributed to elevated TG and reduced HDL-C levels—key components captured by AIP (33, 34). Elevated TG is metabolized into triglyceride-rich lipoproteins (TRLs), and small, dense, low-density lipoprotein (sdLDL) particles are formed (32). TRLs deposit cholesterol in the arterial wall and mediate foam cell formation, while oxidized sdLDL further triggers an immune response and vascular inflammation (35). Conversely, HDL confers cardiovascular protection by mediating reverse cholesterol transport, reducing oxidative stress, and preserving endothelial function (36, 37). AIP has been considered more effective than individual lipid indices in predicting cardiovascular disease risk and has shown significant potential for prognosis prediction and diagnosis (38, 39). Our study revealed that elevated AIP levels significantly increased the risk of CCS in NAFLD patients, even after adjusting for traditional confounders, providing new evidence for the clinical application of AIP as a CCS risk assessment biomarker.

In addition to inflammation and lipid metabolism, ALB also emerged as an independent predictor of CCS in this study. ALB is the most abundant protein in plasma, responsible for preserving colloid osmolarity and exerting anti-inflammatory and antioxidant effects (40, 41). Our study found that among NAFLD patients, lower ALB levels were significantly linked to higher CCS risk. Although ALB levels may not decrease significantly in early NAFLD, structural alterations may impair its physiological activity (42). As the disease progresses, reduced ALB levels may further weaken the body's antioxidant and anti-inflammatory defenses, thus exacerbating the risk of CCS.

To further confirm the link between lnPIV, AIP levels, and coronary artery severity lesions, we applied quantile regression analysis. The results indicated significance for lnPIV at the 50^{th} and 75^{th} percentiles, but significance was noted only for AIP at the 75^{th} percentile. These findings confirmed the potential of lnPIV and AIP in predicting the severity of coronary atherosclerosis, aligning with earlier research findings (43, 44), and may serve as valuable indicators for identifying individuals at greater cardiovascular risk.

While traditional cardiovascular risk factors remain essential for risk assessment, our results highlight the added value of composite indices such as lnPIV and AIP in refining the prediction of CCS, particularly among NAFLD patients. The nomogram constructed based on these biomarkers showed strong predictive accuracy and calibration, and may offer a novel, clinically applicable tool for individualized CCS risk stratification.

Several limitations should be acknowledged in this study. First, the retrospective, single-center design may introduce potential selection bias and limit the generalizability of the findings. Second, a small sample size may reduce statistical power, affecting the precision of some estimates. Third, residual confounding from unmeasured variables may influence the observed associations. Therefore, future studies should address these limitations through large-scale, multi-center cohorts and longitudinal designs to better understand the causal relationship between biomarkers and CCS. Monitoring dynamic changes in these biomarkers over time would also provide valuable insights into their role in disease progression and risk stratification.

5 Conclusions

Elevated PIV and AIP levels were found to be independent risk factors for CCS in NAFLD patients, showing significant associations between their quartiles and the severity of coronary lesions (Gensini scores). The nomogram developed in this study offers a valuable predictive tool, enhancing the identification of high-risk individuals. These findings have important implications for risk stratification and the development of management strategies for CCS in NAFLD patients.

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 Second Hospital of Shanxi Medical University. 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

BY: Writing – review & editing, Methodology, Writing – original draft, Formal analysis, Data curation. JZ: Data curation, Methodology, Writing – review & editing. WZ: Data curation, Writing – review & editing, Formal analysis. LW: Data curation, Writing – review & editing. XZ: Data curation, Writing – review & editing. XL: Writing – review & editing, Data curation. ZY: Data curation, Writing – review & editing. YS: Writing – review & editing, Data curation. ZR: Data curation, Writing – review & editing. BL: 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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Regulation of osteogenic differentiation in vascular smooth muscle cells under high-glucose condition

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Diabetic patients have a higher tendency for vascular calcification (VC). This indicates a possible link between abnormal glucose metabolism and the development of VC. High glucose levels are a major cause of vascular calcification in diabetic patients. Vascular smooth muscle cells (VSMCs) are important functional units of the arterial media and show heterogeneity. Sustained hyperglycemia drives VSMCs to undergo a phenotypic transition from contractile state to osteo-/chondrogenic lineages through multiple pathophysiological mechanisms. Specifically, hyperglycemia stimulates metabolic reprogramming. This includes enhancing advanced glycation end products (AGEs), activating the diacylglycerol-dependent protein kinase C (PKC) pathway, disrupting the pentose phosphate flux (PPP), and dysregulating the hexosamine biosynthesis pathway (HBP). These changes trigger vesicles-mediated mineralization (including matrix/extracellular vesicles), oxidative stress, inflammatory cascades, and an imbalance between autophagy and apoptosis. This review systematically describes the metabolic remodelling induced by high glucose and its regulatory mechanisms in vascular calcification.

KEYWORDS

atherosclerosis, calcification, osteogenic transformation, vascular smooth muscle cells, hyperglycemia research insights

Highlights

What is currently known about this topic?

- Diabetic patients face a higher risk of coronary artery calcification, which is related to hyperglycemia.
- VSMCs play a key role in vascular calcification and can differentiate into osteoblast-like cells.

- VSMCs osteogenic differentiation is likely driven by specific diabetes mellitus–associated mechanisms. These include oxidative stress, PKC activation, PPP, and HBP. These processes regulated by key enzymes such as hexokinase 2 (HK2), pyruvate kinase M (PKM), β-N-acetylglucosaminidase (OGA) and β-N-acetylglucosaminyltransferase (OGT).

What is the key research question?

- How does hyperglycemia induce the osteogenic differentiation of VSMCs?
- what are the underlying molecular mechanisms?

What is new?

- Elucidation of the complex regulatory network of metabolic reprogramming in VSMCs under diabetic conditions.
- Discovery of the role of various microRNAs and extracellular vesicles in regulating VSMCs osteogenic differentiation.

1 Introduction

Forecasts indicate that by 2030, 552 million people will be diabetes (1–3) Cardiovascular calcification was found in 81.2% of diabetic patients and 33.7% of nondiabetic patients. Therefore, diabetic patients are highly prone to VC (4, 5). A better understanding of the molecular processes between high glucose and VC may accelerate the development of new biomarkers and targeted drugs for calcification.

VC is mainly divided into initial and medial calcification (6). VSMCs are important components of the vascular media. In diabetes, hyperglycemia disrupts redox homeostasis and triggers inflammatory signaling, oxidative stress, formation of Ca-Pi crystals, O-GlcnAcylation, promoting the osteogenic differentiation of VSMCs (7–10).

During the osteogenic differentiation of VSMC, hyperglycemia upregulates expression of osteopontin (OPN) and osteoprotegerin (OPG) and then activates Msh homeobox-2 (MSX2) and Runt-related transcription factor 2 (RUNX2) through the wingless - type MMTV integration site family (WNT)/β-catenin and bone morphogenetic protein-2 (BMP-2) pathways (11–14). The mechanisms of VSMCs calcification caused by diabetes have been a hot topic of research in recent years, which mainly include oxidative stress, inflammation, death regulation, matrix vesicle formation, mineral deposition (15–17).Under the high glucose condition, glucose metabolic reprogramming is crucial for the phenotypic transformation of VSMCs and contributes to vascular remodeling (18–20). The complex interaction between metabolic reprogramming, signaling pathway activation, cell fate decisions, and post-transcriptional regulation underlies the osteogenic differentiation of VSMCs in diabetes. Besides, high glucose impairs the pyrophosphate-to-phosphate ratio and induce calcium deposition, disrupts extracellular pyrophosphate and calcium metabolism (21). Despite some progress in recent years, the impact of hyperglycemia on VSMCs osteogenic differentiation remains unclear. In-depth studies are needed to clarify the detailed mechanisms of VSMCs osteogenic differentiation in diabetes. Therefore, this reviewer pays attention to the pathophysiology of VSMCs osteogenic differentiation induced by hyperglycemia.

2 VSMCs' osteogenic differentiation: a key event in VC

The etiology of VC involves the osteogenic differentiation of VSMCs (22). VSMCs exhibit phenotypic plasticity (23). With the development of high-throughput detection technologies such as single-cell and transcriptomics sequencing analysis, it is realized that VSMCs can be transformed into pro-inflammatory chemotactic like, macrophage-like/foam-like, and fibroblast/chondroblast-like smooth muscle cells (24–26). Among them, the osteogenic transformation of VSMCs is an important link in vascular calcification. During VSMCs' osteogenic differentiation, the levels of MSX2, BMP2, RUNX2, osterix, sex-determining region Y-box 9 (SOX9) increase. These upregulate osteocytic and chondrocyte markers [such as OC (osteocalcin), Col1α1 (collagen type I α1), OPN, and alkaline phosphatase (ALP)] and downregulates contractile markers like smooth muscle 22 α (SM22α), calponin, and smooth muscle myosin heavy chain (SM-MHC) (27–31) (Figure 1). With the deepening of scientific research, a large number of regulatory factors will be discovered, which will provide new therapeutic targets for osteogenic transformation of VSMCs. For example, high-mobility group box-1 (HMGB-1) promotes vascular calcification in diabetic mice via endoplasmic reticulum stress (15). Non-POU domain-containing octamer-binding protein (NONO) or octamer-binding transcription factor 4 (OCT4) directly bound to the BMP2 promoter and inhibited BMP2 transcription, which protected against osteogenic differentiation of VSMCs (32, 33).

3 Glucose metabolic reprogramming and VSMCs osteogenic differentiation

Diabetic patients display elevated glucose in the blood, which lead to VSMCs dysfunction and significantly alter their metabolism. Previous studies have shown that in calcified VSMCs, glucose consumption and lactate generation increase due to a shift towards glycolysis (34, 35). During this process, high glucose promotes glucose uptake through glucose transporter 1 (GLUT1) and reprograms glucose metabolism by regulating activity of HK2, PDK4, 6-phosphofructokinase isozyme 1 (PFK1), PKM2, and lactate dehydrogenase A (LDHA) in VSMCs (12) (Figure 2). Therefore, clarifying these metabolic changes could help identify new therapeutic targets for vascular calcification.

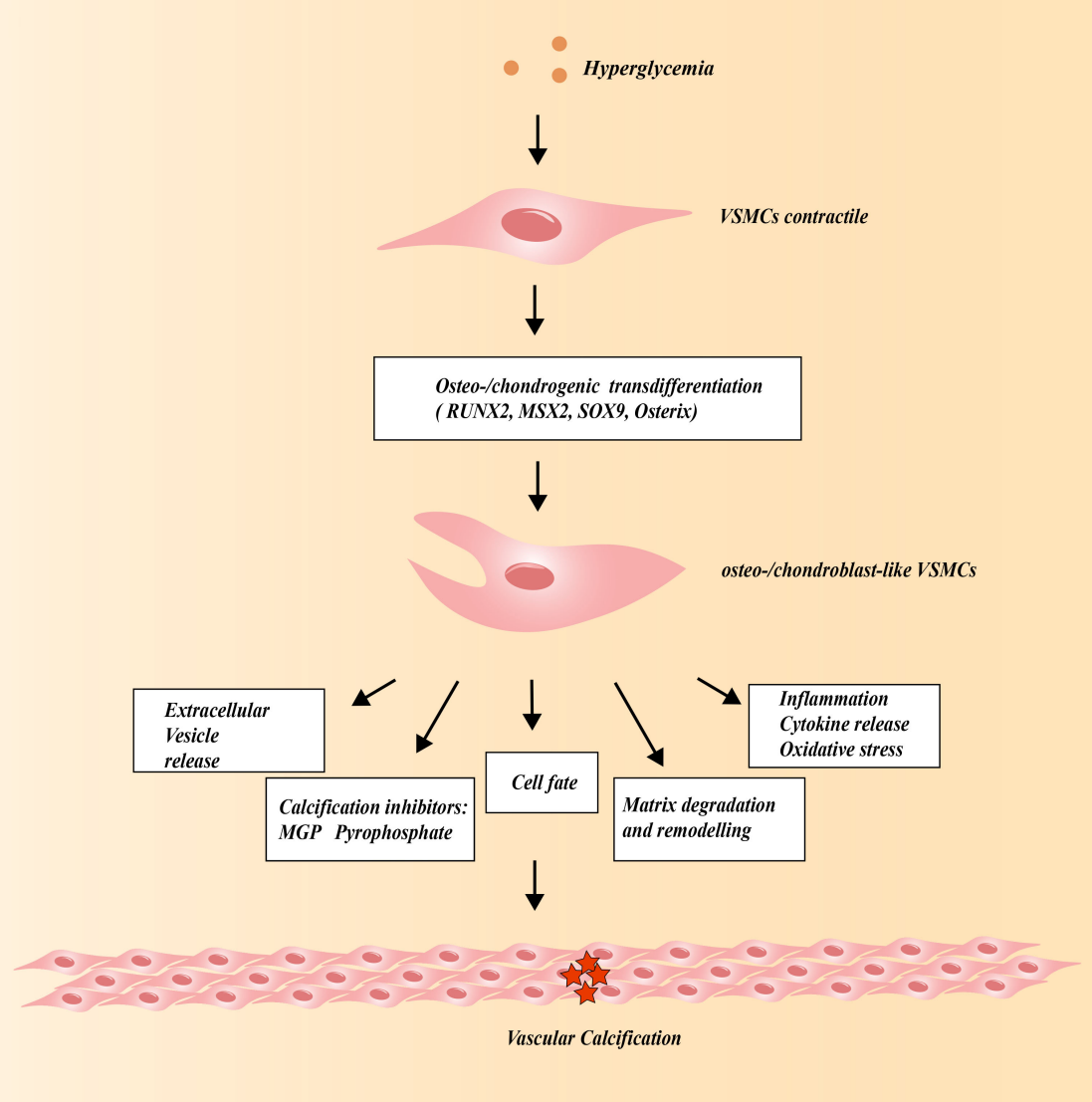

FIGURE 1
The role of VSMCs in Vascular calcification under the high glucose condition.

3.1 GLUT1: the gateway for glucose uptake in VSMCs

GLUT1 is the main isoform of the facilitative GLUT family and mediates glucose uptake in VSMCs (36). It is highly expressed in calcified VSMCs (37). In rodent human arterial smooth muscle cells (HASMCs) and aortic smooth muscle cell lines (A7r5), GLUT1 overexpression increased the intracellular glucose concentration by 44% and enhanced glycolytic flux and tricarboxylic acid cycle activity (TCA) (38–41). Hyperglycemia increase the GLUT1 expression (42). Downregulating GLUT can prevent excessive glucose influx, reducing intracellular protein glycation and free radical generation; both of these are harmful in the development of vascular disease in diabetes (43). High Mobility Group Box 2 (HMGB2) decreased GLUT1 expression and promoted GLUT4 translocation through PPAperoxisome proliferator-activated receptor-γ (PPAR-γ)/silent mating type information regulation 2 homolog 1(SIRT1) (44). Glycogen synthase kinase-3 (GSK-3), an enzyme that hinders the conversion of glucose to glycogen, can inhibit GLUT1 expression and glucose uptake through the tuberous sclerosis complex subunit 2 (TSC2)/mammalian target of rapamycin (mTOR) pathway (38). Ya-Rong Zhang et al. highlighted that intermedin alleviated diabetic vascular calcification by inhibiting GLUT1 through the activation of cyclic AMP (cAMP)/protein kinase A (PKA) signaling pathway (42) (Figure 3; Table 1). Therefore, GLUT1 serves as the first line of defense against VSMCs calcification induced by high glucose. Therefore, developing targets for inhibiting the regulatory expression of GLUT1 is of great clinical significance.

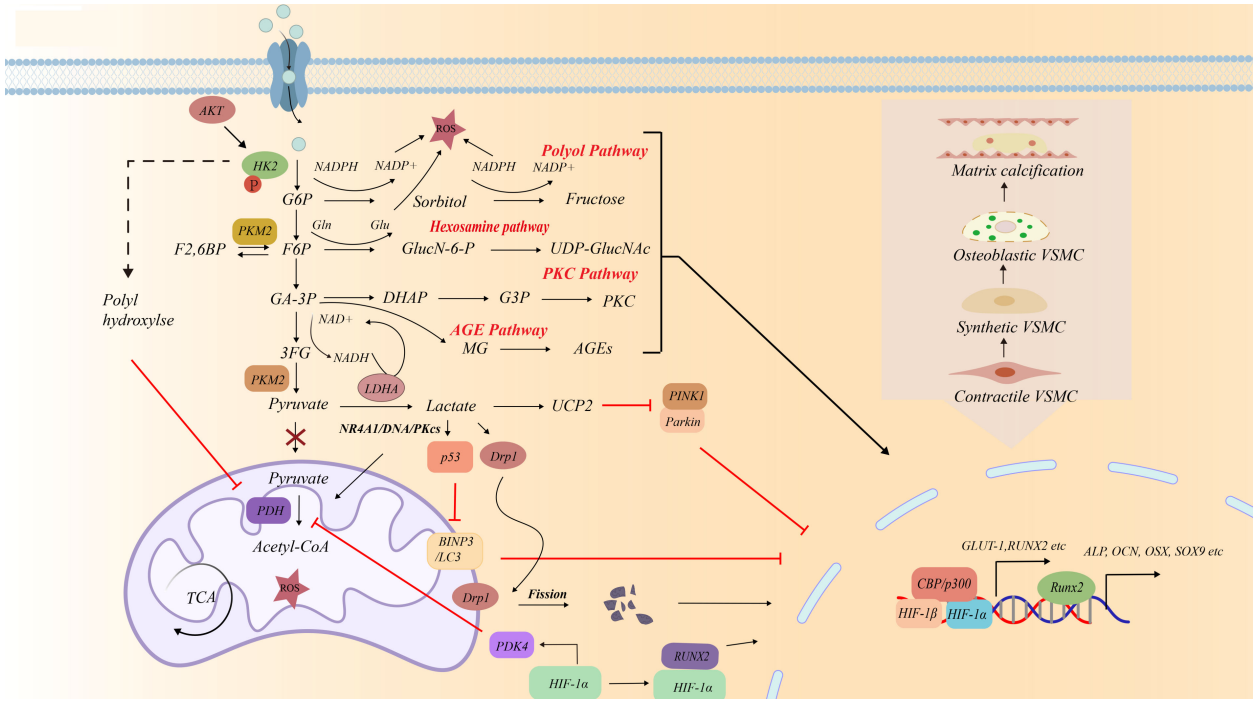

FIGURE 2
The contribution of unscheduled glycolysis to osteogenic differentiation of vascular smooth muscle cells.

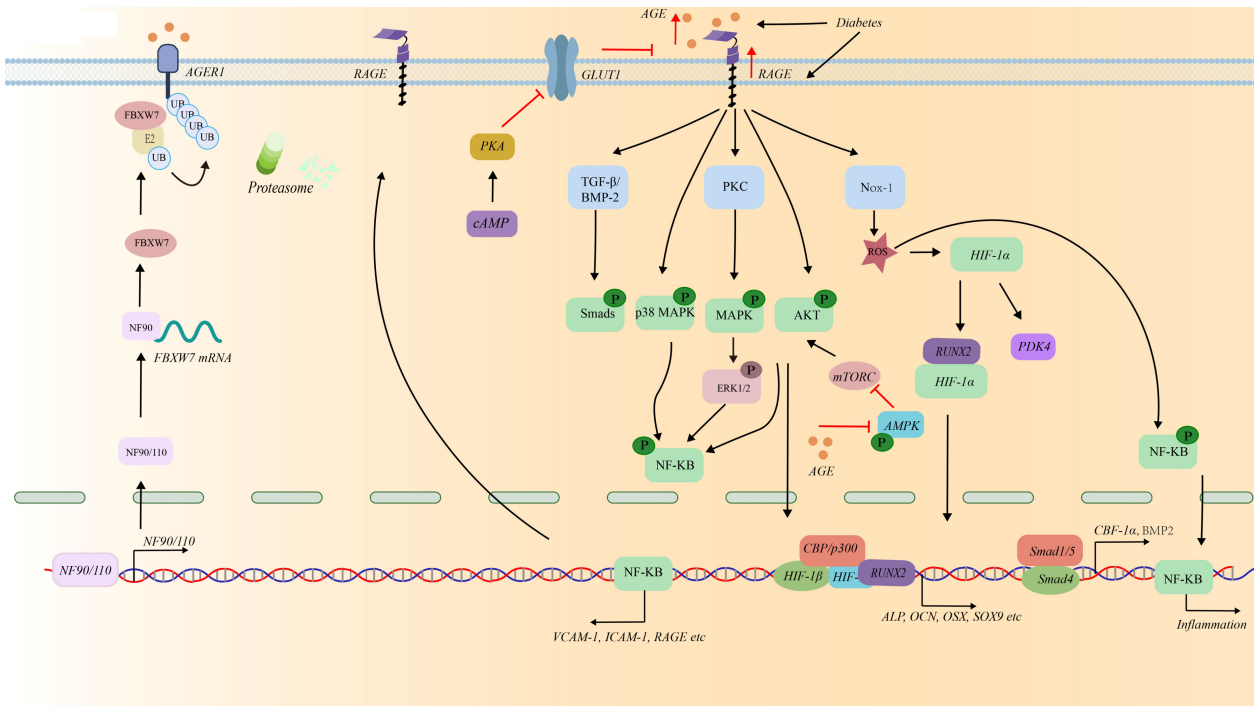

FIGURE 3
The role of AGEs/RAGE in mediating osteogenic differentiation of VSMCs under the high glucose condition.

TABLE 1 Glucose metabolic pathways involved in VSMCs osteogenic differentiation.

Metabolic Pathways	Key Molecules/ Enzymes	Biological Effect	Related Research Examples/Mechanisms
Glucose uptake	GLUT1	Increased glucose uptake intracellular protein glycation and free radical generation	1 HMGB2 decreased GLUT1 expression through PPAR-γ/SIRT1 (44). 2 GSK-3 can inhibit GLUT1 expression and glucose uptake throughTSC2/mTOR pathway (38). 3 Intermedin alleviated diabetic vascular calcification by inhibiting GLUT1 through the activation cAMP/PKA signaling pathway (42).
Pentose Phosphate Pathway (PPP)	HK2	ROS MMP hyperpolarization apoptosis suppression	1 PVT1 affects the glycolysis and phenotypic switch of VSMCs through HK2 (50). 2 Indirubin-3′-monoxime reduced HK2 expression and glycolysis in VSMCs induced by PDGF-BB (51).
	G6PD	Activation of NADPH oxidase Inflammation Apoptosis inhibition	1 Role of G6PD in tumor necrosis factor receptor-associated factor 6-induced SM22α ubiquitination and mitochondrial apoptosis inhibition through the voltage-dependent anion channel 1-Bcl-2 associated X protein pathway (54, 55). 2 Inhibiting Ca^{2+} uniporter or mitochondrial calcium uptake 1 overexpression on VSMCs from diabetic mice decreased activity of G6PD, and normalized cell proliferation (56).
Hexosamine Biosynthetic Pathway (HBP)	OGT, OGA	Upregulation of VCAM-1and RUNX2, Migration Autophagy inhibition	1 Polymerase delta interacting protein 2 deficiency enhanced OGT-mediated protein O-GlcNAcylation (63). 2 STIM1 deficiency-induced impairment of calcium homeostasis and ER stress enhances protein *O*-GlcNAcylation in VSMCs (71).
Advanced Glycation End Products (AGEs)	AGEs, RAGE	ROS Autophagy and apoptosis	1 Metformin inhibits upregulation of ALP and RUNX2 and downregulation of SM22α induced AGEs surplus (74, 80). 2 Intermedin exerts anti-calcification effects by inhibiting RAGEs via cAMP/PKA signaling pathway activation in diabetic vascular calcification (42). 3 USP10 alleviates CEL-induced vascular calcification and atherogenesis in diabetes mellitus by promoting AMPK activation (89). 4 The natural compound thonningianin A decreases expression of RUNX2, BMP2 and OPN via ATG7-dependent autophagy in HG-stimulated MASMCs (167).
Diacylglycerol-dependent PKC pathway activation	GADPH	Inducing intracellular Ca^{2+} Inflammation	1 Activation of PKC-? inducing by AGE-RAGEs activates TGF-?, NF-?B, and p38 MAPK, inducing VSMCs to switch their phenotype into osteoblast-like (9, 29, 79, 95–98).
Aerobic glycolysis	LDHA	Inducing fission of mitochondria mitophagy inhibition	1 Activation of κ-Opioid receptor impedes the calcification of VSMCs through decreasing lactate and PFKFB3 (116). 2 Prohibitin 2 deficiency facilitated PKM1/2 mRNA splicing and reversion from PKM1 to PKM2, and enhanced glycolysis in VSMCs (123). 3 GMRSP inhibits hnRNPA2B1-mediated alternative splicing PKM pre-mRNA, leading to reduced PKM2 production and glycolysis (124). 4 Deficiency of March2 lessened PKM2 dimer-to-tetramer conversion in VSMCs and promoted p53-driven apoptotic transcriptional response (125).

VSMCs, Vascular smooth muscle cells; GSK-3, Glycogen synthase kinase-3; TSC2/mTOR, tuberous sclerosis complex subunit 2/mammalian target of rapamycin; cAMP/PKA, activation of cyclic AMP/protein kinase A; PVT1, Plasmacytoma variant translocation 1; PDGF-BB, platelet-derived growth factor-BB; PKM, pyruvate kinase M; HK2, Hexokinase 2; GLUT 1, Glucose transporter 1; G6PD, Glucose-6-phosphate dehydrogenase; AGEs, Advanced glycation end products; RAGE, Receptor for AGEs; MMP, mitochondrial me mbrane potential; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; ROS, Reactive Oxygen Species; TCA, Tricarboxylic Acid Cycle; ATP, Adenosine Triphosphate; NADPH, Nicotinamide adenine dinucleotide phosphate; HIF-1α, Hypoxia-Inducible Factor-1α; PPAR, Peroxisome Proliferator-Activated Receptor; SIRT, Sirtuin; PI3K, Phosphatidylinositol 3-Kinase; AKT, Protein Kinase B; MAPK, Mitogen-activated protein kinase; hnRNP, heterogeneous nuclear ribonucleoprotein; March2, membrane-associated RING finger protein 2; PFKFB3, Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; GMRSP, Glucose metabolism regulatory protein; LDHA, Lactate dehydrogenase A; GADPH, Glyceraldehyde-3-Phosphate Dehydrogenase; PVTC1, Plasmacytoma variant translocation 1; STIM1, Stromal interaction molecule 1; SM22α, Smooth muscle 22 α; Atg7, Autophagy Related 7; CEL, Carboxyethyl lysine; OGT, β-N-acetylglucosaminyltransferase; OGA, β-N-acetylglucosaminidase; UPS10, Ubiquitin-Specific Protease 10; VCAM-1, vascular cell adhesion molecule-1; TGF-β, Transforming growth factor-β.

3.2 Upstream glycolysis overload and VSMCs osteogenic differentiation

In the upper glycolysis process, hyperglycemia disrupts glycolytic flux, causing the accumulation of intermediate metabolites such as dihydroxyacetone phosphate (DHAP), glyceraldehyde-3-phosphate (GA3P), glucose-6-phosphate (G6P), and pyruvate. 6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), AMP-activated protein kinase (AMPK) strictly regulates glycolytic flux. PFKFB3 - mediated glycolysis enhances the osteogenic trans-differentiation of VSMCs by modulating Forkhead box O3(FoxO3) expression and lactate generation (45). AMPK regulates glucose metabolism reprogramming and osteogenic differentiation of VSMCs by affecting pathways like PPP and HBP and increasing lactate production. High risk human carotid atherosclerotic plaques,

characterized as symptomatic, vulnerable, and inflamed, were reported to exhibit enhanced glycolysis and PPP pathways and elevated amino acid utilization (45). However, little is known about the mechanisms by how VSMCs regulate this complex network. The following part mainly introduces the main metabolic links of glucose metabolism and the influence of their interactions on the calcification process of vascular smooth muscle cells.

3.2.1 PPP and oxidative stress

In rat pulmonary artery smooth muscle cells (PASMCs) cultured in high glucose, the activation of the pentose phosphate pathway (PPP) affects upper glycolytic metabolites (46). Over-activation of the PPP is a key mechanism for the vascular damage related to hyperglycemia (47).

HK2, a key enzyme that phosphorylates glucose into glucose-6-phosphate, has become the predominant regulator of glycolysis in VSMCs. When high glucose levels exceed the catalytic ability of hexokinase, the surplus glucose enters the polyol pathway. These processes lead to the accumulation of reactive oxygen species (ROS), increasing oxidative stress (19, 48) (Figure 2). Over-expression of HK2 in human umbilical vein smooth muscle cells results in the mitochondrial membrane potential hyperpolarization and apoptosis suppression (49). Mengying Wu et al. showed that plasmacytoma variant translocation 1 (PVT1) affects the glycolysis and phenotypic switch of VSMCs through HK2 (50). Elke H. Heiss et al. found that indirubin-3′-monoxime reduced HK2 expression and glycolysis in VSMCs induced by platelet-derived growth factor (PDGF) (Table 1). Activation of signal transducer and activator of transcription (STAT) 3 could be identified as crucial event in upregulation of HK2 and glycolytic activity in PDGF-stimulated VSMCs (51). Xiao-Fei Gao et al. found m^6A modification of profilin-1 interacted with the phosphorylation of ANXA2 (annexin A2) by recruiting SRC proto-oncogene, nonreceptor tyrosine kinase (Src), promoting the phosphorylation of signal transducer and activator of transcription 3 (STAT3) in VSMCs (52). Yanlin Huang et al. demonstrates that ANXA2 promotes osteogenic differentiation and inhibits cellular senescence of periodontal ligament cells (PDLCs) in high glucose conditions (53). The function of ANXA2/Src/STAT pathway on VSMCs calcification is need further study. Suppressing glycolytic enzymes such as phosphofructokinase (PFK)1 and PKM2 can redirect glycolysis towards the PPP (46). Glucose-6-phosphate dehydrogenase (G6PD) is PPP's rate-limiting enzyme. Inhibition of G6PD in vascular cells not only prevents the over-activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase but also reduces subsequent inflammation (47). Recent studies have highlighted the role of G6PD in tumor necrosis factor receptor-associated factor 6-induced SM22α ubiquitination and mitochondrial apoptosis inhibition through the voltage-dependent anion channel 1-Bcl-2 associated X protein (Bax) pathway (54, 55). Inhibiting Ca^{2+} uniporter or mitochondrial calcium uptake 1 overexpression on VSMCs from diabetic mice decreased activity of G6PD, and normalized cell proliferation (56; Table 1). Tumor protein 53 (p53) plays a role in inhibiting cancer cell proliferation and promoting apoptosis by inhibiting G6PD (57, 58). Additionally, p53 can regulate cell apoptosis by binding to VDAC1 (59, 60). However, it is still unclear whether p53 is involved in G6PD-VDAC1 mediated VSMC apoptosis.

Under high glucose conditions, the excessive activation of PPP is associated with the dysregulated regulation of HK2 and G6PD. Inhibition of 6-phosphofructokinase-1(PFK1) and PKM2 can redirect glycolysis to the PPP. Future studies could delve into the specific molecular mechanisms of ANXA2 and G6PD in glucose metabolism remodeling and calcification of VSMCs, as well as the synergistic regulatory network among key enzymes of different glucose metabolic pathways (Figure 2).

3.2.2 HBP and protein O-GlcNAcylation

The HBP can metabolize glucose into the active O-GlcNAcylation sugar donor UDP-β-D-N-acetylglucosamine. This pathway is dynamically regulated by OGT and OGA (61) (Figure 2). In hyperglycemic $ApoE^{-/-}$ mice fed a Western diet, deletion of smooth muscle-specific OGT prevents atherosclerosis development (62). F., et al. found polymerase delta interacting protein 2 (Poldip2) deficiency enhanced OGT-mediated protein O-GlcNAcylation, which inversely promoted myocardin, MRTFA (myocardin-related transcription factor A), and SRF (serum response factor) expressions (63; Table 1). These decreased the myocardin-dependent VSMCs marker gene expression and increased RUNX2-dependent osteogenic gene expression (64–67).

Under high glucose conditions, O-GlcNAcylation of nuclear factor-κB (NF-κB) in rat VSMCs induces upregulation of vascular cell adhesion molecule-1(VCAM-1) (68). Meanwhile, Barnes et al. demonstrated that higher O-GlcNAcylation of specificity protein 1 (sp1) in PASMCs promotes cell migration (69). Jack M Heath et al. demonstrated O-GlcNAcylation of protein kinase B (AKT) at two new sites, T430 and T479, promotes AKT phosphorylation, and then promotes RUNX2 trans-activity and VSMCs calcification (70). Besides, stromal interaction molecule 1 (STIM1) deficiency-induced impairment of calcium homeostasis and ER stress enhances protein *O*-GlcNAcylation in VSMC, which promotes VSMCs osteogenic differentiation and calcification in diabetes (71; Table 1). In other hand, O-GlcNAc signaling enhanced the osteogenic conversion of VSMCs through regulation of canonical Wnt/β-catenin pathway. Indeed, O-GlcNAcylation of β-catenin further increased it transcriptional activity in VSMCs (72). Besides, OGT enhances O- GlcNAcylation of kelch like ECH associated protein 1(KEAP1), leading to nuclear factor erythroid 2-related factor 2 (NRF2) degradation and subsequently inhibiting autophagy in VSMCs (73).

O-GlcNAcylation of cellular proteins such as Sp1, NF-κB, and Runx2 regulates VSMCs calcification, inflammation, migration, and the development of atherosclerosis. Future studies can further explore the specific targets and functions of O-GlcNAcylation modification, such as RUNX2.

3.2.3 Increased formation of AGEs

Notably, type II diabetes patients have much higher AGEs concentrations than non-diabetics (29–31). Accumulated studies have shown AGEs surplus promote osteogenic phenotype transformation of VSMCs by increasing the levels of ALP and

RUNX2 and decreasing the expression of SM22α (74–79). This effect can be inhibited by metformin (80; Table 1). Poetsch, F., et al. reported that AGEs increased the expression of serum and glucocorticoid-inducible kinase 1 (SGK1) and induced the osteogenic trans-differentiation of VSMCs under high glucose conditions in a NF-κB-dependent manner (81). Besides, AGEs upregulate the expression of PDK4, which inhibits the conversion of pyruvate to acetyl-CoA, ultimately reducing Kreb's cycle flux and exacerbating calcium deposition during VSMCs calcification (7) (Figures 2, 3). This effect further promotes the production of AGEs, thereby further expanding the role of AGEs in promoting VSMCs calcification.

AGEs bind to corresponding receptors, such as the receptor for AGEs (RAGE), AGE receptor 1(AGE - R1), AGE - R2, and AGE - R3, to trigger intracellular signaling cascades or exert their effects (82). RAGEs have been reported to exist in unstable plaques with microcalcifications by co-localizing with inflammatory cells and VSMCs undergoing osteochondrogenic differentiation (83). AGEs/RAGEs initiate the activation of PKC-ζ, which then activates the downstream signaling pathways mediated by p38 mitogen-activated protein kinase (p38 MAPK) and NF-κB (83, 84). (Figure 3). Intermedin exerts anti-calcification effects by inhibiting RAGEs via cAMP/PKA signaling pathway activation in diabetic vascular calcification (42; Table 1). AGEs/RAGE induce autophagy in HASMCs via the mechanistic target of rapamycin (mTOR) signaling pathway and trigger apoptosis, contributing to calcification (85). MTMR7 suppresses this effect (86). Recent study revealed that AGEs increased the activity of nuclear factor 90 (NF90), thereby promoting AGER1 degradation and ubiquitination via WD repeat domain-containing 7 and E3 ubiquitin ligase F-box's mRNA stabilization in VSMCs induced by high glucose (87). (Figure 3) Therefore, AGEs receptors play important role in VSMCs calcification, death and inflammation. AGER and RAGEs may be targets to protect against VC.

Currently, carboxyethyl lysine (CEL), pentosidine, carboxymethyl-lysine (CML), and more than twenty other kinds of AGEs have been identified (88). CML was significantly increased in calcified ateries from diabetic atherosclerosis ApoE$^{-/-}$ mice fed with high-fat diets (89). The study found that CML promoted vascular calcification through different pathways in diabetes, including p38 MAPK pathway and the nuclear factor of activated T-cells 1 (NFATc1) (90, 91). In NFATc1pathway, Protein tyrosine kinase 2 (FAK) and SIRT3 affected the nuclear translocation of NFATc1 by regulating the acetylation-phosphorylation crosstalk. Besides, CML mediates vascular calcification in diabetic plaques by impaired osteoclastic bone resorption through NFATc1-N-acetylglucosamine-1-phosphate transferase (GNPTAB) (92). Ubiquitin-Specific Protease 10 (USP10) alleviates CEL-induced vascular calcification and atherogenesis in diabetes mellitus by promoting AMPK activation (89; Table 1). Furthermore, CML increased the expression of PDK4 by increasing ROS (35).

3.2.4 Diacylglycerol-dependent PKC pathway activation

Hyperglycemia induces accumulation of upper glycolytic intermediate glyceraldehyde-3-phosphate and increases diacylglycerol (DAG) production, which activates the PKC pathway, including PKCβ, PKCδ, and PKCα (93). G6PD can be activated by PKC to induce intracellular free Ca^{2+} to enhance the contraction of

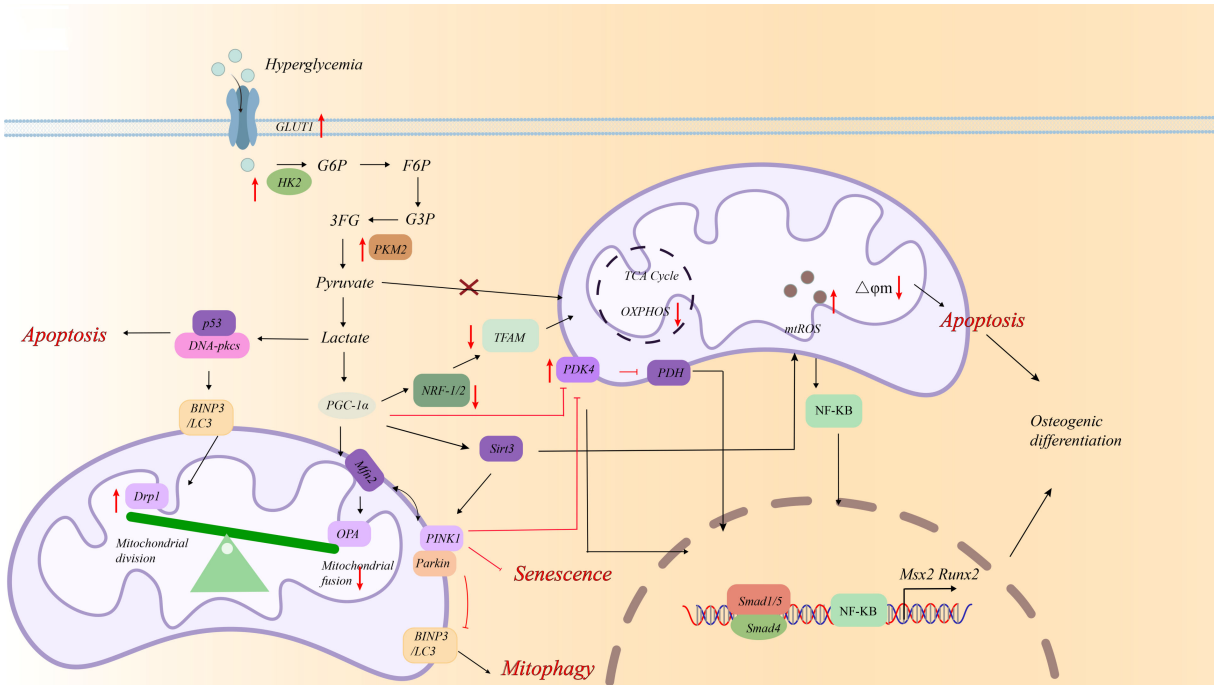

FIGURE 4
The fate and potential mechanism of VSMCs under the high glucose condition.

VSMCs (94). Additionally, activation of PKC-ζ inducing by AGE-RAGEs further activates transforming grow factor-β (TGF-β), NF-κB, and p38 MAPK, inducing VSMCs to switch their phenotype into osteoblast-like (9, 29, 79, 95–98) (Figure 3; Table 1).

3.3 Involvement of lower glycolysis overload in DR

Once pyruvate is generated, it can be converted to CO_2 and acetyl-CoA, which enter the tricarboxylic apvt1cid cycle (TCA). Another fate of pyruvate is to be converted into lactate catalyzed by LDHA (99). The pyruvate dehydrogenase enzymatic complex (PDH) is an important link between glycolysis and the TCA (100). Reprogramming of glucose metabolism from mitochondrial oxidative phosphorylation (OXPHOS) to aerobic glycolysis has been observed during VSMCs phenotype switching (45). As regulators of mitochondrial glucose metabolism, PDKs inhibit the activity of PDH, slowing down the TCA and mediating the glucose metabolic switch of glucose metabolism from OXPHOS (100, 101). It has been made sure that PDK4 regulates VSMCs' metabolic reprogramming towards a higher glycolysis rate, promoting lactic acid generation in the cytosol. This triggers mitochondrial dysfunction, calcium deposition and apoptosis and autophagy, inducing the osteogenic differentiation of VSMCs via direct SMAD1/5/8 phosphorylation and enhancing CBFα1 and BMP2 signaling (7, 35, 48, 102, 103).

3.3.1 LDHA

LDHA is key regulatory enzyme that catalyzes the production of lactate (100). Previous studies have shown that knockout of LDHA suppresses the survival, proliferation, migration, and invasive abilities of VSMCs (104, 105). Further investigations revealed that LDHA expression is regulated by forkhead box M1(FOXM1) via binding to the LDHA promoter (106). Recent study found that YTH N6-Methyladenosine RNA Binding Protein F1 (YTHDF1) recognized vir like M6A methyltransferase associated (KIAA1429)-methylated FOXM1 mRNA and raised FOXM1 stability. This promotes the levels of glycolysis-enhancing genes (GLUT1 and LDHA) and lactate production in multiple myeloma. There is no report on whether GLUT1/LDHA regulated by stabilizing FOXM1 mRNA is involved in the calcification of smooth muscle cells.

Upregulation of LDHA inducing surplus of lactate indue fission of mitochondria associated with dynamin-related protein 1 (Drp1) and impedes phosphatase and tensin homolog (PTEN)-induced mitophagy. PTEN-induced mitophagy mediate through putative kinase 1/parkin via the poly (ADP-ribose) polymerase 1 (PARP1)/DNA polymerase gamma (POLG)/uncoupling protein 2(UCP2) axis. Therefore, knockdown of UCP2 impedes fission of mitochondria as mediated by Drp1, while also partially restoring mitophagy via PTEN-induced putative kinase 1(PINK1)/Parkin in VSMC calcification (107) (Figure 4). Recent study found that PARP-1 is subjected to NEDD8 conjugation, leading to an increase in PARP-1 activity during VC. During this process, PARP-1 NEDDylation is mediated by the E3 ligase CBL proto-oncogene B (CBL-b) and is reversed by NEDD8-specific protease 1 (NEDP-1) during VC (108). Besides, lactate also accelerates VSMCs calcification through suppression of Bcl-2–19 kDa interacting protein (BNIP3)-mediated mitophagy (109). High glucose triggers lactate/G protein-coupled receptor 81(GPR81) and inhibits peroxisome proliferator-activated receptor-γ (PPAR-γ)/SIRT1 pathway, promoting vascular remodeling. HMGB2 promotes HASMC proliferation and vascular remodeling by regulating glucose metabolism through the PPAR-γ/SIRT1/PGC-1α pathway (44, 110–112). As downstream targets of the above two pathways, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) overexpression can reduce ROS-mediated VSMC migration. PGC-1α/NRF2/STAT3 is involved in decreasing VC by increasing superoxide dismutase 2 (SOD2) (110–112). PPAR-γ agonists alleviated periostin-promoted VSMCs calcification and corrected abnormal glycolysis and unbalanced mitochondrial homeostasis (113). 12,13-diHOME suppressed the up-regulation of carnitine O-palmitoyltransferase 1 (CPT1A) and CPT1A-induced succinylation of HMGB1. The succinylation of HMGB1 at the K90 promoted the protein stability and induced the enrichment of HMGB1 in cytoplasm, which induced the calcification in VSMCs (114). PFKFB3 is associated with diabetic atherosclerosis and vascular remodeling through increasing lactic acid and LDHA levels (115). Activation of κ-Opioid receptor impedes the calcification of VSMCs through decreasing lactate and PFKFB3, thus becoming a possible medicinal approach and target for vascular calcification treatment (116; Table 1). Besides, lactate induces lactylation at the K18 site of the H3 histone protein to up-regulate chitinase 3 like 1 (CHI3L1). CHI3L1 forms a polymer complex with interleukin 13 receptor subunit alpha 2 and interleukin 13 (IL-13), activates the janus kinase 1(JAK1)/STAT3/RUNX2 signaling pathway. These findings indicate that regulating lactylation and targeting inhibition of CHI3L1 and IL-13 represent a new therapeutic strategy to reduce arterial calcification in diabetes (117).

Therefore, as an important regulatory element in lactate metabolism regulation, PGC-1α serves as a hub for cell death regulation and is involved in apoptosis, senescence, and autophagy caused by mitochondrial dysfunction (Figure 4).

3.3.2 PKM2

The expression of PKM2 is greater in the VSMCs of atherosclerotic plaques than in those of in normal arteries (118). Tetrameric PKM2 is known to facilitate lactate production by regulating aerobic glycolysis, facilitating VSMC phenotypic switching (119). During this process, elevating crotonylation of PKM2 at K305 promotes the PKM2 dimeric form (120). Interestingly, nuclear dimeric PKM2 is implicated in the activation of the hypoxia-inducible factor-1 alpha (HIF-1α), STAT3, and β-catenin signaling pathways (121, 122). Prohibitin 2, through its C-terminus, directly interacts with heterogeneous nuclear ribonucleoprotein A1, a key modulator of PKM1/2 mRNA splicing that promotes PKM2 expression and glycolysis. Prohibitin 2 deficiency facilitated PKM1/2 mRNA splicing and reversion from PKM1 to PKM2, and enhanced glycolysis in VSMCs (123; Table 1). In PDGF-BB-induced synthetic VSMCs, PKM2 crotonylation (at K305) was upregulated and promotes its nuclear translocation, thereby facilitating

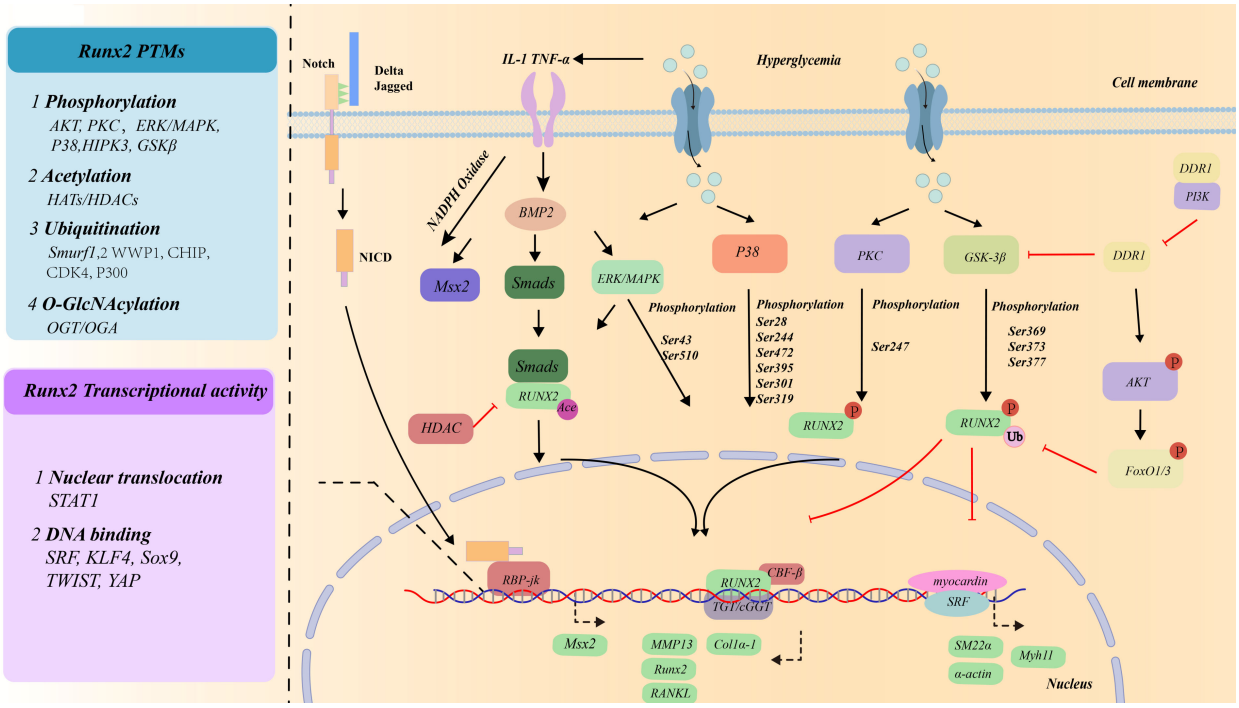

FIGURE 5
Transcriptional factors/co-factors mediating osteogenic differentiation of VSMCs under the high glucose condition.

the expression of GLUT1 and LDHA (120). Therefore, PKM2 crotonylation (at K305) may participate VSMCs calcification induced by high glucose. However, conclusive evidence on the role of PKM2 in VSMCs calcification induced by high glucose is lacking. Glucose metabolism regulatory protein (GMRSP) inhibits heterogeneous nuclear ribonucleoprotein (hnRNP) A2B1-mediated alternative splicing of pyruvate kinase M (PKM) pre-mRNA, leading to reduced PKM2 production and glycolysis. This reprogramming preserves the contractile phenotype of VSMCs and prevents their transition to a proliferative state (124; Table 1). Besides, membrane-associated RING finger protein 2 (March2) interacted with PKM2 to promote K33-linked polyubiquitination. Deficiency of March2 lessened PKM2 dimer-to-tetramer conversion in aortic aneurysm/dissection (AAD) and overtly exacerbated AAD-induced histone H3K18 lactylation in VSMCs by fostering glucose metabolism reprogramming, thereby promoting p53-driven apoptotic transcriptional response (Table 1). TEPP-46 (tetraethyl pyrophosphate), a PKM2-specific activator, pronouncedly alleviated March2 deficiency-deteriorated AAD pathology (125). Therefore, PKM2 dimer-to-tetramer conversion is one of important treatment targets.

4 Signaling pathways orchestrating VSMC osteogenic differentiation

The etiology of VC involves VSMCs' osteogenic differentiation (22). The exposure of VSMCs to high glucose activates the WNT signaling pathway and BMPs via upregulation of transcription factors RUNX2 and MSX2 (126). Previous studies reveal that upregulation of MSX2 induced by high glucose increases expression of Wnt3a and Wnt7a and suppresses Dickkopf-1 (Dkk1) gene expression, which subsequently upregulates ALP and pituitary-specific positive transcription factor 1 (PIT1) gene expression. These promote osteogenic trans-differentiation and calcification of VSMCs (127–130). Based on existing evidence, elevated levels of glucose participate in regulating phosphatidylinositol 3-kinase (PI3K), AMPK signaling pathway, cell death, oxidative stress and inflammation, microRNAs and extracellular vesicles, which enable chondrogenic/osteogenic phenotypic transition of VSMCs.

4.1 Vascular inflammation and oxidative stress

Streptozotocin-induced diabetes increases ROS and the adventitial inflammatory response (Tumor Necrosis Factor-α(TNF-α), interleukin IL-1β, IL-6, and IL-18), playing crucial roles in osteochondral differentiation of VSMCs (131–135). This increase MSX2, BMP2, Wnt7a, and Wnt3a expressions in the aorta and accelerates calcification of the aorta (136). PGC-1α/NRF2/STAT3 is involved in decreasing VC by increasing superoxide dismutase 2 (SOD2) (110–112). In contrast, in a diabetic mouse model, vascular parathyroid hormone receptor (PTH1R) activation can also partly restrict calcification via oxidant stress reduction (32). High glucose (HG)-induced VSMC inflammation increases the level of AKT/FoxO1/3, which leads the upregulation of RUNX2 via inhibiting RUNX2 ubiquitination and subsequent degradation (65) (Figure 5). Oxidative stress and inflammation participate VSMCs calcification in dependent NF-kB transcriptional activation in VSMCs cultured in

high glucose (68, 81, 137, 138). Accumulated studies suggest that oxidative stress and inflammatory cytokines activate monocyte chemotactic protein-1(MCP-1)/chemokine (C-C motif) receptor 2 (CCR2) and receptor of nuclear factor-κB ligand (RANKL) through RUNX2 (65, 139–143). Recent study found the leucine-rich repeat-containing G-protein-coupled receptor 4 (LGR4), a novel receptor for RANKL, also regulates VSMCs calcification (144). Mice deficient in a decoy receptor for RANKL, osteoprotegerin (OPG), develop extensive vascular calcification which is reduced by OPG treatment (145). Palmdelphin (PALMD) promoted the adjustment of glycolysis and NF-κB-mediated inflammation (137, 138). Zinc elevated TNFα-induced protein 3 (TNFAIP3) expression that was dependent on NF-κB transcriptional activation in VSMCs cultured in high glucose. This change was inhibited by zinc-sensing receptor G protein-coupled receptor 39 (GPR39) silencing (146). Empagliflozin attenuated HG-induced osteogenic differentiation and calcium deposition by increasing Bhlhe40/NLRP3 in MOVASs (147). During this process, the stability and the nuclear translocation of Bhlhe40 protein is regulated by Long noncoding RNA SNHG1 (148).

4.2 AMPK

AMPK is a sophisticated regulator of diabetic atherosclerosis, especially in VSMCs (149). Under high glucose condition, AMPK strictly regulates glycolytic flux via glucose uptake and mitochondrial dysfunction in VSMCs (150). For example, intermedin inhibited the expression of RAGE and GLUT1 via the cAMP/PKA signaling pathway in diabetic VC (42). Mitochondrial fission and oxidative stress enhancing VC in diabetes are blocked by the AMPK activator metformin (151–153). The glucagon-like peptide-1 receptor (GLP-1R) agonist exendin-4 promotes mitophagy by activating AMPK, inhibiting the osteogenic phenotype switching of VSMCs (5). Based on the aforementioned discussions, AMPK signaling induction is an ideal strategy in improving glucose metabolism and ameliorating diabetic complications.

4.3 AKT signaling pathway

HG activates of PI3K/AKT/Glycogen Synthase Kinase 3 Beta (GSK3β) (154). This process is associated with discoidin domain receptor 1(DDR1). Restoring DDR1 expression in DDR1-null VSMCs rescues Akt activation (155). In contrast, DDR1-deficient VSMCs increase GSK-3β activation and impair microtubule organization, which may account for reduced RUNX2 activity and nuclear localization (155) (Figure 5). In diabetic mice, AKT activation via O-GlcNAcylation enables vascular calcification induced by hyperglycemia (70, 156). AKT O-GlcNAcylation at T479 and T430 has been identified as a potential regulator of diabetes-induced calcification (70). As the AKT target, FoxO1/3 promotes RUNX2 ubiquitination and subsequent degradation, inhibits VSMCs calcification (65) (Figure 5). Therefore, SMC-specific tensin homologue (PTEN) (a primary negative AKT regulator)/FOXO promotes RUNX2 upregulation and VSMCs calcification (157). Sal B exhibits substantial anti-inflammatory effects by modulating the miR-486a-5p/FOXO1 axis under HG conditions in VSMCs (158). Besides, GLP-1R mediates VSMCs calcification in diabetes through inhibiting ERK1/2 and PI3K/Akt signaling pathways (159).

4.4 Cell fate

High glucose triggers autophagy, apoptosis, defect mitophagy and senescence. This finding underscores the pivotal role of metabolic disturbances in vascular pathology (160). High glucose triggers autophagy in VSMCs through two distinct signaling pathways: HIF-1α/PDK4 axis and the cyclic guanosine monophosphate (cGMP)-protein kinase G (PKG) pathway (161, 162) (Figure 4). These partly contribute to AGEs accumulation (163, 164). Notably, Hu-Qiang He et al. confirmed that impaired autophagy effectively inhibited AGE-induced calcification in HASMCs (85). Xu, Z.J., et al. showed autophagic dysregulation is mechanistically also governed by the Notch receptor 3 (NOTCH3)/RAN binding protein 1(RANBP1) axis in high glucose-stimulated VSMCs (165). Dickkopf1 (Dkk1) slowed vascular calcification by promoting the degradation of PLD1 via the regulating autophagosome formation and maturation (166). The natural compound thonningianin A (TA) decreases expression of RUNX2, BMP2 and OPN via autophagy related 7 (ATG7)-dependent autophagy in HG-stimulated MASMCs (167; Table 1). AGEs also facilitate apoptosis to release more matrix vesicles and establish a calcium–phosphorus deposition microenvironment (168). The enhanced expression of HK2 in HASMCs results in the hyperpolarization of mitochondrial membrane potential and the suppression of apoptosis (49). PKM2 dimer-to-tetramer conversion foster glucose metabolism reprogramming and promote p53-driven apoptotic transcriptional response (125).

High glucose promotes surplus of lactate. Accumulated studies confirmed that lactate paly a core role in regulated cell fate in diabetes. In one hand, lactate accelerates Drp1-regulated fission of the mitochondria. On the other hand, lactate inhibits mitophagy via BNIP3 and PTEN-PINK1/Parkin. All promote the osteoblastic phenotype transition of VSMCs and calcium deposition (151). PARP1 knockdown inhibited Drp1-mediated mitochondrial fission and partially restored PINK1/Parkin-mediated mitophagy. Further study found lactate promote PARP1 expression and nuclear transfer and then activate POLG/UCP2 pathway, inhibiting mitochondrial DNA synthesis (107). Metformin reduces the advancement of diabetes-induced atherosclerosis by blocking Drp1-mediated mitochondrial fission (152) (Figure 4). The glucagon-like peptide-1 receptor (GLP-1R) agonist exendin 4 (EX4) inhibited osteogenic differentiation of HG/β-GP-induced VSMCs through promoting mitophagy by activating the AMPK signaling pathway (5).

VSMCs isolated from diabetic patients show elevated DNA damage and senescence. PGC-1α plays a causative role in the pathogenesis of senescence (169). Hyperglycaemic conditions induced DNA damage and enhanced senescence in VSMCs *in vitro*. CML caused these changes via stimulator of interferon

response cyclic guanosine monophosphate - adenosine monophosphate (cGAMP) interactor 1 activation (170). DNA damage-induced calcification is accelerated within a diabetic environment and can be attenuated *in vitro* by SIRT1/ATM activation (171). DNA damage and senescence promote vascular calcification through SIRT1/PGC-1α pathway in VSMCs (44). PGC-1α and O- GlcNAcylation of KEAP1 lead to NRF2 degradation, thereby inhibiting the negative regulatory effect of NRF2 on the stability of STING mRNA and ultimately promoting STING expression (110–112, 172). Besides, Hyperglycemia stimulates vascular endothelial cells to upregulate cyclin-dependent kinase inhibitor 1A (p21) and p53, thereby exacerbating VSMC senescence and calcification (173).

4.5 miRNAs that regulates VSMC osteogenic differentiation

MicroRNAs (miRNAs) are small non-coding RNAs approximately 22 nucleotides in length. These molecules bind to complementary seed sequences located within the 3' untranslated region (3'UTR) of target messenger RNAs (mRNAs). MicroRNAs have emerged as crucial post-transcriptional regulators in the process of VSMCs re-differentiation from contractile to osteoblast-like phenotype in diabetics (174).

miRNAs effectively silence gene expression, such as RUNX2, MSX2. Overexpression of miR-34a activates NF-κB, subsequently increasing the expression of RUNX2 and osteocalcin (175–177). Meanwhile, microRNA-126-3p impedes the osteogenic trans-differentiation of VSMCs by post-transcriptionally interfering with BMP2 gene expression (178). High glucose levels were shown to induce the upregulation of miR-32-5p by activating CCAAT/enhancer binding protein beta (CEBPB). Overexpression of GATA6 antagonized the effects of miR-32-5p on vascular calcification (179). By modulating the translation efficiency or stability of their target mRNAs, miRNAs are involved in key functions including cell growth, proliferation, differentiation, metabolic regulation, immune responses, and the regulation of cell death pathways (180). In high glucose conditions, the expression of miR142-3p (181), miR21-5p (182), and miR19a (183) are promoted. In contrast, miR24 (184) and miR9 (185) expression is inhibited. These miRNAs participate in regulating proliferation and migration of VSMCs. For example, miR-24 overexpression can mitigate proliferation of VSMCs in diabetic

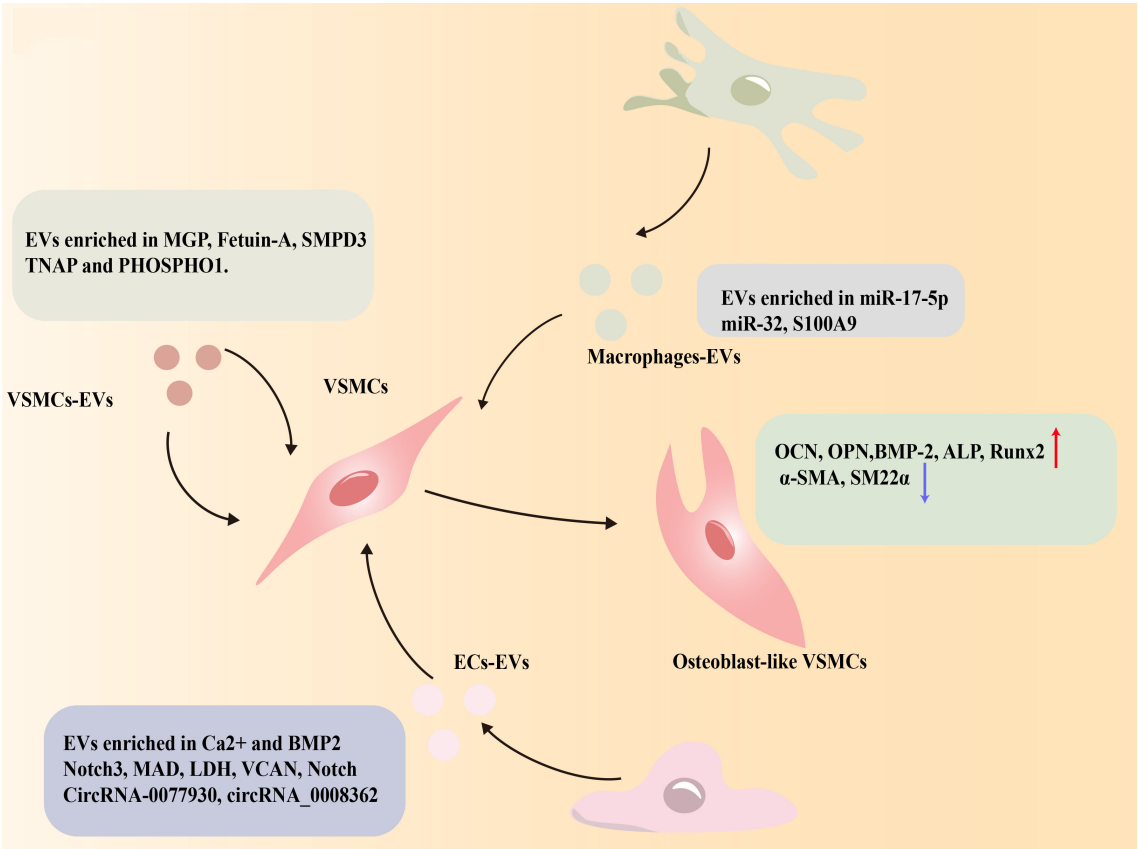

FIGURE 6
Potential mechanism of EVs regulating osteogenic differentiation of VSMCs under the high glucose condition.

rats through the Wnt4/Dishevelled-1(Dvl-1)/β-catenin signaling pathway (186). Decreasing miR125a expression promotes VSMCs migration and proliferation by upregulating 3-hydroxy-3-methylglutaryl coenzyme A reductase (187). Additionally, miR210 inhibits the carbohydrate-responsive element-binding protein (ChREBP)/HIF-1α signaling pathway, regulating glycolysis and apoptosis (188). The binding of RNA-ES3 to Bhlhe40 suppresses the expression of miR-6776-5p, miR-95-5p, miR-4747-5p, and miR-3620-5p, leading to VSMCs senescence and calcification (189). In contrast, MiR-15a/15b/16 specifically target the 3'UTR of nuclear factor of activated T cells (**3**NFATc3) mRNA, and downregulate OCN expression. Therefore, MiR-15a/15b/16 inhibits human VSMCs osteogenic trans-differentiation (162).

Matrix vesicles and circulating miRNAs also play an important role in VSMCs calcification. A deficiency in Hsa_circRNA_0008028 exacerbates high glucose-induced calcification, autophagy, and proliferation in VSMCs by upregulating miR-182-5p. During this process, miR-182-5p targets tribbles pseudokinase 3 (TRIB3). TRIB3 plays a critical role in the induction and maintenance of contractile phenotype in VSMCs (180). Similarly, extracellular vesicles (EVs) carrying circ_0008362 elevated in diabetic patients. It increases the expression of RUNX2 through miR-1251-5p in VSMCs (190). Additionally, macrophage-derived miR-32 inhibits autophagy in type 2 diabetic mice's arterial calcification (162). And MAEC-derived exosomal circHIPK3 increases high glucose-induced VSMCs proliferation via the miR-106a-5p/Foxo1/vascular cell adhesion molecule 1(VCAM1) pathway (190).

4.6 EVs

Mineral homeostasis disruption under high glucose conditions is closely associated with the dysregulation of EVs, including exosomes and matrix vesicles (MVs) (191). Emerging evidence highlights the critical role of EVs in mediating vascular calcification exacerbated by hyperglycemia (192). Therefore, EVs may be potential therapeutic targets in diabetic vascular complications.

4.6.1 EVs of VSMCs: high glucose-induced pro-calcific transformation

Extracellular vesicles coming from VSMCs contain calcification-promoting protein tissue-nonspecific alkaline phosphatase (TNAP) (193) and sortilin (194).The sortilin 1 (SORT1) and neutral sphingomyelinase 2 (nSMase2, also called sphingomyelin phosphodiesterase 3; SMPD3) are crucial enzymes in the generation of EVs and cargo sorting (195). Treatment with anti-sortilin antibodies may considerably lessen EV-induced VC (196). Inhibiting nSMase2 pharmacologically decreases VSMCs EVs secretion and VSMC-driven calcification (197, 198). High quantities of Nε-carboxymethyl-lysine increased release of EVs coming from VSMCs and recruitment of sortilin to EVs (196). Additionally, galectin-3 overexpression in macrophages, triggered by high glucose, facilitates the migration of VSMC-derived EVs to the intima, further exacerbating diabetic vascular intimal calcification (199).

4.6.2 EVs of ECs: bidirectional regulation under high glucose stimulation

Through EVs, endothelial cells (ECs) can communicate with VSMCs (200). High glucose-exposed human umbilical vein endothelial cells (HUVECs) secrete EVs that act as key mediators in VSMC calcification. These EVs deliver Notch3 to VSMCs via the mTOR signaling pathway, promoting VSMCs phenotypic transition towards an osteoblast-like state (201). HG-HUVECs-EVs also contain versican (VCAN), which induce mitochondrial dysfunction, oxidative stress and senescence, which accelerates VSMCs calcification (173). Moreover, high glucose induces the production of EC-derived EVs containing malondialdehyde (MDA), LDH, CircRNA-0077930, and circ_0008362, which promote VSMCs calcification (173, 190, 201–203). Notably, contrary to earlier research suggesting that AGEs were detrimental to vascular cells, Guo et al. demonstrated that AGEs might actually prevent diabetic media calcification by inducing HUVECs to release small EVs carrying abundant miR-126-5p. This miRNA targets bone morphogenetic protein receptor type 1 (BMPR1) and blocks the SMAD1/5/9 signaling pathway (203).

4.6.3 EVs of macrophages: molecular link between pro-inflammation and pro-calcification in high glucose environment

In the high glucose-induced inflammatory microenvironment, macrophage-derived EVs play a pivotal role in VSMCs osteogenic differentiation. MiR-17-5p, macrophage S100A9 and miR-32 are derived from EVs of macrophage. MiR-17-5p attenuates VSMCs osteogenesis through suppressing TGF-β signaling (204). Macrophage S100A9 controls diabetic vascular calcification via NRF-2 and NF-κB (205) (Figure 6). MiR-32 accelerates vascular calcification in type 2 diabetes by inhibiting VSMCs autophagy (162).

5 Conclusions and future perspectives

Vascular calcification has emerged as a vital mortality or morbidity indicator in the cardiovascular system, particularly in diabetes. Osteogenic differentiation of VSMCs is considered a significant mechanism of diabetic macrovascular disease and the initiation mechanism of vascular calcification (65, 206–208). HG activates multiple signaling pathways, like Ca^{2+} signaling, Wnt/β-catenin, BMP/Smad, and Notch through AMPK, PI3K-AKT, oxidative stress and inflammation, microRNA, and EVs pathways (209–211). These activations contribute to glucose metabolic reprogramming such as (a) intracellular PKC overactivity; (b) increased polyol pathway flux; (c) increased the hexosamine pathway flux; and (d) generation of AGEs and other glycated compounds derived from both glucose oxidation in arterial VSMCs (212). These changes promote osteogenic transformation of VSMCs and the development of VC.

RUNX2 is the core of the regulatory network for VSMCs calcification. During glucose metabolism reprogramming, PPP,

HBP, and AGEs/AGER activate ERK1/2, MAPK, AKT, NF-κB and BMP2 in VSMCs. These pathways mainly participate in RUNX2 expression and transcriptional activity through regulate RUNX2 protein structure, and the multilateral genetic, epigenetic and posttranslational modifications (PTMs) regulatory mechanisms control RUNX2 expression (213) (in Figure 2). Further investigations are warranted to address these unanswered questions, which should provide new breakthroughs in the understanding of RUNX2-dependent transcriptional reprogramming of vascular cells and their contributions to the development of arteriosclerosis. For example, it is unknown whether RUNX2 is upregulated in all VSMCs or exclusively in selective VSMCs subpopulations. Of particular interest, RUNX2-regulated expression of RANKL by VSMCs functions as a chemoattractant that induces macrophage/monocyte migration towards VSMCs; and further induces the differentiation of the macrophage/monocyte into bone-resorbing osteoclast-like cells.

Under the high glucose condition, the expression of GLUT, HK2, G6PD, PKM2 and LDHA increase, which enhances glycolytic activity and decreases OXPHOS in VSMCs. During VSMCs calcification, upregulation of PKM2 promote the expression of GLUT1 and LDHA (120). PDK4 inhibit the activity of PDH, slowing down the TCA and towards a higher glycolysis rate. Besides, GLUT1/LDHA may regulate aerobic glycolysis. These explain the preference of VSMCs for the less ATP-efficient metabolic mode of glycolysis. Future efforts will likely focus on identifying key regulatory points and interactions between mechanisms linked to VSMCs transformation that can be targeted to reduce calcification, and, thereby, improve vascular compliance and reduce cardiovascular risk.

There are still many difficult problems to be solved in future research. Specifically, the representation of cultured cells in *in vivo* studies is limited because of the lack of a suitable microenvironment, such as cell–cell interactions, extracellular elastin fibers, hemodynamic factors, and cytokines (214–216). In addition, animal models cannot successfully recapitulate the physiology and pathology in humans. Therefore, the trend of VSMCs transformation in diabetic patients and metabolic reprogramming remains to be further explored and has recently attracted attention.

Author contributions

JG: Writing – original draft, Writing – review & editing. LD: Funding acquisition, Writing – review & editing.

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Conflict of interest

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Association between peripheral thyroid sensitivity defined by the FT3/FT4 ratio and composite adverse outcome among inpatients with heart failure

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Objective: The free triiodothyronine to free thyroxine (FT3/FT4) ratio is an indicator of peripheral thyroid hormone sensitivity. However, its prognostic value in heart failure (HF) remains unclear.

Methods: This single center prospective cohort study included a total of 402 HF patients. The primary composite outcome was established as either mortality from any cause or HF-related hospitalization within one year. Multivariate Cox regression and Kaplan-Meier analysis assessed associations between the FT3/FT4 ratio and composite endpoint risks, with restricted cubic splines (RCS) exploring potential non-linear relationships.

Results: Among 402 heart failure patients, 188 (46.8%) experienced the primary composite endpoint. The highest FT3/FT4 tertile (T3) had 38% lower risk than the lowest tertile (T1) (adjusted HR 0.62, 95% CI 0.41-0.94). In the subgroup of patients with subclinical hypothyroidism (SCH), T3 individuals showed an 84% lower risk compared to T1 (adjusted HR 0.16, 95% CI 0.03–0.81). Both the overall cohort and SCH subgroup exhibited an inverse association between FT3/FT4 ratios and adverse outcomes, whereas euthyroid patients demonstrated a U-shaped relationship with composite endpoint hazards (P for nonlinear = 0.004).

Conclusions: Our findings suggest that maintaining or restoring higher FT3/FT4 levels may improve clinical outcomes in HF patients. Regular monitoring of this ratio, coupled with tailored interventions based on thyroid functional status, could enhance risk stratification and therapeutic decision-making.

KEYWORDS

FT3/FT4 ratio, heart failure, mortality, readmission, peripheral thyroid sensitivity

Introduction

Thyroid hormones directly modulate cardiovascular function by enhancing myocardial contractility while also exerting significant indirect effects through sympathetic nervous system activation (1). Even subtle disturbances in thyroid homeostasis are linked to adverse cardiovascular outcomes (2). Heart failure (HF) patients frequently exhibit alterations in thyroid hormone metabolism, including low T3 syndrome and subclinical hypothyroidism (SCH), both established predictors of poor prognosis (3–5). Furthermore, thyrotropin (TSH) levels above 7.0 mU/L show dose-dependent associations with increased coronary heart disease mortality (6, 7), overt hyperthyroidism elevates cardiovascular mortality (8), and high-normal free thyroxine (FT4) correlates with increased mortality in the elderly (9).

Thyroid hormone homeostasis is regulated by the hypothalamic-pituitary-thyroid (HPT) axis (10). Triiodothyronine (T3), the biologically active hormone, is predominantly generated peripherally via deiodination of thyroxine (T4) (11). The FT3/FT4 ratio quantifies peripheral T4-to-T3 conversion efficiency and tissue-level thyroid hormone bioavailability (12, 13), serving as a surrogate marker of peripheral thyroid sensitivity (14, 15). This ratio may be more sensitive than isolated FT3 or FT4 measurements in detecting subtle thyroid metabolic perturbations (16). Emerging evidence supports the FT3/FT4 ratio's prognostic value in cardiovascular disease for predicting adverse events across multiple populations, including euthyroid acute coronary syndrome patients (17, 18), general cardiovascular disease cohorts (19), and specific groups such as dilated cardiomyopathy (20).

Despite this, the prognostic significance of FT3/FT4 across the spectrum of thyroid function in HF remains underexplored. Notably, HF has an average 1-year mortality rate of up to 33% (21), underscoring the prognostic usefulness for precise, thyroid status-specific risk stratification tools. Defining thyroid function-dependent FT3/FT4 thresholds could enable personalized risk assessment and guide targeted therapies (22).

To address these gaps, this study aimed to: (1) Elucidate the relationship between the FT3/FT4 ratio and composite endpoint risk, and (2) Characterize the nature (linear *vs.* non-linear) and magnitude of associations of the FT3/FT4 ratio with adverse outcomes.

Methods

Study population

This prospective cohort study consecutively enrolled 1,300 patients admitted to the Cardiology Department of Heze Hospital, Affiliated to Shandong First Medical University, between January 2022 and December 2023. Inclusion criteria required participants to be ≥18 years old, fulfilling both the 2018 Chinese HF diagnostic guidelines (23) and the 2021 European Society of Cardiology (ESC) HF criteria (24), and New York Heart Association (NYHA) functional class I-IV. Exclusion criteria comprised: (1) unavailable baseline thyroid function data; (2) pre-existing thyroid disorders, malignancy, or severe infections; (3) pregnancy; (4) loss to follow-up; (5) use of thyroid-affecting medications. After exclusions, 402 patients constituted the final analytical cohort. Approved by the Ethics Committee of Heze Hospital Affiliated to Shandong First Medical University (No. 2024-KY001-079). All participants provided written informed consent.

Data collection

Detailed clinical information was retrieved from the electronic medical records. Clinical information included sex, age, body mass index (BMI), lifestyle factors (smoking, alcohol use), parameters including heart rate (HR), systolic/diastolic blood pressure (SBP/DBP), NYHA class, HF etiology (hypertension, diabetes, coronary heart disease), along with medication records of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), β-blockers, and statins. Venous blood collected within 24 hours of admission underwent analysis for: lipid profiles (total cholesterol [TC], triglycerides [TG], high-density lipoprotein [HDL-C], low-density lipoprotein [LDL-C]), fasting blood glucose [FBG], uric acid [UA], creatinine [Cr], N-terminal pro-B-type natriuretic peptide [NT-proBNP], aspartate aminotransferase [AST], and thyroid function (TSH, FT3, FT4 via direct chemiluminescence; reference ranges: FT3 1.8-4.2 pg/ml, FT4 0.87-1.85 ng/dL, TSH 0.35-5.1 μIU/ml) (Roche Diagnostics Gmbh, Japan). The study population included euthyroid patients and those with thyroid dysfunction (hyperthyroidism, hypothyroidism, subclinical thyroid dysfunction, and other thyroid abnormalities). Euthyroid status is defined as having TSH, FT4, and FT3 all within their respective normal ranges. SCH is characterized by elevated TSH levels (>5.1 uIU/ml) in conjunction with normal FT4. Echocardiography assessed left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVDD) using the Biplane Simpson method. All missing values for these covariates are less than 1%.

Outcomes

The key composite outcome was defined as death from any cause or rehospitalization due to HF within 1 year, selected based on established prognostic relevance in prior studies (25, 26). Endpoint assessors were not blinded to thyroid data.

Statistical analysis

Statistical analyses were performed using SPSS 25.0 and R 0.5.6 (rms package). Patients were stratified into tertiles based on FT3/FT4 ratio. This equidistant grouping method produced consistent intervals and automatically assigned samples into groups of nearly equal size, due to the continuous distribution of values in the population. Similar approaches have been used in previous

studies, such as those by Okoye et al. and Qin et al., which also reported balanced sample distributions across groups as a result of this method (27, 28). Continuous variables were summarized as median and interquartile range (IQR) and compared using the non-parametric Kruskal-Wallis test; categorical variables were presented as counts and percentages, with group comparisons performed using χ^2 or Fisher's exact test as appropriate (29). Cox regression was used to assess the association between FT3/FT4 and composite outcomes. Model 1 remained unadjusted, whereas Model 2 incorporated adjustments for sex, age, and BMI. Model 3 added smoking, drinking, SBP, DBP, HR, NYHA class, LVEF, LVDD, TC, TG, LDL-C, HDL-C, FBG, UA, Cr, logNT-proBNP, AST, comorbidities (hypertension, diabetes, coronary heart disease), and HF medications (ACEIs/ARBs, β-blockers, statins). The results are presented as hazard ratios (HRs) along with 95% confidence intervals (CIs). Survival differences were tested with Kaplan-Meier/log-rank methods, while RCS (knots: 10th/50th/90th percentiles) examined nonlinear associations using Model 3 adjustments. Statistical significance threshold was P<0.05.

Results

FT3/FT4 ratio in the overall cohort

The patient selection flowchart is shown in Figure 1. The final analysis included 402 HF patients with a median age of 73 years (IQR: 67-79), of whom 58.0% were male. During follow-up, 188 (46.8%) experienced the composite events. Participants were stratified into tertiles: T1 (≤0.18), (0.18<T2<0.22), and T3 (≥0.22). Baseline characteristics across tertiles are detailed in Table 1. Higher FT3/FT4 ratios were associated with elevated BMI, SBP, DBP, LDL-C, and HDL-C levels, alongside lower uric acid, creatinine, NT-proBNP, and AST levels (all P <0.05) (Table 1). Notably, the T3 group demonstrated the lowest incidence of composite events (T1: 56.7% vs. T3: 38.1%; P=0.009).

In Cox regression analyses, both T2 and T3 groups exhibited progressively lower risks of composite outcomes compared to T1. In unadjusted Cox analysis, the T3 group had significantly lower composite risk compared to T1 (HR=0.57, 95% CI 0.40-0.81; P for trend=0.002). Adjustment for sex, age, and BMI (Model 2) yielded similar results. In the fully adjusted model (Model 3), the T2 (HR=0.68, 95%CI 0.46-0.99, P=0.047) and T3 (HR=0.62, 95%CI 0.41-0.94, P=0.023) groups both showed significantly lower risks than the T1 group, with a significant decreasing trend across tertiles (P for trend=0.02) (Figure 2). When analyzed as a continuous variable, the FT3/FT4 ratio demonstrated an inverse association with composite outcomes after multivariable adjustment (adjusted HR:0.11, 95%CI: 0.07-0.99, P=0.049). Kaplan-Meier analysis confirmed significantly better event-free survival with higher FT3/FT4 ratios (log-rank P=0.009; Figure 3A). RCS analysis demonstrated an inverse association between the continuous FT3/FT4 ratio and composite risk (P for nonlinear=0.568; Figure 4A).

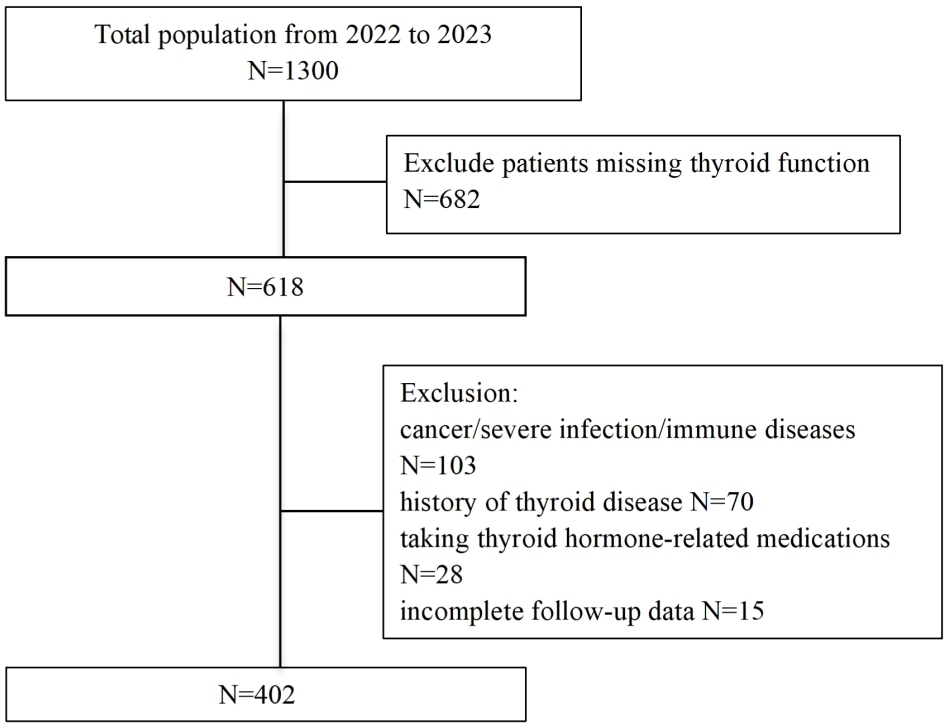

FIGURE 1
Flow chart of patient selection.

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TABLE 1 Baseline characteristics by tertiles of the FT3/FT4 ratio in the main sample (N=402).

FT3/FT4 tertiles	T1 ≤ 0.18 (N=134)	0.18<T2<0.22 (N=134)	T3 ≥0.22 (N=134)	P
Age (years), (IQR)	73 (68, 81)	74 (68, 79)	72 (60, 78)	0.059
Gender, n (%)				
Male	70 (52.2)	76 (56.7)	87 (64.9)	0.103
Female	64 (47.8)	58 (43.3)	47 (35.1)	
BMI (kg/m^2)	22.6 (20.4, 25.2)	23.4 (20.6, 26.3)	24.0 (21.2, 26.6)	**0.032**
Smoking (%)	30 (22.3)	34 (25.4)	44 (32.8)	0.139
Drinking (%)	16 (11.9)	14 (10.4)	23 (17.2)	0.233
Heart rate (bpm)	86 (70, 100)	89 (73, 103)	84 (72, 98)	0.155
NYHA(III-IV) (%)	119 (88.8)	124 (92.6)	115 (85.8)	0.211
LVEF,%	42 (34, 52)	44 (34, 53)	42 (34, 52)	0.600
LVDD (cm)	56 (48, 62)	56 (49, 64)	57 (50, 64)	0.489
NT-proBNP (ng/L)	9569 (4750, 18942)	5957 (2773, 9144)	3395 (2018, 6820)	**<0.001**
SBP (mmHg)	127 (108, 144)	133 (112, 148)	134 (120, 153)	**0.018**
DBP (mmHg)	78 (68, 89)	83 (75, 91)	81 (73, 91)	**0.044**
FT4 (ng/dl)	1.61 (1.45, 1.84)	1.50 (1.39, 1.63)	1.32 (1.16, 1.48)	**<0.001**
FT3 (pg/ml)	1.84 (1.60, 2.22)	2.44 (2.34, 2.73)	2.85 (2.58, 3.18)	**<0.001**
TSH (uIU/ml)	2.77 (1.74, 4.38)	3.18 (1.92, 5.20)	2.95 (1.87, 4.77)	0.353
TC (mmol/L)	3.47 (2.76, 4.14)	3.53 (3.02, 4.21)	3.83 (3.15, 4.46)	**0.004**
TG (mmol/L)	0.91 (0.72, 1.22)	0.90 (0.71, 1.17)	0.98 (0.72, 1.40)	0.197
LDL-C (mmol/L)	1.93 (1.50, 2.59)	2.15 (1.56, 2.69)	2.17 (1.68, 2.93)	**0.015**
HDL-C (mmol/L)	0.91 (0.75, 1.14)	0.96 (0.81, 1.25)	1.02 (0.84, 1.28)	**0.014**
FBG (mmol/L)	4.75 (4.21, 6.36)	4.78 (4.17, 5.68)	4.90 (4.40, 5.78)	0.491
SUA (umol/L)	420 (294, 519)	325 (259, 404)	327 (274, 429)	**<0.001**
Creatinine (mg/dl)	93 (75, 113)	83 (68, 101)	77 (64, 100)	**<0.001**
AST (U/L)	26 (18, 41)	21 (15, 28)	22 (16, 32)	**0.002**
Hypertension (%)	65 (48.5)	64 (47.8)	73 (54.5)	0.484
Diabetes (%)	43 (32.1)	34 (25.4)	27 (20.1)	0.082
Coronary heart disease (%)	72 (53.7)	63 (47.0)	74 (55.2)	0.358
Statins (%)	94 (70.1)	106 (79.1)	104 (77.6)	0.188
ACEI/ARB (%)	91 (67.9)	96 (71.6)	95 (70.9)	0.779
β-Blocker (%)	100 (74.6)	103 (76.9)	105 (78.4)	0.768
Death or readmission (%)	76 (56.7)	61 (45.5)	51 (38.1)	**0.009**

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association (NYHA); LVEF, left ventricular ejection fraction; LVDD, left ventricular end diastolic dimension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood-glucose; SUA, serum uric acid; AST, aspartate aminotransferase; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Bold indicates P value < 0.05.

FT3/FT4 ratio in euthyroid population

Of all the participants included in the analysis, 275 had normal thyroid function and a subgroup analysis was performed for this euthyroid cohort. Subjects had a median age of 73 years (IQR: 65-79), with 58.20% being male. A total of 130 composite outcomes were recorded. Baseline characteristics across tertiles (T1 ≤ 0.18; (0.18<T2<0.22); T3≥0.22) are shown in Table 2. Elevated FT3/FT4 ratio demonstrated positive associations with BMI, TC, and LDL levels, while correlating inversely with UA, Cr, NT-proBNP, AST, and incidence of composite events (Table 2). In addition, euthyroid individuals exhibiting elevated FT3/FT4 ratios were typically

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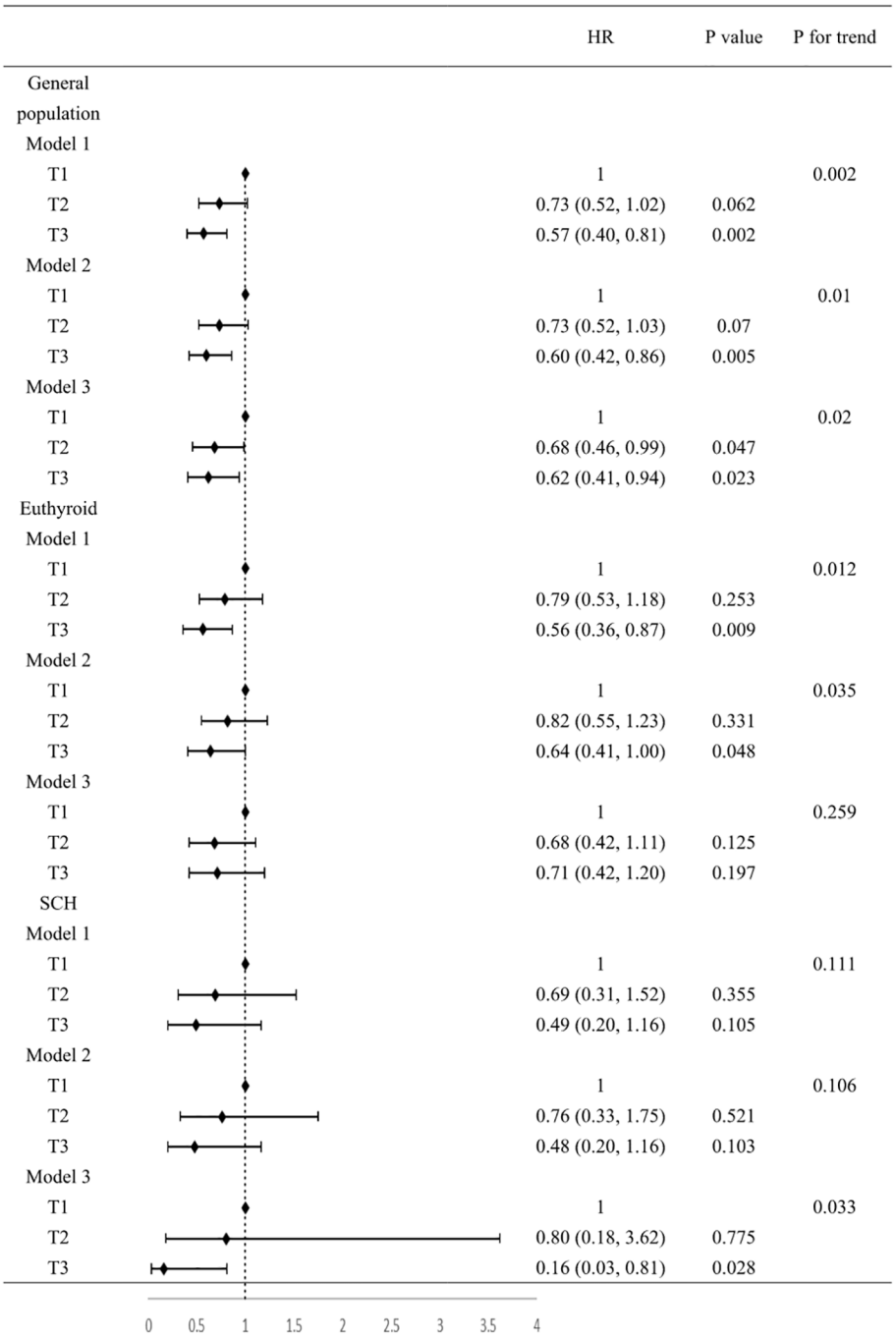

FIGURE 2
Association between FT3/FT4 value and composite outcomes. Model 1, no covariates were adjusted. Model 2, age, gender, BMI were adjusted. Model 3, age, gender, BMI, smoking, drinking, SBP, DBP, HR, NYHA class, LVEF, LVDD, TC, TG, LDL-C, HDL-C, FBG, UA, Cr, NT-proBNP, AST, ACEI/ARB, β-blockers, statins, hypertension, diabetes, coronary heart disease were adjusted. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart ratio; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; FBG, fasting blood glucose; UA, uric acid; Cr, creatinine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; AST, aspartate aminotransferase; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

younger, predominantly male, and demonstrated higher alcohol consumption prevalence, and elevated LVDD (all P <0.05). Model 1 showed the T3 group exhibited a significant risk reduction in contrast to the T1 group (HR: 0.56, 95% CI 0.36-0.87, P=0.009, P for trend=0.012). This association persisted after sex/age/BMI adjustment in Model 2 (HR: 0.64, 95% CI 0.41-1.00, P=0.048). However, after fully adjusting for variables, no significant association was observed (HR: 0.71, 95% CI 0.42-1.20, P=0.197; Figure 2). When analyzed as a continuous variable, the FT3/FT4 ratio showed no significant association with composite outcomes in

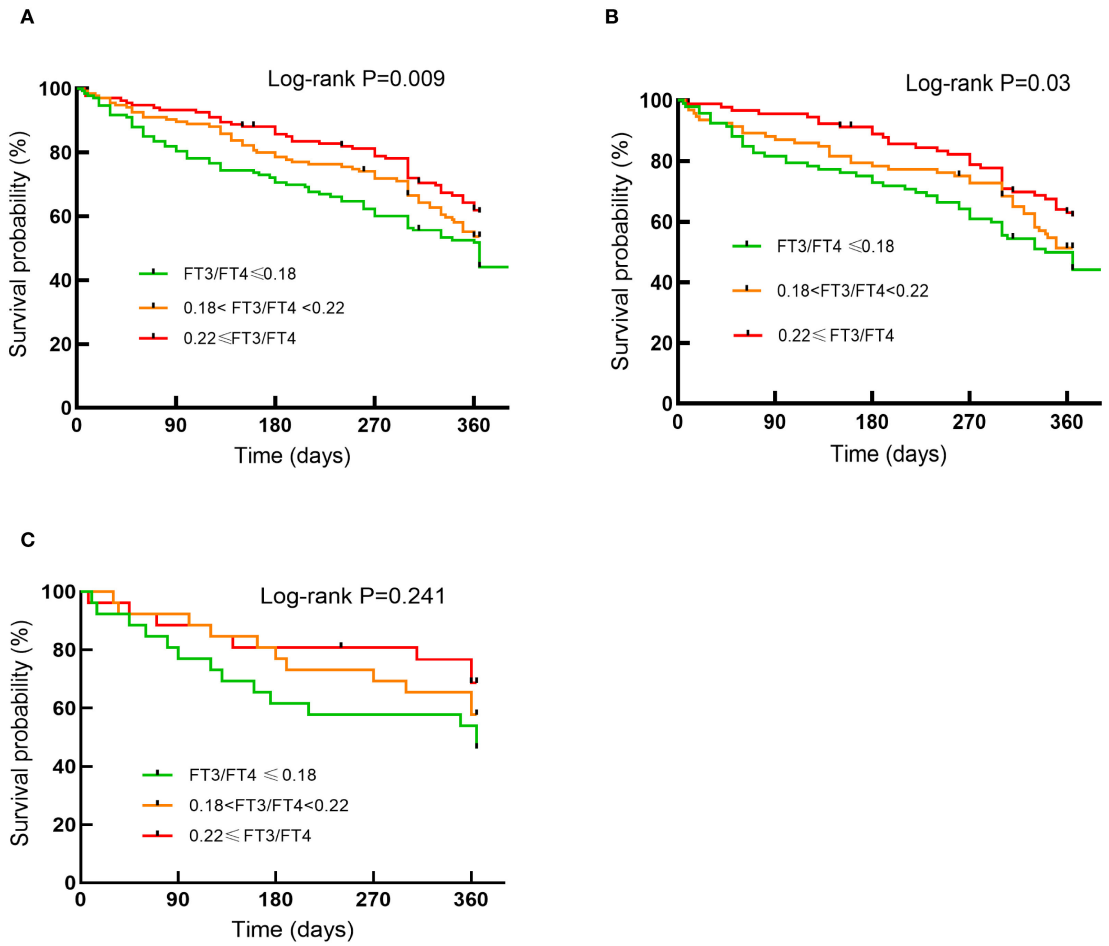

FIGURE 3
Kaplan-Meier curves for endpoint events by tertiles of FT3/FT4 ratio in the general population **(A)** in the euthyroid population **(B)** in the SCH population **(C)**.

the multivariable-adjusted model (adjusted HR: 0.17, 95% CI: 0.71–9.72, P=0.394). Kaplan-Meier analysis revealed significant survival disparities across groups (log-rank test: P=0.03, Figure 3B). RCS analysis, however, uncovered a U-shaped relationship (P for nonlinear=0.005; Figure 4B). The minimum risk was observed when the FT3/FT4 ratio was 0.22 (HR: 0.95, 95% CI: 0.77-1.18).

FT3/FT4 ratio in SCH population

The SCH subgroup included 78 patients with median age 75 years (IQR:68-80); 57.8% male), with 33 composite events (42.3%). Increasing FT3/FT4 ratios predicted increased SBP and NT-proBNP levels (P<0.05) (Table 3). In Model 3, the T3 group (≥0.22) had a substantially lower composite risk compared to T1 (≤0.18) (HR: 0.16, 95% CI 0.03–0.81; P=0.028) with progressive risk attenuation (P for trend=0.033; Figure 2). When analyzed as a continuous variable, the FT3/FT4 ratio demonstrated an inverse association with composite outcomes after multivariable adjustment (adjusted HR:0.45, 95%CI: 0.23-0.87, P=0.018). Kaplan-Meier survival curves showed no significant difference (log-rank P=0.241; Figure 3C), but RCS analysis demonstrated an inverse correlation (P for nonlinear=0.759; Figure 4C).

FT3/FT4 ratio in the remaining 49 patients

Among the remaining 49 patients, the median age was 74 (IQR:65-78) years, 57.1% were male, and 25 composite endpoint events were recorded. Baseline characteristics across tertiles are detailed in Supplementary Table 1. Since our initial exclusion criteria applied only to patients with pre-existing thyroid disease, rather than those with newly identified dysfunction in this study, the 49 patients were included in the overall population but were not analyzed separately due to limited sample size, so as not to compromise statistical power in subgroup analyses.

Discussion

This prospective study demonstrates that the FT3/FT4 ratio, a marker of peripheral thyroid hormone sensitivity, exhibits

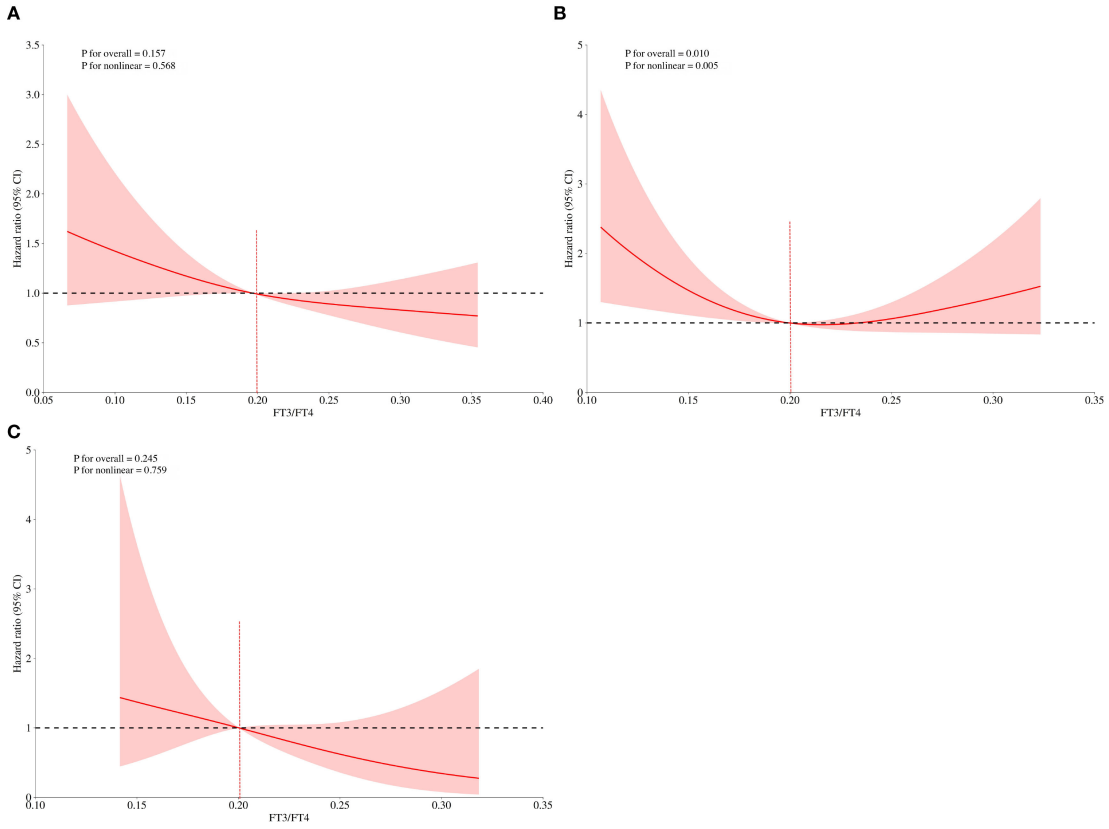

FIGURE 4
FT3/FT4 and the risk of composite endpoints derived from RCS with 3 knots in the general population **(A)** in the euthyroid population **(B)** in the SCH **(C)**. The dotted lines represent 95% confidence intervals. Spline analyses were adjusted for age, gender, BMI, smoking, drinking, SBP, DBP, HR, NYHA class, LVEF, LVDD, TC, TG, LDL-C, HDL-C, FBG, UA, Cr, NT-proBNP, AST, ACEI/ARB, β-blockers, statins, hypertension, diabetes, coronary heart disease. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart ratio; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; FBG, fasting blood glucose; UA, uric acid; Cr, creatinine; NT-proBNP, N-terminal pro-B-type natriuretic peptide; AST, aspartate aminotransferase; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

thyroid status-dependent associations with 1-year mortality rehospitalization risk in heart failure patients. Our key novel findings are: (1) An inverse relationship was observed between the FT3/FT4 ratio and composite risk across the overall HF cohort, particularly among patients with SCH; (2) A significant U-shaped relationship is observed in euthyroid HF patients.

HF is characterized by metabolic derangements including reduced nutrient intake (30), chronic inflammation, and oxidative stress (31), which can impair micronutrient absorption (iodine, selenium, zinc, iron) crucial for thyroid hormone synthesis and conversion (32). Thyroid hormones, in turn, profoundly impact cardiac electrophysiology, contractility, and structure (33). Hence, Subtle fluctuations in thyroid hormone bioavailability can therefore significantly influence cardiac function and HF progression (34). The inverse FT3/FT4 ratio-adverse outcome relationship likely involves multifactorial pathways. Reduced ratios indicate impaired peripheral T4-to-T3 conversion, directly contributing to tissue-level hypothyroidism during acute/chronic disease states (18). T3, acting via nuclear receptors (TRα/TRβ) in the heart, enhances the expression of key proteins involved in calcium handling (SERCA2a, RYR2) and mitochondrial function/biogenesis; processes often compromised in HF (35). Lower FT3 levels directly contributes to HF pathogenesis by impairing left ventricular relaxation and increasing myocardial stiffness (36). Furthermore, HF is associated with sympathetic overactivation and Renin-Angiotensin-Aldosterone System (RASS) hyperactivity (37); T3 restores autonomic balance in heart failure by: (1) Attenuating sympathetic overactivation through downregulation of myocardial β adrenergic receptor density and reduction of circulating norepinephrine levels (38); (2) Recovering baroreflex function via upregulation of neuronal nitric oxide synthase (nNOS) in the nucleus tractus solitarius (39), thereby mitigating these detrimental neurohormonal axes (40).

Our findings align with and extend previous research. Studies linked lower FT3/FT4 ratios to increased mortality in dilated cardiomyopathy (20). A study using propensity matching demonstrated that a reduced ratio of FT3/FT4 is a robust predictor of all-cause mortality in heart failure patients (41). Another study discovered that the FT3/FT4 ratio independently predicts all-cause mortality in the general population. In addition, a study noted that in euthyroid patients with type 2 diabetes mellitus, a low FT3/FT4 ratio independently contributed to major adverse

TABLE 2 Baseline characteristics by tertiles of the FT3/FT4 ratio in the euthyroid samples.

FT3/FT4 tertiles	T1 ≤ 0.18 (N=92)	0.18<T2<0.22 (N=92)	T3≥0.22 (N=91)	P
Age (years), (IQR)	76 (69, 83)	74 (67, 79)	69(60.77)	**<0.001**
Gender, n(%)				
Male	44 (47.8)	52 (56.5)	64 (70.3)	**0.008**
Female	48 (52.2)	40 (43.5)	27 (29.7)	
BMI (kg/m^2)	22.3 (20.6, 25.2)	23.4 (20.8, 26.3)	24.5 (21.5, 26.7)	**0.029**
Smoking (%)	18 (19.6)	23 (25)	31 (34.1)	0.587
Drinking (%)	9 (9.8)	8 (8.7)	18 (19.8)	**0.046**
Heart rate (bpm)	89 (74, 104)	88 (73, 102)	85 (74, 98)	0.492
NYHA(III-IV) (%)	82 (89.1)	86 (93.5)	77 (84.6)	0.157
LVEF,%	43 (35, 55)	42 (33, 51)	40 (33, 52)	0.351
LVDD (cm)	56 (48, 61)	58 (50, 66)	59 (52, 66)	**0.033**
NT-proBNP (ng/L)	8795 (4461, 19401)	5368 (2563, 8671)	3260 (1952, 6013)	**<0.001**
SBP (mmHg)	127 (108, 142)	136 (108, 152)	130 (120, 147)	0.126
DBP (mmHg)	79 (68, 89)	84 (70, 93)	81 (73, 90)	0.272
FT4 (ng/dl)	1.56 (1.41, 1.67)	1.49 (1.37, 1.62)	1.32 (1.21, 1.48)	**<0.001**
FT3 (pg/ml)	1.92 (1.60, 2.12)	2.45 (2.27, 2.76)	2.88 (2.53, 3.28)	**<0.001**
TSH (uIU/ml)	2.36 (1.48, 3.69)	2.49 (1.64, 3.70)	2.33 (1.61, 3.29)	0.676
TC (mmol/L)	3.38 (2.78, 3.93)	3.72 (3.08, 4.28)	3.68 (3.06, 4.42)	**0.018**
TG (mmol/L)	0.89 (0.72, 1.18)	0.94 (0.70, 1.17)	0.97 (0.72, 1.39)	0.464
LDL-C (mmol/L)	1.92 (1.51, 2.51)	2.19 (1.65, 2.79)	2.15 (1.65, 2.95)	**0.047**
HDL-C (mmol/L)	0.91 (0.77, 1.12)	0.96 (0.79, 1.25)	1.01 (0.79, 1.27)	0.083
FBG (mmol/L)	4.67 (4.26, 6.46)	4.79 (4.31, 5.75)	4.98 (4.42, 5.50)	0.794
SUA (umol/L)	411 (274, 508)	327 (263, 422)	324 (272, 427)	**0.033**
Creatinine (mg/dl)	88 (73, 113)	83 (66, 105)	75 (64, 95)	**0.005**
AST (U/L)	26 (18, 42)	21 (15, 27)	21 (16, 31)	**0.001**
Hypertension (%)	43 (46.7)	45 (48.9)	47 (51.6)	0.801
Diabetes (%)	29 (31.5)	25 (27.2)	16 (17.6)	0.086
Coronary heart disease (%)	47 (51.1)	45 (48.9)	46 (50.5)	0.954
Statins (%)	65 (70.7)	77 (83.7)	72 (79.1)	0.097
ACEI/ARB (%)	64 (69.6)	68 (73.9)	67 (73.6)	0.762
β-Blocker (%)	71 (77.2)	71 (77.2)	74 (81.3)	0.733
Death or readmission (%)	52 (56.5)	44 (47.8)	34 (37.4)	**0.034**

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association (NYHA); LVEF, left ventricular ejection fraction; LVDD, left ventricular end diastolic dimension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood-glucose; SUA, serum uric acid; AST, aspartate aminotransferase; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Bold indicates P value < 0.05.

cardiac events following acute myocardial infarction (42). However, our study is the first to comprehensively evaluate this ratio across distinct thyroid functional states (euthyroid vs. SCH) within an HF cohort and to identify state-specific risk patterns. The protective association observed in SCH patients is particularly noteworthy and suggests that maintaining adequate peripheral conversion is crucial in this subgroup, potentially outweighing the risks associated with mildly elevated TSH. This finding resonates with experimental data showing T3 reduces infarct size and activates cardio-protection during ischemia/reperfusion (43), and clinical evidence that low-dose T3 replacement improved LV function post-AMI (44). Notably, in patients with SCH, multivariate Cox regression

TABLE 3 Baseline characteristics by tertiles of the FT3/FT4 ratio in the SCH samples.

FT3/FT4 tertiles	T1 ≤ 0.18 (N=26)	0.18<T2<0.22 (N=26)	T3≥0.22 (N=26)	P
Age (years), (IQR)	74(70,80)	72(67,79)	77(72,83)	0.324
Gender, n (%)				
Male	12 (46.2)	18 (69.2)	15 (57.7)	0.242
Female	14 (53.8)	8 (30.8)	11 (42.3)	
BMI (kg/m^2)	22.5 (20.3, 25.6)	22.9 (19.9, 24.4)	23.7 (19.5, 26.3)	0.675
Smoking (%)	5 (19.2)	7 (26.9)	8 (30.8)	0.625
Drinking (%)	2 (7.7)	4 (15.4)	5 (19.2)	0.477
Heart rate (bpm)	84 (71, 92)	90 (78, 108)	84 (70, 103)	0.524
NYHA(III-IV) (%)	24 (92.3)	23 (88.5)	24 (92.3)	0.855
LVEF, %	46 (36, 58)	44 (37, 54)	46 (40, 55)	0.845
LVDD (cm)	56 (47, 60)	56 (51, 63)	52 (48, 59)	0.492
NT-proBNP (ng/L)	9898 (5624, 16957)	6036 (2580, 9655)	5671 (2076, 8868)	**0.005**
SBP (mmHg)	126 (109, 147)	128 (114, 140)	151 (119, 172)	**0.017**
DBP (mmHg)	78 (70, 90)	81 (76, 87)	81 (70, 97)	0.605
FT4 (ng/dl)	1.54 (1.45, 1.73)	1.51 (1.28, 1.56)	1.22 (1.09, 1.34)	**<0.001**
FT3 (pg/ml)	2.09 (1.90, 2.27)	2.46 (2.20, 2.63)	2.82 (2.58, 2.99)	**<0.001**
TSH (uIU/ml)	6.31 (5.47, 8.53)	7.26 (6.12, 10.39)	7.66 (6.45, 12.67)	0.087
TC (mmol/L)	3.68 (2.57, 4.55)	3.30 (2.85, 4.14)	4.01 (3.13, 4.47)	0.264
TG (mmol/L)	0.92 (0.64, 1.32)	0.89 (0.77, 1.21)	0.94 (0.71, 1.39)	0.869
LDL-C (mmol/L)	1.73 (1.32, 2.92)	1.74 (1.45, 2.32)	2.21 (1.80, 2.74)	0.143
HDL-C (mmol/L)	1.03 (0.68, 1.26)	0.97 (0.86, 1.31)	1.10 (0.96, 1.39)	0.252
FBG (mmol/L)	4.67 (4.00, 5.97)	4.62 (3.93, 5.17)	5.16 (4.32, 7.13)	0.270
SUA (umol/L)	381 (294, 478)	320 (262, 385)	386 (273, 484)	0.299
Creatinine (mg/dl)	96 (82, 114)	83 (70, 101)	94 (67, 150)	0.091
AST (U/L)	26 (18, 37)	19 (15, 26)	22 (15, 31)	0.092
Hypertension (%)	16 (61.5)	10 (38.5)	17 (65.4)	0.108
Diabetes (%)	10 (38.5)	7 (26.9)	7 (26.9)	0.582
CHD (%)	14 (53.9)	12 (46.2)	16 (61.5)	0.538
Statins (%)	21 (80.8)	17 (65.4)	20 (76.9)	0.417
ACEI/ARB (%)	15 (57.7)	19 (73.1)	17 (65.4)	0.507
β-Blocker (%)	20 (76.9)	19 (73.1)	18 (69.2)	0.822
Death or readmission (%)	14 (53.8)	11 (42.3)	8 (30.8)	0.110

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association (NYHA); LVEF, left ventricular ejection fraction; LVDD, left ventricular end diastolic dimension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood-glucose; SUA, serum uric acid; AST, aspartate aminotransferase; CHD, coronary heart disease ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Bold indicates P value < 0.05.

demonstrated an inverse association between the FT3/FT4 ratio and the risk of composite outcomes, whereas KM analysis revealed no significant survival difference among the three groups. This discordance likely reflects the inherent limitation of KM analysis: as a non-parametric method estimating unadjusted survival probabilities from observed events, it does not account for confounding factors.

The U-shaped relationship observed in euthyroid patients is a novel and significant finding. The loss of significance in the fully adjusted multivariate Cox model for the euthyroid subgroup,

particularly after accounting for age and NT-proBNP-both strongly associated with the ratio and outcomes, suggesting that the univariate association was partly confounded. This interpretation is primarily informed by the simultaneous measurement of NT-proBNP and thyroid indicators during the same blood draw, which inherently precludes establishing the temporal sequence required for mediation (where exposure must precede the mediator, which subsequently influences the outcome) (45). However, the highly significant U-curve revealed by RCS analysis indicates a complex, non-monotonic relationship. This suggests an optimal range for peripheral thyroid sensitivity in euthyroid HF. Ratios significantly below 0.22 likely indicate impaired conversion and tissue hypothyroidism, increasing risk. Conversely, ratios significantly above this point might reflect excessive peripheral conversion, potentially linked to hypermetabolic states or impaired hormone clearance, which could paradoxically increase cardiovascular strain or indicate other underlying metabolic disturbances detrimental in HF. Compensatory mechanisms preserving tissue-level thyroid hormone action within the normal functional range might also buffer the impact of ratio variations, except at the extremes (46). Potential mechanisms involve: (1) impaired enzymatic efficiency due to the Thr92Ala DIO2 polymorphism at low FT4/FT3 ratios, whereas DIO2 overexpression under high-T4 conditions depletes essential cofactors (e.g., glutathione), thereby exacerbating T4-to-T3 conversion failure (47); (2) pro-inflammatory cytokines (TNF-α, IL-6) suppressing deiodinase activity through NF-κB-mediated downregulation of DIO1 and DIO2 expression, impairing T3 generation and promoting thyroid hormone resistance during chronic inflammation (48). Further research is needed to elucidate the mechanisms underlying this U-shape.

To our knowledge, this is the first study to identify the optimal FT3/FT4 for stratifying mortality/readmission risk in HF patients with varying thyroid states. Limitations should be acknowledged. First, the single-center design necessitates cautious interpretation regarding generalizability. As iodine sufficiency varies significantly across global regions, and Asian populations often exhibit distinct iodine nutritional status compared to Western cohorts, our results should be interpreted within this contextual framework. Second, only baseline thyroid function was assessed; serial measurements might better capture dynamic changes relevant to prognosis. Third, the mechanisms linking the FT3/FT4 ratio to HF outcomes, particularly the U-shape in euthyroidism, require further elucidation. Fourth, In the SCH cohort, the observed hazard ratio (HR) of 0.16 should be interpreted with caution due to the limited sample size. Finally, observational design precludes causal inference.

In conclusion, the FT3/FT4 ratio is a thyroid status-dependent predictor of 1-year mortality and HF rehospitalization risk. Monitoring the FT3/FT4 ratio, offers a valuable tool for risk stratification. Future studies should validate these thresholds in diverse populations and explore whether interventions aimed at optimizing peripheral thyroid hormone sensitivity.

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 Heze Hospital Affiliated to Shandong First Medical University (No. 2024-KY001-079). 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: Writing – original draft, Formal analysis, Conceptualization. MG: Formal analysis, Writing – review & editing, Data curation. XL: Writing – review & editing, Supervision. LD: Conceptualization, Writing – review & editing, Supervision, Methodology. CM: Conceptualization, Writing – review & editing, Data curation, Formal analysis.

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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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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1652749/full#supplementary-material

SUPPLEMENTARY TABLE 1
Baseline characteristics of the remaining 49 patients by FT3/FT4 tertiles.

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Obesity's systemic impact: exploring molecular and physiological links to diabetes, cardiovascular disease, and heart failure

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Obesity prevalence continues to climb globally, driving healthcare costs ever higher. Over the past decade, significant strides have been made in understanding the causes of obesity, revealing that primary obesity is rooted in a complex interplay of genetic/developmental and epigenetic/environmental factors. Despite this progress, a critical gap remains in our understanding of the precise molecular pathways that translate adipose tissue expansion into the vast spectrum of associated comorbidities and heterogeneous patient outcomes. This review aims to synthesize recent mechanistic insights that bridge this gap. We summarize findings from extensive literature searches to highlight recent discoveries in the mechanisms underlying obesity and elucidate how these mechanisms contribute to various comorbidities. This review explores key pathways, including inflammation, insulin resistance, adipokine dysregulation, and complement system activation, that link obesity to diabetes, cardiovascular diseases, and metabolic syndrome. We provide a focused analysis of how these pathways drive two major obesity-related conditions: type 2 diabetes and cardiovascular disease, with particular emphasis on the pathophysiological mechanisms leading to heart failure. Additionally, we discuss the pathophysiological changes induced by obesity that directly contribute to the development of heart failure, including alterations in cardiac structure and function. Our findings highlight the intricate relationships between obesity and its comorbidities, emphasizing the need for a deeper understanding of these mechanisms to inform targeted interventions, druggable pathways, and improve management strategies for affected individuals.

KEYWORDS

obesity, inflammation, insulin resistance, atherosclerosis, heart failure

1 Introduction

Obesity prevalence continues to climb globally, posing an unprecedented public health challenge and significantly escalating healthcare costs. It is now recognized as one of the leading preventable causes of morbidity and mortality worldwide. Since the 1970s, the global rate of obesity has nearly tripled, making it an epidemic of the 21st century. In 2016 alone, over 1.9 billion adults—equating to 39% of the global adult population—were overweight, with more than 650 million categorized as obese (1). Alarmingly, this trend is not confined to adults; over 41 million children under the age of five and 340 million children and adolescents aged 5–19 were overweight or obese, pointing to early-life origins of metabolic disease (1). In the United States, the situation is particularly dire, where 40% of adults and about 20% of children and adolescents (ages 6–19) met criteria for obesity during the 2015–2016 reporting cycle (2, 3).

Recent epidemiological studies confirm that obesity contributes to approximately 2.8–3.4 million deaths annually, with growing recognition that it serves as a primary driver for a constellation of chronic diseases—including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and multiple types of cancer (2, 3). The pathophysiological basis of these associations has become increasingly clear over the past decade, highlighting obesity not merely as an excess of adipose tissue but as a chronic low-grade inflammatory and endocrine disease that disrupts systemic homeostasis.

Obesity is characterized by a pathological expansion of adipose tissue through both hypertrophy (increase in adipocyte size) and hyperplasia (increase in adipocyte number) (4, 5). This expansion is not metabolically inert: adipocytes secrete a range of adipokines, cytokines, and chemokines that exert local and systemic effects on metabolism, immunity, and organ function. Obese individuals—especially those with visceral fat accumulation—are significantly more likely to develop comorbid conditions that cluster into a high-risk phenotype known as *cardiometabolic multimorbidity* (6, 7) (Figure 1). A major multicohort study of over 120,000 adults found that individuals with even mild obesity (BMI 30–34.9 kg/m^2) were over four times more likely to exhibit two or more of the following conditions: myocardial infarction, stroke, and T2DM (8, 9). Similarly, another study of more than 11,000 participants demonstrated that overweight and obese individuals had a twofold increased risk of developing hypertension, dyslipidemia, atherosclerosis, and cardiomyopathy (10, 11).

Despite decades of epidemiological and mechanistic research, investigations have only begun to delineate the molecular pathways by which obesity triggers and accelerates these comorbidities. A critical knowledge gap remains in understanding how obesity—beyond its definition as excess adiposity—translates into heterogeneous health outcomes. While visceral fat accumulation, chronic inflammation, and adipokine dysregulation are recognized as central drivers of cardiometabolic disease, the precise mechanisms linking adipose tissue expansion to organ-specific pathologies, multimorbidity, and differential risk profiles remain incompletely

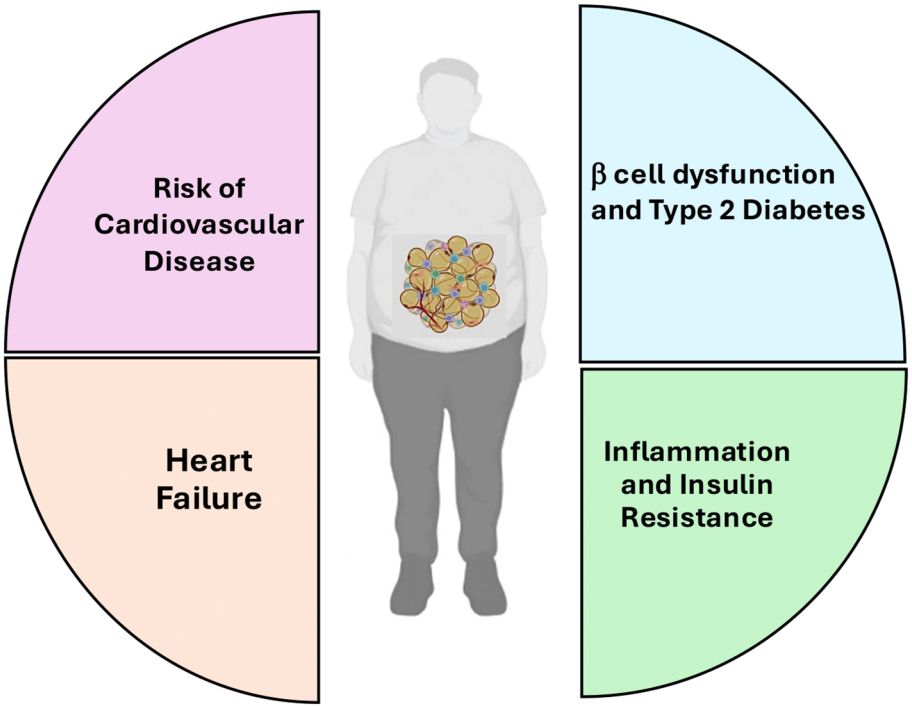

FIGURE 1
The multifaceted impact of obesity on health. This diagram illustrates how obesity contributes to several major health complications. These include an increased risk of cardiovascular disease, the development of heart failure, β-cell dysfunction leading to Type 2 Diabetes, and systemic inflammation and insulin resistance.

defined. Furthermore, paradoxical observations—such as protective effects of subcutaneous fat or the "obesity paradox" in certain populations—highlight unresolved questions about fat distribution, metabolic adaptability, and individual variability in disease progression. Addressing this gap is essential to move beyond BMI-centric definitions and toward mechanistic insights that can inform precision prevention and targeted therapies.

In this review, we synthesize recent findings to elucidate the biological mechanisms by which obesity contributes to a wide spectrum of systemic pathologies. A central feature of obesity is chronic, low-grade inflammation, which not only promotes insulin resistance but also drives endothelial dysfunction, thereby linking excess adiposity to both metabolic and cardiovascular complications. Another critical pathway is adipokine dysregulation. Obesity alters the secretion of adipose-derived hormones such as leptin, adiponectin, and resistin, and these imbalances have profound effects on metabolic homeostasis and cardiovascular health. Insulin resistance represents a further hallmark of obesity, disrupting both glucose and lipid metabolism and forming the core defect in the pathogenesis of type 2 diabetes mellitus. Beyond these established mechanisms, complement system activation has recently emerged as an additional contributor, with growing evidence implicating complement components in adipose tissue inflammation, metabolic dysregulation, and lipid handling. Together, these interlinked pathways highlight the multifactorial nature of obesity-associated disease and underscore the importance of integrating emerging insights with established paradigms.

We also explore how these mechanisms converge to cause structural and functional changes in the cardiovascular system—ranging from endothelial injury and atherosclerotic plaque development to cardiac fibrosis and heart failure. Furthermore, we evaluate how obesity may disrupt organ crosstalk (e.g., between adipose tissue, the liver, and pancreas), giving rise to systemic metabolic derangements such as dyslipidemia, hepatic steatosis, and β-cell dysfunction.

A particular emphasis is placed on the role of the *innate immune system*, including macrophage polarization, toll-like receptor (TLR) signaling, and the activation of complement factors such as C3a, C3adesArg (also known as acylation-stimulating protein, ASP), and C5a—all of which have emerged as critical modulators of adipose tissue inflammation, insulin sensitivity, and cardiovascular health.

Together, these insights illuminate how obesity-induced perturbations in immune, endocrine, and metabolic pathways culminate in a state of *multisystem dysfunction*. Our aim is to provide an integrative and up-to-date overview of the mechanisms linking obesity to comorbid diseases and to highlight how this knowledge may inform the development of *targeted pharmacological and lifestyle-based interventions*. In doing so, we also advocate for a paradigm shift—moving from viewing obesity as an isolated condition to recognizing it as a *root cause of complex chronic multimorbidity*.

2 Inflammation and insulin resistance promote T2DM

Obesity arises when caloric intake persistently exceeds energy expenditure, resulting in excess energy being stored as triglycerides within adipose tissue. This positive energy balance is influenced by a constellation of factors—environmental (e.g., sedentary lifestyle), neurological (e.g., hypothalamic regulation of appetite), genetic predispositions, and hormonal or metabolic imbalances. The resultant expansion of adipose tissue leads to profound systemic metabolic disturbances, including chronic inflammation, oxidative stress, and dyslipidemia. These early hallmarks of obesity—characterized by elevated circulating triacylglycerols (TAG), increased low-density lipoprotein (LDL), reduced high-density lipoprotein (HDL), and insulin resistance—constitute the metabolic syndrome (12, 13). If left unchecked, these perturbations set the stage for the progression to type 2 diabetes mellitus (T2DM), cardiovascular disease, and premature death, particularly in genetically or environmentally susceptible individuals.

Obesity more than doubles the risk of developing metabolic syndrome and increases the risk of T2DM by fourfold (14). T2DM—accounting for over 90% of all diabetes cases—is driven by a dual pathology: *peripheral insulin resistance and pancreatic β-cell dysfunction*, both of which are profoundly influenced by chronic inflammation. In obesity, the ability of peripheral tissues (e.g., skeletal muscle, liver, adipose) to respond to insulin is impaired, increasing the insulin demand on β-cells. Initially, β-cells compensate by enhancing insulin secretion, but over time, they become dysfunctional, fail to meet metabolic demands, and undergo apoptosis—culminating in overt hyperglycemia and diabetes.

2.1 β-cell physiology in an obese condition

Obesity is associated with increased fat infiltration in multiple organs, including the pancreas. As ectopic lipid accumulation intensifies within islets, pancreatic β-cells are exposed to lipotoxic stress. In rodent models, this leads to β-cell dysfunction, dedifferentiation, and apoptosis (15, 16). Paradoxically, in the early stages of obesity, β-cells adapt by increasing their mass in response to insulin resistance—a process that occurs via β-cell replication and neogenesis from progenitors.

Experimental studies in rats have shown that high-fat diet (HFD)-induced obesity can cause a threefold increase in β-cell mass, mainly due to enhanced proliferation (17). Similar findings were reported in mouse models, where diet-induced obesity (DIO) leads to an increase in β-cell area and insulin-positive cells. In human autopsy studies, obese individuals without diabetes often show a 20–90% increase in β-cell mass compared to lean individuals (18). However, the exact timing, extent, and sustainability of this compensation vary between individuals and are influenced by age, duration of obesity, and genetic factors.

2.2 β-cell dysfunction and the onset of T2DM

Although β-cell compensation initially delays the onset of hyperglycemia, progressive β-cell failure marks the transition from insulin resistance to overt T2DM. In individuals with diabetes, β-cell loss is attributed to several mechanisms:

- Apoptosis, which is elevated in human T2DM islets (15);
- Reduced proliferation or regenerative capacity, which is limited in adult humans (19).
- Oxidative stress and endoplasmic reticulum (ER) stress, which impair protein folding and insulin biosynthesis (18);
- Inflammatory cytokines (e.g., IL-1β, TNF-α) produced locally or systemically, which activate β-cell death pathways (20);
- Lipotoxicity, where prolonged exposure to free fatty acids, especially saturated fats, impairs insulin gene expression and mitochondrial function (21);
- Glucotoxicity, where chronic hyperglycemia induces β-cell oxidative damage (22);
- Amyloid deposition, which disrupts β-cell membranes (23);
- Autophagy defects, reducing the clearance of damaged organelles (24).

An emerging mechanism of β-cell loss involves *transdifferentiation*—where β-cells lose their identity or convert into other cell types, such as α-cells (Figure 2A). Rodent studies have confirmed this phenomenon under stress conditions (25), and human studies suggest that dedifferentiated β-cells—marked by the loss of insulin and gain of progenitor-like markers—are more frequent in T2DM islets (26).

2.3 Adipose tissue biology and insulin resistance

Adipose tissue is a dynamic endocrine organ that secretes adipokines, cytokines, and extracellular vesicles to regulate systemic metabolism, energy homeostasis, and immune responses. In lean states, adipocytes maintain insulin sensitivity and release anti-inflammatory adipokines such as adiponectin. However, during chronic overnutrition, adipocytes undergo hypertrophy, triggering tissue remodeling, hypoxia, and immune cell infiltration. This environment transforms adipose tissue into a site of low-grade, chronic inflammation—a hallmark of insulin resistance (27, 28).

In obese individuals, there is a marked shift in adipose-resident immune cell populations. Macrophages, which typically comprise ~10% of cells in lean adipose tissue, increase to over 40–50% in obesity. Furthermore, there is a phenotypic switch from anti-inflammatory M2-like macrophages to proinflammatory M1-like macrophages, which produce TNF-α, IL-6, and inducible nitric oxide synthase (iNOS), directly impairing insulin signaling in adipocytes (29–31).

Compounding this, adipocyte hypoxia, driven by rapid adipose expansion outpacing vascular supply, leads to fibrosis and increased chemokine secretion (e.g., MCP-1), promoting monocyte recruitment and further macrophage accumulation (32). These macrophages form crown-like structures around dead or dying adipocytes—a histological hallmark of inflamed adipose tissue.

The proinflammatory milieu increases circulating free fatty acids (FFAs) through enhanced lipolysis (33), which, in turn, activate toll-like receptors (TLRs) and stress signaling pathways in peripheral tissues, exacerbating insulin resistance (Figure 2B).

2.4 Hypoxia-mediated insulin resistance

Hypoxia plays a central role in adipose tissue dysfunction. As adipocytes expand, oxygen diffusion becomes limited, inducing hypoxia-inducible factor-1 alpha (HIF1α) expression. HIF1α activates transcription of genes involved in glycolysis, angiogenesis, and inflammation. In obese adipose tissue, overexpression of HIF1α has been linked to upregulation of chemokines such as MCP-1 and leukotriene B4 (LTB4), which recruit proinflammatory macrophages (34–36).

Mechanistically, hypoxia activates the JNK and NF-κB pathways, which disrupt insulin signaling by promoting serine phosphorylation of insulin receptor substrate-1 (IRS-1), impairing downstream AKT activation (37–39). These stress pathways also enhance the expression of inducible nitric oxide synthase (iNOS), further compromising vascular function and insulin action.

2.5 Dietary fatty acids in insulin resistance

High-fat diets rich in saturated fatty acids (e.g., palmitate) are potent inducers of insulin resistance. Saturated fats activate pattern recognition receptors such as TLR2 and TLR4, triggering inflammatory cascades via the MyD88-dependent NF-κB and JNK pathways. These pathways upregulate inflammatory cytokines, impair insulin receptor signaling, and induce endoplasmic reticulum stress (40, 41).

Moreover, saturated fats activate the NLRP3 inflammasome, leading to IL-1β and IL-18 maturation. These cytokines not only promote insulin resistance but also induce β-cell dysfunction and apoptosis. In contrast, unsaturated fatty acids (e.g., oleate) have anti-inflammatory effects, underscoring the importance of fat quality in metabolic health.

2.6 Hypothalamic insulin resistance

Obesity, particularly abdominal obesity, elevates circulating free fatty acids and pro-inflammatory mediators that impair insulin signaling in both peripheral tissues and the central nervous system. Peripheral insulin resistance drives hyperinsulinemia, which can exacerbate central insulin resistance by disrupting hypothalamic leptin signaling and glucose sensing. Central insulin resistance, in

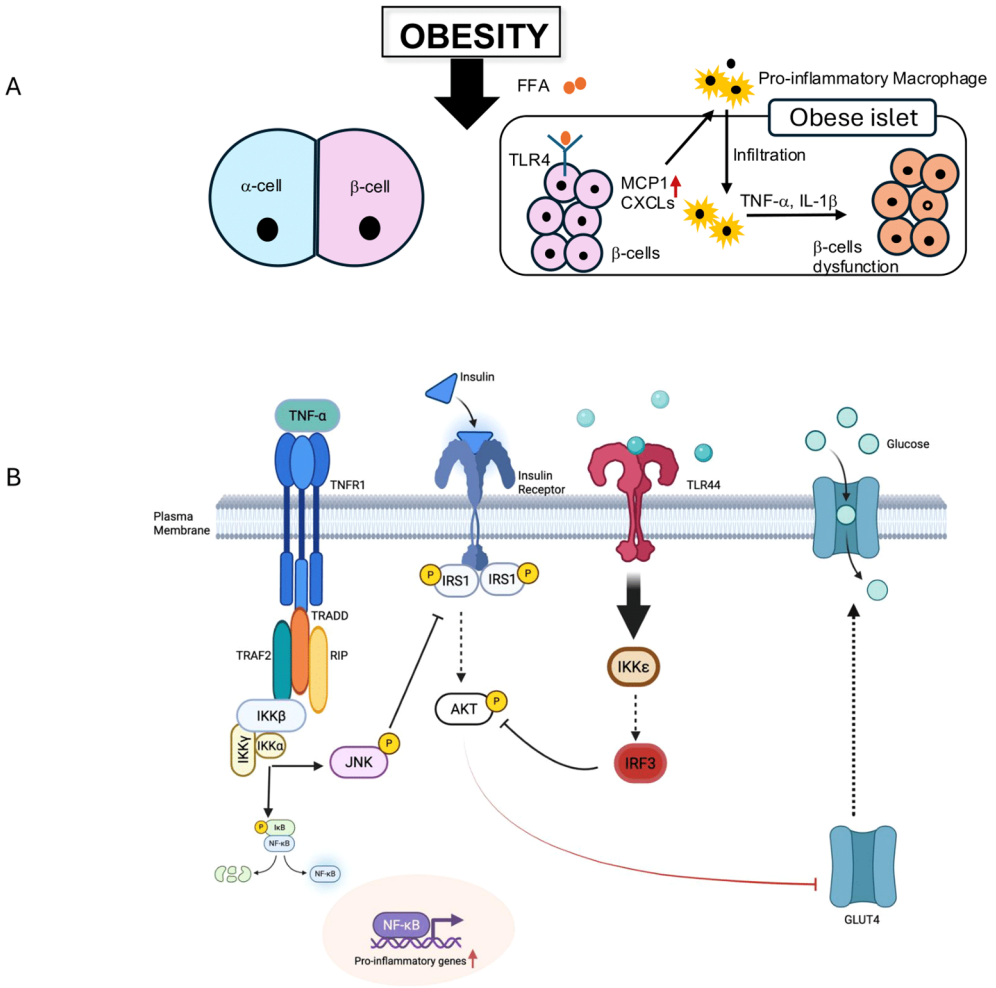

FIGURE 2
Mechanisms of obesity-induced β-cell dysfunction and insulin resistance. **(A)** Obesity leads to increased free fatty acids (FFAs), which activate TLR4 on pancreatic β-cells. This activation, along with other signals, promotes the recruitment of pro-inflammatory macrophages and the production of pro-inflammatory cytokines like TNF-α and IL-1β, leading to infiltration of immune cells into the islet and resulting in β-cell dysfunction. **(B)** A schematic illustrating molecular pathways contributing to insulin resistance and inflammation. TNF-α binds to TNFR1, activating a signaling cascade involving TRADD, TRAF2, RIP, IKKβ, and JNK. IKKβ activation leads to NF-κB activation and the transcription of pro-inflammatory genes. JNK activation phosphorylates IRS1 at Serine residue, inhibiting its ability to signal downstream through AKT, thereby impairing insulin signaling and glucose uptake via GLUT4. Additionally, TLR4 activation by FFAs can directly activate IKKε and IRF3, further contributing to inflammatory responses and insulin resistance.

turn, compromises hypothalamic regulation of appetite, promoting hyperphagia and further weight gain (42). This interplay establishes a self-reinforcing cycle in which peripheral and central insulin resistance mutually exacerbate one another. Dysregulated appetite arises as a key consequence: hyperinsulinemia may enhance hunger, while impaired central insulin signaling reduces the brain's responsiveness to satiety cues, collectively contributing to obesity progression and metabolic dysfunction. In rodent models, overnutrition activates the IKKβ/NF-κB signaling axis in hypothalamic neurons, promoting the production of IL-6 and TNF-α, which disrupt insulin receptor signaling (43, 44).

ER stress and JNK activation impair leptin and insulin action, contributing to hyperphagia and weight gain (45–47). Inflammatory adipokines such as *resistin* and FFAs reach the hypothalamus via the circulation and cerebrospinal fluid, triggering TLR4 activation and promoting serine phosphorylation of IRS-1, which blocks downstream PI3K/AKT signaling (48, 49). Management of insulin resistance targets both peripheral and central mechanisms through lifestyle interventions—caloric restriction, balanced diet, and regular physical activity—which improve peripheral insulin sensitivity and enhance central insulin and leptin signaling, complemented by pharmacological agents when lifestyle measures are insufficient.

2.7 Complement system activation

The complement system, traditionally known for its role in innate immunity, also plays a pivotal role in adipose tissue biology and insulin resistance. Adipose tissue produces complement

components such as *adipsin (Factor D)* and C3, both of which are upregulated in obesity (50–52). Adipsin is required for adipocyte differentiation and survival, while C3-derived products such as C3a and C3adesArg (ASP) influence lipid storage and glucose metabolism (53, 54).

Obese individuals exhibit elevated levels of C3a, which signals through the C3a receptor (C3aR) to promote inflammation and macrophage activation (55). Similarly, C5a and its receptor C5aR mediate immune cell recruitment and cytokine production. While ASP exerts insulin-like effects in lean individuals by promoting triglyceride synthesis, ASP resistance develops in obesity, contributing to dysregulated lipid storage and insulin resistance (56). Dedifferentiation of islet β-cells is increasingly recognized as a central event in the progression of type 2 diabetes mellitus (T2DM) (57). It was observed that complement C3 is elevated in the circulation and islets of T2DM patients and mice, where it drives β-cell dedifferentiation (50). Conversely, treatment with insulin, gliclazide, or metformin lowered C3, Nga3, and Oct4 expression while restoring Pdx1 and MafA, thereby protecting β-cell identity. Mechanistic studies revealed that C3 activates Wnt/β-catenin signaling through phosphorylation of β-catenin, and pathway inhibition effectively blocked C3-induced dedifferentiation. Collectively, these results identify C3 as a key mediator of β-cell dedifferentiation in T2DM and support its inhibition as a potential strategy to preserve β-cell function (58).

3 Obesity in the development and progression of CVDs

Obesity significantly increases the risk of cardiovascular diseases (CVDs) through the complex interplay of metabolic, hemodynamic, inflammatory, and neurohormonal mechanisms. Multiple epidemiological studies have established obesity as a major risk factor for hypertension, dyslipidemia, atherosclerosis, coronary artery disease, and stroke (7, 59). One of the central pathological processes linking obesity to CVD is atherosclerosis, which is exacerbated by the chronic low-grade inflammation, oxidative stress, and metabolic dysregulation characteristic of obesity.

In individuals with obesity, adipose tissue—especially visceral fat—acts as an active endocrine organ that secretes various adipokines (e.g., leptin, resistin, adiponectin), pro-inflammatory cytokines (e.g., TNF-α, IL-6), and chemokines (e.g., MCP-1) (60). These factors promote endothelial dysfunction, vascular inflammation, and lipid accumulation within the arterial wall. Endothelial cells exposed to inflammatory signals upregulate adhesion molecules such as VCAM-1 and ICAM-1, which recruit circulating monocytes into the subendothelial space. These monocytes differentiate into macrophages that engulf oxidized low-density lipoprotein (OxLDL) via scavenger receptors such as CD36 and scavenger receptor A (SRA), transforming into foam cells and initiating fatty streak formation—the earliest visible lesion of atherosclerosis (61) (Figure 3).

Over time, continued lipid accumulation, cellular apoptosis, and inflammatory activation promote the progression of fatty streaks into fibrous plaques. Leptin and resistin, which are elevated in obesity, further aggravate plaque instability by inducing reactive oxygen species (ROS), smooth muscle cell proliferation, and extracellular matrix remodeling. Leptin also enhances platelet aggregation and thrombosis, while resistin impairs endothelial nitric oxide (NO) production, increasing vasoconstriction and reducing vascular repair capacity (62).

Dyslipidemia in obesity—characterized by elevated triglycerides, increased LDL particles (especially small dense LDL), and reduced high-density lipoprotein (HDL)—contributes further to atherogenesis. Insulin resistance exacerbates this dyslipidemia by increasing hepatic very-low-density lipoprotein (VLDL) production and reducing HDL synthesis.

Thus, obesity accelerates every stage of atherogenesis, from endothelial dysfunction to plaque rupture, ultimately heightening the risk of myocardial infarction, stroke, and peripheral arterial disease. Moreover, obesity-related metabolic and inflammatory factors interfere with normal cardiac and vascular physiology even in the absence of overt atherosclerosis, increasing susceptibility to various forms of cardiovascular pathology.

4 Obesity as a pathogenic driver of heart failure

Heart failure (HF) is a major complication of obesity, with pathophysiology extending beyond the contributions of traditional risk factors like hypertension and diabetes. The development of obesity-related HF is a multifactorial process involving hemodynamic overload, structural cardiac remodeling, metabolic derangements, chronic inflammation, and neurohormonal activation (63). In the early stages of obesity, increased blood volume and cardiac output due to expanded adipose tissue mass impose a chronic volume and pressure load on the heart. This hemodynamic stress triggers adaptive left ventricular hypertrophy (LVH) to maintain cardiac output. However, prolonged overload results in maladaptive remodeling, characterized by cardiomyocyte hypertrophy, interstitial fibrosis, and impaired diastolic filling, hallmark features of heart failure with preserved ejection fraction (HFpEF), which is highly prevalent in obese individuals (64).

Chronic low-grade inflammation and oxidative stress, common in obesity, directly contribute to myocardial injury and remodeling. Pro-inflammatory cytokines such as TNF-α and IL-6 activate cardiac fibroblasts, promote extracellular matrix deposition, and reduce myocardial compliance. Insulin resistance induces metabolic inflexibility in the heart, impairing glucose uptake and increasing reliance on fatty acid oxidation. This shift leads to mitochondrial dysfunction and the accumulation of lipotoxic intermediates, which damage cardiomyocytes. Locally, epicardial adipose tissue (EAT), significantly increased in obesity, secretes pro-inflammatory adipokines and cytokines in proximity to the myocardium, exacerbating myocardial fibrosis and coronary microvascular dysfunction.

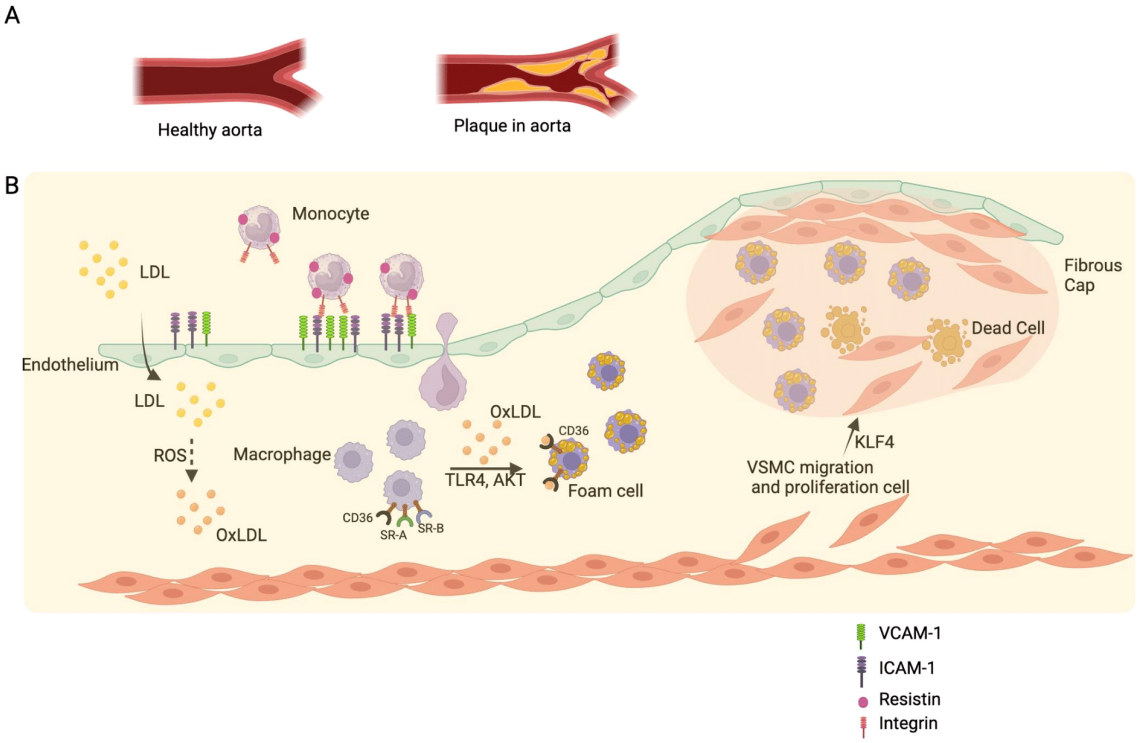

FIGURE 3
Pathogenesis of atherosclerosis. **(A)** Comparison of a healthy aorta with an aorta affected by atherosclerotic plaque. **(B)** Schematic representation of atherosclerotic plaque formation. Low-density lipoprotein (LDL) particles infiltrate the subendothelial space and become oxidized (OxLDL) due to reactive oxygen species (ROS) produced by endothelial cells. Endothelial cells, activated by OxLDL, express adhesion molecules such as VCAM-1 and ICAM-1, which facilitate the recruitment and adhesion of circulating monocytes. Monocytes differentiate into macrophages and engulf OxLDL via scavenger receptors (SR-A, SR-B, CD36) and through TLR4-mediated signaling pathways. This uptake transforms macrophages into foam cells, which accumulate in the subendothelial space. As the lesion progresses, smooth muscle cells (VSMCs) migrate from the media into the intima and proliferate, influenced by factors like KLF4. The accumulation of foam cells, VSMCs, and extracellular matrix components leads to the formation of a fibrous cap overlying a necrotic core composed of dead cells and lipid debris, characteristic of an advanced atherosclerotic plaque.

Neurohormonal systems, including the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS), are activated in obesity. Elevated leptin levels stimulate sympathetic activity, contributing to increased heart rate, vasoconstriction, and sodium retention, thereby increasing cardiac workload (65). Over time, this metabolic and structural strain can lead to a deterioration of systolic function, resulting in heart failure with reduced ejection fraction (HFrEF). Obesity induces significant structural changes in the heart, collectively called cardiac remodeling. These include left ventricular hypertrophy (LVH), increased left ventricular mass, chamber dilation, and concentric or eccentric remodeling. Echocardiographic and MRI studies consistently show that obese individuals exhibit a higher prevalence of LVH, which initially maintains cardiac output but ultimately compromises diastolic filling (66).

Furthermore, obesity significantly elevates the risk of arrhythmias, particularly atrial fibrillation (AF), which contributes to HF morbidity. Arrhythmogenesis is driven by systemic and local myocardial inflammation, oxidative stress, abnormal autonomic tone, and structural changes (67). Leptin and other adipokines can alter cardiomyocyte ion channel expression and electrophysiological properties, prolonging action potential duration and delaying repolarization. Critically, adipose infiltration into the atrial myocardium and interstitial fibrosis create areas of conduction block and re-entry circuits, predisposing to AF. Obesity-related sleep apnea and intermittent hypoxia further exacerbate this arrhythmogenic substrate by increasing sympathetic activity and ROS production (Figure 4).

In summary, obesity drives HF through a convergent path of hemodynamic, metabolic, inflammatory, and structural insults that remodel the heart and disrupt its electrophysiological stability.

5 Conclusion

This review underscores the intricate relationship between obesity and its associated comorbidities, including type 2 diabetes mellitus (T2DM), atherosclerosis, and cardiomyopathy, highlighting potential underlying mechanisms. Numerous studies have shown that obesity promotes chronic low-grade inflammation across multiple tissues. This inflammatory state is characterized by the accumulation and polarization of both innate and adaptive immune cells toward pro-inflammatory phenotypes. Sustained inflammation contributes significantly to the development of insulin resistance and the progression to T2DM.

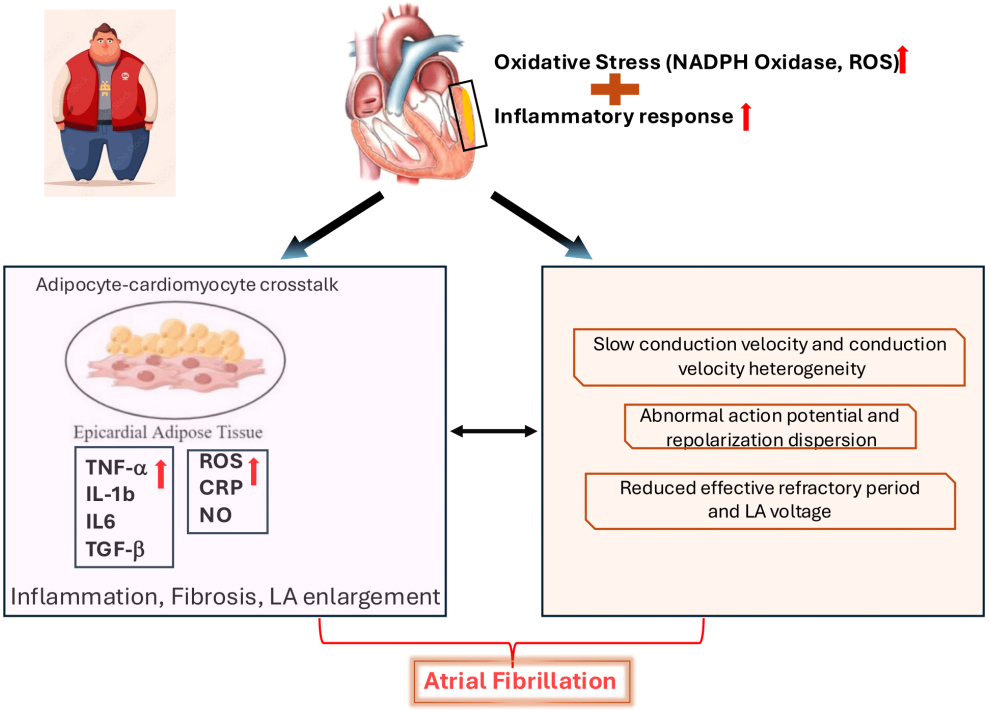

FIGURE 4
Mechanisms linking obesity and atrial fibrillation. In the heart, obesity is associated with increased oxidative stress, primarily through NADPH oxidase and reactive oxygen species (ROS) production, as well as an elevated inflammatory response. These factors directly contribute to electrophysiological abnormalities in the atria, including slow and heterogeneous conduction velocity, abnormal action potentials, increased repolarization dispersion, reduced effective refractory period, and decreased left atrial (LA) voltage, all of which are pro-arrhythmic. Furthermore, obesity leads to changes in epicardial adipose tissue, fostering "adipocyte-cardiomyocyte crosstalk." This involves increased secretion of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6, along with elevated ROS and CRP, while nitric oxide (NO) levels may be altered. This crosstalk promotes inflammation and fibrosis within the atria, leading to LA enlargement. Both the direct cardiac effects (oxidative stress, inflammation, and electrophysiological changes) and the effects mediated by epicardial adipose tissue contribute to the development and maintenance of atrial fibrillation.

In addition to peripheral insulin resistance, obesity impairs insulin sensitivity in the hypothalamus, where the central Resistin/TLR4 signaling axis has been implicated in promoting hypothalamic inflammation and systemic metabolic dysfunction.

Emerging research also emphasizes the multifaceted role of the complement system in obesity-related pathologies. Traditionally recognized for its role in immune surveillance and host defense, the complement system also modulates metabolic inflammation by clearing pathogens and cellular debris. Although it may not serve as a primary driver of disease, the complement system can influence both the initiation and resolution of inflammatory responses, increasingly being recognized as a key contributor to obesity-induced insulin resistance and metabolic dysregulation.

Obesity also heightens the risk of cardiovascular diseases, including hypertension, atherosclerosis, atrial fibrillation, left ventricular remodeling, and heart failure (HF). These risks arise from a complex interplay of metabolic, hemodynamic, and inflammatory mechanisms. Interestingly, despite these risks, multiple studies have observed a lower mortality rate among overweight and obese individuals with pre-existing cardiovascular conditions compared to their leaner counterparts—a phenomenon known as the "obesity paradox."

Although obesity is a well-established risk factor for cardiovascular disease, diabetes, and overall mortality, multiple epidemiological studies have reported an "obesity paradox," in which overweight or moderately obese individuals exhibit better survival in certain chronic conditions, including heart failure, coronary artery disease, chronic kidney disease, and type 2 diabetes. Large cohort studies of heart failure and post–myocardial infarction populations consistently show lower all-cause and cardiovascular mortality among overweight and mildly obese patients compared with those of normal weight. However, these observations are largely derived from observational data and may be influenced by biases such as reverse causation, selection bias, and residual confounding, as well as limitations of body mass index (BMI) in capturing fat distribution and lean mass.

Several mechanisms have been proposed to explain this paradox. Excess adiposity may provide metabolic reserves during acute illness or catabolic stress, protecting against tissue breakdown and malnutrition. Fat distribution is also critical: while visceral fat is strongly associated with adverse metabolic and cardiovascular outcomes, subcutaneous fat may exert protective effects by modulating systemic inflammation and maintaining insulin sensitivity. Adipose tissue secretes bioactive hormones, or

adipokines, such as adiponectin, which possess anti-inflammatory and cardioprotective properties, potentially moderating disease severity. Furthermore, obese individuals often present earlier in the disease course and may receive more intensive medical care, while preserved skeletal muscle mass and higher cardiorespiratory fitness may enhance resilience and survival (68–70).

Recent studies using more precise measures of body composition, including visceral fat quantification, waist-to-hip ratio, and lean mass assessment, suggest that the apparent protective effects of obesity are largely limited to individuals with greater subcutaneous fat and preserved muscle mass. Collectively, these findings indicate that the obesity paradox arises from a combination of physiological mechanisms, fat distribution and adipokine effects, methodological biases, and limitations of traditional anthropometric measures, underscoring the need for nuanced interpretation in clinical practice (71, 72).

Nevertheless, in most individuals, obesity creates a pro-inflammatory milieu that facilitates monocyte recruitment into the vascular wall. These monocytes differentiate into macrophages, which contribute to foam cell formation by engulfing oxidized LDL, initiating the development of atherosclerotic plaques. As global obesity rates rise, so too does the number of individuals at heightened risk for heart failure. Obesity promotes several metabolic disturbances—such as insulin resistance, dysregulated adipokine production, chronic inflammation, and myocardial lipotoxicity—all of which contribute to cardiac dysfunction.

Furthermore, obesity is a key contributor to secondary conditions that exacerbate HF risk, including obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS). It also drives structural, functional, and electrophysiological changes in the myocardium, including ventricular hypertrophy, fibrosis, and arrhythmias. Understanding these interlinked mechanisms is essential for the prevention and management of HF. Moreover, addressing the paradoxical impact of obesity on heart failure outcomes is crucial for guiding evidence-based weight management strategies tailored to individual patient profiles.

6 Future research directions

Future research on obesity must adopt a more holistic and integrative framework that captures its biological complexity and clinical heterogeneity. Rather than focusing solely on BMI as a risk marker, efforts should shift toward understanding how fat distribution, tissue-specific signaling, and systemic inflammatory and endocrine networks interact to shape disease trajectories. Emerging tools—including single-cell and spatial omics, advanced imaging, and systems biology approaches—offer unprecedented opportunities to dissect these pathways in detail and uncover novel therapeutic targets. A deeper exploration of paradoxical observations, such as the protective role of subcutaneous adiposity or the survival advantage seen in certain obese populations, may reveal adaptive mechanisms with broad clinical relevance. Equally important is the integration of mechanistic insights with population-level data to refine risk prediction and guide precision interventions. By embracing this multidimensional approach, the field can move closer to transforming obesity research into actionable strategies that not only prevent and treat comorbidities but also improve long-term health outcomes on a global scale.

Author contributions

DB: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. AM: Funding acquisition, 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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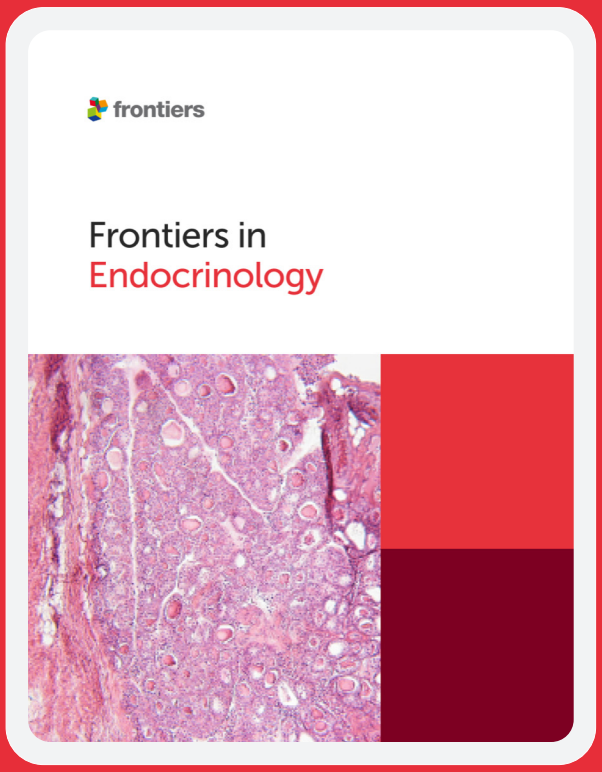

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