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Clinical implications of obesity and lipid-related parameters on cardiometabolic diseases, volume II

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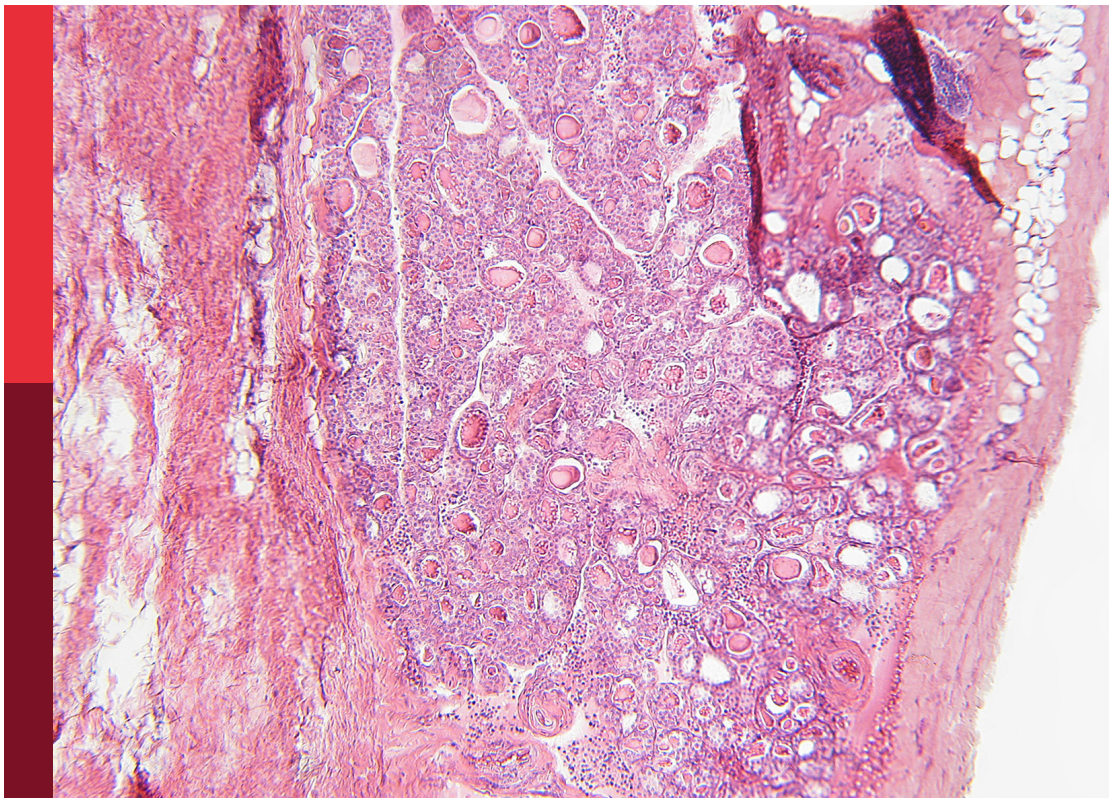

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Clinical implications of obesity and lipid-related parameters on cardiometabolic diseases, volume II

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The association between Chinese visceral adiposity index and cardiometabolic multimorbidity among Chinese middle-aged and older adults: a national cohort study

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Objective: This study aimed to explore the association between the Chinese visceral adiposity index (CVAI) and cardiometabolic multimorbidity in middle-aged and older Chinese adults.

Methods: The data used in this study were obtained from a national cohort, the China Health and Retirement Longitudinal Study (CHARLS, 2011-2018 wave). The CVAI was measured using previously validated biomarker estimation formulas, which included sex, age, body mass index, waist circumference, triglycerides, and high-density lipoprotein cholesterol. The presence of two or more of these cardiometabolic diseases (diabetes, heart disease, and stroke) is considered as cardiometabolic multimorbidity. We used Cox proportional hazard regression models to examine the association between CVAI and cardiometabolic multimorbidity, adjusting for a set of covariates. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to show the strength of the associations. We also conducted a subgroup analysis between age and sex, as well as two sensitivity analyses. Receiver operator characteristic curves (ROC) were used to test the predictive capabilities and cutoff value of the CVAI for cardiometabolic multimorbidity.

Results: A total of 9028 participants were included in the final analysis, with a mean age of 59.3 years (standard deviation: 9.3) and women accounting for 53.7% of the sample population. In the fully-adjusted model, compared with participants in the Q1 of CVAI, the Q3 (HR = 2.203, 95% CI = 1.039 – 3.774) and Q4 of CVAI (HR = 3.547, 95% CI = 2.100 – 5.992) were associated with an increased risk of cardiometabolic multimorbidity. There was no evidence of an interaction between the CVAI quartiles and sex or age in association with cardiometabolic multimorbidity (P >0.05). The results of both sensitivity analyses suggested that the association between CVAI and cardiometabolic multimorbidity was robust. In addition, the area under ROC and ideal cutoff value for CVAI prediction of cardiometabolic multimorbidity were 0.685 (95% CI = 0.649-0.722) and 121.388.

Conclusion: The CVAI is a valid biomarker with good predictive capability for cardiometabolic multimorbidity and can be used by primary healthcare organizations in the future for early warning, prevention, and intervention with regard to cardiometabolic multimorbidity.

KEYWORDS

Chinese visceral adiposity index, cardiometabolic multimorbidity, diabetes, heart disease, stroke, middle-aged and older adults, cohort study

1 Introduction

The prevalence of cardiometabolic diseases, such as cardiovascular diseases, diabetes, and stroke, is an important threat to human health (1), especially among middle-aged and older populations. In recent years, the rate of cardiometabolic multimorbidity (defined herein as the presence of two or more the following cardiometabolic diseases: diabetes, heart disease, and stroke) has increased due to rising global obesity rates (2, 3). A previous large survey of nearly 40,000 people in sub-Saharan Africa showed that the prevalence of cardiometabolic multimorbidity among respondents aged 15-69 years was 4.8% (4), with a prevalence of 14.1% in the 55-69 age group (4). In China, results from a population-based survey of 500,000 people aged 30-79 years showed that the prevalence of cardiometabolic multimorbidity was 6.0% (5). Moreover, multiple studies have confirmed that cardiometabolic multimorbidity is associated with the risk of cognitive decline and dementia (6), higher mortality (7, 8), higher depressive symptoms (9), and lower quality of life (10) compared to single cardiometabolic diseases. Given these health hazards and high prevalence trends, it is important to elucidate the potential risk factors for cardiometabolic multimorbidity and target these factors for early prevention and intervention, which may help reduce the incidence of cardiometabolic multimorbidity.

Evidences from basic biological research and observational studies have identified poor socioeconomic factors (e.g., low income, low education, and a single civil status), unhealthy lifestyles (e.g., smoking, alcohol consumption, and unhealthy diet), and gut metabolite as important factors related to cardiometabolic multimorbidity (11–16). Additionally, studies have explored the association between body measures, such as grip strength (17). Obesity is now widely recognized as the most relevant risk factor for cardiometabolic multimorbidity. A review of 16 cohort studies involving 0.12 million adults in Europe and the United States found that elevated BMI was associated with an increased risk of cardiometabolic multimorbidity (18). Obesity was an important risk factor for cardiometabolic multimorbidity in middle-aged and older people (19). Furthermore, visceral adipose tissue distribution, but not overall obesity, is an independent predictor of cardiometabolic disease (20). Previous Chinese scholars constructed a Chinese visceral adiposity index (CVAI) based on a sample of Chinese people using age, BMI, waist circumference, total triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) (21). The CVAI is a superior predictor of cardiometabolic diseases, such as stroke, diabetes, and cardiovascular disease, compared with BMI (22–24). However, it is unclear whether the CVAI predicts the development of cardiometabolic multimorbidity.

To fill the aforementioned gap in the literature and provide new biomarkers for the prevention of cardiometabolic multimorbidity, our study aimed to explore the association between CVAI and cardiometabolic multimorbidity based on a national cohort.

2 Materials and methods

2.1 Participants

The data used in this study were obtained from a national cohort, the China Health and Retirement Longitudinal Study (CHARLS, 2011-2018 wave). The CHARLS is a nationally representative survey of middle-aged and older adults aged 45 years and older in China. Specific sampling and design details have been reported in the literature (25). We used 17708 participants from the 2011 CHARLS as potential study participants; a total of 9540 participants were included at baseline after excluding participants aged <45 years and those with missing data on CVAI, cardiometabolic multimorbidity, and covariates. We selected the 2013, 2015, and 2018 CHARLS as a follow-up survey, and 9028 participants were included in the cohort analysis after excluding participants with cardiometabolic multimorbidity at baseline, those lost to follow-up, and those with missing cardiometabolic multimorbidity data. CHARLS was approved by the Biomedical Ethics Review Committee of Peking University. Figure 1 shows the selection of participants from the CHARLS cohort.

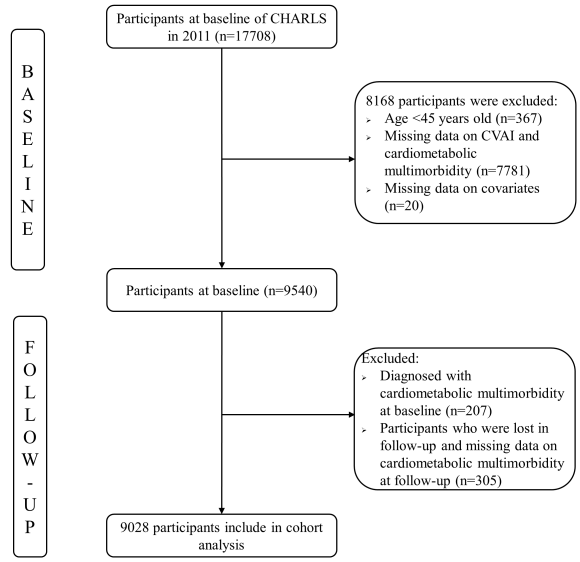

FIGURE 1
The selection process of the participants.

2.2 Measures

2.2.1 CVAI

CVAI was measured using previously validated biomarker estimation formulas (21).

Males: CVAI = −267.93 + 0.68 * age + 0.03 * BMI(kg/m2) + 4.00 * WC(cm) + 22.00 * Log10TG(mmol/L) − 16.32 * HDL-C(mmol/L);

Females: CVAI = −187.32 + 1.71 * age + 4.23 * BMI(kg/m2) + 1.12 * WC(cm) + 39.76 * Log10TG(mmol/L) − 11.66 * HDL-C(mmol/L).

2.2.2 Cardiometabolic multimorbidity

In alignment with previous studies (26), we focused on three cardiometabolic diseases: diabetes, heart disease, and stroke, excluding hypertension. Participants were asked 'Have you been diagnosed with diabetes by a doctor?', 'Have you been diagnosed with heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems by a doctor?' and 'Have you been diagnosed with stroke by a doctor?', respectively. If the participants' answer were yes, they were considered as having the disease. The presence of two or more of these three diseases is considered as cardiometabolic multimorbidity.

2.2.3 Covariates

Socio-demographic characteristics, lifestyle, health status, and blood biomarkers were included as potential covariates. Socio-demographic characteristics included age, sex, residence, marital status, educational level, and family income (truncated by the median into low and high). Lifestyle included smoking, drinking, exercise, and participation in social activities. Health status included pain, self-rated health, health insurance, hypertension, respiratory disease, kidney disease, digestive disease, mental illness, current use of antihypertensive drugs, current use of antidiabetic drugs, and current use of antidyslipidemia drugs. Blood biomarkers included low-density lipoprotein cholesterol (LDL-C, unit: mg/dL), total cholesterol (unit: mg/dL), and fasting blood glucose (unit: mg/dL).

2.3 Statistical methods

In this study, we used the mean ± standard deviation (SD) to describe the distribution status of continuous variables, such as BMI and frequency (composition ratio), to characterize the distribution status of categorical variables, such as sex. To clearly distinguish the association between CVAI values and cardiometabolic multimorbidity, we divided the CVAI into four equal parts according to quartiles: Q1, Q2, Q3, and Q4. We used the Cox proportional hazard regression model to explore the association between CVAI quartiles and cardiometabolic multimorbidity, adjusting for covariates. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to show the strength of the associations. To demonstrate this association, after controlling for different covariates, we constructed three Cox models. Model 1 is not adjusted for any of the variables. Model 2 was adjusted for socio-demographic characteristics. Model 3 was adjusted for lifestyles, health status, and blood biomarkers, which was initially based on Model 2. We conducted subgroup analysis to explore sex and age heterogeneity in the association between CVAI and cardiometabolic multimorbidity. Additionally, two sensitivity analyses were conducted to further assess the robustness of the association. We first excluded participants with hypertension, respiratory disease, kidney disease, digestive disease, mental illness and reran the Cox regression analyses since the CVAIs of these participants may be extremely high or low. Second, we included the CVAI as a continuous variable in the model to determine whether the association between the specific value of the CVAI and cardiometabolic multimorbidity remained statistically significant to exclude artificial loss of information due to the classifications. Finally, we also conducted the receiver operating characteristic curve (ROC) analysis and calculated area under ROC (AUC) to assess the predictive capabilities of the CVAI for cardiometabolic multimorbidity. We used the maximal Youden index to determine ideal cutoff values for CVAI prediction of cardiometabolic multimorbidity by overall, age and sex. All statistical analyses were conducted using STATA 16.0, and the test level for statistical significance was set at $P < 0.05$.

3 Results

3.1 Descriptive statistics

The mean age of the 9028 participants included in the final analysis was 59.3 years (SD: 9.3), with a range of 45–96 years. Of these, 4183 (46.3%) were male, and 4845 (53.7%) were female. The mean CVAI was 98.39 (SD: 50.30). The chi-square test showed statistically significant differences in the distribution of CVAI according to age, sex, residence, marital status, educational level, smoking, drinking, social activity participation, hypertension, kidney disease, digestive disease, cardiometabolic multimorbidity, body mass index, waist circumference, triglyceride level, and high-density lipoprotein cholesterol level. The participants' characteristics are shown in Table 1.

TABLE 1 Characteristics of participants according to CVAI.

Characteristics	Total	Quartiles of CVAI				*P* value
		Q1	Q2	Q3	Q4	
Total sample	9028 (100.0)	2257 (25.0)	2257 (25.0)	2257 (25.0)	2257 (25.0)	
Age, yeas						<0.001
45-59	4921 (54.5)	1421 (63.0)	1299 (57.6)	1194 (52.9)	1007 (44.6)	
≥60	4107 (45.5)	836 (37.0)	958 (42.4)	1063 (47.1)	1250 (55.4)	
Sex						<0.001
Male	4183 (46.3)	1320 (58.5)	1022 (45.3)	883 (39.1)	958 (42.4)	
Female	4845 (53.7)	937 (41.5)	1235 (54.7)	1374 (60.9)	1299 (57.6)	
Residence						<0.001
Rural	7545 (83.6)	2040 (90.4)	1948 (86.3)	1824 (80.8)	1733 (76.8)	
Urban	1483 (16.4)	217 (9.6)	309 (13.7)	433 (19.2)	524 (23.2)	
Marital status						0.003
Married	7922 (87.7)	2020 (89.5)	1989 (88.1)	1975 (87.5)	1938 (85.9)	
Unmarried	1106 (12.3)	237 (10.5)	268 (11.9)	282 (12.5)	319 (14.1)	
Educational level						<0.001
Illiteracy	2612 (28.9)	564 (25.0)	672 (29.8)	698 (30.9)	678 (30.0)	
Middle school below	3738 (41.4)	1007 (44.6)	961 (42.6)	872 (38.6)	898 (39.8)	
Middle school and above	2678 (29.7)	686 (30.4)	624 (27.6)	687 (30.4)	681 (30.2)	
Family income						0.228
Low	4316 (47.8)	1120 (49.6)	1072 (47.5)	1070 (47.4)	1054 (46.7)	
High	4712 (52.2)	1137 (50.4)	1185 (52.5)	1187 (52.6)	1203 (53.3)	
Smoking						<0.001
No	5509 (61.0)	1137 (50.4)	1397 (61.9)	1517 (67.2)	1458 (64.6)	
Yes	3519 (39.0)	1120 (49.6)	860 (38.1)	740 (32.8)	799 (35.4)	
Drinking						<0.001
No	6050 (67.0)	1315 (58.3)	1517 (67.2)	1618 (71.7)	1600 (70.9)	
Yes	2978 (33.0)	942 (41.7)	740 (32.8)	639 (28.3)	657 (29.1)	
Exercise						0.161
Hardly	5303 (58.7)	1343 (59.5)	1343 (59.5)	1280 (56.7)	1337 (59.2)	
Regularly	3725 (41.3)	914 (40.5)	914 (40.5)	977 (43.3)	920 (40.8)	
Social activity participation						<0.001
No	4441 (49.2)	1208 (53.5)	1185 (52.5)	1051 (46.6)	997 (44.2)	
Yes	4587 (50.8)	1049 (46.5)	1072 (47.5)	1206 (53.4)	1260 (55.8)	
Pain						0.678
No	5889 (65.2)	1464 (64.9)	1461 (64.7)	1468 (65.0)	1496 (66.3)	
Yes	3139 (34.8)	793 (35.1)	796 (35.3)	789 (35.0)	761 (33.7)	
Self-rated health						0.077
Excellent	603 (6.7)	128 (5.7)	146 (6.5)	165 (7.3)	164 (7.3)	
Very good	1393 (15.4)	344 (15.2)	336 (14.9)	342 (15.2)	371 (16.4)	

(Continued)

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TABLE 1 Continued

Characteristics	Total	Quartiles of CVAI				*P* value
		Q1	Q2	Q3	Q4	
Good	4394 (48.7)	1158 (51.3)	1119 (49.6)	1069 (47.4)	1048 (46.4)	
Fair	2424 (26.8)	569 (25.2)	609 (27.0)	628 (27.8)	618 (27.4)	
Poor	214 (2.4)	58 (2.6)	47 (2.1)	53 (2.3)	56 (2.5)	
Health insurance						0.338
No	508 (5.6)	112 (5.0)	140 (6.2)	130 (5.8)	126 (5.6)	
Yes	8520 (94.4)	2145 (95.0)	2117 (93.8)	2127 (94.2)	2131 (94.4)	
Hypertension						<0.001
No	6884 (76.3)	1997 (88.5)	1882 (83.4)	1704 (75.5)	1301 (57.6)	
Yes	2144 (23.7)	260 (11.5)	375 (16.6)	553 (24.5)	956 (42.4)	
Respiratory disease						0.128
No	7970 (88.3)	1966 (87.1)	1987 (88.0)	2015 (89.3)	2002 (88.7)	
Yes	1058 (11.7)	291 (12.9)	270 (12.0)	242 (10.7)	255 (11.3)	
Kidney disease						0.001
No	8447 (93.6)	2073 (91.8)	2117 (93.8)	2123 (94.1)	2134 (94.6)	
Yes	581 (6.4)	184 (8.2)	140 (6.2)	134 (5.9)	123 (5.4)	
Digestive disease						<0.001
No	6659 (73.8)	1574 (69.7)	1663 (73.7)	1695 (75.1)	1727 (76.5)	
Yes	2369 (26.2)	683 (30.3)	594 (26.3)	562 (24.9)	530 (23.5)	
Mental illness						0.475
No	8908 (98.7)	2227 (98.7)	2224 (98.5)	2223 (98.5)	2234 (99.0)	
Yes	120 (1.3)	30 (1.3)	33 (1.5)	34 (1.5)	23 (1.0)	
Diabetes						<0.001
No	8167 (90.5)	2162 (95.8)	2120 (93.9)	2021 (89.5)	1864 (82.6)	
Yes	861 (9.5)	95 (4.2)	137 (6.1)	236 (10.5)	393 (17.4)	
Heart diseases						<0.001
No	7463 (82.7)	1966 (87.1)	1897 (84.1)	1849 (81.9)	1751 (77.6)	
Yes	1565 (17.3)	291 (12.9)	360 (15.9)	408 (18.1)	506 (22.4)	
Stroke						<0.001
No	8388 (92.9)	2166 (96.0)	2131 (94.4)	2082 (92.3)	2009 (89.0)	
Yes	640 (7.1)	91 (4.0)	126 (5.6)	175 (7.7)	248 (11.0)	
Cardiometabolic multimorbidity						<0.001
No	8828 (97.8)	2238 (99.2)	2228 (98.7)	2205 (97.7)	2157 (95.6)	
Yes	200 (2.2)	19 (0.8)	29 (1.3)	52 (2.3)	100 (4.4)	
Current use of antihypertensive drugs						<0.001
No	7346 (81.4)	2089 (92.6)	1979 (87.7)	1821 (80.7)	1457 (64.6)	
Yes	1682 (18.6)	168 (7.4)	278 (12.3)	436 (19.3)	800 (35.4)	
Current use of antidiabetic drugs						<0.001
No	8797 (97.4)	2237 (99.1)	2218 (98.3)	2208 (97.8)	2134 (94.6)	

(Continued)

TABLE 1 Continued

Characteristics	Total	Quartiles of CVAI				*P* value
		Q1	Q2	Q3	Q4	
Yes	231 (2.6)	20 (0.9)	39 (1.7)	49 (2.2)	123 (5.4)	
Current use of antidyslipidemia drugs						<0.001
No	8613 (95.4)	2224 (98.5)	2196 (97.3)	2156 (95.5)	2037 (90.3)	
Yes	415 (4.6)	33 (1.5)	61 (2.7)	101 (4.5)	220 (9.7)	
Body Mass Index, kg/m^2	23.47 ± 3.68	20.47 ± 2.44	22.23 ± 2.47	24.12 ± 2.69	27.07 ± 3.31	<0.001
Waist circumference, cm	84.26 ± 12.52	72.11 ± 12.64	81.11 ± 7.47	87.45 ± 6.3	96.37 ± 7.55	<0.001
Triglyceride, mg/dl	133.09 ± 108.47	78.29 ± 36.4	102.29 ± 47.37	134.48 ± 64.05	217.3 ± 168.4	<0.001
HDL-C, mg/dl	51.33 ± 15.32	61.75 ± 16.08	54.5 ± 13.16	48.43 ± 12.11	40.62 ± 10.87	<0.001
LDL-C, mg/dl	116.64 ± 35.02	109.65 ± 30.88	117.04 ± 32.77	121.99 ± 33.83	117.89 ± 40.71	<0.001
Total cholesterol, mg/dl	193.87 ± 38.90	184.86 ± 35.20	190.35 ± 37.28	196.40 ± 37.56	203.88 ± 42.61	<0.001
Fasting blood glucose, mg/dl	109.62 ± 35.24	101.93 ± 23.50	106.50 ± 35.18	109.04 ± 31.84	121.01 ± 44.35	<0.001
CVAI	98.39 ± 50.30	37.85 ± 35.89	81.57 ± 8.71	113.17 ± 9.94	160.96 ± 24.01	<0.001

HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; CVAI, Chinese visceral adiposity index.

3.2 Cox hazard model

Table 2 displays the associations between CVAI quartiles and cardiometabolic multimorbidity. In the unadjusted model, compared with the Q1 of CVAI, the Q3 and Q4 of CVAI were all significantly associated with a high incidence of cardiometabolic multimorbidity. After adjusting for age, sex, residence, marital status, educational level, and family income, the association between CVAI quartiles and cardiometabolic multimorbidity remained significant. In the fully-adjusted model, compared with participants in the Q1 of CVAI, the HRs (95% CIs) of participants in Q2, Q3, and Q4 of the CVAI for the risk of cardiometabolic multimorbidity were 1.358 (0.758 – 2.433), 2.203 (1.286 – 3.774), and 3.547 (2.100 – 5.992), respectively. Additionally, a linear association was observed between the CVAI quartiles and the incidence of cardiometabolic multimorbidity in all Cox models (P <0.001).

3.3 Subgroup analyses

The results of the subgroup analyses for sex and age are presented in Table 3. The association found between the CVAI quartiles and cardiometabolic multimorbidity remained statistically significant (P<0.05) in males and middle-aged adults aged 45-59 years. Meanwhile, only the Q4 of CVAI was associated with an increased risk of cardiometabolic multimorbidity in females and older adults aged 60 years or more. Additionally, there was no evidence of an interaction between the CVAI quartiles and sex or age in association with cardiometabolic multimorbidity (P for interaction >0.05).

3.4 Sensitivity analysis

In the first sensitivity analysis, we excluded participants with hypertension, respiratory disease, kidney disease, digestive disease,

TABLE 2 Associations between CVAI and cardiometabolic multimorbidity.

Quartiles of CVAI	Model 1		Model 2		Model 3	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Q1 (reference)						
Q2	1.529 (0.857-2.727)	0.150	1.450 (0.812-2.592)	0.209	1.358 (0.758-2.433)	0.303
Q3	2.742 (1.622-4.638)	<0.001	2.515 (1.479-4.277)	0.001	2.203 (1.286-3.774)	0.004
Q4	5.308 (3.250-8.669)	<0.001	4.718 (2.861-7.780)	<0.001	3.547 (2.100-5.992)	<0.001
P for trend	<0.001		<0.001		<0.001	

Model 1 is not adjusted for any of the variables. Model 2 was adjusted for socio-demographic characteristics. Model 3 was adjusted for lifestyles, health status, and blood biomarkers, which was initially based on Model 2.

TABLE 3 Subgroup analyses of CVAI and cardiometabolic multimorbidity.

Subgroup	HR (95%CI)	*P*-value	*P* for interaction
Male			
Q1 of CVAI (reference)			
Q2 of CVAI	1.727 (0.692-4.309)	0.242	
Q3 of CVAI	3.655 (1.600-8.347)	0.002	
Q4 of CVAI	5.541 (2.487-12.347)	<0.001	
Female			
Q1 of CVAI (reference)			
Q2 of CVAI	1.053 (0.494-2.244)	0.894	0.495
Q3 of CVAI	1.365 (0.671-2.775)	0.391	0.103
Q4 of CVAI	2.288 (1.130-4.636)	0.022	0.172
Age <60 years			
Q1 of CVAI (reference)			
Q2 of CVAI	0.896 (0.377-2.128)	0.803	
Q3 of CVAI	2.663 (1.307-5.428)	0.007	
Q4 of CVAI	3.223 (1.561-6.658)	0.002	
Age ≥60 years			
Q1 of CVAI (reference)			
Q2 of CVAI	1.725 (0.750-3.966)	0.200	0.235
Q3 of CVAI	1.609 (0.700-3.696)	0.263	0.462
Q4 of CVAI	3.387 (1.548-7.414)	0.002	0.979

and mental illness, and performed a fully-adjusted Cox model. The results showed no substantial change in the association between CVAI quartiles and cardiometabolic multimorbidity (compared with Q1, the HRs of the participants in Q3 and Q4 were 2.708 [95%CI= 1.039-7.055], 3.966 [95%CI= 1.505-10.450]). Additionally, we conducted a second sensitivity analysis using CVAI as a continuous variable. The results suggested that the elevated CVAI values were associated with an increased risk of cardiometabolic multimorbidity (HR= 1.011, 95%CI= 1.007-1.014). The results of both sensitivity analyses suggested that the association between CVAI and cardiometabolic multimorbidity was robust.

3.5 Predictive capability of the CVAI for cardiometabolic multimorbidity

The results of predictive capability of the CVAI for cardiometabolic multimorbidity are presented in Table 4. The AUC of overall, male group, female group, the aged <60 years, and the aged ≥60 was 0.685 (95% CI = 0.649-0.722), 0.702 (95% CI = 0.649-0.759), 0.668 (95% CI = 0.618-0.728), 0.701 (95% CI = 0.647-0.756), and 0.660 (95% CI = 0.610-0.711), respectively. The ideal cutoff value for CVAI prediction of cardiometabolic multimorbidity was 121.388 in total sample. For each group, the following cutoff values were 102.378 in male, 136.554 in female, 101.927 in the aged <60 years group, and 132.568 in the aged ≥60 years group. More details are displayed in Table 4.

4 Discussion

Our study explored the association between CVAI and cardiometabolic multimorbidity among middle-aged and older Chinese adults based on a national cohort. We found a linear association between the CVAI quartiles and the risk of cardiometabolic multimorbidity. Compared with the participants in Q1 of the CVAI, those in Q3 and Q4 had a 135% and 278% higher risk of future cardiometabolic multimorbidity, respectively. The results of ROC analyses indicate that CVAI has good predictive

TABLE 4 Predictive capability of the CVAI for cardiometabolic multimorbidity.

Sample	AUC	95%CI of AUC	Sensitivity	Specificity	Cut-off value	*P*-value
Overtall	0.685	0.649-0.722	0.600	0.691	121.388	<0.001
By sex						
Male	0.702	0.649-0.759	0.741	0.604	102.378	<0.001
Female	0.668	0.618-0.728	0.487	0.772	136.554	<0.001
By age						
Age <60 years	0.701	0.647-0.756	0.742	0.600	101.927	<0.001
Age ≥60 years	0.660	0.610-0.711	0.559	0.711	132.568	<0.001
By sex and age						
Male aged <60 years	0.753	0.675-0.831	0.872	0.583	98.679	<0.001
Male aged ≥60 years	0.653	0.574-0.732	0.833	0.416	78.803	<0.001
Female aged <60 years	0.654	0.580-0.728	0.800	0.479	89.305	<0.001
Female aged ≥60 years	0.652	0.584-0.720	0.609	0.671	136.535	<0.001

capability for cardiometabolic multimorbidity. This study suggests that the CVAI may be a reliable biomarker for predicting the occurrence of cardiometabolic multimorbidities in clinical settings.

The association between CVAI and cardiometabolic diseases has been confirmed in several previous studies. For example, a recent study based on the CHARLS found that an increase in the CVAI predicted the risk of developing future strokes among middle-aged and older adults (23). A U-shaped relationship was also found between CVAI and type 2 diabetes mellitus (27). Additionally, evidence suggests that the CVAI is associated with cardiometabolic multimorbidity. In a cohort study involving more than 2,000 patients with type 2 diabetes, elevated CVAI was found to increase the risk of cardiovascular events (28). Additionally, the risk of stroke in patients with metabolic syndrome increased with increased CVAI (29). A cross-sectional study of Chinese older adults showed a linear association between CVAI and the prevalence of hypertension and diabetes mellitus (30). This observational study provides strong support for our findings. According to the capacity–load model, the risk of cardiometabolic diseases is a combination of the interaction between the metabolic capacity and the load of the body (2). Obesity is thought to increase the metabolic load, leading to impaired metabolic capacity of the body and imbalances in metabolic homeostasis, leading to an increased risk of cardiometabolic diseases (31, 32). Visceral fat is mainly located in the abdominal cavity, and its increase can cause fat cells to spill over into the surrounding organs (liver, kidneys, and heart), resulting in insulin resistance, which impairs the metabolic function of these organs (20). Furthermore, elevated CVAI produces insulin resistance, leading to renal cytokine imbalance and damage to the glomerular basement membrane, initiating metabolic dysfunction in the kidneys (33–35). Additionally, a UK Biobank-based study found that pericardial adipose tissue objectively measured using cardiovascular magnetic resonance imaging significantly and positively correlated with abnormal cardiovascular structure and function (36). It has also been found that increased abdominal adipose tissue induces the production of inflammatory cytokines, leading to an inflammatory response and oxidative stress that impairs vascular endothelial function (37).

The results of the subgroup analysis revealed interesting findings. First, this study found that the association between the CVAI quartiles and cardiometabolic multimorbidity was stronger in males than in females, wherein both the Q3 and Q4 of the CVAI were associated with an increased risk of cardiometabolic multimorbidity, whereas in females only Q4 showed an association. A previous animal study based on obese mice found a stronger pro-inflammatory state in the adipose endothelial cells of male mice than in female mice, indicating that male mice are put at higher risk due to obesity (38). Additionally, animal experiments have shown that obese female mice have a higher glucose tolerance than male mice due to the anti-inflammatory properties of estrogen, which reduces immune cell infiltration and oxidative stress in the adipose tissue of female mice (39). Evidence from animal studies may partially explain our findings, but more population-based studies are needed to further elucidate the causes of these differences due to sex. Another interesting finding was that the association between CVAI quartiles and cardiometabolic multimorbidity was stronger in the middle-aged group aged 45-59 years, compared to that of older adults aged ≥ 60 years. Two previous studies reported similar findings in that the CVAI was more strongly associated with new-onset diabetes (27) and stroke (40) in the middle-aged adults compared to older adults. There exists the persistence of the "obesity paradox" in older adults, wherein the all-cause mortality is lower in the overweight BMI group compared with the normal BMI group (41). It has also been found that overweight and mildly obese individuals have a lower prevalence of cardiovascular disease and a better prognosis (42, 43). This may partially support our finding that the Q4 of the CVAI is associated with a higher risk of cardiometabolic multimorbidity in the older adult group, but not Q3. Given that only a few studies have directly explored the associations and biological mechanisms of CVAI with health outcomes in older adults, future in-depth animal experiments or long-term cohort studies are required to validate our findings.

This study has strengths in terms of its research design and analytical strategy. First, it used population-representative data from a large national epidemiological survey, which may allow our findings to be extrapolated to the entire Chinese middle-aged and elderly population. The findings of this study have a high practical value in guiding the early warning and prevention of cardiometabolic morbidity in middle-aged and elderly people, such as the incorporation of CVAI as a biomarker for cardiometabolic morbidity in primary health care. Additionally, several confounders in our statistical analyses were controlled, and subgroup analyses for age and sex were also performed, which allowed us to detect possible differences in different groups and to estimate more accurately the association between CVAI and cardiometabolic multimorbidity. A sensitivity analysis was also conducted to test the robustness of the findings. Finally, we also analyzed the predictive capability and optimal cutoff value of CVAI for cardiometabolic multimorbidity, which can be used by healthcare professionals. However, this study has some limitations. First, although we used a cohort study with a high level of evidence to explore the association between CVAI and cardiometabolic multimorbidity, observational studies were limited since these could not infer causality. In the future, causal inference methods, such as Mendelian randomization or experimental study designs, should be used to elucidate the causal relationship between the two. Second, due to database limitations, the CHARLS did not have records on the dietary, precise physical activity, specific drug usage (such as statins and antiplatelet drugs) from the participants at the time of the survey, which may lead to the omission of covariates in our study, resulting in confounding bias. Third, we excluded participants with missing variables in the baseline survey and those lost to follow-up, which created a selection bias. Finally, cardiometabolic multimorbidity was self-reported. Since the participants were tasked to report their physician-diagnosed disease, this may have been subject to recall bias.

5 Conclusions

Elevated CVAI was significantly associated with a higher risk of cardiometabolic multimorbidity in middle-aged and older Chinese adults. The CVAI was found to be a valid biomarker with good

predictive capability for cardiometabolic multimorbidity and can be used by primary healthcare organizations in the future for early warning, prevention, and intervention in cardiometabolic multimorbidity.

Data availability statement

The datasets presented in this article are not readily available because the data of this study can be obtained on the official website of CHARLS. Requests to access the datasets should be directed to http://charls.pku.edu.cn/.

Ethics statement

The studies involving humans were approved by Biomedical Ethics Review Committee of Peking University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XY: Conceptualization, Formal Analysis, Methodology, Software, Writing – original draft. GZ: Formal Analysis, Methodology, Writing – original draft. CH: Validation, Writing – review & editing. PW: Validation, Writing – review & editing. JL: Supervision, Writing – review & editing. MZ: Supervision, Writing – review & editing, Funding acquisition, Project administration.

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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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Influence of nonalcoholic fatty liver disease severity on carotid adventitial vasa vasorum

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Introduction: Nonalcoholic fatty liver disease (NAFLD) affects a quarter of the world's population and encompasses a spectrum of liver conditions, from non-alcoholic steatohepatitis (NASH) to inflammation and fibrosis. In addition, NAFLD also links to extrahepatic conditions like diabetes or obesity. However, it remains unclear if NAFLD independently correlates with the onset and progression of atherosclerosis.

Material and methods: This cross-sectional study aimed to explore the relationship between NAFLD severity, assessed via liver biopsy, and early atherosclerosis using adventitial vasa vasorum (VV) density. It included 44 patients with obesity (33 with steatosis, 11 with NASH) undergoing bariatric surgery.

Results: Results revealed no significant differences in adventitial VV density between steatosis and NASH groups, neither in the mean values [0.759 $\pm$ 0.104 vs. 0.780 $\pm$ 0.043, P=0.702] nor left-right sides. Similarly, carotid intima-media thickness (cIMT) did not vary between these groups. Additionally, no linear correlation existed between VV density and cIMT. Only gender showed an association with VV density.

Conclusion: These findings suggest that NASH severity doesn't independently drive early atherosclerosis or affects cIMT. Gender might play a role in early atherosclerotic disease in NAFLD, impacting VV density and cIMT. This highlights the need to consider other risk factors when evaluating cardiovascular risk in NAFLD patients.

KEYWORDS

atherosclerosis, vasa vasorum, vascular disease, nonalcoholic fatty liver disease, obesity

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent and potentially life-threatening illness that has become the world's most common chronic liver disease, as well as the second most common indication for liver transplant (1, 2). It affects around a quarter of the world's population (95% CI 22.1-28.6), and this prevalence continues to increase globally, exacerbated by the obesity epidemic (3, 4). NAFLD is a heterogeneous disease that encompasses a spectrum of conditions, ranging from simple steatosis to cirrhosis and hepatocellular carcinoma with an intermediate stage known as non-alcoholic steatohepatitis (NASH) (5). NASH is characterized by inflammation, fibrosis and the onset of structural changes in the liver (6, 7). In addition to its impact on liver health, NAFLD is strongly associated with extrahepatic diseases such as obesity, insulin resistance, type 2 diabetes mellitus, hypertension, atherogenic dyslipidemia, and alterations in the gut microbiome (8). Furthermore, certain studies have demonstrated the involvement of oxidative stress, procoagulant factors, and systemic inflammation mediators, including interleukin 6, tumor necrosis factor α, and C-reactive protein, in NAFLD pathogenesis (9, 10).

It has been proposed that the presence of NAFLD also contributes to vascular inflammation and tone, thereby promoting the development of endothelial dysfunction and atherosclerotic plaques, ultimately heightening the risk of cardiovascular (CV) disease (9–11). However, a consensus regarding whether NAFLD is independently associated with an increased CV risk in the absence of other established risk factors is lacking (12). Furthermore, its correlation with surrogate markers of CV disease, such as carotid intima-media thickness (cIMT), aortic stiffness, brachial artery vasodilatory responsiveness, and coronary artery calcification, remains to be fully elucidated (9, 10, 13, 14).

While cIMT currently stands as one of the most widely employed predictors of atheromatosis (15), a growing body of evidence substantiates the notion that the atheromatous process initiates earlier, involving hyperplasia and pathological expansion of the adventitial vasa vasorum (VV) into the avascular intima (16). Consequently, the visualization of adventitial VV holds the potential to detect atherosclerosis development well in advance of any discernible increase in cIMT, thereby facilitating the early identification of individuals at elevated risk of CV disease. Despite this, the impact of NAFLD on VV structure and function remains unexplored.

Thus, the objective of our study was to assess whether the severity of NAFLD, diagnosed via liver biopsy, correlates with the onset and progression of atherosclerosis by examining the VV. To achieve this, we conducted a single-center cross-sectional study involving 44 patients with severe obesity (33 patients with simple hepatic steatosis and 11 patients with NASH) who subsequently underwent bariatric surgery.

Materials and methods

Ethical considerations

The research conducted in this study received approval from the Human Ethics Committee at Arnau de Vilanova University Hospital (CEIC-1275). The details of the study protocol were provided to all patients scheduled for a bariatric procedure in 2017, and they were extended an invitation to take part. Those patients who chose to participate provided their informed consent through a signed written document. The study adheres to the ethical principles outlined in the 1975 Declaration of Helsinki. Importantly, this was an observational study, and as such, it did not necessitate registration as a clinical trial.

Study population

We assessed the density of adventitial VV based on the presence of NAFLD in a single-center analytical cross-sectional study involving 33 individuals with simple steatosis and 11 cases with NASH. The study was conducted at the Arnau de Vilanova University Hospital from Lleida (Lleida, Spain). Using the standard deviation (SD) of adventitial VV determined from a previous investigation, we calculated that a minimum sample size of 35 subjects was required (17). Thus, we contacted all 73 individuals scheduled for a programmed bariatric procedure in 2017 and invited them to participate in an outpatient clinic visit before the procedure.

While all 73 patients met the eligibility criteria for gastrointestinal surgery as outlined in the National Institutes of Health Consensus Conference guidelines (18), we excluded nine individuals for various reasons: previous bariatric surgery or use of anti-obesity medication (n=3), history of prior cardiovascular event (n=2), reported alcohol consumption ≥20g/day in women or 30mg/day in men (n=2), glomerular filtration rate below 60 ml/min/per 1.73 m^2 (n=1), and chronic steroid treatment (n=1). See the flowchart of the study in Figure 1. Additionally, 6 patients declined to participate, and 6 patients were excluded from the final analysis due to technical issues (rapid contrast clearance impeding proper VV density assessment or missing reports of VV or cIMT).

Upon availability of liver biopsy data, 4 patients were excluded for having a healthy liver and 4 patients were excluded due to hepatic conditions others than NAFLD (2 cirrhosis and 2 hemochromatosis). Ultimately, a total of 44 patients who underwent bariatric surgery were included in the study. Pregnant women and individuals with active neoplasms, recent cardiac instability, severe pulmonary hypertension, or class III or IV heart failure were not included.

Data collection

All measurements, including anthropometric assessments, blood tests, medical history documentation, and contrast-enhanced ultrasound (CEU) of the carotid artery were conducted during the month prior to the scheduled surgery, except for the liver biopsy, which was performed during the surgery itself.

Height and weight were conducted following established protocols, and body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m^2) (19). Blood samples were obtained after an overnight fast, typically between 8:00 and 10:00 AM, from the antecubital vein. Subsequently, the samples were subjected to centrifugation (2000g at 4 °C for 20 minutes), and aliquots were stored at -80°C for later batched analyses. Standard techniques were employed for the determination of biochemical parameter at the clinical biochemistry laboratory within our hospital. Smoking status (never, former, or current smoker) was also obtained. Smokers who quit smoking a year or more before the visit were considered non-smokers.

Standard and contrast-enhanced carotid ultrasound

CEU was utilized to assess carotid adventitial VV density, employing a Siemens Sequoia 512 ultrasound system equipped with a 15L8W linear array probe and ultrasound contrast software utilizing cadence-contrast pulse sequencing technology. A contrast agent composed of a phospholipid shell encapsulating sulphur hexafluoride was introduced (Sonovue; Bracco Spa, Milan, Italy). Following solubilization in 5 ml of saline, a 2.5ml bolus of the contrast agent was administered via the antecubital vein for each explored carotid artery, using a 20-gauge needle to prevent microbubble rupture.

Quantification of adventitial VV content in the far adventitial layer involved determining the average ratios of intensities above the intima-lumen boundary by 2mm and the intensities below the media-adventitia boundary by 2mm within the common carotid artery, situated 1cm proximal to the bifurcation. The resulting value, denoted as VV signal, was computed as the average of the t10 to t20 ratios derived from diastolic frames characterized by both

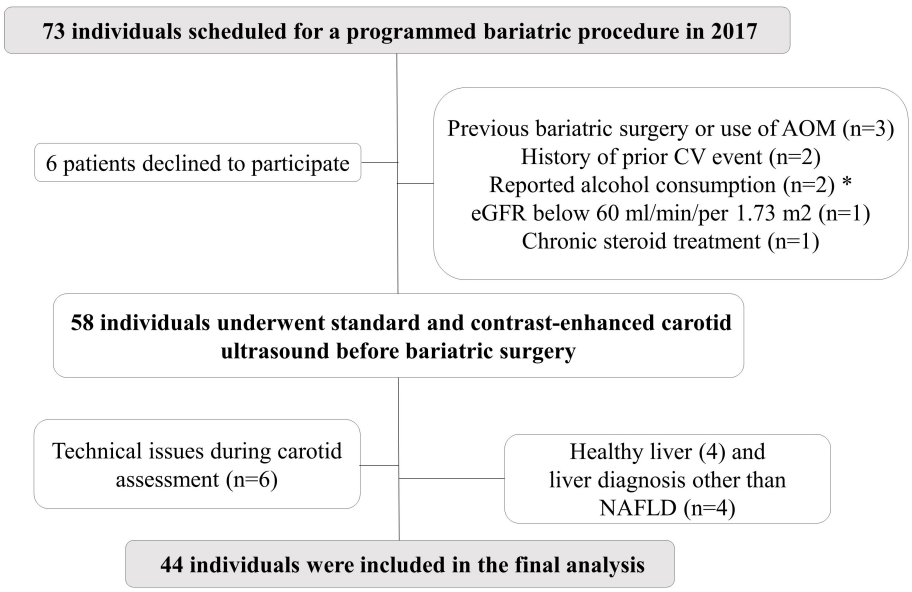

FIGURE 1
Flowchart of the study population. AOM, anti-obesity medications; CV, cardiovascular; eGFR, estimated glomerular filtration rate; NAFLD, nonalcoholic fatty liver disease. *: ≥20g/day in women or 30mg/day in men.

high and stable lumen and adventitial intensities within a 1-minute video recording (17, 20). VV measurements were performed for both the right and left carotid arteries, and the mean signal for both sides was presented. As a ratio, VV signal lacks units. All CEU studies were digitally stored for subsequent analysis and quantified by an investigator who remained blind to the data.

Additionally, all participants underwent B-mode ultrasound examination of the extracranial carotid arteries to determine the common carotid arteries far wall cIMT, in accordance with previous descriptions (21). We used a Vivid-I ultrasound machine (General Electric Healthcare, Waukesha, WI, USA) coupled with a 12 L-RS linear array transducer probe (5–13 MHz). Measurements of cIMT were taken at 1 cm proximal to the bifurcation, at 1 cm within the bifurcation, and in the initial cm of the internal carotid (22). Segments with atheromatous plaques, denoted by a focal intima-media thickness 1.5 mm extending into the lumen, were excluded from these measurements.

Liver biopsy

During the bariatric surgery, a wedge liver biopsy was conducted following the established routine surgical protocol. A tissue sample measuring approximately 10x5 mm was obtained from the subcapsular region of the left lobe, specifically segment III as per the Couinaud classification (23). The liver biopsy specimens were fixed in formalin and subsequently embedded in paraffin. An experienced pathologist performed the histopathological evaluation using a semiquantitative approach in accordance with the Clinical Research Network for Nonalcoholic Liver Disease recommendations (24). The reported histopathological findings encompassed the percentage of hepatocytes with both macro and microvesicular steatosis, the identification of Mallory bodies, the presence of fibrosis, as well as the existence of lobular or portal inflammation. The quantification of hepatocytes with steatosis was accomplished through a visual semiquantitative method, with liver steatosis defined as the presence of fatty infiltration in over 5% of hepatocytes. Additionally, the NAFLD activity score (NAS) was determined, along with the presence or absence of nonalcoholic steatohepatitis (NASH). A NAS score of ≥5 and the occurrence of hepatocyte ballooning, on the other hand, identified NASH (24).

Statistical analysis

The normal distribution of variables was assessed using the Shapiro-Wilk test and evaluating skewness and kurtosis. Continuous variables with a normal distribution were presented as mean values ± SD, while non-normally distributed variables were reported as median and interquartile range (IQR). Categorical variables were presented as percentages. Group differences were compared using the Student t-test for normally distributed data, the Mann-Whitney U test for non-normally distributed data, and χ^2 for categorical variables. Prior to conducting the Student t-test, the homogeneity of variances was examined using the Levene test. Furthermore, a correlation analysis between VV density and the other variables was conducted by calculating Spearman's correlation coefficient (rho).

To explore variables independently associated with adventitial VV density, stepwise multivariate regression analyses were employed. The independent variables included in the analyses were age, gender, blood pressure, type 2 diabetes, BMI, serum aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, glycated hemoglobin, fasting plasma glucose, low density lipoproteins cholesterol, triglycerides, and the presence of simple steatosis or NASH. A separate analysis was conducted to explore the independent variables associated with cIMT. All p-values were derived from two-sided tests of statistical significance, and significance was accepted at the level of $P < 0.05$. The statistical analyses were carried out using the Stata statistical package (StataC version 16).

Results

Table 1 displays the primary clinical characteristics and metabolic data of the study population. Among the participants, thirty-three individuals (75%) exhibited simple steatosis, while eleven were diagnosed with NASH based on liver biopsy findings. Although a greater proportion of males was noted among patients with NASH, no discernible distinctions were observed in terms of age, BMI, and smoking history. Likewise, both groups showed similarities in metabolic parameters encompassing glucose metabolism, lipid metabolism, and liver profile.

TABLE 1 Baseline main clinical and metabolic characteristics of patients in the study.

	Simple steatosis (n=33)	Nonalcoholic steatohepatitis (n=11)	P
Age (years)	46.3 ± 11.3	51.1 ± 9.6	0.884
Woman, n (%)	30 (90.9)	3 (27.2)	0.034
BMI (kg/m^2)	45.3 ± 6.3	42.3 ± 6.2	0.086
Non-smoker, n (%)	10 (30.3)	6 (54.5)	0.975
Type 2 diabetes, n (%)	21 (63.6)	7 (63.6)	0.635
Fasting plasma glucose (mg/dl)	104 (96 to 116)	114 (95 to 175)	0.349
HbA1c (%)	5.7 (5.2 to 6.3)	6.9 (5.7 to 7.9)	0.109
c-LDL (mg/dl)	110.4 ± 33.0	104.5 ± 33.8	0.307
Triglycerides (mg/dl)	140 (106 to 157)	142 (94 to 223)	0.550
Hypertension, n (%)	18 (54.5)	5 (45.4)	0.601
AST (UI/I)	21 (18 to 25)	22 (16 to 27)	0.817
ALT (UI/I)	27 (17 to 33)	23 (15 to 35)	0.455
GGT (UI/I)	29 (17 to 33)	30 (19 to 49)	0.870

Data are mean ± SD, median (interquartile range) or n (percentage). BMI, body mass index; HbA1c, glycated hemoglobin; c-LDL, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl aminotransferase.

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TABLE 2 Baseline mean adventitial VV density according to steatosis or steatohepatitis condition.

	Simple steatosis (n=33)	Nonalcoholic steatohepatitis (n=11)	P
VV mean	0.759 ± 0.104	0.780 ± 0.043	0.702
VV right	0.765 (0.693 to 0.850)	0.762 (0.647 to 0.952)	0.654
VV left	0.717 (0.639 to 0.783)	0.678 (0.624 to 0.882)	0.935
cIMT mean (mm)	0.702 ± 0.140	0.775 ± 0.112	0.934
cIMT right (mm)	0.700 ± 0.150	0.769 ± 0.132	0.903
cIMT left (mm)	0.718 ± 0.163	0.801 ± 0.147	0.916

Data are mean ± SD or median (interquartile range). VV, vasa vasorum; cIMT, carotid intima-media thickness. Regarding the data from the four patients who were initially excluded due to a diagnosis of healthy liver from the liver biopsy, their mean VV and cIMT were 0.691 ± 0.092 and 0.666 ± 0.171, respectively. There were no significant differences between the groups (healthy liver, simple steatosis, and nonalcoholic steatohepatitis) in the ANOVA analysis (p = 0.471 and p = 0.689, respectively).

Upon evaluating adventitial VV density in both groups, no discernible differences emerged between patients with simple steatosis and NASH, neither in the mean values [0.759 ± 0.104 vs. 0.780 ± 0.043, P=0.702] nor in the left nor right side (Table 2). Similarly, no variations were observed when measuring cIMT in both groups.

In the univariate analysis, we did not observe any significant correlations between mean adventitial VV and cIMT (r=0.041, P=0.795), BMI (r=-0.017, P=0.908), and systolic blood pressure (r=0.028, P=0.854), nor with the other analytical variables (Table 3; Figure 2).

TABLE 3 Linear correlations between mean adventitial vasa vasorum density and clinical, anthropometric, and analytical variables in the entire study population.

	r	P-value
GGT (UI/I)	-0.193	0.208
HbA1c (%)	0.192	0.210
Triglycerides	0.153	0.321
Fasting plasma glucose (mg/dl)	0.106	0.493
c-LDL (mg/dl)	-0.102	0.508
AST (UI/I)	-0.076	0.623
cIMT (mm)	0.041	0.795
ALT (UI/I)	-0.034	0.823
Systolic blood pressure (mmHg)	0.028	0.854
BMI (kg/m^2)	-0.017	0.908

GGT, gamma-glutamyl aminotransferase; HbA1c, glycated hemoglobin; c-LDL, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; cIMT, carotid intima-media thickness; ALT, alanine aminotransferase; BMI, body mass index;

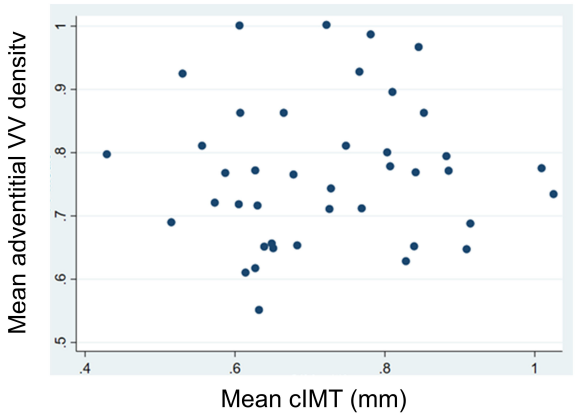

FIGURE 2
Linear correlations between mean adventitial vasa vasorum (VV) density and mean carotid intima-media thickness (cIMT).

In the stepwise multiple linear regression analysis, only gender demonstrated an association with the mean adventitial VV density, while the degree of NAFLD and the other variables did not show significant associations (Table 4). Indeed, the mean adventitial VV density was significantly higher in men when compared to women within the entire group (0.856 ± 0.137 vs. 0.747 ± 0.102, P=0.009), as well as in patients with steatosis (0.881 ± 0.096 vs. 0.747 ± 0.784, P=0.016). On the other hand, age and gender but not the severity of NAFLD were found to be the sole variables independently associated with cIMT, with no significant association observed with the mean VV density (Table 5).

TABLE 4 Stepwise multiple linear regression analysis of variables associated with the mean adventitial VV density.

Mean adventitial vasa vasorum density		
	Point Estimation (beta)	P-value
Gender (women)	-0.206	0.005
GGT (UI/I)	-0.001	0.106
BMI (kg/m^2)	0.006	0.154
Systolic BP (mmHg)	-0.027	0.154
c-LDL (mg/dl)	<0.001	0.195
Steatosis/Steatohepatitis	-0.061	0.199
Age (years)	0.003	0.255
HbA1c (%)	0.042	0.291
AST (UI/I)	0.004	0.306
Triglycerides (mg/dl)	<0.001	0.347
Fasting plasma glucose (mg/dl)	-0.000	0.434
ALT (UI/I)	-0.002	0.457

GGT, gamma-glutamyl aminotransferase; BMI, body mass index; BP, blood pressure; c-LDL, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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TABLE 5 Stepwise multiple linear regression analysis of variables associated with the mean carotid intima-media thickness.

Mean carotid intima-media thickness		
	Point Estimation	P-value
Age (years)	0.008	0.001
Gender (women)	-0.016	0.033
c-LDL (mg/dl)	0.001	0.106
Fasting plasma glucose (mg/dl)	-0.001	0.121
Triglycerides (mg/dl)	<0.001	0.184
BMI (kg/m^2)	0.004	0.277
VV mean (mm)	-0.210	0.280
HbA1c (%)	0.041	0.299
Steatosis/Steatohepatitis	-0.028	0.556
AST (UI/I)	0.001	0.718
GGT (UI/I)	<0.001	0.910
ALT (UI/I)	<0.001	0.934
Systolic BP (mmHg)	-0.003	0.945

c-LDL, low-density lipoprotein cholesterol; BMI, body mass index; VV, vasa vasorum; HbA1c, glycated hemoglobin; AST, aspartate aminotransferase; GGT, gamma-glutamyl aminotransferase; ALT, alanine aminotransferase; BP, blood pressure.

Discussion

To the best of our knowledge, this study represents the first attempt to evaluate whether NAFLD itself plays a role in the initiation of atherosclerosis, as assessed by adventitial VV density, in patients with severe obesity. Our findings indicate that early stages of atheromatosis are not conditioned by the presence of inflammation and fibrosis within the liver. In our investigation, a comparison of adventitial VV density (mean, right, and left sides) between patients with simple steatosis and those with NASH, characterized by inflammation progressing through fibrosis and structural liver changes, failed to reveal significant differences. Likewise, there was minimal discernible difference in cIMT between patients diagnosed with simple steatosis and NASH.

While CV disease stands as the primary cause of mortality in individuals with NAFLD, consensus remains elusive regarding whether NAFLD confers increased cardiovascular risk independently of established risk factors (10, 12). The co-occurrence of NAFLD and these CV risk factors complicates epidemiological studies seeking to discern whether liver changes contribute to CV disease. In line with this, a 2020 expert consensus has proposed replacing the term NAFLD with a more accurate descriptor: Metabolic Associated Fatty Liver Disease (MAFLD) (25, 26). Targher et al., through a meta-analysis encompassing 16 studies and 34,043 subjects, found NAFLD to correlate with fatal and non-fatal cardiac events, a relationship that intensified with NAFLD severity (27). Conversely, Wu et al. reported, in a meta-analysis of 34 studies and 164,949 subjects, significant associations between NAFLD and increased prevalence of atherosclerosis and CV disease, while failing to establish significant NAFLD-CV disease mortality or overall mortality links (28). In concurrence, a more recent meta-analysis by Liu et al. involving 24 studies and 498,501 subjects demonstrated elevated all-cause mortality risk in NAFLD patients (HR = 1.34, 95% CI 1.17-1.54), but again failed to establish a significant link between NAFLD and CVD mortality (29). In our study, we did not observe any differences in the prevalence of CV risk factors, such as type 2 diabetes, hypertension, or dyslipidemia, between patients with simple steatosis and NASH. This reinforces the idea that the severity of NAFLD does not have an impact in the initial phases of atheromatous disease.

Prior studies have explored the relationship between NAFLD and surrogate markers of CV disease and endothelial dysfunction, such as cIMT, aortic stiffness, brachial artery vasodilatory responsiveness, and coronary artery calcification (30–36). However, our study is unique in its assessment of early morphofunctional changes in the arterial wall based on NAFLD stage, showing that NASH is not associated with increased VV density. In advanced stages of atherosclerotic disease, a study involving 4,222 individuals in Germany revealed a notable increase in carotid atherosclerotic plaque prevalence among those diagnosed with hepatic steatosis through ultrasound (30). However, even after accounting for CV risk factors, no significant differences in cIMT were observed (30). Additionally, Styczycnski et al.'s study of 120 patients with severe obesity who underwent bariatric surgery found no association between aortic stiffness and NAFLD severity defined by wedge liver biopsy (36). Conversely, other studies have yielded affirmative findings in the association between steatosis and atherosclerotic disease. For example, a 5 years longitudinal study including 728 men and 497 women free of hypertension and type 2 diabetes at the baseline noted accelerated arterial stiffness progression in NAFLD individuals, regardless of metabolic syndrome presence (35). Similarly, in 52 NAFLD cases and 28 age- and sex-matched controls, NAFLD correlated with reduced brachial artery vasodilatory response to ischemia (31). Two Korean studies involving 1,854 and 10,153 individuals, respectively, reported elevated coronary artery calcification scores in NAFLD patients (32, 33). While our approach aligns with the gold standard method for diagnosing non-alcoholic fatty liver disease, most of these studies relied on ultrasound-based NAFLD diagnoses, potentially skewing participant inclusion toward advanced steatosis and metabolic abnormalities (30, 32–35).

Our study also demonstrated the absence of a linear correlation between adventitial VV density and cIMT in patients with severe obesity, suggesting that we may be assessing different stages in the development of atheromatous disease, with different etiopathogenic factors and clinical situations responsible for their stimulation. This data further supports the notion that NAFLD exerts limited influence on the early phases of atheromatous disease when evaluated in two different ways. Insights into the absence of association between NAFLD and CV disease association may also emerge from naturally occurring mutations in genes affecting liver fat content (11, 37, 38). Recent evidence highlights genetic variants predisposing to NAFLD that lack a corresponding elevated CV disease risk in the absence of metabolic syndrome components (39, 40). Supporting this, a mendelian randomization study of two large European cohorts found no causal link between NAFLD and CV disease (40).

Surprisingly, modifiable factors such as blood pressure, type 2 diabetes, and lipid profile did not emerge as independent predictors

of VV density, with only gender demonstrating such influence. Therefore, our results underscore gender's role in atherosclerotic disease, influencing etiology, clinical presentation, and prognosis of patients with cardiovascular disease (41–43). Evidence suggests that atheromatous disease manifests 10 to 15 years earlier in men than women, particularly during reproductive age. Postmenopausal women face increased CV disease risk due to estrogen secretion cessation, leading to comparable incidence rates between older women and men (42, 44). In our relatively younger study population with severe obesity, over half of whom exhibited type 2 diabetes or hypertension, gender may contribute to VV density differences. These results align with previous research by Akabame et al. and Wong et al., which indicated a gender imbalance in CV disease rates (65% male vs. 35% female; 70.8% male vs. 29.2% female, respectively) (45, 46). Moreover, our study suggests that male gender's negative impact may extend to initial CV disease stages, as indicated by an independent association with increased VV density and increased cIMT in multiple regression analysis.

Several limitations merit discussion regarding our study. Primarily, its cross-sectional design precludes both causality and longitudinal follow-up. Additionally, data collection from a single hospital potentially limits representation of the broader fatty liver disease population. Notably, VV density and cIMT were measured solely in NAFLD patients, precluding a comparison to histologically normal liver individuals. However, measurements from 141 overweight men and women without established coronary heart disease or a risk equivalent, such as diabetes, from a multiracial and multiethnic population in the metropolitan area of Chicago, Illinois, showed results similar to those described in our study for both for the average median adventitial VV ratio (0.80 ± 0.19) and cIMT (0.82 ± 0.22) (47). Second, our study's small sample size, including 11 NASH patients and 33 with simple steatosis, constitutes a further limitation and precludes to generalize our results to the entire population. However, both groups exhibited comparable clinical and biochemical profiles except for gender, bolstering our findings. Of significant note, our study utilized incidental liver biopsies conducted during scheduled bariatric procedures to diagnose cases of simple steatosis and steatohepatitis. While this approach aligns with the gold standard method for diagnosing NAFLD, it is worth mentioning that certain other liver biopsy studies employed a selection criterion of elevated transaminase levels, suggestive of the presence of NASH and more advanced metabolic abnormalities. Finally, previous studies have demonstrated the negative impact of BMI on VV density and cIMT (48). In our study, although BMI does not appear as a variable independently associated with adventitial VV density, the lack of BMI variability among the study population, which consists of individuals with severe obesity who underwent bariatric surgery, should be kept in mind for future studies.

In summary, our findings suggest that NASH does not contribute to increased VV density or cIMT compared to simple steatosis. This study emphasizes the complex interplay between NAFLD and CV disease, highlighting the importance of considering other risk factors when evaluating cardiovascular risk in NAFLD patients. Further research is needed to understand the nuanced relationships between NAFLD, atherosclerosis, and gender in larger, more diverse populations.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Human Ethics Committee at Arnau de Vilanova University Hospital (CEIC-1275). 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

JL-M: Conceptualization, Formal analysis, Investigation, Software, Writing – original draft, Writing – review & editing. ES: Conceptualization, Investigation, Writing – review & editing. FH: Investigation, Writing – review & editing. MC: Investigation, Writing – review & editing. MS: Investigation, Writing – review & editing. JV: Methodology, Writing – review & editing. MB-L: Data curation, Methodology, Writing – review & editing. EC: Conceptualization, Investigation, Writing – review & editing. JP: Investigation, Writing – review & editing. XM-G: Investigation, Writing – review & editing. FV: Investigation, Writing – review & editing. AC: Supervision, Writing – review & editing. MBu: Data curation, Writing – review & editing. RM: Data curation, Writing – review & editing. AL: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, 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

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Association between the triglyceride glucose index and atherosclerotic cardiovascular disease in the general population: analysis of the national health and nutrition examination survey 1999–2004

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Objective: The triglyceride-glucose (TyG) index, a reliable substitute indicator of insulin resistance (IR), is considered an independent risk factor for long-term outcomes in patients with cardiovascular disease. However, studies investigating the association between TyG and atherosclerotic cardiovascular disease (ASCVD) are limited and lack direct evidence. We aim to examine the relationship between the TyG index and ASCVD through a comprehensive cross-sectional study.

Methods: Overall, 7212 participants from the 1999–2004 National Health and Nutrition Examination Survey were included. The baseline TyG index was calculated as ln [fasting triglyceride (mg/dL) × fasting blood glucose (mg/dL)/2]. Restricted cubic spline (RCS) regression, univariate logistic regression, and multivariate logistic regression analysis were used to evaluate the association between the TyG index and ASCVD.

Results: In the overall population, a multivariate logistic regression analysis showed that the TyG level was not only positively associated with ASCVD [OR (95%CI): 1.29 (1.01,1.64), *P*=0.042], coronary artery disease (CAD) [OR (95%CI): 1.82(1.33,2.48), *P*<0.001], and stroke [OR (95%CI): 2.68(1.54,4.69), *P*=0.002], but also linearly correlated with all three (*P*-overall<0.001; *P*-non-linear >0.05). Although the TyG index was not associated with peripheral arterial disease (PAD) [OR (95%CI): 1.00 (0.73,1.36), *P*>0.900], it showed a U-shaped correlation with PAD (*P*-overall <0.001; *P*-non-linear= 0.0085), and the risk of PAD was minimized when TyG=8.67. By incorporating the TyG index into the baseline risk model, the accuracy of ASCVD prediction was improved [AUC: baseline risk model, 0.7183 vs. baseline risk model + TyG index, 0.7203, *P* for comparison=0.034]. The results of the subgroup analysis were consistent with those of the main analysis.

Conclusion: The TyG index was independently associated with ASCVD, CAD, and stroke, suggesting that it may serve as a valid indicator for predicting ASCVD in the entire population.

KEYWORDS

triglyceride-glucose index, atherosclerotic cardiovascular disease, coronary artery disease, ischemic stroke, peripheral arterial disease

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a general term for a group of diseases caused by atherosclerosis that involve blood vessels and the heart throughout the body (1–4), including coronary artery disease (CAD), ischemic stroke, and peripheral arterial disease (PAD), which is the leading cause of death (5–8). It is well known that both triglyceride (TG) and fasting blood glucose (FBG) abnormalities are prone to ASCVD. However, FBG and TG as single indicators are limited in predicting the occurrence of ASCVD, and invasive tests, such as angiography are time-consuming and costly. If a simple and inexpensive clinical indicator can be developed for the early identification of ASCVD risk groups, it will be of great clinical value for the prevention and treatment of this disease.

Insulin resistance (IR) contributes to CAD and plays a key role in the development of type 2 diabetes and atherosclerotic disease (9–11). The hyperinsulinemic hyperglycemic clamp is considered to be the gold standard for quantifying insulin sensitivity. However, it is not commonly used in clinical practice because it is not only expensive, but also time-consuming and labor-intensive to measure. Thus, the homeostasis model assessment of insulin resistance (HOMA-IR) has been proposed as an alternative. Notably, the clinical utility of HOMA-IR is limited owing to the limitations of the insulin measurement methods and their susceptibility to confounding factors. Patients with IR tend to have disturbed glucose and lipid metabolism, which induces a series of inflammatory responses and oxidative stress (12, 13). Based on this theoretical background, the triglyceride-glucose (TyG) index calculated using TG and FBG was proposed as a convenient IR marker in 2008 (14). Similar to other IR markers, the TyG index has been shown to be associated with the risk of several chronic diseases related to diabetes, cardiovascular disease, stroke, and renal microvascular injury (15–20). However, there is limited research on the relationship between the TyG index and ASCVD, particularly due to the lack of validation in large-scale studies based on the general population. To address this knowledge gap, this study selected 7212 adults in the United States who participated in the National Health and Nutrition Examination Survey (NHANES) survey from 1999–2004 to explore the relationship between the TyG index and ASCVD by a cross-sectional study.

Materials and methods

Study population

The data for this cross-sectional study were obtained from the NHANES database, a large general population-based cross-sectional survey led by the National Center for Health Statistics (NCHS) that collected information on the health and nutrition of household populations in the United States. This national survey used a complex, multistage, stratified sampling design to identify participants, and oversampled certain populations to ensure a representative sample. This survey has been released every two years since 1999; additionally, all data were validated by the National Center for Health Statistics before being made public and available to the entire population. The NHANES survey was approved by the National Health and NCHS Research Ethics Review Board, and informed consent was obtained from all participants. The NHANES survey data for each period and detailed survey operation manuals, consent forms, and brochures are publicly available on the NHANES website (https://www.cdc.gov/nchs/nhanes).

Adult participants from the 1999–2004 NHANES database were selected to investigate the relationship between the TyG index and ASCVD risk. A total of 31,126 NHANES participants from to 1999–2004 were initially included in this study; 11,518 participants with missing TG and FBG and 12,396 participants with missing outcome indicators of CAD, stroke, or PAD were excluded, and a final total of 7,212 participants were included in this study (Figure 1).

Exposure variable and outcomes

The baseline information of the participants, such as sex, age, ethnicity, household income, education, alcohol and smoking status, and medical history (including hypertension, diabetes, cardiovascular diseases, stroke, and prescription medication use) were obtained from the household interview questionnaire. Physical examination information, such as height, weight, and blood pressure was obtained at mobile screening centers. After resting for at least 5 min, the technician measured the blood pressure in the participant's right arm using an automated manometer. The systolic

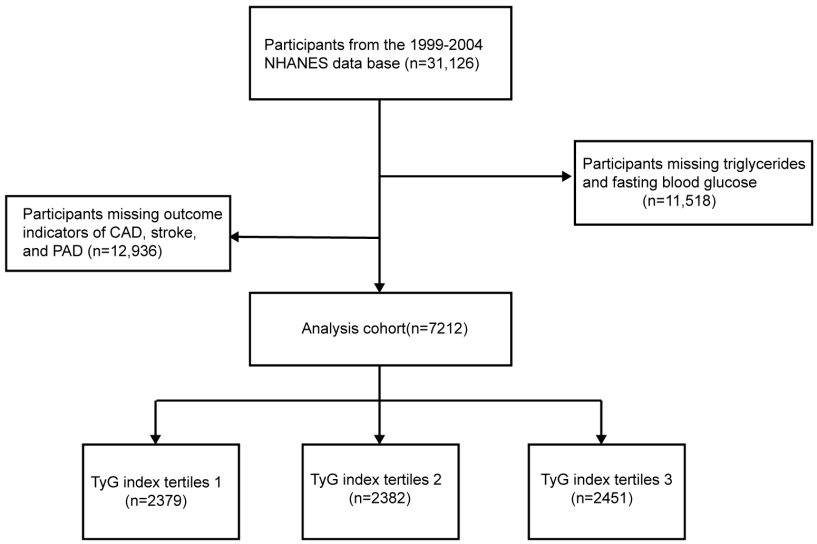

FIGURE 1
Flow chart for the enrollment of study population.

blood pressure was measured in both arms (brachial artery) and ankles (posterior tibial artery) using an 8 MHz Doppler probe. The ankle-brachial blood pressure index (ABPI) was calculated as the ratio of the mean systolic pressure of the tibial artery to that of the brachial artery. The participants were requested to fast for more than 8 h before blood samples were drawn to determine the total cholesterol (TC), TG, FBG, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glycosylated hemoglobin A1C (HbA1C) levels, a process that took place at a mobile examination center (MEC). All biological samples were sent to the nearest collaborating laboratory for testing, and all physical examinations and laboratory tests were performed in accordance with the relevant guidelines.

ASCVD was defined as CAD, stroke, or PAD in arterial disease. The diagnosis of CAD and stroke was based on the patients' previous diagnoses or current symptoms due to data constraints from the NHANES survey. CAD was defined as a previous diagnosis of coronary heart disease, angina pectoris, or a heart attack. Stroke was defined as having been diagnosed by a doctor or professional health advisor that had a stroke. As no questionnaires specifically related to the PAD diagnosis and symptoms were available, we relied on the ABPI as a measurement to define PAD. ABPI provides an effective means of assessing the stenosis between the aorta and ankle by measuring the ratio of ankle artery pressure to the central blood pressure. It exhibits a higher sensitivity than symptomatic diagnosis and has been widely adopted (21, 22). In line with the consensus document by the American Diabetes Association, we defined ABPI<0.9 as indicative of Peripheral Arterial Disease (PAD) (23). The primary outcome was ASCVD and the secondary outcomes were CAD, stroke, and PAD. Notably, the following were used for analyses: 1) HOMA-IR = fasting blood glucose (FBG, mmol/L) × fasting insulin (μU/mL)/22.5; 2) TyG index= ln [fasting TG (mg/dL) × FBG (mg/dL)/2]. Diabetes was defined as follows: 1. Previous diagnosis of diabetes or current use of oral hypoglycemic medication/insulin; 2. Fasting blood glucose level >7 mmol/L; and 3. HbA1c>6.5%. Hypertension was defined as a history of hypertension, current antihypertensive medication use, or maximum systolic blood pressure greater than 140 mmHg/ maximum diastolic blood pressure greater than 90 mmHg. Alcohol consumption was defined as a frequency of alcohol consumption >=1 drink/month in the past 12 months.

Statistical analysis

Statistical analyses were performed using R 4.3.0, and a *P*-value <0.05 was considered statistically significant. While performing the data analyses, we considered sample weights to correct for differential selection probabilities, compensate for possible deficiencies in the eligible population, and adjust for non-coverage and non-response. The missing covariates were supplemented using random forest-based multiple interpolation. TyG was categorized as T1, T2, or T3 based on the tertiles. Quantitative information was expressed using mean ± standard deviation (SD), and qualitative information was expressed as a percentage. Differences in the baseline information between groups with different TyG indices were explored using a variance analysis or the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. In addition, a restricted cubic spline (RCS) curve was constructed to evaluate the linear or nonlinear relationships between the TyG index and ASCVD, CAD, stroke, and PAD. The associations between TyG levels and ASCVD, CAD, stroke, and PAD were estimated using multifactorial logistic regression models with 95% confidence intervals (CI). The confounding variables were selected based on the significant differences between the TyG index and risk factors significantly associated with ASCVD. Model 1 is unadjusted. Model 2 was

adjusted for age, sex, race, education, and household poverty index (PIR) based on Model 1. Model 3 was adjusted for smoking, alcohol consumption, hypertension, diabetes, HDL-C, LDL-C, FBG, HbA1c, TG, TC, and insulin levels based on Model 2. To evaluate the improvement of the TyG index compared to HOMA-IR, FBG, and TG in traditional ASCVD prediction models, we combined the baseline risk model with each of them to create four new models, analyzed the diagnostic value using receiver operating characteristic curves (ROCs), and calculated the area under the curve to quantify the predictive effect of the four models. The Net Reclassification Improvement (NRI) and Integrated Discriminant Improvement (IDI) were also tested to explore the predictive efficacies of HOMA-IR, FBG, and TG for ASCVD. In addition, we performed sensitivity analyses for specific subgroups, such as sex, age, hypertension, diabetes, and BMI, and used *P* interaction tests to determine whether the confounders interacted with exposure factors.

Results

Characteristics of the population stratified by the triglyceride glucose index

The baseline characteristics of the study population are presented according to the TyG tertiles in Table 1. A total of 7212 participants were enrolled in this study, of which 3691 (51.2%) participants were male, with a mean age of 60.26 years. Notably, 1841 (25.5%) participants were eligible for the diagnosis of ASCVD, 840 (11.6%) participants had CAD, 300 (4.2%) participants had stroke, and 1054 (14.6%) participants had PAD. The ranges of TyG index for T1-T3 were <8.41, 8.41–8.93, and >8.93, respectively. Individuals with higher TyG levels included more non-Hispanic whites, more males, were older on average, and had a higher prevalence of a variety of disorders, such as hypertension, diabetes, CAD, stroke, PAD, and ASCVD. In

TABLE 1 The characteristics of participants according to TyG index.

Variable	Overall (n=7212)	T1 (n=2379)	T2 (n=2382)	T3 (n=2451)	*P* value
Male (%)	3691 (51.2)	1086 (45.6)	1207(50.7)	1398 (57.0)	<0.001
Race (%)					<0.001
Mexican American	1530 (21.2)	341 (14.3)	528 (22.2)	661 (27.0)	
Other Hispanic	275 (3.8)	68 (2.9)	104 (4.4)	103 (4.2)	
Non-Hispanic White	3959 (54.9)	1313 (55.2)	1322 (55.5)	1324 (54.0)	
Non-Hispanic Black	1238 (17.2)	593 (24.9)	356 (14.9)	289 (11.8)	
Other/multiracial	210 (2.9)	64 (2.7)	72 (3.0)	74 (3.0)	
Age (years)	60.26(13.08)	58.30 (13.53)	61.49 (13.10)	60.96 (12.39)	<0.001
Education (%)					<0.001
Less than high school	2423 (33.6)	680 (28.6)	819 (34.4)	924 (37.7)	
High school graduate or equivalent	1678 (23.3)	540(22.7)	561 (23.6)	577 (23.5)	
Some college or above	3111 (43.1)	1159 (48.7)	1002 (42.1)	950 (38.8)	
PIR	2.78 (1.61)	2.98 (1.64)	2.76 (1.59)	2.60 (1.59)	<0.001
BMI (kg/m2)	28.43 (5.62)	26.71 (5.37)	28.83 (5.85)	29.72(5.18)	<0.001
HbA1c	5.78 (1.13)	5.41 (0.52)	5.59 (0.64)	6.31 (1.63)	<0.001
FBG (mg/dl)	102.23(38.16)	89.44 (11.02)	95.58 (16.13)	121.12(57.93)	<0.001
TG (mg/dl)	154.45(145.94)	73.26 (18.05)	125.45(23.77)	261.45(207.72)	<0.001
HDL-C (mg/dl)	52.66 (16.19)	61.49 (16.87)	52.52 (14.43)	44.23 (12.09)	<0.001
LDL-C (mg/dl)	126.47 (37.76)	118.47 (32.13)	129.44(34.33)	131.35(39.02)	<0.001
ALT (u/l)	25.95 (30.72)	24.22 (45.34)	25.48 (20.21)	28.07 (19.45)	<0.001
AST (u/l)	25.94 (25.47)	26.07 (36.95)	25.80 (19.87)	25.94 (14.17)	0.934
TC (mg/dl)	207.55 (41.05)	195.29 (35.91)	206.97(37.15)	220.02 (45.44)	<0.001
Insulin (uU/ml)	13.03 (15.79)	9.47 (17.05)	17.42 (16.47)	12.08 (12.35)	<0.001

(Continued)

TABLE 1 Continued

Variable	Overall (n=7212)	T1 (n=2379)	T2 (n=2382)	T3 (n=2451)	*P* value
Smoke (%)					<0.001
Never	3338 (46.3)	1177 (49.5)	1128 (47.4)	1033 (42.1)	
Past	1397 (19.4)	463 (19.5)	408 (17.1)	526 (21.5)	
Current	2477 (34.3)	739 (31.1)	846 (35.5)	892 (36.4)	
Drinking (%)	4828 (66.9)	1648 (69.3)	1573 (66.0)	1607 (65.6)	0.012
HOMA-IR	3.61 (5.86)	2.15 (4.70)	2.92 (3.28)	5.71 (7.88)	<0.001
Diabetes (%)	1266 (17.6)	139 (5.8)	296 (12.4)	831 (33.9)	<0.001
Hypertension (%)	4295 (59.6)	1232 (51.8)	1467 (61.6)	1596 (65.1)	<0.001
CAD (%)	840 (11.6)	191 (8.0)	283 (11.9)	366 (14.9)	<0.001
Stroke (%)	300 (4.2)	59 (2.5)	116 (4.9)	125 (5.1)	<0.001
PAD (%)	1054 (14.6)	326 (13.7)	333 (14.0)	395 (16.1)	0.034
ASCVD (%)	1841 (25.5)	509 (21.4)	608 (25.5)	724 (29.5)	<0.001

PIR, poverty index; BMI, body mass index; HbA1c, Glycosylated Hemoglobin, Type A1C; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; CAD, coronary artery disease; PAD, peripheral arterial disease; ASCVD, atherosclerotic cardiovascular disease; T, tertile.

addition, a higher TyG index was associated with higher blood indices including FBG, TG, HOMA-IR, ALT, HbA1c, LDL-C, TC, and other blood markers. Table 2 demonstrated the baseline characteristics of the population grouped according to ASCVD, and the results showed that ASCVD was more common in people who were Non-Hispanic White, older, male, less educated, poorer, smokers, alcohol drinkers, hypertensive, and diabetic. Moreover, patients with ASCVD tended to have higher blood biochemicals, such as TyG, FBG, TG, and HbA1C.

Trend test between TyG index and primary and secondary outcomes

RCS regression was used to explore the dose-response relationship between the TyG index and primary and secondary outcomes (Figure 2). The results showed that the TyG index was linearly correlated with ASCVD (*P* for nonlinearity=0.088), CAD (*P* for nonlinearity=0.592), and stroke (*P* for nonlinearity=0.442). Therefore, T1 was chosen as the reference when constructing the

TABLE 2 The characteristics of participants according to ASCVD.

Variable	Overall (n=7212)	Non-ASCVD (n=5371)	ASCVD (n=1841)	*P* value
Male (%)	3691 (51.2)	2623 (48.8)	1068(58.0)	<0.001
Race (%)				<0.001
Mexican American	1530 (21.2)	1186 (22.1)	344 (18.7)	
Other Hispanic	275 (3.8)	231 (4.3)	44 (2.4)	
Non-Hispanic White	3959 (54.9)	2829 (52.7)	1130(61.4)	
Non-Hispanic Black	1238 (17.2)	963 (17.9)	275 (14.9)	
Other/multiracial	210 (2.9)	162 (3.0)	48 (2.6)	
Age (years)	60.26(13.08)	58.08 (12.53)	66.59 (12.56)	<0.001
Education (%)				<0.001
Less than high school	2423 (33.6)	1709 (31.8)	714 (38.8)	
High school graduate or equivalent	1678 (23.3)	1257(23.4)	421 (22.9)	
Some college or above	3111 (43.1)	2405 (44.8)	706 (38.3)	

(Continued)

TABLE 2 Continued

Variable	Overall (n=7212)	Non-ASCVD (n=5371)	ASCVD (n=1841)	*P* value
PIR	2.78 (1.61)	2.86 (1.62)	2.55 (1.58)	<0.001
BMI (kg/m2)	28.43 (5.62)	28.39 (5.63)	28.56 (5.58)	0.250
HbA1c	5.78 (1.13)	5.72 (1.10)	5.93 (1.20)	<0.001
FBG (mg/dl)	102.23(38.16)	100.44 (36.12)	107.45 (43.16)	<0.001
TG (mg/dl)	154.45(145.94)	152.17 (146.79)	161.12(143.24)	0.023
HDL-C (mg/dl)	52.66 (16.19)	53.44 (16.38)	50.38 (15.42)	<0.001
LDL-C (mg/dl)	126.47 (35.76)	128.46 (35.51)	120.66(35.87)	<0.001
ALT (u/l)	25.94 (30.72)	26.64 (34.52)	23.90 (14.7)	<0.001
AST (u/l)	25.94 (25.47)	26.25 (28.81)	25.02 (10.92)	0.074
Cholesterol (mg/dl)	207.55 (41.05)	209.88 (39.91)	200.77(43.52)	<0.001
Insulin (uU/ml)	13.03 (15.79)	12.08 (10.89)	15.80 (24.92)	<0.001
Smoke (%)				<0.001
Never	3338 (46.3)	2600(48.4)	738 (40.1)	
Past	1397 (19.4)	1082 (20.1)	315 (17.1)	
Current	2477 (34.3)	1689(31.4)	788 (42.8)	
Drinking (%)	4828 (66.9)	3637 (67.7)	1191 (64.7)	0.012
Diabetes (%)	1266 (17.6)	798 (14.9)	468 (25.4)	<0.001
Hypertension (%)	4295 (59.6)	2960 (55.1)	1335 (72.5)	<0.001

The abbreviations are annotated as in Table 1.

multivariable logistic regression models for ASCVD, CAD, and stroke. Additionally, the TyG index demonstrated a U-shaped relationship with PAD (*P* for nonlinearity=0.009), with the smallest odds ratio at TyG = 8.67. Therefore, T2 was selected as the reference for developing the PAD model.

Association of TyG index with ASCVD in overall population

The final confounders included in the model were sex; age; race; education; PIR; FBG, TG, HbA1c, AST, ALT, LDL-C, HDL-C and TC levels; creatinine; hypertension; diabetes mellitus; smoking; and alcohol consumption. The multivariate logistic regression analysis demonstrated an association between the TyG levels and the risk of ASCVD, CAD, stroke, and PAD (Table 3). Regarding the risk of ASCVD, the OR and 95% CI for the largest tertile (T3) over the smallest tertile (T1) was [1.75 (1.46,2.11); *P*<0.001) in the unadjusted model 1, [1.47 (1.19,1.81); *P*<0.001) in the partially adjusted model 2, and [1.29 (1.01, 1.64], *P*=0.042) in the fully adjusted model 3. Compared with T1, the risk of CAD in T3 was significantly higher in the unadjusted model 1 [OR (95%CI): 2.52 (1.96, 3.25), *P*<0.001], partially adjusted model 2 [OR (95%CI): 2.12 (1.61, 2.79), *P*<0.001], and fully adjusted model 3 [OR (95%CI): 1.82 (1.33, 2.48), *P*<0.001] The risk of stroke was significantly increased at the highest TyG level compared to the lowest TyG level in model1 [OR (95%CI): 2.71(1.82, 4.03), *P*<0.001], model2 [OR (95%CI): 2.43 (1.57, 3.75), *P*<0.001], and model3[OR (95%CI): 2.68(1.54, 4.69), *P*=0.002]. The risk of PAD with different TyG levels was not statistically significant in the all-adjusted model [OR (95%CI): 1.00 (0.73, 1.36), *P*>0.900] (Table 3). In addition, individuals with higher TyG levels have a greater risk of ASCVD (*P* for trend<0.001), CAD (*P* for trend<0.001), and stroke (*P* for trend=0.002) (Table 3).

Incremental effect of the TyG index for predicting ASCVD

We incorporated traditional cardiovascular risk factors, such as sex, age, race, total cholesterol, LDL-C, hypertension, diabetes, smoking, and alcohol consumption, into the baseline risk model. Subsequently, we individually introduced the TyG index, HOMA-IR, FBG level, and TG level to construct four new models. The predictive performance of these models was evaluated by plotting ROC curves and calculating the AUC. Notably, our analysis revealed that only the inclusion of the TyG index [AUC: baseline risk model, 0.7183 vs. baseline risk model + TyG index, 0.7203, *P*=0.034] significantly improved the base model, with an NRI of 0.009 (*P*=0.110) and an IDI of 0.002 (*P*<0.001) (Table 4). However, the addition of HOMA-IR [AUC: baseline risk model, 0.7183 vs. baseline risk model + HOMA-IR index, 0.7184, *P*=0.747], FBG [AUC: baseline risk model, 0.7183 vs. baseline risk model + FBG, 0.7185, *P*=0.516], and TG

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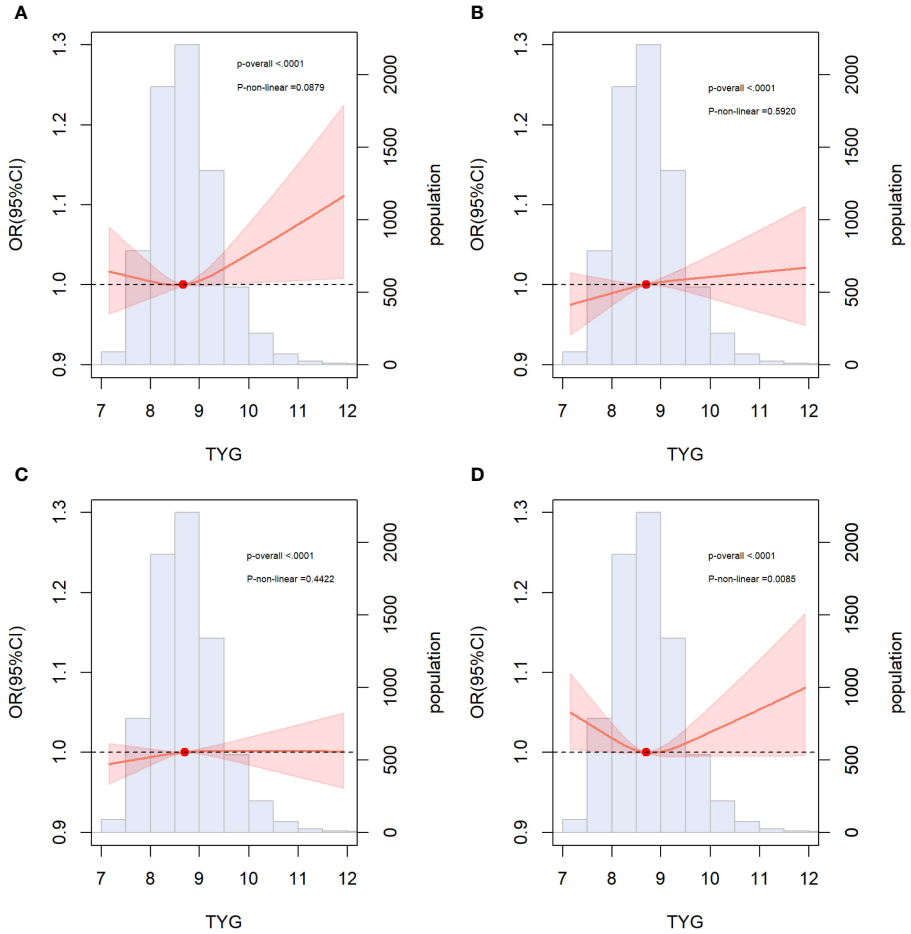

FIGURE 2
Restricted cubic spline curves for ASCVD, CAD, stroke and PAD by TyG index after covariate adjustment. **(A)** Relationship between TyG index and ASCVD; **(B)** Relationship between TyG index and CAD; **(C)** Relationship between TyG index and stroke **(D)** Relationship between TyG index and PAD. The threshold of statistical significance was set as $P<0.05$. The histograms represented the distribution of people with different TYG index. ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; PAD, peripheral arterial disease.

[AUC: baseline risk model, 0.7183 vs. baseline risk model + TG index, 0.7196, $P=0.095$] did not lead to a statistically significant enhancement in model performance (Figure 3).

Sensitive analysis of association of TyG with ASCVD

The results of the subgroup analysis stratified by sex, age, diabetes, hypertension, and BMI are shown in Figure 4. Overall, the participants in the highest TyG index tertile had significantly higher odds of developing ASCVD in subgroups. Notably, significant interactions were observed between the TyG index and sex (P for interaction <0.001) and age (P for interaction = 0.032), and no interaction was found for the other confounding variables. Furthermore, the TyG index was positively associated with the incidence of ASCVD in female individuals [OR (95% CI): 1.66 (1.11,2.47) and middle-aged individuals [OR (95% CI): 1.54 (1.02, 2.34]). Building upon these findings, we further explored the relationship between the TyG index and ASCVD in subgroups stratified by sex and age using multivariate-adjusted RCS analysis. As shown in Figure 5, while a linear association trend between the TyG index and ASCVD was observed in all subgroups (P for overall <0.001, all P for nonlinear >0.05), a significant positive correlation between the TyG index and ASCVD was evident specifically in the female and middle-aged subgroups.

Discussion

To the best of our knowledge, this is the first large-scale cross-sectional study to explore the relationship between TyG index and ASCVD. The results showed that The TyG index remained positively associated with the risks of ASCVD, CAD, and stroke after correcting for various confounders. The TyG index was U-shaped and associated with the risk of PAD, with the lowest risk occurring when the TyG index was 8.67. The addition of the TyG index significantly increased the predictive efficacy of the basic model compared with HOMA-IR, FBG, and TG. In summary, the TyG index can serve as a reliable tool for predicting ASCVD risk,

TABLE 3 Association of TyG index with the risk of ASCVD, Stroke, CAD, and PAD.

	Case	N	Model1		Model2		Model3	
			OR (95%CI)	*P* value	OR (95%CI)	*P* value	OR (95%CI)	*P* value
ASCVD								
T1	509	2379	Ref		Ref		Ref	
T2	608	2382	1.42 (1.14,1.78)	0.003	1.17 (0.94,1.47)	0.200	1.13 (0.88,1.45)	0.300
T3	724	2451	1.75 (1.46,2.11)	<0.001	1.47 (1.19,1.81)	<0.001	1.29 (1.01,1.64)	0.042
P for trend				<0.001		<0.001		<0.001
CAD								
T1	191	2379	Ref		Ref		Ref	
T2	283	2382	1.59 (1.22,2.08)	0.001	1.27 (0.98,1.65)	0.068	1.23 (0.92,1.65)	0.200
T3	366	2451	2.52 (1.96,3.25)	<0.001	2.12 (1.61,2.79)	<0.001	1.82 (1.33,2.48)	<0.001
P for trend				<0.001		<0.001		<0.001
Stroke								
T1	59	2379	Ref		Ref		Ref	
T2	116	2382	2.43 (1.6,3.70)	<0.001	2.1 (1.39,3.18)	<0.001	2.23 (1.49,3.33)	<0.001
T3	125	2451	2.71 (1.82,4.03)	<0.001	2.43 (1.57,3.75)	<0.001	2.68 (1.54,4.69)	0.002
P for trend				<0.001		<0.001		0.002
PAD								
T1	326	2379	Ref		Ref		Ref	
T2	333	2382	1.19 (0.91,1.54)	0.200	1.02 (0.79,1.33)	0.900	0.99 (0.73,1.35)	>0.900
T3	395	2451	1.27 (1.00,1.62)	0.054	1.09 (0.85,1.40)	0.500	1.00 (0.73,1.36)	>0.900
P for trend				<0.001		<0.001		0.931

OR, odds ratio; CI, Confidence Interval; Other abbreviations are shown in Table 1.

thereby optimizing ASCVD prevalence stratification in the general population.

Numerous scholars have focused on the association between the TyG index and the risk of single diseases, such as CAD, stroke, PAD, and atherosclerosis; however little attention has been paid to ASCVD. ASCVD, as a composite outcome, is more closely associated with all-cause mortality and adverse cardiovascular event outcomes than a single disease (24–26), and the early identification and management of patients with high-risk ASCVD is of greater clinical value. Hua et al. simulated the incidence of ASCVD in participants over the next 10 years and found that the TyG index was associated with an increased risk of ASCVD (27). Previous studies have demonstrated the promising potential of the TyG index in predicting the risk of CAD (28, 29) and the prognosis of adverse cardiovascular events in patients with acute coronary syndrome (ACS) (30, 31), stable CAD (32, 33), or non-obstructive CAD (34). A high TyG index is also independently associated with stroke (35). In contrast, Wu et al. found no statistically significant differences in the risk of stroke in those with the highest TyG index compared to those with the lowest TyG index; however, there was a significant linear trend (36). In our study, the TyG index was not only positively correlated with the risk of stroke, but also showed an

TABLE 4 Incremental effect of TYG, HOMA.IR, FBG and TG for predicting ASCVD.

	AUC	P for comparisons	NRI (95%CI)	p value	IDI (95%CI)	p value
Baseline risk model	0.7183	Ref	Ref	Ref	Ref	Ref
+TYG	0.7203	0.034	0.009 (-0.002,0.020)	0.110	0.002 (0.001,0.004)	<0.001
+HOMA.IR	0.7184	0.747	0.002 (-0.003,0.007)	0.339	0.001 (-0.001,0.001)	0.156
+FBG	0.7185	0.516	0.001 (-0.001,0.005)	0.792	0.001 (-0.001,0.001)	0.465
+TG	0.7196	0.095	0.001 (-0.008, 0.009)	0.933	0.002 (0.001, 0.003)	<0.001

NRI, Net Reclassification Improvement; IDI, Integrated Discriminant Improvement; AUC, area under the curve. Other abbreviations are listed in Table 1.

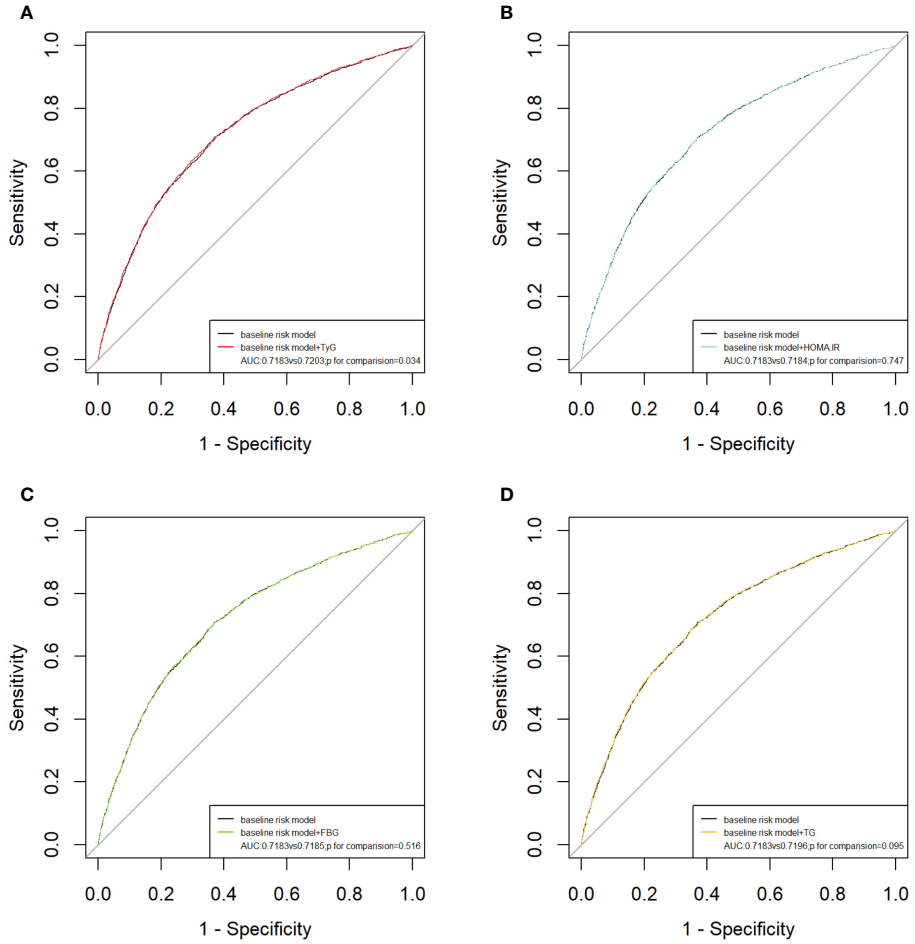

FIGURE 3
ROC curves for the evaluation of TyG index and other risk factors on the diagnostic performance of ASCVD. **(A)** Baseline risk model vs baseline risk model + TyG index groups; **(B)** Baseline risk model vs baseline risk model + HOMA-IR groups; **(C)** Baseline risk model vs baseline risk model + FBG; **(D)** Baseline risk model vs baseline risk model + TG. Baseline risk models included sex, age, LDL-C, ALT, AST, TC, insulin, hypertension, diabetes, smoking, alcohol consumption. AUC, area under the curve; TyG, triglyceride-glucose; TG, triglyceride; FBG, fasting blood glucose. HOMA-IR, homeostasis model assessment of insulin resistance.

overall linear trend. From the available studies, it is inconclusive whether the TyG index can be used as an independent predictor of stroke; however, individuals with higher TyG levels tend to have a higher risk of stroke. Evidence of the relationship between the TyG index and PAD is limited. Gao et al. found that in 12,320 non-PAD community participants, a higher TyG index was associated with an increased risk of PAD (37). However, after adjusting for relevant risk factors, we did not find a significant correlation between the TyG index and the risk of PAD, but only observed a U-shaped trend between the TyG index and PAD risk. This difference may be due to our diagnosis of PAD being based on ABPI rather than angiography or symptomatic standards, which could lead to missed diagnoses of mild-to-moderate or early stage PAD, thereby affecting the assessment of the correlation between the TyG index and PAD risk. Second, from a statistical perspective, artificially categorizing the TyG index as a categorical variable in our study may have led to the loss of some information, reducing the sensitivity and accuracy of the analysis, and thereby affecting the discovery of a correlation between the TyG index and risk of PAD. Additionally, the TyG index can represent, to some extent, the nutritional level of participants; both malnutrition and over-nutrition could increase the risk of PAD, which may explain the U-shaped correlation between TyG and PAD (38–40).

Notably, sex and age interacted with the TyG index to predict ASCVD, and the relationship between TyG levels and ASCVD was prominent in the female and middle-aged groups, but not in the male and older groups. Previous studies have repeatedly mentioned the superiority of the TyG index in predicting cardiovascular and atherosclerosis-related diseases in the female population (41, 42), which is generally in line with the results of our study. This difference can be explained by the gender insulin hypothesis (43). Previous studies have found that individuals of female sex tend to be more insulin resistant than male individuals because of the differences in hormone levels, fat distribution, metabolism, genetic and hereditary factors and lifestyle factors (44–46). As the amount of estrogen wanes,IR is observed to increase in women after entering menopause (47), explaining why there are more women with type 2 diabetes. Besides, the interaction between TyG and age has also drawn our attention. After a 7-year

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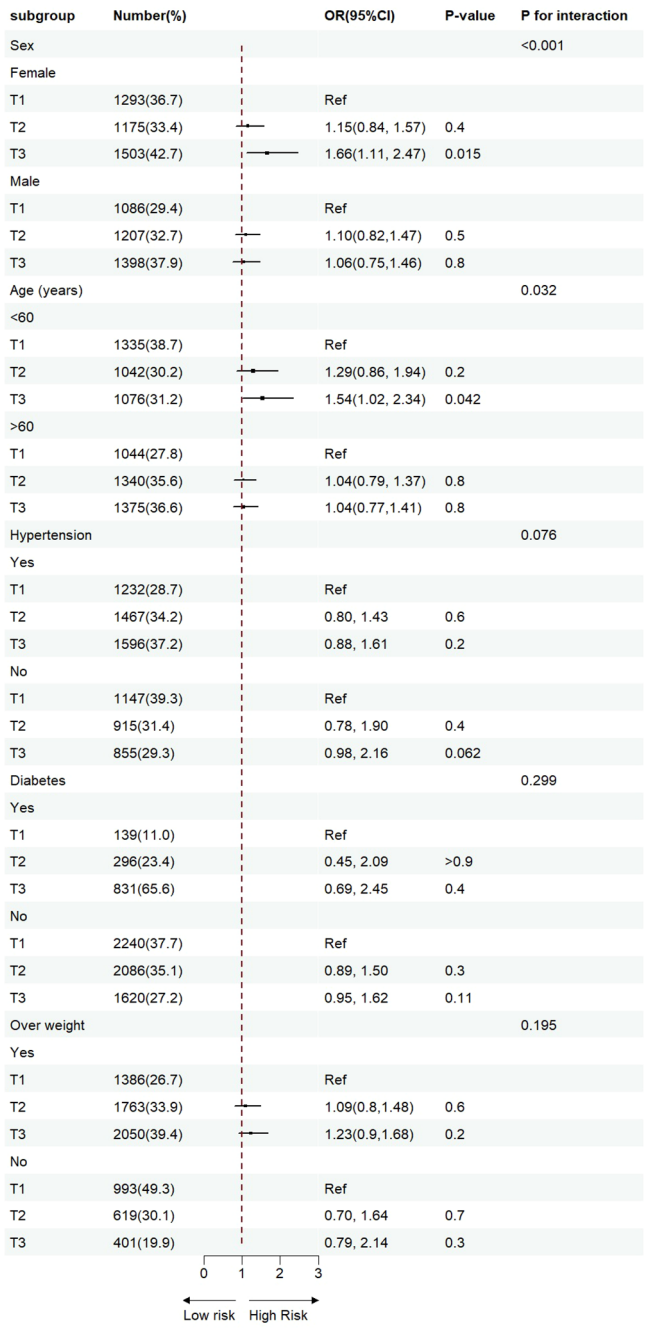

FIGURE 4
Sensitivity analysis for the impact of TyG index on ASCVD. The red vertical solid line represents OR= 1. The threshold of statistical significance was set as $P<0.05$.

follow-up of 2923 patients with cardiovascular disease, Wang et al. found that the TyG levels were a promising marker for predicting the all-cause mortality in middle-aged patients, but not in elderly patients (48). Similarly, middle-aged patients with higher levels of TyG index awere more likely to experience major adverse cardiovascular events (49). However, the exact reasons for this pattern remain to be discussed. The most likely reasons are two-fold. Firstly, younger individuals were more likely to developing IR (50), leading to elevated TyG levels in this population (51, 52). Secondly, the TyG index measurements in the elderly awere susceptible to more confounding factors, such as the presence of various diseases, concomitant poor nutritional status, and altered lipid levels. Therefore, the TyG index might not accurately reflect the IR in older adults compared to younger adults. Overall, the reasons why the female and middle-aged individuals are more prone to IR are likely multifaceted, and further research is needed for a comprehensive understanding of its mechanisms

The mechanism underlying the correlation between the TyG index and ASCVD has not yet been clearly elucidated; however, we believe that this could be explained by the IR doctrine. First, an imbalance in the glucose and lipid metabolism induced by IR leads

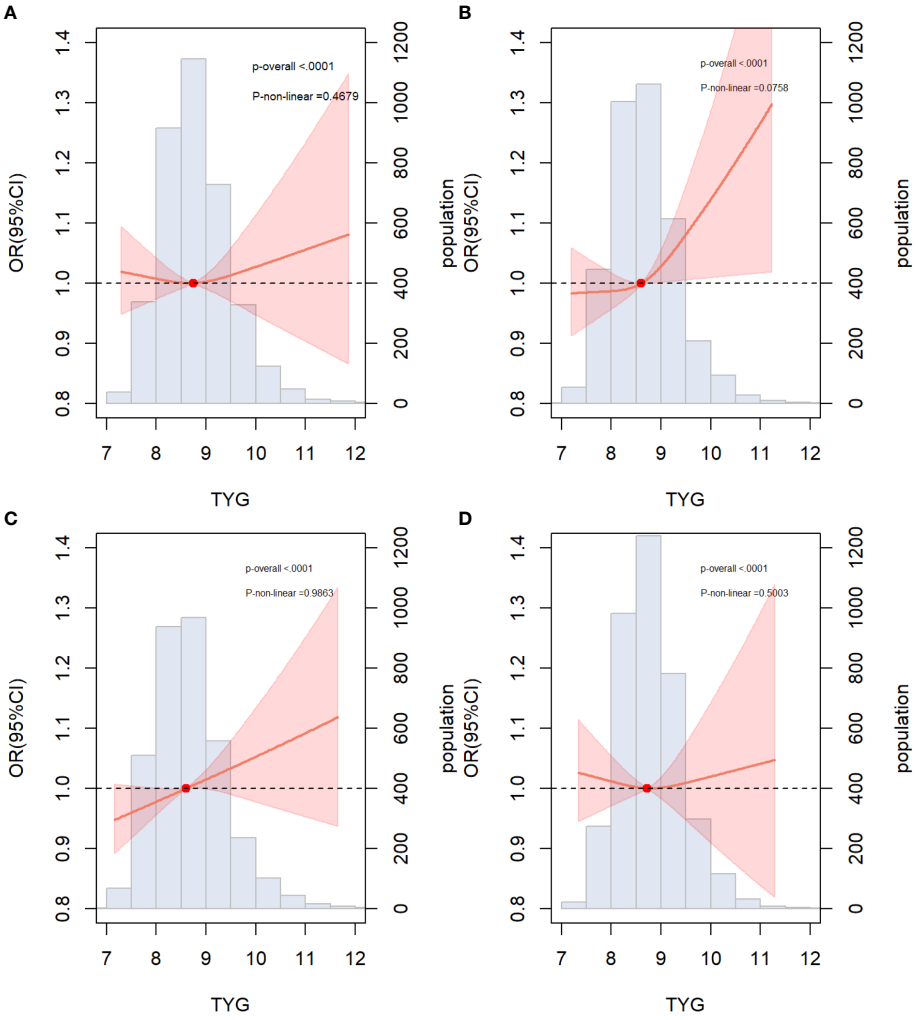

FIGURE 5
Associations between TYG index and ASCVD in specific subgroups **(A)** Male; **(B)** Female; **(C)** Non-elderly (age<60); **(D)** Elderly (age≥60); The threshold of statistical significance was set as $P<0.05$. The histograms represented the distribution of people with different TYG index levels. ASCVD, atherosclerotic cardiovascular disease.

to inflammation and oxidative stress, resulting in the development of atherosclerosis (53, 54). Second, IR plays a key role in the progression of atherosclerosis by promoting the apoptosis of macrophages, endothelial cells, and vascular smooth muscle cells. In addition, IR with hyperglycemia induces hyperglycosylation, which promotes smooth muscle cell proliferation, collagen cross-linking, and collagen deposition, and is closely associated with a substantial increase in the incidence of vascular fibrosis and stiffness. The cascade of pathological changes associated with IR ultimately leads to an increased incidence of atherosclerosis, cardiovascular diseases, and all-cause mortality.

We also found that after the addition of HOMA-IR, FBG, TG, and TyG grades to the base model, only the TyG index optimized the model, whereas HOMA-IR, FBG, and TG failed to optimize the model, indicating that the TyG index, although calculated from FBG and TG, has a higher diagnostic value, probably because it represents both lipid and glycemic factors and has a higher correlation with IR. HOMA-IR is commonly used for the indirect assessment of IR. However, its clinical utility is limited by the testing methods and costs. Compared to HOMA-IR, the TyG index not only has a higher predictive value for ASCVD, but also does not increase medical expenses, offering significant clinical applicability. However, it has to be mentioned that ASCVD is a dynamic, progressive disease and treatment should be initiated according to the patient's specific situation, which makes the use of baseline TyG index as a prognostic marker less certain.

This study had several limitations. First, this was an observational study; therefore, it was difficult to exclude the effects of confounding factors. Second, the diagnoses of CAD and stroke are based on self-reported medical history, whereas the diagnosis of PAD is based on ABPI rather than angiography, which may miss patients in the early stages of the disease or those who have not sought medical attention. Third, the data on triglyceride and glucose levels were measured only at baseline and the effect of changes in TyG levels over time on ASCVD was not considered. Furthermore, the use of lipid- and glucose-lowering medications was not considered. Finally, due to the cross-sectional nature of this study, the research results can only indicate an association between the TyG index and high ASCVD risk, but cannot establish a causal relationship between the two. Further

longitudinal studies are required to clarify the causal relationship between TyG index and ASCVD.

Conclusion

In the general population, our study demonstrated that the TyG index was positively associated with the occurrence of ASCVD and had a certain predictive value. However, ASCVD is a dynamic and progressive disease; therefore, enabling the use of the TyG index in real time to dynamically predict the risk of ASCVD is the next challenge for our team.

Data availability statement

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

Ethics statement

The studies involving humans were approved by National Health and Nutrition Examination Survey. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

JS: Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing, Conceptualization. XC: Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing, Investigation. HL: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. YZ: Data curation, Investigation, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Correlation of cardiometabolic index and sarcopenia with cardiometabolic multimorbidity in middle-aged and older adult: a prospective study

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Background: Research has demonstrated that sarcopenia and visceral obesity are significant risk factors for chronic disease in middle-aged and older adults. However, the relationship between sarcopenia, the cardiac metabolic index (CMI), a novel measure of visceral obesity, and cardiometabolic multimorbidity (CMM) remains unclear. In this study, data from the China Longitudinal Study of Health and Retirement (CHARLS) were analyzed to investigate the association between sarcopenia and CMI with CMM in the middle-aged and older adult population.

Methods: The study included 4,959 participants aged 45 and over. Sarcopenia was defined using the criteria of the Asian Sarcopenia Working Group 2019. CMM is defined as having two or more of the following conditions: physician-diagnosed heart disease, diabetes, stroke, and/or hypertension. CMI was calculated using the formula: CMI = (TG/HDL-C) × WHtR. To explore the association between CMI and sarcopenia and CMM, cox proportional risk regression models were used.

Results: The median age of all participants was 57 years, with 47.1% being male. Over the 8-year follow-up, 1,362 individuals developed CMM. The incidence of CMM was 8.7/1,000 person-years in the group without sarcopenia or high CMI, 17.37/1,000 person-years in those with high CMI, 14.22/1,000 person-years in the sarcopenia group, and 22.34/1,000 person-years in the group with both conditions. After adjusting for covariates, the group with both sarcopenia and high CMI had a significantly increased risk of CMM (HR 2.48, 95% CI 1.12-5.51) and heart disease (HR 2.04, 95% CI 1.05-3.98). Among those over 65 years, sarcopenia was discovered to be associated with an increased risk of CMM [HR (95% CI: 4.83 (1.22, 19.06)]. The risk of CMM was further increased to 7.31-fold (95% CI:1.72, 31.15) when combined with high CMI.

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Conclusions: The combination of sarcopenia and high CMI is associated with an increased risk of developing CMM. Early identification and intervention of sarcopenia and CMI not only enable the development of targeted therapeutic strategies but also provide potential opportunities to reduce the morbidity and mortality of CMM.

KEYWORDS

CHARLS, cardiometabolic multimorbidity, cardiac metabolic index, visceral obesity, sarcopenia

Introduction

With the increasing global urbanization and changes in lifestyles and diet, the prevalence of cardiometabolic diseases is on the rise, presenting a significant public health challenge worldwide (1). Several large-scale population-based cohort studies have identified a high degree of comorbidity between cardiovascular disease and abnormal glucose metabolism, which increases the risk of cardiovascular disease (2–4). The EUROASPIRE IV study conducted in Europe found that approximately 25% of patients with coronary heart disease patients who had not been previously diagnosed with diabetes were newly diagnosed with the condition. Additionally, 46% to 66% were found to be in the pre-diabetes stage, while only 10.5% to 26.6% had completely normal glucose metabolism (5). In China, it is estimated that approximately 500,000 cardiovascular deaths per year can be attributed to diabetes, making the co-morbidity of cardiovascular disease and diabetes/pre-diabetes a significant concern. Scientists have introduced the concept of 'cardiometabolic multimorbidity (CMM)' to describe this phenomenon (6). CMM is defined as the simultaneous occurrence of two or more cardiovascular metabolic diseases (CMD) (7). In the United States, the prevalence of CMM is 14.4%, and it is higher in men and older adults (8). It is worth noting that the health implications associated with CMM are considerably more severe than those associated with single CMD (9). Older adults with any cardiometabolic disease or two cardiometabolic diseases had a significantly shorter life expectancy of 7 and 12 years, respectively, compared to those without heart disease (10). Furthermore, individuals with one CMD or CMM were 1.41 and 1.89 times more likely to experience higher levels of mental stress than those without cardiometabolic disease (11). Therefore, the early prevention and treatment of CMM remain a critical challenge that requires further attention.

Sarcopenia is a syndrome that is characterized by a progressive age-related decline in skeletal muscle mass (SMM) and strength, which leads to dysfunction in the body. According to the 2019 report from the European Working Group on Sarcopenia in Older People (EWGSOP), the prevalence of sarcopenia is 6%-12% globally, 14%-33% in older adults aged 65 years and older, and as high as 78% among hospitalized patients (12). The 2019 report by the Asian Sarcopenia Working Group indicates that the prevalence of sarcopenia in the Asian older adult population ranges from 5.5% to 25.7% (13). There is increasing evidence linking sarcopenia to various adverse outcomes, such as falls, debility, frequent medical visits, and a higher risk of mortality (14). Sarcopenia has also been identified as a risk factor for the development of cardiovascular disease (15). A comprehensive study conducted in a Chinese population found a significant association between sarcopenia and an increased risk of cardiovascular disease, including both heart disease and stroke (16). Sarcopenia often coexists with an accumulation of adipose tissue, particularly abdominal obesity (17). Severe muscle loss and obesity can synergistically increase metabolic disturbances and the risk of adverse outcomes such as myocardial infarction, stroke, and death more than sarcopenia or simple obesity alone (18). Obesity is recognized as a key modifiable risk factor for CMM (19). Although high Body Mass Index (BMI) is currently a widely used international metric for assessing the extent of human obesity, it does not accurately reflect body composition or the distribution of visceral fat. Furthermore, it should be noted that BMI is not a reliable predictor of cardiovascular disease risk in certain populations. Body fat distribution, rather than the degree of overall obesity, leads to greater cardiovascular risk (20). In 2015, Ichiro et al. proposed the Cardiometabolic Index (CMI) as an obesity-related anthropometric index which combines height (m) and waist circumference (m) and offers a more precise representation of a person's body shape than traditional indicators such as Body Mass Index (BMI), waist circumference, and hip circumference (21). Several studies have demonstrated a significant association between and hypertension, carotid atherosclerosis, and diabetes mellitus (22–24). However, previous studies have primarily focused on the association of sarcopenia or CMI with a single CMD and have mostly employed cross-sectional survey methods instead of prospective studies with a higher level of evidence. Unfortunately, there are no comprehensive studies that investigate the relationship between sarcopenia and/or CMI and CMM. Consequently, substantial knowledge gaps and uncertainties persist regarding the interactions and potential mechanisms between sarcopenia and/or CMI and CMM.

This study aims to investigate the association between sarcopenia and CMI, both alone and in combination with CMM. The goal is to determine whether the coexistence of sarcopenia and CMI increases the risk of developing CMM. The findings will

provide a solid and reliable foundation for clinical prevention and treatment strategies, and may facilitate the medical community make new breakthroughs in related fields.

Methods

Study design and population

The China Longitudinal Study of Health and Retirement (CHARLS)is a long-term survey that documents the social, economic, and health status of middle-aged and older adults in China aged 45 and above, along with their families. The study enrolled 17,708 participants in 2011, with follow-up surveys conducted every two years. Ethical approval for CHARLS was obtained from the Ethical Review Committee of Peking University (IRB 00001052 -11015), and all participants provided informed consent. When performing research involving human subjects, all procedures were following institutional and national research council ethical standards as well as the Declaration of Helsinki and its subsequent amendments or similar ethical standards. For further details and raw data, please visit https://charls.pku.edu.cn.

This study commenced in 2011 with a base sample of 17,708 respondents and four follow-up surveys. To guarantee the dependability and comprehensiveness of our results, we established the following exclusion criteria. These criteria excluded 1) individuals with incomplete data or a diagnosis of a specific illness (heart disease, diabetes, stroke, hypertension); 2) those with unknown age information; 3) those without gender-related details; and 4) those lacking sarcopenia-related data. After a rigorous screening process, our final analytical sample consisted of 4959 participants. None of the individuals had cardiovascular-metabolic diseases at the time of the 2011 CHARLS survey and continued to participate in the 2013, 2015, and 2018 follow-up surveys. The detailed selection process is outlined in Figure 1, providing a visual representation of the screening procedures.

Definition of sarcopenia

The Asian Working Group on Sarcopenia (AWGS) 2019 criteria were used to assess sarcopenia. The measurements included grip strength, gait speed, the five-chair rise test, the Simple Physical Performance Battery (SPPB) and appendicular skeletal muscle mass (ASM) values. Grip strength served as the primary indicator of muscle strength, with cutoff values of <28 kg for men and <18 kg for women. To estimate muscle mass, we used the ASM formula, which considers weight, height, sex, and age. Previous studies have demonstrated high agreement between the ASM formula and double x-ray absorptiometry (DXA). The threshold for low muscle mass was based on the lowest 20% of gender-specific height-adjusted muscle mass (ASM/Ht^2) in the study population (25). Therefore, we considered ASM/Ht^2 values <5.27 kg/m^2 for females and ASM/Ht2 <7.01 kg/m^2 for males as indicators of low muscle mass. The assessment of somatic functioning included gait speed, the five-chair rise test, and SPPB scores. Reduced somatic function were defined as gait speed less than 1.0 m/s, the five-chair rise test taking 12 seconds or more, or an SPPB score less than 9. The study cohort comprised 3084 non-sarcopenia, 1290 possible sarcopenia, 434 sarcopenia, and 151 severe sarcopenia cases. For the purpose of this study, individuals diagnosed with sarcopenia and severe sarcopenia were grouped together. This decision was made to ensure adequate sample size for statistical analysis and to reflect the shared clinical significance and physiological characteristics of these conditions in the context of increased risk for cardiometabolic multimorbidity.

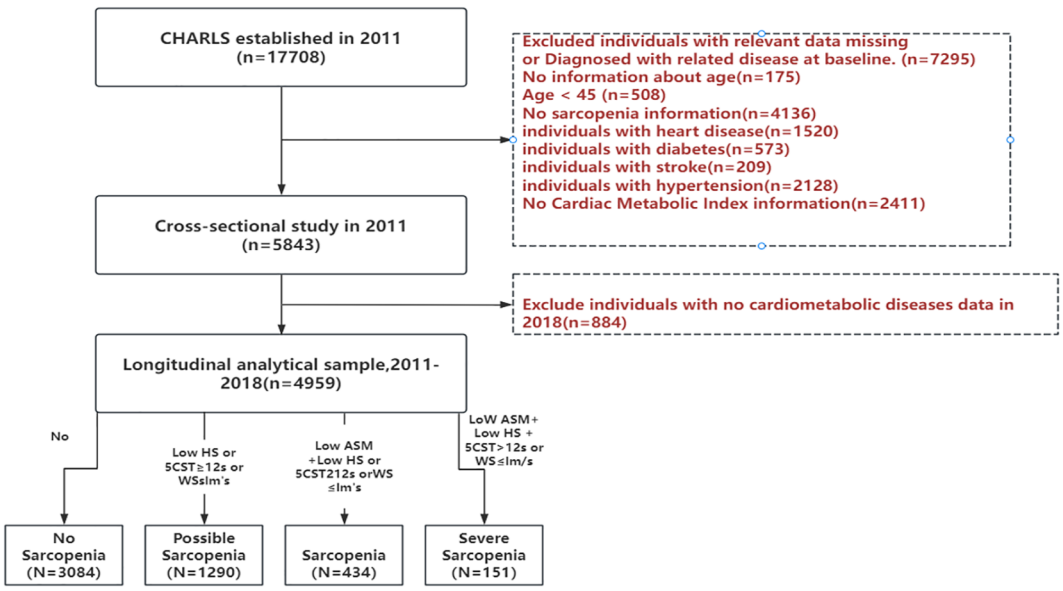

FIGURE 1
Flowchart for participants of this current study.

Cardiac metabolic index

CMI = TG/HDL-C × WHtR, TG: triglycerides, HDL-C: high-density lipoprotein cholesterol, WHtR: waist circumference to height ratio. Both waist circumference and height are measured in centimeters. To classify CMI, we used an interquartile approach due to the lack of a uniform classification standard. We selected the 75th percentile as the cutoff point based on the distribution of CMI in the study population. Individuals with CMI above the 75th quartile were defined as having 'high CMI'. This aim of this classification was to identify individuals with high CMI levels for further investigation of their association with CMM. This will enable a more accurate assessment of an individual's cardio-metabolic risk and provide a basis for developing appropriate interventions.

Definitions of CMM

CMM is defined as the coexistence of two or more cardiovascular and metabolic diseases, such as hypertension, diabetes, heart disease, and stroke. To determine whether an individual has any of these diseases, we ask, 'Has your doctor informed you that you have hypertension?', 'Have you been diagnosed with diabetes mellitus or elevated blood glucose levels (including abnormal glucose tolerance and raised fasting blood glucose)?', 'Have you been with heart disease (such as myocardial infarction, coronary heart disease, angina pectoris, congestive heart failure, or other heart conditions)?', and 'Have you experienced a stroke (including cerebral infarction and cerebral hemorrhage) as diagnosed by a doctor?'.

Covariates

This study collected baseline data on socio-demographic status and health-related information using a structured questionnaire. The data aimed to provide a comprehensive overview of the socio-demographic characteristics and health status. Gender, age, education level, marital status, place of residence, and exercise habits were collected as socio-demographic variables. These variables are important for understanding the social background and lifestyle of the subjects, which can help identify potential correlations with their health status. Health-related factors include physiological indicators such as BMI, smoking and drinking status, blood pressure levels, blood counts, CRP, lipids, renal function, fasting blood glucose, and uric acid.

Statistical analysis

In the follow-up study, participants were subdivided into four groups based on their health status: 1) no sarcopenia and normal CMI, 2) high CMI only, 3) sarcopenia only, and 4) both sarcopenia and high CMI. To explore the differences in baseline characteristics among the groups, we flexibly used chi-square ($\chi 2$) tests as well as the Pearson $\chi 2$ test or Fisher exact test. To assess the potential association between sarcopenia and CMI status at baseline and subsequent CMM events, we applied the Cox proportional risk model to calculate the corresponding hazard ratios (HR) and 95% confidence intervals.

For the longitudinal data analysis, we constructed three increasingly comprehensive models. Model 1 served as the unadjusted baseline model. Model 2 was adjusted based on Model 1 by incorporating age and gender as covariates. Model 3 further integrated additional adjustments based on Model 2, including education, residence, marital status, smoking habits, alcohol consumption, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), white blood cell count, hemoglobin, platelet count, C-reactive protein, total cholesterol, low-density lipoprotein (LDL), blood urea nitrogen (BUN), creatinine, blood glucose, and uric acid. Statistical analysis was conducted using R studio (version 4.3.2). A P value less than 0.05 was considered statistically significant.

Results

Characteristics of the study participants

Table 1 presents the characteristics of the participants based on the quartiles of CMI (Q1 <0.27 mmol/l, 0.27 <Q2 <0.44 mmol/l, 0.44 <Q3 <0.75 mmol/l, Q4 >0.75 mmol/l). After screening by exclusion criteria, a total of 4959 participants aged 45 or above and free of cardiometabolic disease events at baseline were included. The median age of the study population was 57(50.8 63), and 2338 (47.1%) were male. Participants with higher CMI levels were more likely to be female, reside in rural areas, have lower levels of education, have a higher BMI, and engage in less physical activity. Additionally, they also had higher levels of C-reactive protein (CRP), blood glucose, total cholesterol (TC), triglycerides (TG), as well as higher levels of low-density lipoprotein cholesterol (LDL-C). According to AWGS 2019 criteria, the cohort comprised 3084 (62.1%) non-sarcopenia, 1290(26%) possible sarcopenia, 434 (8.8%) sarcopenia and 151(3%) severe sarcopenia cases. Over the 8-year follow-up period, there were 1362 individuals who developed CMM and 3108 individuals who developed one type of CMD.

The longitudinal association of sarcopenia and CMI and CMM

Table 2 shows the relationship between CMI, sarcopenia, and CMM incident. After adjusting for socio-demographic characteristics and health-related factors, higher CMI values were associated with an increased risk of heart disease [HR (95%CI): 1.13 (0.78, 1.49)], stroke [HR (95%CI): 1.65(1.07, 2.60)], hypertension [HR (95%CI): 1.11(0.92, 1.33)], CMM [HR (95%CI): 1.48(0.92, 1.33)], and diabetes [HR (95%CI): 1.89(1.33, 2.68)]. Notably, CMI had the strongest association with an elevated risk of diabetes and CMM development, at 1.89-fold and 1.48-fold respectively.

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TABLE 1 Characteristics of 4959 participants by CMI.

Characteristics	Q1<0.27 mmol/l	0.27<Q2<0.44 mmol/l	0.44<Q3<0.75 mmol/l	Q4>0.75 mmol/l	Total	P value
Total	1239	1240	1240	1240	4959	
Gender						< 0.001
Female	573 (46.2)	653 (52.7)	708 (57.1)	687 (55.4)	2621 (52.9)	
Male	666 (53.8)	587 (47.3)	532 (42.9)	553 (44.6)	2338 (47.1)	
Age						0.005
median (IQR)	57 (51,64)	57 (50,63)	57 (51,64)	56 (50,62)	57 (50.8,63)	
BMI						< 0.001
median (IQR)	21.1 (19.4,22.9)	22.1 (20.3,24)	23.2 (21.2,25.5)	24.6 (22.5,27.1)	22.7 (20.6,25)	
Education						0.048
low	861 (69.5)	854 (68.9)	876 (70.6)	817 (65.9)	3408 (68.7)	
middle	372 (30)	373 (30.1)	352 (28.4)	404 (32.6)	1501 (30.3)	
high	6 (0.5)	13 (1)	12 (1)	19 (1.5)	50 (1)	
Marriage						0.591
No	21 (1.8)	15 (1.3)	14 (1.2)	19 (1.6)	69 (1.5)	
Yes	1163 (98.2)	1168 (98.7)	1158 (98.8)	1147 (98.4)	4636 (98.5)	
Rural						< 0.001
Urban	329 (26.6)	353 (28.5)	431 (34.8)	476 (38.4)	1589 (32)	
Rural	910 (73.4)	887 (71.5)	809 (65.2)	764 (61.6)	3370 (68)	
strenuous exercise						< 0.001
No	259 (47.9)	279 (54)	310 (61)	344 (63.8)	1192 (56.6)	
Yes	282 (52.1)	238 (46)	198 (39)	195 (36.2)	913 (43.4)	
moderate intensity exercise						0.027
No	176 (32.5)	200 (38.7)	201 (39.6)	219 (40.7)	796 (37.8)	
Yes	365 (67.5)	317 (61.3)	307 (60.4)	319 (59.3)	1308 (62.2)	
light intensity exercise						0.59
No	92 (17.1)	95 (18.4)	94 (18.5)	109 (20.3)	390 (18.6)	
Yes	447 (82.9)	421 (81.6)	413 (81.5)	427 (79.7)	1708 (81.4)	
Smoking						0.001
No	697 (56.3)	753 (60.7)	792 (63.9)	764 (61.6)	3006 (60.6)	
Yes	542 (43.7)	487 (39.3)	448 (36.1)	476 (38.4)	1953 (39.4)	
Drinking						< 0.001
No	668 (54)	768 (62)	793 (64)	797 (64.3)	3026 (61.1)	
Yes	570 (46)	471 (38)	446 (36)	443 (35.7)	1930 (38.9)	
SBP, mmHg						< 0.001
median (IQR)	119 (108,130.5)	119.5 (109.8,131)	123 (112.5,135.2)	124.5 (113.8,137.5)	121.5 (110.5,134)	
DPB, mmHg						< 0.001
mean (SD)	70.5 (63.5,77.5)	71.5 (64.5,79)	73 (66.5,81)	74.5 (67.5,82)	72.5 (65.5,80)	

(Continued)

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TABLE 1 Continued

Characteristics	Q1<0.27 mmol/l	0.27<Q2<0.44 mmol/l	0.44<Q3<0.75 mmol/l	Q4>0.75 mmol/l	Total	P value
White Blood Cell, 10^9/L						< 0.001
median (IQR)	5.6 (4.7,6.7)	5.9 (4.8,7.1)	6 (5,7.1)	6.2 (5.2,7.5)	5.9 (4.9,7.1)	
Hemoglobin, g/dL						< 0.001
median (IQR)	14 (12.8,15.2)	14.1 (12.9,15.3)	14.2 (13,15.4)	14.5 (13.2,15.8)	14.2 (13,15.5)	
Platelets, 10^9/L						0.005
median (IQR)	202 (162,248)	210 (163.2,259)	206 (162,254)	213 (163,264)	208 (163,255)	
CRP , mg/L						< 0.001
median (IQR)	0.7 (0.4,1.4)	0.8 (0.5,1.7)	0.9 (0.5,1.8)	1.2 (0.7,2.3)	0.9 (0.5,1.8)	
HDL-c, mg/dL						< 0.001
median (IQR)	65.7 (57.2,75.2)	54.9 (48.3,61.9)	47.9 (42.1,53.7)	37.5 (32.5,43.7)	50.6 (41.7,61.1)	
Total Cholesterol, mg/dL						< 0.001
median (IQR)	184 (163.9,207.6)	187.1 (164.2,209.5)	191 (166.6,213.4)	194.8 (170.9,222.7)	189.4 (166.2,213.4)	
LDL-c, mg/dL						< 0.001
median (IQR)	107.5 (89.3,127.1)	116.4 (95.9,138.8)	119.5 (99.2,140.7)	112.7 (87.8,135.3)	113.7 (93.2,135.3)	
Triglycerides						< 0.001
median (IQR)	60.2 (49.6,70.8)	85 (74.3,98.2)	114.2 (100,133.6)	193.4 (154,257.5)	100 (71.7,144.3)	
BUN, mg/dl						< 0.001
median (IQR)	16 (13.3,19)	15.1 (12.5,18.5)	14.8 (12.4,17.7)	14.7 (12.2,17.4)	15.2 (12.5,18.2)	
Creatinine, mg/dl						0.011
median (IQR)	0.7 (0.6,0.9)	0.7 (0.6,0.9)	0.7 (0.6,0.9)	0.8 (0.7,0.9)	0.7 (0.6,0.9)	
Glucose, mg/dl						< 0.001
median (IQR)	98.6 (91.6,106.7)	99.5 (93.1,107.8)	100.6 (93.6,109.5)	105.8 (97.4,117.6)	101.2 (93.8,110.2)	
Uric Acid, mg/dl						< 0.001
median (IQR)	4.1 (3.4,4.9)	4 (3.4,4.8)	4.2 (3.5,5)	4.5 (3.8,5.4)	4.2 (3.5,5)	
Sarcopenia						< 0.001
No	773 (62.4)	757 (61)	747 (60.2)	807 (65.1)	3084 (62.2)	
Possible	242 (19.5)	312 (25.2)	367 (29.6)	369 (29.8)	1290 (26)	
Severe	51 (4.1)	41 (3.3)	39 (3.1)	20 (1.6)	151 (3)	
Yes	173 (14)	130 (10.5)	87 (7)	44 (3.5)	434 (8.8)	
Number of CMM						< 0.001
0	69 (5.6)	105 (8.5)	142 (11.5)	173 (14)	489 (9.9)	
1	865 (69.8)	819 (66)	744 (60)	680 (54.8)	3108 (62.7)	
>=2	305 (24.6)	316 (25.5)	354 (28.5)	387 (31.2)	1362 (27.5)	

However, after adjusting for covariates, there was no statistically difference in risk between those with and without sarcopenia for developing CMM, diabetes, heart disease, stroke, and hypertension.

Figure 2 displays the change in annual incidence of CMM among all participants from 2011 to 2018. Our findings suggest that the incidence of CMM may significantly in individuals with sarcopenia and high CMI, either alone or in combination. The group with sarcopenia combined with high CMI had the highest prevalence at all time points and showed a significant upward trend. This result highlights the significant threat to individual health

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TABLE 2 Associations of the CMI and sarcopenia with the risk of CMM.

Factors	HR(95%CI)				
	Diabetes	Heart disease	Stroke	Hypertension	CMM
Sarcopenia	**0.96 (0.46,1.96)**	**1.52 (0.87,1.48)**	**0.84 (0.35,2.03)**	**1.31 (0.90,1.89)**	**1.76 (0.95,3.26)**
CMI	**1.89 (1.33,2.68)*** **	**1.13 (0.78,1.49)**	**1.67 (1.07,2.60)***	**1.11 (0.92,1.33)**	**1.48 (1.09,2.01)***
P for interaction	**0.61**	**0.06**	**0.97**	**0.45**	**0.39**

Low CMI and no-sarcopenia were used as control groups.
HR, hazard ratio; CMM, Cardiometabolic multimorbidity; CMI, cardiac metabolic index;
Model: adjusted age, sex, residence, education, marital status, smoking, drinking, BMI, SBP, DBP, strenuous exercise, moderate intensity exercise, White Blood cell, Hemoglobin, Platelets, CRP, Total Cholesterol, LDL-c, BUN, Creatinine, Glucose, Uric Acid.
* indicates P<0.05, *** indicates P<0.001.

posed by the combination of sarcopenia and high CMI. Table 3 shows the relationships between different combinations of sarcopenia, CMI, and CMM components. In the longitudinal analyses, the prevalence of CMM was 8.7/1000 person-years in the group with neither sarcopenia nor high CMI, 17.37/1000 person-years in the high CMI group, 14.22/1000 person-years in the sarcopenia group, and 22.34/1000 person-years in the group with both sarcopenia reduction and high CMI. Model 1 found that the group with sarcopenia and high CMI group had an increased risk of CMM, heart disease, diabetes, stroke, and hypertension. After adjusting for age and sex in Model 2, the group with sarcopenia and high CMI still had an increased risk of CMM, diabetes, and stroke. After adjusting for all covariates in model 3, the combination of sarcopenia and high CMI was found to be associated with an increased risk of heart disease [HR (95% CI): 2.04 (1.05, 3.98)] and CMM [HR (95% CI): 2.48 (1.12, 5.51)], compared to those with neither sarcopenia nor CMI. However, no significant associations were found with the attenuated outcomes of diabetes, stroke, and hypertension. High CMI was only associated with a 1.86-fold (95% CI: 1.14,3.01) probability of developing diabetes. There were no significant longitudinal associations between sarcopenia alone and different components of CMM.

Subgroup analysis

Among males, high CMI was found to be associated with an increased risk of stroke [HR (95% CI): 3.15 (1.24, 8.01)]. The risk of stroke was further increased to 5.85-fold [95% CI: 1.20, 25.59] when comorbid sarcopenia was present. In females, the combination of sarcopenia and high CMI was associated with a higher risk of heart disease [HR (95% CI): 2.75 (1.18, 6.41)]. The longitudinal association between sarcopenia combined with high CMI and CMM was not significant for both genders (Table 4). However, subgroup analyses stratified by age reflected distinct patterns of association. Among those aged below 65 years, sarcopenia combined with high CMI was associated with an elevated risk of heart disease only [HR (95% CI): 2.95 (1.18, 7.40)], while the longitudinal association with CMM was not significant after adjusting for model 2. In contrast, for those aged 65 years or older, sarcopenia was found to be associated with a higher risk of CMM [HR (95% CI): 4.83 (1.22, 19.06)]. This risk was further elevated to 7.31-fold (95% CI: 1.72, 31.15) when combined with high CMI (Table 5). These findings suggest that the association between sarcopenia and high CMI with CMM may vary depending on age, and that the association appears to be more pronounced in the older adult population.

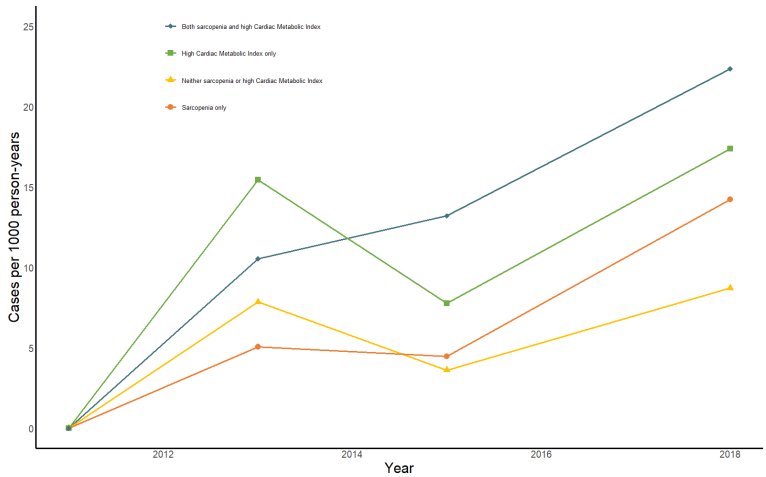

FIGURE 2
Impact of sarcopenia, high CMI, and sarcopenia combined with high CMI on person-year incidence of CMM from 2011-2018. Bule line: Sarcopenia combined with high CMI; Green line: high CMI only; Yellow line: No sarcopenia or high CMI; orange line: Sarcopenia only.

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TABLE 3 Associations of the CMI and sarcopenia with the incidence of CMM.

Factors	cases	Incidence rate (per 1000 person-year)	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)
Heart disease					
Neither sarcopenia or high Cardiac Metabolic Index	159	15.19	Ref.	Ref.	Ref.
High Cardiac Metabolic Index only	193	18.27	1.21 (0.98,1.49)	1.19 (0.97,1.47)	1.15 (0.78,1.70)
Sarcopenia only	60	22.42	1.50 (1.11,2.02)**	1.15 (0.83,1.59)	1.41 (0.80,2.51)
Both sarcopenia and high Cardiac Metabolic Index	38	30.11	2.04 (1.44,2.91)***	1.40 (0.94,2.09)	2.04 (1.05,3.98)*
Diabetes					
Neither sarcopenia or high Cardiac Metabolic Index	69	6.5	Ref.	Ref.	Ref.
High Cardiac Metabolic Index only	188	17.74	2.80 (2.12,3.68)***	2.78 (2.11,3.66)***	1.86 (1.14,3.01)*
Sarcopenia only	26	9.48	1.47 (0.94,2.31)	1.52 (0.93,2.46)	0.84 (0.32,2.23)
Both sarcopenia and high Cardiac Metabolic Index	18	13.92	2.17 (1.29,3.65)**	2.22 (1.26,3.92)**	2.18 (0.88,5.41)
Stroke					
Neither sarcopenia or high Cardiac Metabolic Index	46	4.3	Ref.	Ref.	Ref.
High Cardiac Metabolic Index only	76	7.02	1.64 (1.14,2.37)**	1.70 (1.18,2.45)**	1.31 (0.69,2.48)
Sarcopenia only	23	8.35	1.97 (1.19,3.24)**	1.41 (0.81,2.43)	0.77 (0.27,2.19)
Both sarcopenia and high Cardiac Metabolic Index	18	13.71	3.28 (1.90,5.65)***	2.27 (1.22,4.21)**	1.32 (0.41,4.27)
Hypertension					
Neither sarcopenia or high Cardiac Metabolic Index	323	31.43	Ref.	Ref.	Ref.
High Cardiac Metabolic Index only	454	44.79	1.47 (1.27,1.69)***	1.49 (1.29,1.72)***	0.98 (0.76,1.26)
Sarcopenia only	93	37.76	1.22 (0.97,1.53)	0.94 (0.74,1.21)	1.23 (0.80,1.89)
Both sarcopenia and high Cardiac Metabolic Index	59	47.23	1.56 (1.18,2.06)**	1.15 (0.85,1.56)	1.43 (0.87,2.36)
CMM					
Neither sarcopenia or high Cardiac Metabolic Index	93	8.7	Ref.	Ref.	Ref.
High Cardiac Metabolic Index only	186	17.37	2.04 (1.59,2.61)***	2.06 (1.61,2.65)***	1.28 (0.81,2.03)
Sarcopenia only	39	14.22	1.65 (1.14,2.40)**	1.31 (0.87,1.96)	1.71 (0.82,3.55)
Both sarcopenia and high Cardiac Metabolic Index	29	22.34	2.66 (1.75,4.03)***	2.01 (1.26,3.20)**	2.48 (1.12,5.51)*

HR, hazard ratio; CMM, Cardiometabolic multimorbidity; CMI, cardiac metabolic index;
Model 1: unadjusted;
Model 2: adjusted for age, sex;
Model 3: adjusted as model 2 with further adjustment for residence, education, marital status, smoking, drinking, BMI, SBP, DBP, strenuous exercise, moderate intensity exercise, White Blood cell, Hemoglobin, Platelets, CRP, Total Cholesterol, LDL-c, BUN, Creatinine, Glucose, Uric Acid.
* indicates P<0.05, ** indicates P<0.01, *** indicates P<0.001.

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TABLE 4 Sex Subgroup Analysis of the Effect of CMI and sarcopenia on CMM.

Factors		Model 1 HR(95%CI)	Model 2 HR(95%CI)
Male	Heart disease		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.64(1.18,2.27)**	1.57(0.87,2.85)
	Sarcopenia only	1.87(1.15,3.03)*	1.54(0.66,3.60)
	Both sarcopenia and high Cardiac Metabolic Index	1.52(0.69,3.33)	0.75(0.16,3.53)
	Diabetes		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	3.32(2.16,5.11)***	1.54(0.67,3.54)
	Sarcopenia only	1.68(0.81,3.46)	1.37(0.26,7.28)
	Both sarcopenia and high Cardiac Metabolic Index	3.84(1.75,8.46)***	3.74(0.73,19.19)
	Stroke		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	2.37(1.43,3.94)***	3.15(1.24,8.01)*
	Sarcopenia only	1.72(0.76,3.89)	2.31(0.61,8.77)
	Both sarcopenia and high Cardiac Metabolic Index	5.00(2.21,11.28)***	5.85(1.20,28.59)*
	Hypertension		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.48(1.22,1.81)***	0.91(0.64,1.31)
	Sarcopenia only	1.25(0.90,1.74)	1.16(0.62,2.16)
	Both sarcopenia and high Cardiac Metabolic Index	1.33(0.81,2.19)	1.75(0.75,4.09)
	CMM		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	2.75(1.90,3.96)***	1.50(0.79,2.86)
	Sarcopenia only	1.74(0.96,3.16)	1.89(0.71,5.05)
	Both sarcopenia and high Cardiac Metabolic Index	3.40(1.70,6.81)***	2.17(0.61,7.71)
Female	Heart disease		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	0.98(0.74,1.29)	0.79(0.46,1.36)
	Sarcopenia only	1.36(0.94,1.95)	1.48(0.70,3.17)
	Both sarcopenia and high Cardiac Metabolic Index	1.82(1.19,2.78)**	2.75(1.18,6.41)*

(Continued)

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TABLE 4 Continued

Factors		Model 1 HR(95%CI)	Model 2 HR(95%CI)
	Diabetes		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	2.22 (1.56,3.17)***	1.78 (0.96,3.28)
	Sarcopenia only	1.33 (0.77,2.29)	1.22 (0.38,3.89)
	Both sarcopenia and high Cardiac Metabolic Index	1.16 (0.54,2.45)	1.77 (0.53,5.90)
	Stroke		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.19 (0.68,2.07)	0.55 (0.19,1.59)
	Sarcopenia only	2.19 (1.15,4.21)*	0.11 (0.01,1.10)
	Both sarcopenia and high Cardiac Metabolic Index	2.87 (1.37,6.03)**	0.31 (0.04,2.13)
	Hypertension		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.43 (1.16,1.75)***	1.01 (0.69,1.48)
	Sarcopenia only	1.19 (0.88,1.62)	1.28 (0.69,2.38)
	Both sarcopenia and high Cardiac Metabolic Index	1.73 (1.22,2.44)**	1.36 (0.70,2.63)
	CMM		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.67 (1.17,2.36)**	1.02 (0.52,2.02)
	Sarcopenia only	1.72 (1.08,2.77)*	2.18 (0.72,6.67)
	Both sarcopenia and high Cardiac Metabolic Index	2.23 (1.29,3.86)**	2.24 (0.72,7.04)

HR, hazard ratio; CMM, Cardiometabolic multimorbidity; CMI, cardiac metabolic index;
Model 1: unadjusted;
Model 2: adjusted age, sex, residence, education, marital status, smoking, drinking, BMI, SBP, DBP, strenuous exercise, moderate intensity exercise, White Blood cell, Hemoglobin, Platelets, CRP, Total Cholesterol, LDL-c, BUN, Creatinine, Glucose, Uric Acid.
* indicates P<0.05, ** indicates P<0.01, *** indicates P<0.001.

Discussion

This study examines the relationship between sarcopenia, CMI, and CMM in 4959 middle-aged and older adults. The findings indicate that sarcopenia combined with high CMI is associated with an increased risk of CMM development, particularly among individuals aged 65 years or older. However, neither sarcopenia nor high CMI alone significantly elevates the risk of CMM. These findings suggest that the coexistence of sarcopenia and high CMI may increase the risk of CMM development.

The study also found a prevalence of possible sarcopenia, sarcopenia, and severe sarcopenia at 26%, 8.8%, and 3% respectively. These rates were notably lower than those reported by Wu et al. (38.5%, 18.6%, and 8%). This discrepancy may be related to the differences in the age and years of age of the participants (26). According to the AWGS criteria, the prevalence of sarcopenia in Asian countries ranges from 5.5% to 25.7%, which is consistent with our findings (13). Previous epidemiological studies have shown that sarcopenia is associated with the risk of several metabolic diseases, including insulin resistance, which is one of the main pathological mechanisms leading to CMM[6] (27),. Skeletal muscle is a major organ for insulin action, and decreased skeletal muscle mass affects insulin-mediated glucose metabolism causing insulin resistance. A recent GWAS study conducted in a European population discovered that insulin resistance mediates the causal link between sarcopenia-related phenotypic grip strength and whole-body muscle mass with five distinct types of chronic metabolic diseases, including type 2 diabetes mellitus, nonalcoholic fatty liver disease, hypertension, coronary heart disease, and myocardial infarction (28). Furthermore, Ke et al. reported that sarcopenia-related phenotypic grip strength independently

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TABLE 5 Age Subgroup Analysis of the Effect of CMI and sarcopenia on CMM.

Factors		Model 1 HR(95%CI)	Model 2 HR(95%CI)
Age<65	Heart disease		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.18 (0.94,1.47)	1.17 (0.77,1.77)
	Sarcopenia only	0.88 (0.51,1.52)	0.92 (0.38,2.23)
	Both sarcopenia and high Cardiac Metabolic Index	2.79 (1.58,4.92)***	2.95 (1.18,7.40)*
	Diabetes		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	2.63 (1.98,3.49)***	1.53 (0.94,2.50)
	Sarcopenia only	1.73 (0.95,3.13)	1.12 (0.33,3.85)
	Both sarcopenia and high Cardiac Metabolic Index	1.21 (0.38,3.83)	2.18 (0.60,7.93)
	Stroke		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.60 (1.07,2.37)*	1.42 (0.68,2.95)
	Sarcopenia only	1.55 (0.70,3.47)	1.04 (0.22,4.90)
	Both sarcopenia and high Cardiac Metabolic Index	1.36 (0.33,5.62)	1.49 (0.18,12.64)
	Hypertension		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.50 (1.28,1.75)***	1.03 (0.78,1.36)
	Sarcopenia only	0.89 (0.60,1.31)	1.09 (0.54,2.22)
	Both sarcopenia and high Cardiac Metabolic Index	0.76 (0.38,1.54)	0.78 (0.24,2.54)
	CMM		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.91 (1.47,2.48)***	1.34 (0.82,2.20)
	Sarcopenia only	1.22 (0.67,2.23)	0.74 (0.17,3.22)
	Both sarcopenia and high Cardiac Metabolic Index	0.61 (0.15,2.49)	1.72 (0.38,7.90)
Age≥65	Heart disease		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.47 (0.82,2.62)	1.05 (0.26,4.19)
	Sarcopenia only	1.65 (0.97,2.80)	2.00 (0.69,5.74)
	Both sarcopenia and high Cardiac Metabolic Index	1.61 (0.90,2.87)	2.33 (0.69,7.83)

(Continued)

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TABLE 5 Continued

Factors		Model 1 HR(95%CI)	Model 2 HR(95%CI)
	Diabetes		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.81 (0.71,4.60)	1.36 (0.20,9.26)
	Sarcopenia only	1.24 (0.49,3.14)	1.90 (0.21,17.46)
	Both sarcopenia and high Cardiac Metabolic Index	2.76 (1.14,6.71)*	10.49 (1.30,84.82)*
	Stroke		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	2.13 (0.80,5.68)	1.33 (0.28,6.29)
	Sarcopenia only	1.97 (0.77,5.02)	1.44 (0.28,7.41)
	Both sarcopenia and high Cardiac Metabolic Index	3.21 (1.26,8.20)*	1.60 (0.29,8.91)
	Hypertension		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	1.48 (0.99,2.18)*	0.74 (0.35,1.56)
	Sarcopenia only	1.13 (0.78,1.65)	0.98 (0.49,1.97)
	Both sarcopenia and high Cardiac Metabolic Index	1.43 (0.96,2.13)	1.30 (0.60,2.81)
	CMM		
	Neither sarcopenia or high Cardiac Metabolic Index	Ref.	Ref.
	High Cardiac Metabolic Index only	3.45 (1.47,8.07)**	1.84 (0.47,7.20)
	Sarcopenia only	2.88 (1.26,6.62)*	4.83 (1.22,19.06)*
	Both sarcopenia and high Cardiac Metabolic Index	4.82 (2.10,11.07)***	7.31 (1.72,31.15)**

HR, hazard ratio; CMM, Cardiometabolic multimorbidity; CMI, cardiac metabolic index;
Model 1: unadjusted;
Model 2: adjusted age, sex, residence, education, marital status, smoking, drinking, BMI, SBP, DBP, strenuous exercise, moderate intensity exercise, White Blood cell, Hemoglobin, Platelets, CRP, Total Cholesterol, LDL-c, BUN, Creatinine, Glucose, Uric Acid.
* indicates P<0.05, ** indicates P<0.01, *** indicates P<0.001.

predicts the morbidity of chronic metabolic diseases and all-cause mortality (29). Similarly, our study found that individuals aged 65 years or older with sarcopenia exhibited a higher propensity for developing CMM compared to those without sarcopenia, aligning with previous findings. However, there was no significant increase in the prevalence of CMM among individuals with sarcopenia who were under 65 years of age compared to participants without sarcopenia. This lack of increase may be due to the small sample size included and the short follow-up period. Therefore, assessment of sarcopenia during community health screening may help identify patients with CMM and is expected to develop early interventions to improve health outcomes, especially in the older adult.

This study found that a high level of CMI increases the risk of CMD, consistent with previous cross-sectional studies (21). In the same cohort study, Zhu et al. suggested that high levels of BRI were associated with a high risk of CVD (30). The BRI index is a measure of abdominal obesity that assesses body fat distribution using waist and hip circumference but cannot distinguish between visceral and subcutaneous fat. It is crucial to consider this when evaluating the health risks associated with obesity. It is important to note that the distribution of fat in the body has a greater impact on human metabolism than total body fat. Visceral obesity, which is characterized by the accumulation of visceral fat, has been identified as a strong predictor of CMM morbidity and mortality (31). WHtR is considered a valuable parameter that reflects both subcutaneous adipose tissue (SAT) and visceral adipose tissue distribution. TG/HDL-C is an atherogenic marker that represents insulin resistance and cardio-metabolic risk. It offers stronger predictive value for stroke, CVD, and all-cause mortality compared to traditional lipid profiles (32). Therefore, CMI may

be an important predictor of metabolic disease and is significantly associated with cumulative cardiometabolic risk factors (33, 34). The longitudinal analysis showed that the incidence of CMM was 8.7/1000 person-years in the group with neither sarcopenia nor high CMI, 17.37/1000 person-years in the high CMI group, 14.22/1000 person-years in the sarcopenia group, and 22.34/1000 person-years in the group with sarcopenia combined with high CMI. These data strongly demonstrate that sarcopenia combined with high CMI is a significant predictor of CMM incidence.

Previous extensive research has demonstrated that the loss of skeletal muscle mass and function is often accompanied by a relative or absolute increase in body fat, a condition known as sarcopenic obesity (SO) (35). So is associated with a higher risk of metabolic and cardiovascular diseases compared to sarcopenia or obesity alone. In a prospective study of 3,366 older adults living in a community, the highest risk of CVD events was associated with SO, assessed using waist circumference and muscle strength (36). Zhou et al. assessed the impact of SO on patients with type 2 diabetes using different measures of obesity. They found that when categorized using percent body fat (BF%), SO was associated with increased cardiometabolic risk in patients. Hye et al. reported that weight-adjusted waist-to-height ratio (WWI) was the most suitable predictor of cardiovascular events in older adults with T2DM and sarcopenia (37). Our study findings revealed that, after adjusting for all relevant variables, individuals with sarcopenia combined with CMI exhibited a significantly increased risk of CMM morbidity compared to those with either condition alone. This risk was particularly pronounced in those aged over 65 years and thus underscores the importance of assessing sarcopenia and CMI in community health screenings and routine clinical practice. It helps identify individuals at a higher risk of developing CMM and enables early intervention measures to minimize its occurrence.

Although our study has yielded several noteworthy observations, there are still some limitations. First, the exclusion of participants with incomplete sarcopenia information and missing CMD data during follow-up may have introduced selection bias, limiting the generalizability of our findings. Second, while we employed equations to estimate muscle mass, validated in Chinese individuals, potential differences in accuracy compared to the AWGS-recommended DAX should be noted;Third, despite adjusting for numerous conventional confounders, residual confounding by unaccounted factors such as body fat mass and medication history may have influenced our results. Four, we acknowledge that our decision to group sarcopenia and severe sarcopenia may impact the interpretation of our results. This approach was taken to maintain statistical power and to align with the clinical focus on the broader implications of muscle wasting on health outcomes. While this may obscure some differences between the two groups, it also provides a more generalizable assessment of the impact of muscle wasting across the spectrum of severity. Future research with larger sample sizes may benefit from distinguishing between sarcopenia and severe sarcopenia to better understand the nuances of their respective contributions to cardiometabolic health. Last, possible excessive use and the reliance on self-reported physician diagnoses for CMM may have introduced information bias. Additionally, our study has chosen to focus on individuals with high CMI, we recognize the potential value in examining the lower end of the CMI spectrum. However, given the specific objectives of this research to investigate the correlation between high CMI and cardiometabolic multimorbidity, we deliberately concentrated our efforts on the group with the greatest clinical relevance. Future studies may consider exploring the implications of low CMI in depth, which could provide a complementary perspective to our findings. Despite these limitations, our study provides valuable insights into the impact of sarcopenia and visceral obesity on cardiometabolic diseases, offering crucial clues for future research. Therefore, the assessment of sarcopenia and CMI should be clinically incorporated into community health screenings and routine clinical practice for older adults.

Conclusion

In summary, the findings suggest a significant correlation between sarcopenia and CMI with CMM in middle-aged and older adults in China. The risk of CMM was significantly higher for sarcopenia combined with high CMI than for either condition alone. It is crucial to emphasize that preventing sarcopenia and/or implementing effective interventions for reducing CMI may contribute to reducing the incidence of CMM and promoting healthy aging.

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://charls.pku.edu.cn.

Ethics statement

The studies involving humans were approved by institutional and national research council ethical. 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

LH: Funding acquisition, Writing – original draft. CL: Formal analysis, Visualization, Writing – original draft. YT: Methodology, Writing – original draft. YY: Data curation, Investigation, Writing – original draft. ML: Formal analysis, Writing – original draft. HT: Writing – review & editing. JL: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Atherogenic index of plasma: a new indicator for assessing the short-term mortality of patients with acute decompensated heart failure

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Objective: Arteriosclerosis is a primary causative factor in cardiovascular diseases. This study aims to explore the correlation between the atherogenic index of plasma (AIP) and the 30-day mortality rate in patients with acute decompensated heart failure (ADHF).

Methods: A total of 1,248 ADHF patients recruited from the Jiangxi-Acute Decompensated Heart Failure1 (JX-ADHF1) cohort between 2019 and 2022 were selected for this study. The primary outcome was the 30-day mortality rate. Multivariable Cox regression, restricted cubic splines (RCS), and stratified analyses were utilized to assess the relationship between AIP and the 30-day mortality rate in ADHF patients. Mediation models were employed for exploratory analysis of the roles of inflammation, oxidative stress, and nutrition in the association between AIP and the 30-day mortality rate in ADHF patients.

Results: During the 30-day follow-up, 42 (3.37%) of the ADHF patients died. The mortality rates corresponding to the quartiles of AIP were as follows: Q1: 1.28%, Q2: 2.88%, Q3: 2.88%, Q4: 6.41%. The multivariable Cox regression revealed a positive correlation between high AIP and the 30-day mortality rate in ADHF patients [Hazard ratio (HR) 3.94, 95% confidence interval (CI): 1.08–14.28], independent of age, gender, heart failure type, cardiac function classification, and comorbidities. It is important to note that there was a U-shaped curve association between AIP (<0.24) and the 30-day mortality rate before the fourth quartile, with the lowest 30-day mortality risk in ADHF patients around an AIP of -0.1. Furthermore, mediation analysis suggested significant mediating effects of inflammation and nutrition on the 30-day mortality rate in ADHF patients related to AIP, with inflammation accounting for approximately 24.29% and nutrition for about 8.16% of the mediation effect.

Conclusion: This retrospective cohort analysis reveals for the first time the association between AIP and the 30-day mortality rate in ADHF patients.

According to our findings, maintaining an AIP around -0.1 in ADHF patients could be crucial for improving poor prognoses from a medical perspective. Additionally, for ADHF patients with high AIP, it is important to assess and, if necessary, enhance nutritional support and anti-inflammatory treatment.

KEYWORDS

arteriosclerosis, atherogenic index of plasma, acute decompensated heart failure, poor prognoses, AIP, ADHF

Introduction

ADHF is characterized by new-onset or worsening symptoms and signs of severe cardiac functional or structural abnormalities, necessitating urgent hospitalization (1). Despite significant advancements in heart failure medications, assistive devices, and therapeutic approaches over the past few decades (2–7), the recurrent hospitalization and mortality risks remain notably high for ADHF patients (8–11). Therefore, early and effective risk stratification using simple factors could be crucial in improving the prognosis for hospitalized ADHF patients.

Arteriosclerosis is a major cause of various cardiovascular and cerebrovascular diseases such as coronary heart disease, heart failure, and stroke (12–14). Early identification of arteriosclerosis is vital in reducing the burden of these diseases (11–15). Clinical follow-up studies have confirmed the importance of assessing arteriosclerosis for risk stratification in heart failure, which includes using measures like carotid intima-media thickness as a marker of carotid arteriosclerosis (16, 17), the ankle-brachial index for peripheral artery disease (18, 19), and coronary artery calcification scoring as a sign of coronary arteriosclerosis (20, 21). The AIP is a novel and simple biological marker for assessing arteriosclerosis, developed by Professors Dobiásová M and Frohlich J, calculated from triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) levels (22). Dobiásová M and colleagues, in their evaluation across 35 cohorts with varying risks of arteriosclerosis, found that the AIP measurements closely matched the values of lipoprotein particle size and the fractional esterification rate of high-density lipoprotein cholesterol, and were directly related to arteriosclerosis risk. Hence, they recommended AIP as an assessment parameter for arteriosclerosis. This recommendation has been validated in numerous subsequent clinical cohorts (23–27), where researchers have highlighted the significance of AIP in assessing cardiovascular and cerebrovascular diseases and their adverse outcomes. However, the role of AIP in the prognosis of ADHF patients remains unclear. To address this question, our current study aims to analyze the association between AIP and the 30-day mortality rate in ADHF patients, exploring key mediating pathways that contribute to this association, through the JX-ADHF1 cohort.

Methods

Subject selection

The JX-ADHF1 study is a retrospective cohort study initiated by medical professionals. Its primary objective is to establish a high-quality cohort of ADHF patients, effectively utilizing clinical records during hospitalization to explore new methods for early risk stratification and improve the prognosis of ADHF patients. Specifically, the JX-ADHF1 study consecutively included 1,790 ADHF patients admitted to Jiangxi Provincial People's Hospital from January 2019 to December 2022. The diagnosis of ADHF was based on the latest European Society of Cardiology guidelines for acute and chronic heart failure available at the time of admission. The exclusion criteria for the study population were as follows: (i) 23 subjects with liver cirrhosis and 99 subjects with stage 5 chronic kidney disease or a history of hemodialysis were excluded due to the potential adverse impact of non-heart failure related fluid retention on the study factors and prognosis. (ii) 42 subjects who underwent percutaneous coronary intervention within the last three months were excluded due to the significant impact of reperfusion therapy on short-term prognosis. (iii) 73 subjects with malignant tumors were excluded due to their potentially life-limiting prognosis impacting the study results. (iv) 63 patients with pacemakers were excluded due to expected autonomic regulatory deficits. (v) 12 minors and 1 pregnant woman were also excluded. Finally, for the current study, 229 subjects with missing baseline AIP information were excluded. Ultimately, the current study evaluated 1,248 ADHF patients, and Figure 1 depicts the detailed screening process for the entire study population.

Ethics and informed consent

The JX-ADHF1 study data, owned by Jiangxi Provincial People's Hospital, is accessible to researchers who have signed a data use agreement. The JX-ADHF1 study protocol was approved by the Ethics Committee of Jiangxi Provincial People's Hospital (IRB: 2024–01), and consent for data use was obtained from the subjects and their families. The research dataset anonymized

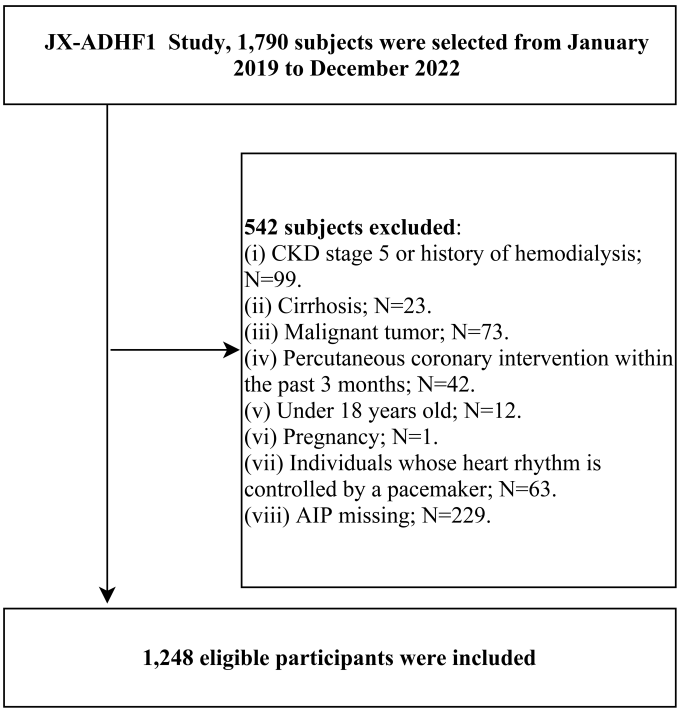

FIGURE 1
Flow chart of study participants.

personal identifiers with identifiable information, adhering to the ethical principles of the Declaration of Helsinki and reported results according to the STROBE guidelines Supplementary Text 1.

Data collection

Demographic (gender and age) and clinical data [comorbidities (hypertension, diabetes, cerebral infarction, coronary heart disease), New York Heart Association (NYHA) classification at admission, systolic and diastolic blood pressure (SBP and DBP), echocardiogram results at admission, and blood sample laboratory parameters] of the subjects at baseline were independently collected and cross-checked by two trained researchers. The blood pressure measurements recorded in the current analysis were the first measurements after admission, taken in a calm environment or bedside using an Omron automatic sphygmomanometer (HBP-1300). Comorbidities were determined based on patient self-report, ongoing medication treatment, or records in the patient's medical history.

Laboratory parameters were measured within 24 hours of admission at the Jiangxi Provincial People's Hospital laboratory center by professional medical laboratory personnel using automatic analyzers. The biochemical indicators measured included albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), creatinine (Cr), uric acid (UA), total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), and HDL-C, routine blood parameters [white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), platelet count (PLT)], and the cardiac function indicator N-terminal pro B-type natriuretic peptide (NT-proBNP). It is important to note that lipid and liver enzyme-related indicators were measured from venous blood samples taken on an empty stomach at admission or the next morning after admission.

Calculation of AIP

AIP = log10 (TG/HDL-C) (22).

Study outcome

The primary outcome of the study is the all-cause 30-day mortality rate. The start of the follow-up for all ADHF patients is set at the time of admission, and their 30-day survival status is obtained by trained medical workers through text messages, phone calls, and face-to-face follow-ups in outpatient and inpatient settings.

Statistical analysis

Data analysis in this study is performed using R language version 4.2.1 and Empower(R) version 2.20 statistical software. Baseline characteristics of the study population were described as counts (%), mean (standard deviation), or median (interquartile range) based on the type and distribution of variables. Differences

between groups were compared using t-tests, one-way ANOVA, and non-parametric tests, with a two-sided $P < 0.05$ set as the threshold for statistical significance.

Kaplan-Meier curve was used to depict the 30-day survival rates of ADHF patients. Cox regression models were constructed to test the association between AIP and the 30-day mortality rate in ADHF patients, in which the variance inflation factors of all covariates were considered in the adjustment of variables (28), and evaluated the suitability of the Cox regression model using Schoenfeld residuals to assess the proportional hazards assumption (29). To test the robustness of the Cox regression analysis, the minimum strength of association needed for an unmeasured confounder to explain the 30-day mortality rate in ADHF patients was calculated based on the final adjusted model (E-value) (30).

Nested within the Cox regression model, RCS with four knots was employed to model the dose-response relationship between AIP and the 30-day mortality rate in ADHF patients. Stratified analysis was further used to explore how the association between AIP and the 30-day mortality rate in ADHF patients varies across different subgroups, with likelihood ratio tests assessing differences between strata.

After establishing the association between AIP and the 30-day mortality rate in ADHF patients, mediation analysis (31) was conducted to explore whether oxidative stress (32), inflammation (33), and nutrition (34) pathways mediate the relationship between AIP and the 30-day mortality rate. The size of the mediation effect was quantified by calculating the ratio of the indirect effect to the total effect, and the significance of the mediation effect was tested using the Bootstrap sampling method (35). Based on previous studies, GGT is selected as a marker of oxidative stress (36), WBC as a marker of inflammation (37), and ALB as an indicator of nutritional status (38).

Results

Follow-up outcomes and baseline characteristics

The analysis included 1,248 ADHF patients with an average age of 68 years and a male-to-female ratio of 1.43:1. During the 30-day observation period, 42 patients (3.37%) experienced mortality events. Figure 2 displays the 30-day survival curve of the study population, indicating a gradual increase in mortality events over time within the 30-day period.

In this analysis, AIP in ADHF patients showed a normal distribution (Supplementary Figure 1), with a median of 0.075. Patients were divided into quartiles based on their AIP, summarizing the baseline characteristics of ADHF patients (Table 1). The results indicated that compared to the group with lower AIP values, those with higher AIP were younger, had lower SBP, left ventricular ejection fraction (LVEF), ALB, and HDL-C levels, and higher levels of WBC, RBC, PLT, ALT, Cr, UA, TC, TG, and LDL-C. Additionally, patients with higher AIP were more likely to have comorbid diabetes and coronary heart disease, a higher proportion of NYHA class IV, and a significantly higher probability

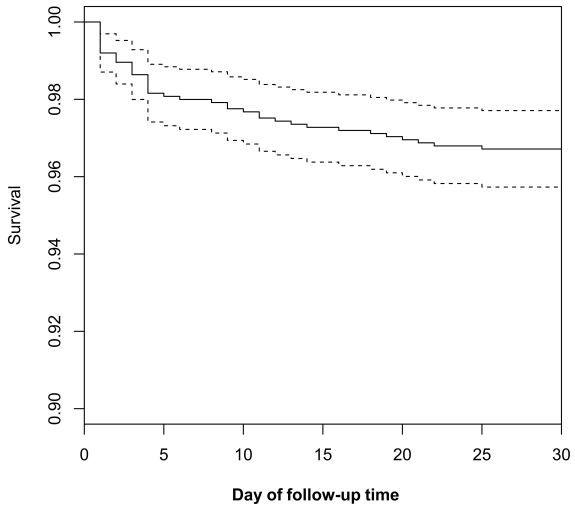

FIGURE 2
30-day survival curve of acute decompensated heart failure patients.

of mortality within 30 days (Q1: 1.28%, Q2: 2.88%, Q3: 2.88%, Q4: 6.41%).

Table 2 further displays the baseline characteristics of the study population based on whether or not the subject experienced mortality within the 30-day follow-up period. In summary: (i) In demographic characteristics, ADHF patients who died within 30 days were significantly older at admission, had a higher proportion of NYHA class IV, and a higher prevalence of cerebral infarction. (ii) In terms of measured data, deceased subjects typically had lower baseline levels of blood pressure, RBC, HGB, PLT, ALB, TC, HDL-C, and LDL-C, but higher levels of WBC, liver enzymes, Cr, UA, TG, NT-proBNP, and AIP (Figure 3).

Association analysis of AIP with 30-day mortality in ADHF patients

Before analyzing the association, we confirmed through Schoenfeld residual plots of AIP over time (Supplementary Figure 2) that the Cox regression model did not violate the proportional hazards assumption. Additionally, the variance inflation factors of each covariate were calculated, identifying collinearity between HGB, ALB, and TC with other covariates, and thus these were not included in the subsequent multivariable models (Supplementary Table 1).

Three progressively adjusted multivariable Cox regression models were constructed to analyze the association between AIP and the 30-day mortality rate in ADHF patients (Table 3). In the first model (Model 1), adjustments were made for age, gender, and comorbidities (hypertension, diabetes, cerebral infarction, and coronary heart disease), showing a positive correlation between AIP and 30-day mortality rate in ADHF patients with an HR of 7.38 (95%CI: 2.55–21.36). Additionally, the HR values corresponding to the AIP quartiles showed a positive trend (P-trend=0.0002). In the second model (Model 2), adjustments were further made for NYHA

TABLE 1 Summary of baseline characteristics of the study population according to AIP quartile group.

	AIP quartiles				*P*-value
	Q1 (-0.73–0.08)	Q2 (-0.08–0.08)	Q3 (0.08–0.24)	Q4 (0.24–1.55)	
No. of subjects	312	312	312	312	
Gender					0.709
Female	129 (41.35%)	134 (42.95%)	130 (41.67%)	120 (38.46%)	
Male	183 (58.65%)	178 (57.05%)	182 (58.33%)	192 (61.54%)	
Age (years)	74.00 (67.00–81.00)	70.00 (60.00–80.00)	69.00 (60.00–78.00)	66.00 (57.00–75.00)	<0.001
Comorbidities					
Hypertension (n,%)	128 (41.03%)	122 (39.10%)	137 (43.91%)	141 (45.19%)	0.405
Diabetes (n,%)	37 (11.86%)	87 (27.88%)	83 (26.60%)	121 (38.78%)	<0.001
Cerebral infarction (n,%)	58 (18.59%)	55 (17.63%)	43 (13.78%)	52 (16.67%)	0.406
CHD (n,%)	82 (26.28%)	98 (31.41%)	92 (29.49%)	123 (39.42%)	0.004
NYHA classification (n,%)					0.310
III	229 (73.40%)	222 (71.15%)	217 (69.55%)	208 (66.67%)	
IV	83 (26.60%)	90 (28.85%)	95 (30.45%)	104 (33.33%)	
SBP (mmHg)	130.80 (25.05)	128.95 (23.47)	127.64 (25.27)	125.53 (24.39)	0.055
DBP (mmHg)	76.70 (15.77)	76.18 (15.09)	76.16 (15.81)	75.20 (16.09)	0.684
LVEF (%)	48.00 (40.00–56.00)	48.00 (39.00–57.00)	46.00 (37.00–55.00)	45.00 (36.00–55.25)	0.026
WBC ($\times10^9$/L)	5.47 (4.49–6.90)	5.80 (4.70–7.48)	6.37 (5.26–7.96)	6.80 (5.60–8.71)	<0.001
RBC ($\times10^{12}$/L)	3.96 (0.69)	4.05 (0.72)	4.16 (0.75)	4.19 (0.88)	<0.001
HGB (g/L)	120.07 (20.66)	122.82 (22.13)	125.50 (22.28)	124.86 (25.37)	0.013
PLT ($\times10^9$/L)	148.00 (115.50–187.00)	161.00 (122.00–202.00)	166.00 (129.00–215.50)	177.50 (136.00–233.75)	<0.001
ALB (g/L)	35.92 (4.33)	35.57 (5.14)	35.37 (4.69)	34.70 (5.67)	0.019
ALT (U/L)	18.00 (12.00–29.75)	22.00 (14.00–35.25)	23.00 (14.00–40.00)	24.50 (14.75–45.00)	<0.001
AST (U/L)	25.00 (19.00–36.00)	25.00 (20.00–36.00)	25.00 (19.00–38.75)	25.00 (19.00–43.25)	0.619
GGT (U/L)	38.50 (22.25–64.25)	44.00 (25.00–83.00)	43.00 (25.00–75.75)	42.50 (25.00–87.25)	0.053
Cr (umol/L)	79.00 (61.50–102.00)	87.00 (66.00–121.00)	90.00 (72.00–120.00)	100.00 (73.00–165.00)	<0.001
UA (umol/L)	404.00 (329.00–504.00)	413.00 (334.50–518.75)	440.00 (361.00–555.00)	465.00 (346.00–606.00)	<0.001
TC (mmol/L)	3.72 (0.91)	3.79 (1.01)	3.77 (1.01)	3.96 (1.24)	0.026
TG (mmol/L)	0.77 (0.65–0.89)	1.06 (0.92–1.21)	1.29 (1.11–1.51)	1.89 (1.55–2.41)	<0.001
HDL-C (mmol/L)	1.26 (0.28)	1.07 (0.23)	0.93 (0.21)	0.77 (0.21)	<0.001
LDL-C (mmol/L)	2.14 (0.76)	2.36 (0.84)	2.45 (0.86)	2.57 (0.96)	<0.001
NT-proBNP (pmol/L)	3769.50 (2413.25–5707.25)	3500.50 (1917.50–5621.00)	3637.50 (2234.75–5519.75)	3875.00 (1971.75–5932.50)	0.468
30-day mortality	4 (1.28%)	9 (2.88%)	9 (2.88%)	20 (6.41%)	0.004

CHD, coronary heart disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipid cholesterol; Cr, creatinine; UA, uric acid; WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; NT-proBNP, N-Terminal Pro-Brain Natriuretic Peptide; AIP, atherogenic index of plasma.

classification, LVEF, DBP, and NT-proBNP, slightly decreasing the HR to 5.87 (95%CI: 1.77–19.44). In Model 2, despite a continuing positive trend in AIP quartiles, the HR value for the second quartile was slightly higher than for the third (HR: Q2 2.38, Q3 2.15). The third model (Model 3), further considered the impact of WBC, RBC, PLT, ALB, AST, GGT, Cr, UA, and LDL-C, with findings similar to Model 2, showing a slight decrease in HR (HR 3.94, 95% CI: 1.08–14.28). Notably, in Model 3, the HR value for the second

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TABLE 2 Characteristics of study subjects surviving versus dying by 30 days.

	Survivors	Nonsurvivors	*P*-value
No. of subjects	1206	42	
Gender			**0.470**
Female	498 (41.29%)	15 (35.71%)	
Male	708 (58.71%)	27 (64.29%)	
Age (years)	70.00 (60.00–78.75)	77.50 (69.00–83.50)	0.001
Comorbidities			
Hypertension (n,%)	509 (42.21%)	19 (45.24%)	0.696
Diabetes (n,%)	313 (25.95%)	15 (35.71%)	0.158
Cerebral infarction (n,%)	194 (16.09%)	14 (33.33%)	0.003
CHD (n,%)	381 (31.59%)	14 (33.33%)	0.811
NYHA classification (n,%)			**<0.001**
III	863 (71.56%)	13 (30.95%)	
IV	343 (28.44%)	29 (69.05%)	
SBP (mmHg)	128.75 (24.41)	113.43 (25.80)	<0.001
DBP (mmHg)	76.42 (15.63)	65.67 (13.52)	<0.001
LVEF (%)	47.00 (38.00–56.00)	50.00 (38.50–53.00)	0.627
WBC ($\times10^9$/L)	6.10 (4.83–7.69)	10.21 (6.29–14.76)	<0.001
RBC ($\times10^{12}$/L)	4.10 (0.76)	3.72 (0.84)	0.001
HGB (g/L)	123.62 (22.69)	114.69 (23.06)	0.012
PLT ($\times10^9$/L)	161.00 (126.00–210.00)	151.50 (98.00–232.25)	0.499
ALB (g/L)	35.52 (4.92)	31.72 (5.63)	<0.001
ALT (U/L)	21.00 (13.00–37.00)	29.00 (15.00–81.50)	0.034
AST (U/L)	25.00 (19.00–37.00)	41.00 (22.00–98.50)	<0.001
GGT (U/L)	41.00 (24.00–76.00)	57.00 (30.00–93.75)	0.049
Cr (umol/L)	87.00 (67.00–120.00)	179.50 (124.00–276.75)	<0.001
UA (umol/L)	426.00 (342.00–539.00)	523.50 (391.25–661.00)	0.003
TC (mmol/L)	3.83 (1.05)	3.34 (0.83)	0.003
TG (mmol/L)	1.14 (0.88–1.55)	1.30 (1.03–1.77)	0.128
HDL-C (mmol/L)	1.01 (0.29)	0.85 (0.28)	<0.001
LDL-C (mmol/L)	2.39 (0.87)	2.01 (0.64)	0.005
AIP	0.09 (0.26)	0.21 (0.25)	0.002
NT-proBNP (pmol/L)	3618.50 (2140.25–5595.50)	6175.00 (3465.75–10123.00)	<0.001

(Continued)

TABLE 2 Continued

CHD, coronary heart disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipid cholesterol; Cr, creatinine; UA, uric acid; WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; NT-proBNP, N-Terminal Pro-Brain Natriuretic Peptide; AIP, atherogenic index of plasma.

quartile was higher than the third but lower than the fourth (HR: Q2: 2.82, Q3: 2.01, Q4: 4.09); suggesting a potential non-linear association before the fourth quartile of AIP. Based on Model 3, the minimum E-value associated with the 30-day mortality rate in ADHF patients was calculated to be 7.34.

Dose-response relationship

Using a RCS with four knots, we further constructed a dose-response relationship curve between AIP in ADHF patients and their 30-day mortality rate (Figure 4). After adequately adjusting for confounding factors, we found that the dose-response curve correlated with the association analysis results in Table 3. It can be observed that the association between the 30-day mortality rate and AIP demonstrated a U-shaped curve before the fourth quartile of AIP (AIP<0.24), with the lowest 30-day mortality risk in ADHF patients occurring at an AIP of approximately -0.1.

Subgroup analysis

We conducted stratified analyses based on age (median), gender, LVEF value (50%), NYHA classification, and comorbidities, assessing the presence of interactions between AIP and stratification factors through likelihood ratio tests. The results (Table 4) indicated no significant interactions in all the subgroups (All *P*-interaction>0.05), suggesting that the association between AIP and the 30-day mortality rate in ADHF patients was relatively stable and unlikely to be influenced by these external factors.

Mediation analysis

Mediated analysis was performed to explore the roles of inflammation, oxidative stress and nutritional pathways in the association between AIP and the 30-day mortality rate in ADHF

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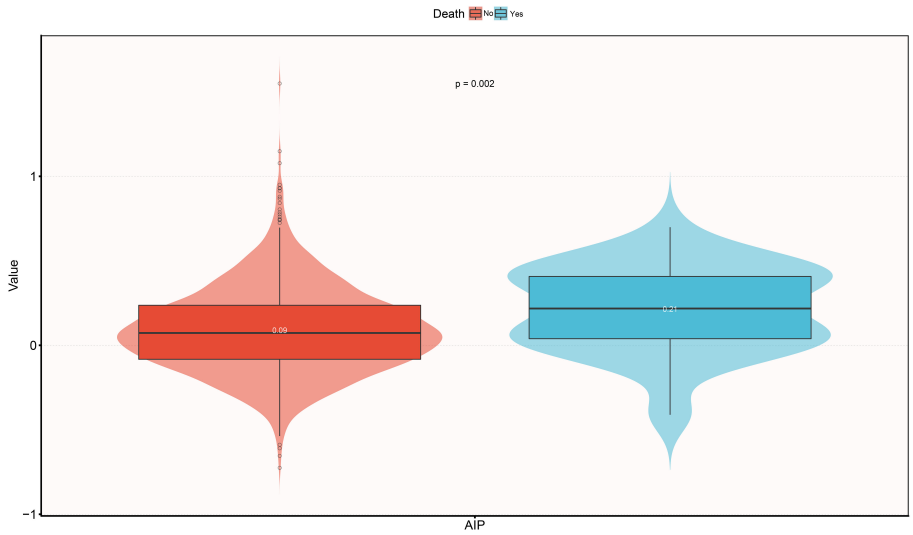

FIGURE 3
Violin diagram showing baseline characteristics of AIP according to whether death occurred during the 30-day follow-up period. AIP, atherogenic index of plasma.

patients. Table 5 presents the detailed results of the mediation analysis, and Figure 5 illustrates the mediation diagram for inflammation (WBC), oxidative stress (GGT), and nutrition (ALB). The exploratory analysis revealed significant mediating effects of inflammation and nutrition in the association between AIP and the 30-day mortality rate in ADHF patients (*P*-value of proportion mediate < 0.05), while the mediating effect of oxidative stress appeared non-significant (*P*-value of proportion mediate > 0.05). Specifically, inflammation accounted for approximately 24.29% of the mediation effect, and nutrition for about 8.16% in the association between AIP and the 30-day mortality rate in ADHF patients.

TABLE 3 Multivariable Cox regression analysis of the association between AIP and 30-day mortality in patients with ADHF.

	Hazard ratios (95% confidence interval)		
	Model 1	Model 2	Model 3
AIP (continuous variable)	7.38 (2.55, 21.36)	5.87 (1.77, 19.44)	3.94 (1.08, 14.28)
AIP (quartiles)			
Q1(-0.73–0.08)	Ref	Ref	Ref
Q2(-0.08–0.08)	2.55 (0.78, 8.36)	2.38 (0.69, 8.15)	2.82 (0.78, 10.15)
Q3(0.08–0.24)	2.81 (0.86, 9.20)	2.15 (0.64, 7.28)	2.01 (0.51, 7.89)
Q4(0.24–1.55)	6.98 (2.31, 21.05)	4.89 (1.60, 14.96)	4.09 (1.25, 13.35)
P-trend	0.0002	0.0035	0.0233

AIP, atherogenic index of plasma; ADHF, acute decompensated heart failure.
Model 1 adjusted for gender, age, hypertension, diabetes, cerebral infarction and CHD.
Model 2 adjusted for model 1 + NYHA classification, LVEF, DBP, NT-proBNP.
Model 3 adjusted for: Model 2+ WBC, RBC, PLT, ALB, AST, GGT, Cr, UA, LDL-C.

Discussion

In this retrospective cohort analysis, we discovered that although the overall association between AIP at admission and 30-day mortality in patients with ADHF was positively correlated and independent of age, gender, heart failure type, cardiac function classification, and comorbidities, further analysis using RCS revealed a U-shaped association before the fourth quartile of AIP (AIP<0.24). The lowest 30-day mortality risk in ADHF patients corresponded to an AIP of approximately -0.1.

ADHF is a common reason for hospitalization or the need for emergency care in the elderly population and is associated with a high risk of adverse outcomes (1, 8–11). Statistics indicate that over 30% of ADHF patients require rehospitalization or face mortality shortly after discharge (within 90 days) (8–11, 39). In China, the 30-day mortality rate for ADHF patients ranges between 1.65% and 13.17% (40–45), while in the JX-ADHF1 cohort, it is approximately 4%, and in the current analysis, it is 3.37% after excluding certain subjects. ADHF has become one of the most challenging cardiovascular diseases to manage appropriately worldwide. Early identification of patients potentially at risk of adverse outcomes and exploration of more effective treatment options may be vital in reducing the disease burden on patients and the healthcare system (38).

AIP is a crucial assessment tool for arteriosclerosis. Many past studies have demonstrated its significant value in assessing the risk of cardiovascular and cerebrovascular diseases (23–26), and in evaluating adverse outcomes in these diseases (46–52). For instance, in assessing adverse outcomes in coronary heart disease patients, an increase of one unit in AIP as a continuous variable is reported to increase the risk of major adverse cardiovascular and cerebrovascular events by 30.8%-114.9% (46, 47). When AIP is considered as a categorical variable, patients with coronary heart disease and high AIP face a 61.4%-689% increased risk of major

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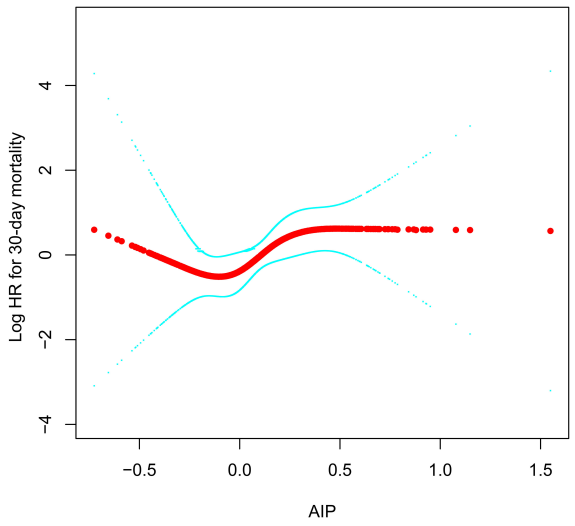

FIGURE 4
Fitting the dose-response relationship between AIP and 30-day mortality in ADHF patients with 4 knots restricted cubic spline. AIP, atherogenic index of plasma; ADHF, acute decompensated heart failure. Adjusted for gender, age, hypertension, diabetes, cerebral infarction, CHD, NYHA classification, LVEF, DBP, NT-proBNP, WBC, RBC, PLT, ALB, AST, GGT, Cr, UA, LDL-C.

TABLE 4 Stratified analysis showed the relationship between AIP and 30-day mortality in patients with ADHF in different age, gender, NYHA class, LVEF and whether combined with hypertension/diabetes/cerebral infarction/CHD.

Subgroup	Adjusted HR (95%CI)	*P* for interaction
Age (years)		0.8800
20–70	6.24 (0.76, 51.04)	
71–96	7.70 (1.38, 42.87)	
Gender		0.8070
Male	4.37 (0.94, 20.19)	
Female	3.13 (0.33, 29.47)	
NYHA		0.9313
III	2.19 (0.16, 29.60)	
IV	2.50 (0.49, 12.67)	
LVEF		0.7670
< 50%	4.51 (0.66, 30.75)	
≥ 50%	3.09 (0.57, 16.80)	
Hypertension		0.9755
Yes	4.03 (0.54, 29.84)	
No	3.87 (0.73, 20.55)	
Diabetes		0.6974
Yes	2.64 (0.24, 29.15)	
No	4.65 (1.00, 21.54)	
Cerebral infarction		0.6899
Yes	5.91 (0.55, 63.24)	
No	3.37 (0.75, 15.16)	
CHD		0.0617
Yes	0.97 (0.13, 7.22)	
No	11.33 (2.22, 57.89)	

AIP, atherogenic index of plasma; ADHF, acute decompensated heart failure; CHD, coronary heart disease.
Models adjusted for the same covariates as in model 3 (Table 3), except for the stratification variable.

adverse cardiovascular and cerebrovascular events compared to those with low AIP (27, 48, 49). Overall, high AIP in patients with coronary heart disease indicates a higher risk of adverse outcomes. Similarly, in patients with baseline hypertension and stroke, high AIP also indicates a high risk of severe adverse outcomes (50–52). Our current study further revealed the role of AIP in assessing the risk of adverse outcomes in ADHF patients. The study showed that for each unit increase in AIP as a continuous variable, the 30-day mortality risk in ADHF patients increased by 294%; compared to those with low AIP, patients with high AIP had a 309% increased risk of 30-day mortality. These new research findings further underscored the significant value of AIP in assessing the risk of adverse outcomes in cardiovascular and cerebrovascular diseases.

An important finding of our current study, derived from the RCS analysis, is the U-shaped association between AIP and the 30-day mortality rate in ADHF patients before the fourth quartile of AIP (<0.24), with the lowest risk of 30-day mortality around an AIP of -0.1. This observation conveyed two crucial messages: (i) The dose-response curve provided a more intuitive understanding of the overall and stage-specific associations between AIP and the 30-day mortality rate in ADHF patients. (ii) The nadir of the U-shaped curve implied the threshold of the lowest short-term mortality risk in ADHF patients. On the one hand, this threshold is significant for risk assessment, and on the other hand, maintaining the AIP around -0.1 in ADHF patients may be beneficial in improving their prognosis. Similar U-shaped associations for AIP have been reported in other diseases; in a study on the adverse prognosis of acute ischemic stroke patients (52), Liu H and colleagues found a U-shaped association between AIP quartiles (Q1-Q4) and 3-month mortality in stroke patients, with the lowest mortality risk associated with AIP values between -0.1 and 0.08. This finding is similar to our current study. Additionally, in a study by Lee MJ et al. (53), examining the relationship between AIP and all-cause mortality in dialysis patients, a U-shaped curve was observed, with the lowest mortality risk in dialysis patients around an AIP of 0.39. The AIP threshold reported by Lee MJ et al. differs from our findings, likely due to differences in study populations. It is well-known that renal impairment leads to changes in cholesterol structure, metabolism, reverse transport, accompanied by increased oxidative stress, electrolyte metabolism disorders, and other metabolic impacts, ultimately leading to dyslipidemia, particularly arteriosclerosis-inducing lipids (54–56). In our current analysis, we excluded patients with stage 5 chronic kidney

TABLE 5 Mediated analysis was performed to explore the roles of inflammation, oxidative stress and nutritional pathways in the association between AIP and the 30-day mortality rate in ADHF patients.

Mediator	Total effect	Mediation effect	Direct effect	PM(%)	*P*-value of PM
WBC	0.015 (0.003, 0.025)	0.004 (0.002, 0.006)	0.011 (0.002, 0.022)	24.29	0.032
GGT	0.015 (0.003, 0.025)	-0.000(-0.000,0.001)	0.015 (0.004, 0.026)	1.51	0.478
ALB	0.015 (0.003, 0.025)	0.002 (0.000, 0.003)	0.013 (0.002, 0.024)	8.16	0.042

PM, proportion mediate; ADHF, acute decompensated heart failure; other abbreviations as in Table 1.
Model adjusted for the same covariates as in model 2 (Table 3), except for the mediator variable.

disease and those undergoing dialysis to minimize the adverse impact of additional fluid and sodium retention on prognosis. Compared to Lee MJ et al.'s study on dialysis patients, our AIP levels were significantly lower [median value of the AIP: 0.075 (ours) vs 0.47 (Lee MJ et al.)].

The mechanism by which high AIP significantly increases the short-term mortality risk in ADHF patients is not entirely clear, but some insights may be provided by existing research evidence and auxiliary analyses in our study. Arteriosclerosis is known to be a pathological process involving long-term accumulation and transformation of lipids, inflammatory cells, smooth muscle cells, and necrotic cell debris beneath the endothelial cells lining the inner walls of arteries (57). Previously, arteriosclerosis was considered a lipid storage disease; however, more recent research has revealed it to be an ongoing inflammatory process (58, 59). Inflammation mediates the appearance of lipid streaks, the formation of arteriosclerosis, and subsequent cardiovascular and cerebrovascular complications, playing a pivotal role in the development of arteriosclerosis (58, 60). Fundamentally, arteriosclerosis can be termed an arteritis (57–60). Based on these established theories, our current study aimed to validate the role of inflammation in adverse cardiovascular outcomes associated with arteriosclerosis in real-world clinical practice. Using a mediation analysis model with WBC as the inflammatory marker (37), our results showed that inflammation significantly mediates the association between AIP and the 30-day mortality rate in ADHF patients, accounting for approximately 24.29% of the effect. This finding further validates the accuracy of basic research and quantifies the mediation effect of inflammation in this process, providing useful clinical data to support the basic mechanisms. Moreover, considering the significant impact of oxidative stress and nutrition on the pathogenesis and prognosis of ADHF patients (32, 34), we assessed the mediating effects of oxidative stress and nutrition. Our findings indicated that nutrition played a mediating role of about 8.16% in the association between AIP and 30-day mortality rate in ADHF patients, while the mediating effect of oxidative stress was not significant. Based on our findings, we recommend that for ADHF patients with high AIP, it is important to assess and manage inflammation and nutritional status, with potential benefits from enhanced nutritional support and anti-inflammatory treatment when necessary.

Study strengths and limitations

Our study has several notable strengths: (i) This is the first report of the relationship between AIP and the prognosis of ADHF patients. (ii) The discovery of a U-shaped curve association is of significant clinical importance, as the AIP threshold indicating the lowest death risk can provide crucial assistance in risk assessment and treatment for ADHF patients. (iii) The findings from the mediation analysis offer a mechanistic explanation for the association between AIP and 30-day mortality risk in ADHF patients and also provide insights for future treatment directions.

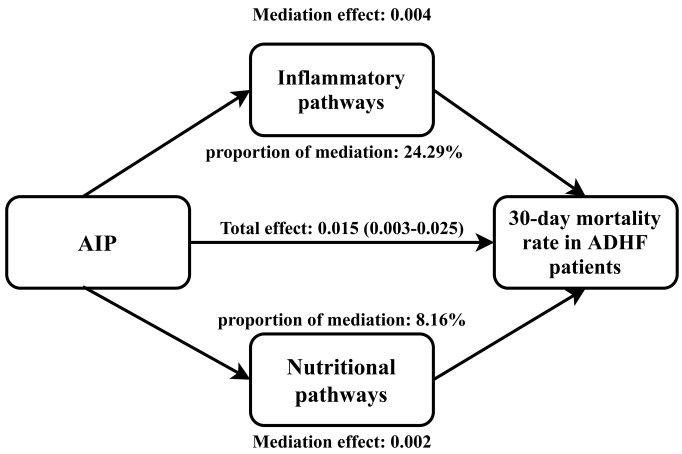

FIGURE 5
Path diagram for mediational model. AIP, atherogenic index of plasma; ADHF, acute decompensated heart failure. Adjusted for gender, age, hypertension, diabetes, cerebral infarction, CHD, NYHA classification, LVEF, DBP and NT-proBNP.

However, our study also has certain limitations: (i) Being observational, it inevitably includes some unmeasured factors leading to residual confounding. Nevertheless, the calculated E-value (7.34) suggests that it is unlikely that any confounding factors could significantly alter our findings. (ii) We lack repeated measurements of AIP, which might be more beneficial for early risk stratification in ADHF patients. (iii) The study evidence is primarily applicable to the population in Jiangxi, and its relevance to other regions and ethnicities should be interpreted with caution. (iv) Due to the limited sample size, we did not observe significant associations in subgroups after further stratification. (v) The observational nature of the study limits our ability to further assess the impact of enhanced nutritional support and anti-inflammatory treatment on adverse outcomes in patients with high AIP. (vi) The causes of ADHF were not distinguished in the current study; considering the significant adverse cardiovascular effects of pre-existent cardiomyopathy, infections, ischemic heart disease, heavy alcohol use or illegal drug use and some chemotherapy medicines in patients with ADHF that were already present prior to the onset of the disease (61–65), this may result in some special populations being unobserved, and further studies are needed.

Conclusion

In this retrospective cohort analysis, we have unveiled for the first time the association between AIP and the 30-day mortality rate in ADHF patients. Notably, this association exhibits a U-shaped curve before AIP<0.24, with the lowest 30-day mortality risk in ADHF patients around an AIP of -0.1. Additionally, based on evidence from mediation analysis, we have identified significant mediating effects of inflammation and nutrition on the association of AIP with the 30-day mortality rate in ADHF patients, with inflammation accounting for approximately 24.29% and nutrition for about 8.16% of the mediation effect.

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 the Ethics Committee of Jiangxi Provincial People's Hospital. 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

MY: Formal analysis, Investigation, Software, Validation, Writing – original draft. HY: Investigation, Writing – original draft. MK: Investigation, Software, Writing – review & editing. JQ: Investigation, Writing – review & editing. CY: Investigation, Writing – review & editing. GX: Data curation, Formal analysis, Investigation, Validation, Writing – review & editing. GS: Data curation, Formal analysis, Validation, Writing – review & editing. YZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, 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/fendo.2024.1393644/full#supplementary-material

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Association between atherogenic dyslipidemia and muscle quality defined by myosteatosis

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Background: Myosteatosis, ectopic fat accumulation in skeletal muscle, is a crucial component of sarcopenia, linked to various cardiometabolic diseases. This study aimed to analyze the association between dyslipidemia and myosteatosis using abdominal computed tomography (CT) in a large population.

Methods: This study included 11,823 patients not taking lipid-lowering medications with abdominal CT taken between 2012 and 2013. Total abdominal muscle area (TAMA), measured at the L3 level, was segmented into skeletal muscle area (SMA) and intramuscular adipose tissue. SMA was further classified into normal attenuation muscle area (NAMA: good quality muscle) and low attenuation muscle area (poor quality muscle). NAMA divided by TAMA (NAMA/TAMA) represents good quality muscle. Atherosclerotic dyslipidemia was defined as high-density lipoprotein cholesterol (HDL-C) less than 40 mg/dL in men and 50 mg/dL in women, low-density lipoprotein cholesterol (LDL-C) greater than 160 mg/dL, triglycerides (TG) greater than 150 mg/dL, small dense LDL-C (sdLDL-C) greater than 50.0 mg/dL, or apolipoprotein B/A1 (apoB/A1) greater than 0.08.

Results: The adjusted odds ratios (ORs) of dyslipidemia according to the HDL-C and sdLDL definitions were greater in both sexes in the lower quartiles (Q1~3) of NAMA/TAMA compared with Q4. As per other definitions, the ORs were significantly increased in only women for LDL-C and only men for TG and ApoB/A1. In men, all lipid parameters were significantly associated with NAMA/TAMA, while TG and ApoB/A1 did not show significant association in women.

Conclusion: Myosteatosis measured in abdominal CT was significantly associated with a higher risk of dyslipidemia. Myosteatosis may be an important risk factor for dyslipidemia and ensuing cardiometabolic diseases.

KEYWORDS

dyslipidemia, skeletal muscle, sarcopenia, lipid, myosteatosis

1 Introduction

Sarcopenia, traditionally defined as low muscle mass, is associated with numerous cardio-metabolic disorders, including atherogenic dyslipidemia (1–3). However, sarcopenia is a more complex condition that cannot be fully explained by the loss of muscle mass (4, 5). Recently, it has gained more attention for its association with muscle strength (4). A lack of muscle strength, a key characteristic of sarcopenia, can be indirectly assessed through muscle quality, encompassing changes in skeletal muscle architecture, composition, and function (5). Indeed, muscle quality evaluated by muscle fat infiltration (called as myosteatosis), is emerging as an important measure of sarcopenia (4, 6–8). Myosteatosis, characterized by ectopic fat deposition in skeletal muscle, disrupts muscle strength and metabolism (6–8).

Although muscle biopsy is the gold standard for detecting myosteatosis, computed tomography (CT) is commonly used to evaluate muscle quality by measuring fat infiltration in muscle through muscle attenuation (7). In CT scans, high attenuation indicates a lower fat content and thus reflects healthy, good-quality muscle, whereas low attenuation represents a higher fat content and indicates unhealthy, poor-quality muscle (7). So far, myosteatosis defined by CT scan has been linked to conditions such as immobilization, metabolic syndrome, type 2 diabetes, coronary artery calcification, and nonalcoholic fatty liver disease (NAFLD) (9–11).

Previous studies, predominantly relying on dual-energy X-ray absorptiometry (DXA) to measure muscle mass for sarcopenia assessment, have explored the relationship between sarcopenia and atherogenic dyslipidemia (12, 13). Individuals with a low muscle mass index had a higher incidence and risk of atherogenic dyslipidemia (with low-density lipoprotein cholesterol, LDL-C, levels higher than the individual risk factor-based target) than those with a normal muscle mass index (12). Similarly, elderly Asian men with low skeletal muscle mass measured by DXA exhibited a higher prevalence and risk of atherogenic dyslipidemia and an overall worse lipid profile than those with normal muscle mass (13).

However, research on the association between dyslipidemia and muscle quality beyond muscle mass is lacking and inconsistent. In a study of Afro-Caribbean men, calf muscle adiposity was positively associated with low-density lipoprotein cholesterol (LDL-C) and inversely associated with high-density lipoprotein cholesterol (HDL-C) (14). The Multi-Ethnic Study of Atherosclerosis demonstrated a positive correlation between total abdominal muscle density and total cholesterol; however, no significant associations were found with LDL-C, HDL-C, or triglycerides (TG) (15). Given the heterogeneity in myosteatosis markers and study populations, findings on the association between myosteatosis and lipid levels are inconsistent. Therefore, we aimed to reevaluate the relationship between myosteatosis and atherogenic dyslipidemia in a large population using CT-measured muscle attenuation.

2 Materials and methods

2.1 Study population

A total of 23,311 subjects who had undergone abdominal CT scans as part of routine health check-ups at the Health Screening and Promotion Center of Asan Medical Center (Seoul, Republic of Korea) between January 2012 and December 2013 were identified. Patients meeting one or more of the following criteria were excluded: those on lipid-lowering medications (n = 2,996), those with overt thyroid dysfunction (n = 110), and those with chronic renal insufficiency (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) (n = 42). Furthermore, subjects with hepatic disorders, cardiovascular disease, malignancy, or those currently taking glucocorticoids or hormone replacement therapy, as well as those with excessive alcohol intake (> 30 grams/day in men; > 20 grams/day in women), were excluded. Finally, 11,823 subjects were included in the analysis (Figure 1).

All participants completed a questionnaire on their medical and surgical history, medications, and health behaviors such as smoking, drinking, and exercise. Smoking behavior was categorized into three groups: current, past, and never smokers. Drinking habits were quantified in grams/day based on the alcohol content of the beverage, frequency of drinking, and amount consumed. Regular exercise was defined as 30 minutes of moderate-intensity aerobic exercise five days a week, 20 minutes of vigorous-intensity aerobic exercise three days a week, or resistance exercises 3 days a week. Hypertension was defined as having a systolic and/or diastolic blood pressure (BP) of 140/90 mmHg or higher or taking antihypertensive medication. Diabetes mellitus was diagnosed if any of the following criteria were met; fasting plasma glucose (FPG) level ≥ 126 mg/dL (7.0 mmol/L), glycated hemoglobin level (HbA1c) ≥ 6.5%, or current use of anti-diabetic medication.

This study adhered to the ethical guidelines outlined in the Declaration of Helsinki and Korea Good Clinical Practice. Written informed consent was obtained from all subjects. The institutional review board of Asan Medical Center approved this study (No. 2020-0343).

2.2 Measurements

Height and weight were measured while subjects were wearing light clothing without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference (WC, cm) was measured midway between the costal margin and the iliac crest at the end of a normal expiration. BP was measured on the right arm after a rest ≥5 min, using an automatic manometer with an appropriate cuff size.

After overnight fasting, early morning blood samples were drawn from the antecubital vein into vacuum tubes and subsequently analyzed at a central, certified laboratory in Asan

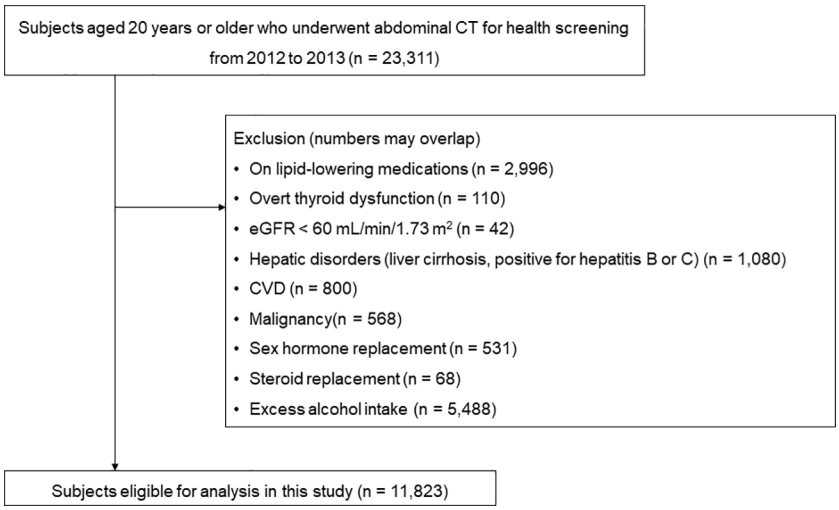

FIGURE 1
Selection process of the study population.

Medical Center. Measurements included the concentrations of uric acid, fasting glucose, high-sensitive C-reactive protein (hsCRP) and lipid parameters including, apolipoprotein B (apoB) and apolipoprotein A1 (apoA1).

Fasting total cholesterol (TC), HDL-C, LDL-C, TG and uric acid were measured by an enzymatic colorimetric method using a Toshiba 200FR Neo (Toshiba Medical System Co., Ltd., Tokyo, Japan). Serum apoB and apoA1 levels were measured by a turbidometric method using Cobas Integra C-6000 analyzer (Roche Diagnostics, Basel, Switzerland). HsCRP was measured by an immunoturbidimetric method (Toshiba). FPG levels were measured via an enzymatic colorimetric method using a Toshiba 200 FR autoanalyzer (Toshiba). Ion-exchange high-performance liquid chromatography (Bio-Rad Laboratories, Inc., Hercules, CA, USA) was used to measure HbA1c levels. All enzyme activities were measured at 37°C.

2.3 Definition of atherogenic dyslipidemia

Atherogenic dyslipidemia was defined as meeting at least one of the following three criteria, as per the guidelines of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (16): low HDL-C < 40 mg/dL in men and < 50 mg/dL in women, high LDL-C ≥ 160 mg/dL, or high TG ≥ 150 mg/dL.

In addition to the classic dyslipidemia criteria, calculated small dense LDL-C (sdLDL-C) was determined using the following equation: 0.580 (non–HDL-C) + 0.407 (dLDL-C) – 0.719 (cLDL-C) – 12.05, where dLDL-C and cLDL-C represent the directly measured and calculated LDL-C, respectively, based on the equation TC – HDL-C – TG/5 (17). Furthermore, apolipoprotein B (ApoB)/apolipoprotein A1 (ApoA1) was measured in 1585 subjects. ApoA1 constitutes HDL-C, while ApoB is in very-low-density lipoprotein, intermediate-density lipoprotein, LDL-C, and lipoprotein(a) (18). Thus, ApoB/ApoA1 represents the balance between proatherogenic and antiatherogenic lipoproteins (18). The sdLDL-C cutoff value of 50.0 mg/dL was used, as established using samples from the MultiEthnic Study of Atherosclerosis (MESA) and was based on the 75th percentile value of sdLDL-C for normolipidemic and dyslipidemic subjects who showed no sign of coronary heart disease or diabetes mellitus at baseline (19). For ApoB/A1, 0.80 was used as the cutoff, as suggested in previous studies (20, 21).

2.4 CT image collection

Abdomen and pelvis CT scans were conducted using the Somatom Definition scanner (Siemens Healthineers, Erlangen, Germany), Discovery CT750 HD scanner (GE Healthcare, Milwaukee, WI, USA), or LightSpeed VCT scanner (GE Healthcare). All CT examinations were performed with the following parameters: 120 kVp; automated dose modulation (CareDose 4D, Siemens Healthineers; automA and smartmA, GE Healthcare); matrix 512 × 512; and collimation of 0.625 mm. Image data were reconstructed with a slice thickness of 5 mm using the filtered back-projection technique and a soft tissue reconstruction algorithm (B30f kernel; Siemens Healthineers; Standard kernel, GE Healthcare). For contrast enhancement, 100–150 mL of iopromide (Ultravist 370 or Ultravist 300; Bayer Schering Pharma, Berlin, Germany) was intravenously administered using an automatic power injector.

2.5 Assessment of body composition and myosteatosis

Body composition was evaluated using automated artificial intelligence software developed with a fully convolutional network

segmentation technique. Since muscle mass, as measured by the lumbar 3rd vertebra (L3) CT, is strongly correlated with whole-body muscle mass (22), the software was programmed to automatically select the L3 vertebrae inferior endplate level. The selected CT images were then segmented automatically to generate the boundaries of the total abdominal muscle area (TAMA), visceral fat area (VFA), and subcutaneous fat area (SFA). All muscles within the selected axial images (including the psoas, para-spinal, transversus abdominis, rectus abdominis, quadratus lumborum, and internal and external obliques) were encompassed by TAMA. An image analyst and a radiologist, blinded to the clinical information, reviewed all selected CT images and verified the segmented areas.

TAMA was categorized based on CT density for myosteatosis measurement: (1) normal attenuation muscle area (NAMA, +30 to +150 Hounsfield Unit [HU]), representing nonfatty muscle with minimal intramuscular fat; (2) low attenuation muscle area (LAMA, −29 to +29 HU), representing fatty muscles with intramuscular lipid deposition; and (3) intermuscular adipose tissue (IMAT, −190 to −30 HU), representing visible fat tissue located between muscle groups and muscle fibers (Supplementary Figure S1) (23). The skeletal muscle area (SMA, −29 to +150 HU) included NAMA and LAMA. The NAMA/TAMA ratio was calculated by dividing NAMA by TAMA and multiplying by 100. VFA and SFA were also evaluated based on specific fat tissue thresholds (−190 to −30 HU).

2.6 Statistical analysis

Statistical analyses were performed for each sex due to the differences in muscle mass and attenuation value (6, 24). Continuous variables with normal distributions are shown as mean ± standard deviation, while those with skewed distributions are shown as median and interquartile range. Categorical variables are expressed as numbers (%). One way analysis of variance was applied to calculate the statistical significance among the quartile groups (Tables 1, 2), while student's t-test and chi-square test were performed to compare two groups (Supplementary Table S2). The sex-specific quartiles (Q1–Q4) of the NAMA/TAMA index were applied as the marker for myosteatosis throughout our analyses. The quartile ranges of the NAMA/TAMA index are presented in Supplementary Table S1. Multiple logistic regression analyses were performed to analyze the odds ratios (ORs) and 95% confidence intervals for dyslipidemia according to HDL-C, LDL-C, TG, sdLDL-C, and ApoB/A1 definitions. The ORs were adjusted for age, sex, smoking status, alcohol consumption, regular exercise, hypertension, diabetes mellitus, and VFA/SFA ratio. Menopausal status was also adjusted in females. Multiple linear regression analysis with the NAMA/TAMA index as a continuous variable was also performed. All statistical analyses were performed using SPSS software version 21.0 for Windows (IBM, Inc., Armonk, NY, USA). P-values of < 0.05 were considered statistically significant.

3 Results

3.1 Baseline characteristics

Of the 11,823 subjects, 6,434 were men and 5,389 were women, among which dyslipidemia was present in 4,773 (40.4%). The baseline characteristics and CT measurements between the NAMA/TAMA index quartiles are presented in Tables 1, 2 for each sex. As the NAMA/TAMA quartile increased, the prevalence of dyslipidemia decreased in both male and female populations. The higher the NAMA/TAMA quartile, the younger the patients, with overall favorable metabolic profiles such as lower BMI, WC, BP, and FPG levels across both sexes. Myosteatosis indices were also the most favorable in the highest quartile group for both men and

TABLE 1 Comparison of baseline characteristics and CT measurements between the quartiles of the NAMA/TAMA index in males.

	Q1 (n = 1,606)	Q2 (n = 1,613)	Q3 (n = 1,606)	Q4 (n = 1,609)	P-value
Dyslipidemia, n (%)	780 (48.6)[a]	746 (46.2)[a,b]	684 (42.6)[b,c]	618 (38.4)[c]	<0.001
Anthropometric data					
Age, years	57.2 ± 9.5	53.9 ± 8.4	52.3 ± 8.6	49.3 ± 8.6	<0.001
Height, cm	170.8 ± 6.0	170.8 ± 5.8	170.5 ± 5.6	170.3 ± 5.7	0.073
Weight, kg	75.0 ± 11.3	71.7 ± 9.0	70.1 ± 8.4	67.1 ± 8.5	<0.001
BMI, kg/m^2	25.7 ± 3.1	24.5 ± 2.6	24.1 ± 2.4	23.1 ± 2.5	<0.001
WC, cm	91.7 ± 8.1	87.7 ± 6.5	85.7 ± 6.3	81.9 ± 7.0	<0.001
SBP, mmHg	126.2 ± 13.7	124.4 ± 12.7	123.1 ± 12.9[a]	121.9 ± 12.5[a]	<0.001
DBP, mmHg	80.4 ± 10.5[a]	79.8 ± 9.9[a]	78.8 ± 10.1[b]	78.0 ± 9.8[b]	<0.001
Skeletal muscle mass, kg	31.3 ± 4.2[a]	31.2 ± 3.7[a,b]	31.2 ± 3.6[a,b]	30.8 ± 3.6	0.003
Body fat mass, kg	19.0 ± 6.3	16.1 ± 4.5	14.7 ± 4.0	12.4 ± 4.1	<0.001

(Continued)

TABLE 1 Continued

	Q1 (n = 1,606)	Q2 (n = 1,613)	Q3 (n = 1,606)	Q4 (n = 1,609)	P-value
Biochemical data					
Fasting glucose, mg/dL	103.3 ± 19.6	101.5 ± 18.6	99.7 ± 16.9[a]	98.4 ± 17.2[a]	<0.001
HbA1c, %	5.8 ± 0.8	5.7 ± 0.7	5.6 ± 0.6	5.5 ± 0.6	<0.001
Total cholesterol, mg/dL	194.4 ± 33.9	196.2 ± 32.4	196.3 ± 33.1	195.2 ± 33.5	0.308
Triglycerides, mg/dL	117 (84–161)[a]	115 (83–159)[a,b]	109 (80–151)[a,b,c]	102 (74–145)[c]	<0.001
HDL-C, mg/dL	48.4 ± 11.6[a]	49.4 ± 12.3[a,b]	50.0 ± 11.9[b]	52.6 ± 13.3	<0.001
LDL-C, mg/dL	126.6 ± 30.0[a]	127.7 ± 28.6[a]	128.1 ± 29.1[a]	125.4 ± 29.5[a]	0.049
AST, IU/L	26 (21–32)[a]	26 (21–31)[a,b,c]	25 (21–31)[a,b,c]	25 (21–30)[c]	0.031
ALT, IU/L	24 (18–33)[a]	24 (18–33)[a,b]	23 (18–33)[a,b]	22 (17–30)	<0.001
hsCRP, mg/dL	0.07 (0.04–0.15)	0.06 (0.03–0.12)[a]	0.05 (0.03–0.11)[a]	0.04 (0.02–0.08)	<0.001
eGFR, mL/min/1.73 cm^2	94.4 ± 16.2[a]	93.4 ± 15.1[a,b]	92.2 ± 14.3[b,c]	92.2 ± 14.4[b,c]	<0.001
Clinical data					
Current smoker, n (%)	485 (30.2)	495 (30.7)	505 (31.5)	535 (33.3)	0.099
Alcohol consumption, g/d	5.3 (0.9–12.4)	6.4 (1.1–13.8)	6.3 (1.2–11.7)	6.8 (1.4–12.1)	0.294
Regular exercise, n (%)	890 (55.5)[a]	936 (58.1)[a,b]	979 (61.1)[b,c]	991 (61.8)[b,c]	<0.001
Diabetes, n (%)	182 (11.3)	142 (8.8)[a]	116 (7.2)[a,b]	99 (6.2)[b]	<0.001
Hypertension, n (%)	492 (30.6)	348 (21.6)[a]	303 (18.9)[a]	218 (13.5)	<0.001
CT measurement data					
SMA, cm^2	158.8 ± 23.0	161.7 ± 20.8[a]	163.5 ± 20.7[a,b]	164.2 ± 21.6[b]	<0.001
SMA/BMI	6.2 ± 0.7	6.6 ± 0.6	6.8 ± 0.6	7.1 ± 0.6	<0.001
NAMA, cm^2	113.4 ± 19.0	128.6 ± 16.7	136.3 ± 17.4	143.9 ± 19.0	<0.001
NAMA/BMI	4.4 ± 0.7	5.2 ± 0.5	5.7 ± 0.5	6.2 ± 0.6	<0.001
LAMA, cm^2	45.4 ± 11.1	33.1 ± 5.3	27.2 ± 4.1	20.3 ± 4.2	<0.001
LAMA/BMI	1.8 ± 0.3	1.3 ± 0.2	1.1 ± 0.1	0.9 ± 0.1	<0.001
NAMA/TAMA index	67.3 ± 6.3	76.7 ± 1.5	81.4 ± 1.2	86.5 ± 2.1	<0.001
VFA/SFA	1.2 ± 0.5	1.1 ± 0.4	1.1 ± 0.4	0.9 ± 0.4	<0.001

Data are presented as mean ± standard deviation or median (interquartile range, 1st–4th) unless otherwise indicated.
CT, computed tomography; NAMA, normal attenuation muscle area; TAMA, total abdominal muscle area; Q, quartile; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; hsCRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; SMA, skeletal muscle area; LAMA, low attenuation muscle area; VFA, visceral fat area; SFA, subcutaneous fat area.
[a,b,c] Superscript letters imply a statistically insignificant difference in the post-hoc analysis between values indicated by the same superscript letter. Otherwise, the post-hoc analysis revealed significant differences between each group.

TABLE 2 Comparison of baseline characteristics and CT measurements between the quartiles of the NAMA/TAMA index in females.

	Q1 (n = 1345)	Q2 (n = 1351)	Q3 (n = 1348)	Q4 (n = 1345)	P-value
Dyslipidemia, n (%)	646 (48.0)	517 (38.3)[a]	482 (35.8)[a]	300 (22.3)	<0.001
Anthropometric data					
Age, years	57.9 ± 8.6	53.3 ± 7.5	51.5 ± 7.6	47.1 ± 7.2	<0.001
Height, cm	157.6 ± 5.4	158.5 ± 5.4[a]	158.4 ± 5.1[a]	159.4 ± 5.2	0.075
Weight, kg	61.1 ± 8.3	57.8 ± 7.2	55.3 ± 6.5	52.7 ± 6.1	<0.001

(Continued)

TABLE 2 Continued

	Q1 (n = 1345)	Q2 (n = 1351)	Q3 (n = 1348)	Q4 (n = 1345)	P-value
Anthropometric data					
BMI, kg/m^2	24.6 ± 3.1	23.0 ± 2.7	22.1 ± 2.4	20.7 ± 2.3	<0.001
WC, cm	84.9 ± 7.8	79.7 ± 6.9	76.7 ± 6.5	72.3 ± 6.3	<0.001
SBP, mmHg	122.9 ± 15.2	117.6 ± 14.5	115.5 ± 13.9	112.2 ± 13.2	<0.001
DBP, mmHg	75.9 ± 10.4	73.3 ± 10.6	72.1 ± 10.6	70.3 ± 10.3	0.727
Skeletal muscle mass, kg	21.6 ± 2.6	21.7 ± 2.4	21.5 ± 2.4	21.5 ± 2.3	<0.001
Body fat mass, kg	20.9 ± 5.7	17.6 ± 4.7	15.7 ± 4.2	13.0 ± 3.9	<0.001
Biochemical data					
Fasting glucose, mg/dL	100.1 ± 19.0	97.1 ± 15.9	95.1 ± 12.9	92.6 ± 11.3	<0.001
HbA1c, %	5.7 ± 0.7	5.6 ± 0.6	5.5 ± 0.5	5.4 ± 0.4	<0.001
Total cholesterol, mg/dL	206.3 ± 34.3[a]	203.3 ± 34.0[a,b]	201.7 ± 33.4[b]	192.4 ± 31.4	0.021
Triglycerides, mg/dL	95 (69–130)	85 (65–120)	82 (62–113)	71 (53–98)	<0.001
HDL-C, mg/dL	57.9 ± 14.0	60.6 ± 14.2	62.2 ± 14.7	66.0 ± 14.8	0.171
LDL-C, mg/dL	132.5 ± 30.8	128.2 ± 30.6[a]	126.1 ± 30.1[a]	115.5 ± 28.2	0.006
AST, IU/L	24 (20–29)[a]	23 (20–29)[a,b]	23 (19–28)[a,b]	22 (19–26)	0.001
ALT, IU/L	19 (15–25)	18 (14–24)[a]	16 (13–22)[a]	15 (12–20)	<0.001
hsCRP, mg/dL	0.06 (0.03–0.13)	0.04 (0.02–0.09)[a]	0.03 (0.02–0.07)[a,b]	0.02 (0.02–0.05)[b]	<0.001
eGFR, mL/min/1.73 cm^2	101.8 ± 19.1[a]	101.8 ± 17.8[a]	100.4 ± 16.7[a]	100.9 ± 16.4[a]	<0.001
Clinical data					
Current smoker, n (%)	34 (2.5)[a]	37 (2.7)[a]	32 (2.4)[a]	52 (3.9)	0.004
Alcohol consumption, g/d	0.0 (0.0–1.2)[a]	0.4 (0.0–1.9)[a,b]	0.4 (0.0–1.9)[b,c]	0.8 (0.0–2.7)[c]	<0.001
Regular exercise, n (%)	691 (51.5)	745 (55.2)[a]	804 (59.8)[b]	763 (56.8)[a,b]	<0.001
Menopause, n (%)	1,095 (81.4)	888 (65.7)	749 (55.6)	459 (34.1)	<0.001
Diabetes, n (%)	106 (7.9)	62 (4.6)	34 (2.5)[a]	22 (1.6)[a]	<0.001
Hypertension, n (%)	319 (23.7)	189 (14.0)	130 (9.6)	78 (5.8)	<0.001
CT measurement data					
SMA, cm^2	105.9 ± 13.3	107.5 ± 12.9[a]	107.3 ± 13.0[a]	108.1 ± 12.8[a]	0.592
SMA/BMI	4.3 ± 0.5	4.7 ± 0.5	4.9 ± 0.5	5.2 ± 0.6	<0.001
NAMA, cm^2	69.0 ± 11.0	80.5 ± 9.8	85.6 ± 10.5	91.8 ± 11.1	0.001
NAMA/BMI	2.8 ± 0.5	3.5 ± 0.4	3.9 ± 0.4	4.4 ± 0.5	<0.001
LAMA, cm^2	37.0 ± 8.2	26.9 ± 4.2	21.7 ± 3.2	16.3 ± 3.2	<0.001
LAMA/BMI	1.5 ± 0.3	1.2 ± 0.2	1.0 ± 0.1	0.8 ± 0.1	<0.001
NAMA/TAMA index	59.7 ± 6.9	71.2 ± 2.0	77.1 ± 1.5	83.3 ± 2.5	<0.001
VFA/SFA	0.6 ± 0.3	0.5 ± 0.2	0.5 ± 0.2	0.3 ± 0.2	<0.001

Data are presented as mean ± standard deviation or median (interquartile range, 1st–4th) unless otherwise indicated.
CT, computed tomography; NAMA, normal attenuation muscle area; TAMA, total abdominal muscle area; Q, quartile; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; hsCRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; SMA, skeletal muscle area; LAMA, low attenuation muscle area; VFA, visceral fat area; SFA, subcutaneous fat area.
[a,b,c]The superscript letters imply a statistically insignificant difference in the post-hoc analysis between values indicated by the same superscript letter. Otherwise, the post-hoc analysis revealed significant differences between each group.

women. Male and female patients with dyslipidemia weighed more and had a larger BMI, WC, and body fat mass than those without dyslipidemia (Supplementary Table S2). Those without dyslipidemia showed greater value of NAMA/TAMA than those with dyslipidemia regardless of sex (Supplementary Table S2).

3.2 Risk of atherogenic dyslipidemia

The risk of atherogenic dyslipidemia according to the quartiles of the NAMA/TAMA index for each sex are shown in Figure 2. In men, as the NAMA/TAMA quartile decreased, the ORs of

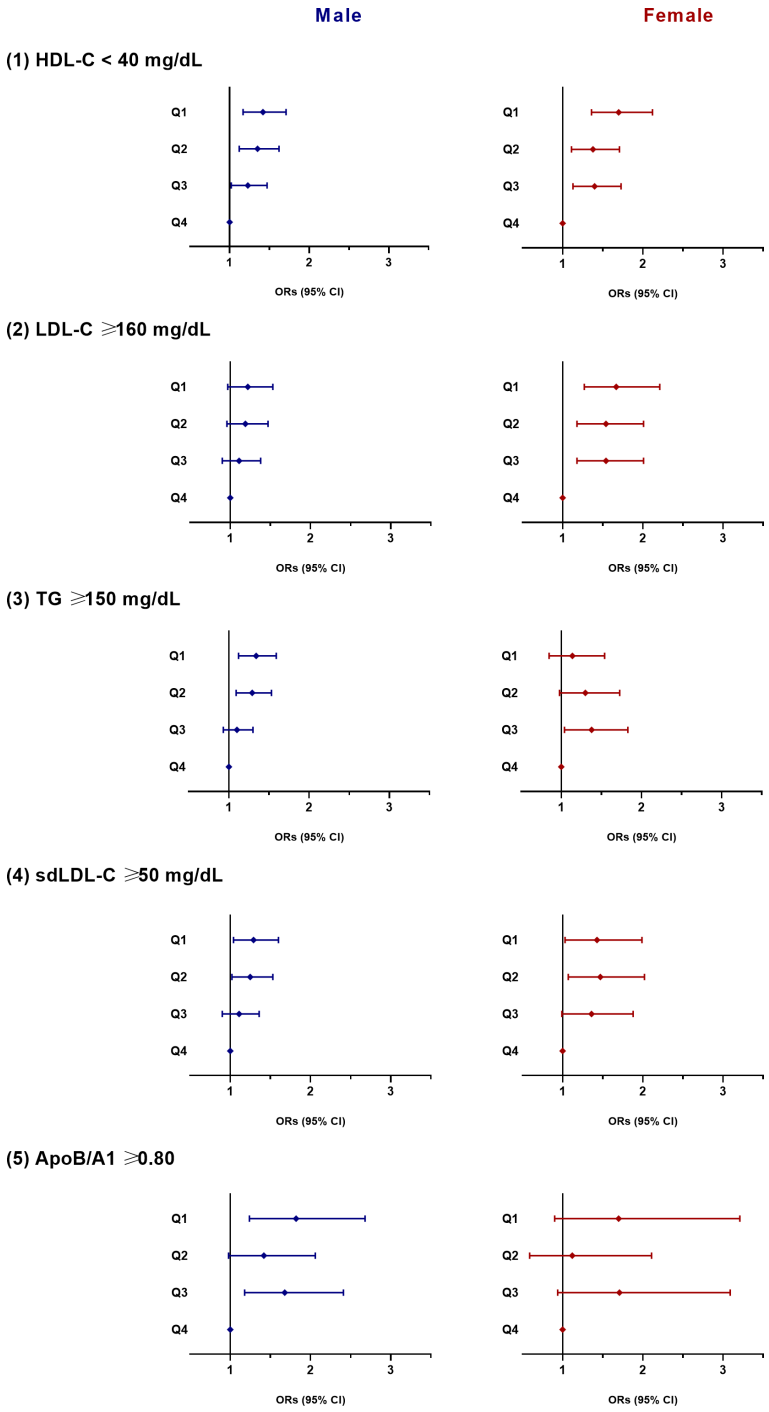

FIGURE 2
ORs for dyslipidemia according to the quartiles of the NAMA/TAMA index. ORs were adjusted for age, smoking, alcohol consumption, exercise, hypertension, diabetes, menopausal status (in female), and VFA to SFA ratio. OR, odds ratio; NAMA, normal attenuation muscle area; TAMA, total abdominal muscle area; Q, quartile; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VFA, visceral fat area; SFA, subcutaneous fat area.

dyslipidemia, according to the HDL-C, TG, sdLDL, and ApoB/A1 definitions, significantly increased (Figure 2). According to the LDL-C definition, the NAMA/TAMA quartiles in males were not significantly associated with a higher risk of dyslipidemia (Figure 2). The NAMA/TAMA index was positively associated with HDL-C and negatively associated with LDL-C, TG, sdLDL, and ApoB/A1, and all of the standardized beta values were statistically significant in the male population (Table 3).

In women, a decrease in the NAMA/TAMA quartile resulted in higher ORs for dyslipidemia according to HDL-C, LDL-C, and sdLDL-C definitions (Figure 2). According to the TG and ApoB/A1 definitions, the ORs for dyslipidemia was not statistically significant in the female population (Figure 2). The NAMA/TAMA index was positively associated with HDL-C and negatively associated with LDL-C, TG, sdLDL-C, and ApoB/A1 in women (Table 3). However, the standardized beta values of TG and ApoB/A1 were not statistically significant (Table 3).

4 Discussion

This cross-sectional analysis of 11,823 patients who participated in routine health examinations showed that muscle quality assessed by the degree of myosteatosis was associated with the risk of atherogenic dyslipidemia. A greater NAMA/TAMA index, which indicates healthy low-fat muscle, was significantly associated with a lower risk of atherogenic dyslipidemia even after adjusting for age, health behaviors, and other ectopic fat distribution.

The value of myosteatosis is on the rise in the research field of sarcopenia. Myosteatosis allows the measurement of muscle

TABLE 3 Multiple linear regression analysis of the lipid parameters.

	Male		Female	
	Standardized β	P value	Standardized β	P value
1) HDL-C				
NAMA/TAMA	0.069	< 0.001	0.080	< 0.001
Age	0.094	< 0.001	0.042	0.013
Smoking	-0.066	< 0.001	0.015	0.215
Alcohol	0.119	< 0.001	0.082	< 0.001
Exercise	0.249	< 0.001	-0.055	< 0.001
Hypertension	0.257	0.077	-0.008	0.532
Diabetes	0.384	< 0.001	-0.063	< 0.001
Menopausal status			0.031	0.031
VFA/SFA	0.267	< 0.001	0.267	< 0.001
2) LDL-C				
NAMA/TAMA	-0.070	< 0.001	-0.065	< 0.001
Age	0.149	< 0.001	0.075	< 0.001
Smoking	-0.030	0.012	-0.030	0.014
Alcohol	-0.006	0.613	-0.007	0.556
Exercise	0.008	0.513	0.010	0.426
Hypertension	-0.045	< 0.001	-0.043	0.001
Diabetes	-0.079	< 0.001	-0.079	< 0.001
Menopausal status			0.127	< 0.001
VFA/SFA	0.180	< 0.001	0.182	< 0.001
3) TG				
NAMA/TAMA	-0.035	< 0.001	-0.017	0.208
Age	-0.178	< 0.001	0.005	0.744
Smoking	0.120	< 0.001	0.042	< 0.001
Alcohol	0.017	< 0.001	-0.021	0.073

(Continued)

TABLE 3 Continued

	Male		Female	
	Standardized β	P value	Standardized β	P value
3) TG				
Exercise	0.077	0.059	0.044	< 0.001
Hypertension	0.086	< 0.001	0.041	0.001
Diabetes	0.046	< 0.001	0.067	< 0.001
Menopausal status			0.047	0.001
VFA/SFA	0.241	< 0.001	0.326	< 0.001
4) sdLDL-C				
NAMA/TAMA	-0.038	0.004	-0.056	<0.001
Age	-0.186	<0.001	0.042	0.019
Smoking	0.101	<0.001	0.012	0.344
Alcohol	-0.021	0.084	-0.037	0.004
Exercise	0.070	<0.001	0.021	0.099
Hypertension	0.019	0.113	-0.005	0.735
Diabetes	-0.052	<0.001	-0.033	0.012
Menopausal status			0.118	<0.001
VFA/SFA	0.230	<0.001	0.315	<0.001
5) ApoB/A1				
NAMA/TAMA	-0.098	0.002	-0.089	0.065
Age	-0.142	<0.001	-0.0789	0.158
Smoking	0.137	<0.001	-0.038	0.368
Alcohol	-0.094	0.002	-0.095	0.030
Exercise	0.081	0.008	0.051	0.220
Hypertension	0.020	0.518	-0.013	0.766
Diabetes	-0.112	<0.001	-0.086	0.044
Menopausal status			0.128	0.008
VFA/SFA	0.164	<0.001	0.300	<0.001

microstructure, which determines muscle strength and metabolism (25, 26). Type 2 diabetes, NAFLD, and cardiovascular disease are some of the unfavorable clinical outcomes associated with myosteatosis (9–11). Patients with type 2 diabetes exhibited increased LAMA and decreased NAMA and NAMA/TAMA index (27). Additionally, those with higher LAMA and lower NAMA/TAMA were at a higher risk of NAFLD and liver fibrosis (11).

Myosteatosis is also associated with mortality. Increased myosteatosis determined by calf muscle density using CT was correlated with increased all-cause and cardiovascular mortality in older men, according to a 7.2-year longitudinal study (28). According to an 8.8-year follow-up study, myosteatosis measured in the thigh muscle using CT was associated with a higher mortality risk (29). Mortality risk decreased in patients with higher abdominal muscle density, highlighting muscle quality as a predictor of mortality (30).

Only a few studies have examined the associations between muscle density measured by CT and lipid levels. Miljkovic et al. demonstrated that calf muscle density was positively associated with LDL-C and negatively associated with HDL-C (14). These findings were additionally partly supported by a longitudinal study that revealed exercise-induced reductions in thigh IMAT were related to changes in HDL-C and LDL-C to larger, less atherogenic lipoprotein particles (31). However, Vella et al. later reported that increases in total cholesterol levels (not LDL-C, HDL-C, or TG) were associated with higher abdominal muscle density and lower abdominal muscle area (15). Such conflicting results regarding the

relationship between lipid parameters and muscle area and density suggest the need for more accurate quantification of muscle quality and myosteatosis.

Although the definition of myosteatosis is not yet standardized, evaluating attenuation density and IMAT through CT is adequate for assessing myosteatosis (7, 9). NAMA has a lower level of fatty infiltration than LAMA, which has a higher quantity of adipocytes and intramyocellular fat within muscle fibers and myocytes, leading to a lower density on CT (32). Kim et al. have introduced the NAMA/TAMA index, calculated by dividing NAMA by TAMA and multiplying by 100 (23). More recent discoveries suggested the clinical value and relevance of this index; a greater NAMA/TAMA index was significantly associated with a lower prevalence of subclinical coronary artery disease and NAFLD (10, 11). The results of this study further suggest that the NAMA/TAMA index is inversely correlated with HDL-C and directly associated with LDL-C (females only) and TG.

LDL-C and sdLDL were inversely correlated with NAMA/TAMA, good quality muscle index, in women, which had been demonstrated in female patients with rheumatoid arthritis using skeletal muscle mass measured using DXA (33). Interestingly, LDL-C and sdLDL-C did not show significant associations with NAMA/TAMA in the male population. The OR of dyslipidemia according to LDL-C definition was only significant in women and did not differ according to NAMA/TAMA quartiles in men, even after adjusting for multiple variables. Hepatic lipase, a lipolytic enzyme hydrolyzing TG and phospholipid into LDL-C and HDL-C, is more active in males with higher intraabdominal fat (34). Since analysis with NAMA/TAMA index includes only inter/intramuscular fat, it might not have shown significant correlations with LDL-C and sdLDL-C in men who have more than twice the visceral fat of women (35, 36). Further studies are needed to elucidate the sex differences in the associations between myosteatosis and LDL-C.

The exact molecular mechanisms underlying the interaction between dyslipidemia and myosteatosis are not fully understood. Increased muscle fat infiltration induces lipotoxicity and chronic inflammation and results in insulin resistance in skeletal muscle (37). Insulin resistance in skeletal muscle alters the processing pattern of ingested carbohydrates by decreasing glycogen synthesis in muscle and increasing lipogenesis in the liver (38). Cytokines such as interleukin-1 and tumor necrosis factor are released, accelerating protein catabolism (39). Consequently, dyslipidemia develops with the rise in plasma TG and fall in HDL-C (38). Further research is warranted to further elucidate the underlying mechanism for the relationship between myosteatosis and dyslipidemia.

This study has several limitations. First, this is a cross-sectional study, so the causal relationship between myosteatosis and dyslipidemia could not be verified. Second, the study population was limited to Koreans, limiting its generalizability to other ethnic groups. Third, muscle quality assessed via CT scan was used to indirectly measure muscle strength without performing a grip strength test, which was not covered by routine health examinations. Lastly, the myosteatosis indices in this study were obtained solely at the L3 level of the abdomen. Although other body parts were not covered, such as the lower extremities (a common focus in previous studies), a cross-sectional area of muscle and adipose tissue from a single lumbar CT or MRI image was highly correlated with that of the whole body in several studies (40, 41). Despite such limitations, this study is the first to examine the association between myosteatosis and dyslipidemia in a large population. Previous studies measuring muscle density using CT were small population studies. Many potential confounders were considered in the statistical analysis to avoid potential bias. This research used previous abdominal CT scans taken as part of a routine health examination, so evaluation of myosteatosis in patients with a previous CT scan is clinically applicable.

Myosteatosis and dyslipidemia are closely related, evidenced by the decline in the risk of dyslipidemia as the healthy muscle component increases. Ectopic fat accumulation in muscle contributes to atherogenic dyslipidemia and ensuing cardiometabolic diseases. Future studies suggesting efficacious ways to screen and treat myosteatosis are needed.

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 Institutional Review Board of Asan Medical Center. 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

HK: Data curation, Formal analysis, Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. YC: Investigation, Methodology, Writing – review & editing. MK: Data curation, Resources, Writing – original draft. ML: Data curation, Investigation, Writing – review & editing. EK: Resources, Software, Validation, Writing – review & editing. WL: Investigation, Resources, Supervision, Validation, Writing – review & editing. HK-K: Data curation, Project administration, Resources, Supervision, Validation, Writing – review & editing. CJ: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1327522/full#supplementary-material

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Association between TyG index and risk of carotid atherosclerosis in NAFLD patients: a retrospective cohort study

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Background: The TyG index, or triglyceride-glucose index, is primarily used as a marker to assess insulin resistance and metabolic health. It increases mortality risk in patients with NAFLD, atherosclerosis, ischemic stroke, or heart failure. However, its association with Carotid Atherosclerosis (CAS) risk in NAFLD patients remains uncertain.

Methods: This retrospective cohort study enrolled 739 individuals who participated comprehensive health evaluations at a large public hospital in Yangzhou, China, between January 2021 and December 2023. Among them, 436 were men and 303 were women, and their mean (SD) age was 51.53 ± 11.46 years. The individuals were categorized into three tertiles (Q1, Q2, and Q3), according to the baseline TyG index. Our investigation focused on exploring the correlativity between the TyG and the occurrence of CAS utilizing Cox regression and RCS analyses.

Results: During a 3-year follow-up period, 199 patients developed CAS (cumulative incidence rate: 26.93%). A statistical model, adjusted for age, gender, BMI, and other confounders indicated that the HR (95%CI) values for CAS risk in the Q2 and Q3 groups were 3.11(1.87-5.17) and 4.51(2.69-7.56), respectively, with P-values <0.001 for both groups. A sensitivity analysis confirmed these results. Kaplan–Meier survival analysis revealed that CAS risk varied across the groups (*P* non-linear < 0.05).

Conclusion: In individuals diagnosed as NAFLD, the possibility for CAS escalates with the elevation of the TyG value. Therefore, the TyG index is an effective marker for assessing the risk of CAS within this demographic. Large-sample prospective studies are needed to confirm this conclusion in the future.

KEYWORDS

triglyceride-glucose index, NAFLD, cohort study, carotid atherosclerosis, insulin resistance

Introduction

Nonalcoholic fatty liver disease (NAFLD) manifests with a staggering global prevalence, estimated at 25% (1). Notably, it stands as the prevailing liver ailment within the people of China (2). Compared with individuals without NAFLD, those with this disease exhibit an elevated rate of mortality (3), with cerebrovascular diseases being the leading factor of death rather than the liver disease itself (1, 4). Although many researchers have explored the correlation between NAFLD and cardiovascular diseases (including ischemic heart disease, cardiac arrhythmias, hypertension) progression (5, 6), the potential risk of carotid atherosclerosis (CAS) has been overlooked. Evidence suggests that >30% of all patients with NAFLD develop CAS (7), a major cause of ischemic stroke, which carries high risks of disability and mortality. Identifying predictive factors for CAS in patients with NAFLD is crucial for reducing stroke incidence.

Insulin resistance (IR) is instrumental in the progression of NAFLD and worsens as the disease progresses (8, 9). It leads to endothelial dysfunction and oxidative stress, promoting atherosclerosis (10). The gold standard for diagnosing it is the hyperinsulinemic-euglycemic clamp (11, 12); however, the complexity of this technique limits its clinical utility and widespread application. The Homeostasis Model Assessment is another common indicator of IR (13), but its variability across populations complicates the determination of an optimal threshold (14). Moreover, this approach is unsuitable for patients receiving insulin therapy. The TyG index emerges as a novel metric for appraising IR within clinical settings (15, 16). In a state of insulin resistance, adipose tissue becomes less sensitive to insulin, leading to increased lipolysis and the release of free fatty acids into the bloodstream, which in turn leads to increased triglyceride synthesis in the liver. In addition, the presence of insulin resistance impairs the ability of insulin to promote glucose uptake and utilization, leading to elevated blood glucose levels. The TyG index indirectly reflects the degree of metabolic abnormalities in the body under insulin resistance by comprehensively assessing two indicators: fasting triglycerides and fasting blood glucose. Substantial evidence emphasizes a notable association between the TyG index and IR using the HIEC technique (17). Because of its reliability and ease of calculation, the TyG index emerges as especially well-suited for utilization resource-limited community hospitals (18). Additionally, research has shown that TyG-WC (waist circumference) can also reflect the state of IR (19).

This study aimed to investigate the correlation between the TyG index and susceptibility to CAS in NAFLD patients. The main goal was to enhance strategies for preventing CAS within this population.

Materials and methods

Study population

Our study included 739 individuals who had undergone routine health examinations at Northern Jiangsu People's Hospital Affiliated to Yangzhou University from January 2021 to December 2023. The study population comprised 436 men and 303 women. The patients' mean (SD) age was 51.53 ± 11.46 years. The inclusion criteria were outlined as follows: undergoing regular health examinations at our hospital at least once; completing baseline carotid artery color Doppler ultrasonography, liver color Doppler ultrasonography, and laboratory examinations; having NAFLD at baseline; and not having CAS at baseline. The exclusion criteria encompassed individuals with a history of stroke, coronary heart disease, or malignant neoplasms; those engaging in excessive drinking; individuals with hepatitis or any type of liver disease; participants lacking questionnaire survey data and laboratory test results; and subjects who did not complete at least one carotid artery color Doppler ultrasonographic examination during the follow-up period. A flowchart depicting the enrollment of patients is presented Figure 1. Our study received approval from the Ethics Committee of Northern Jiangsu People's Hospital Affiliated to Yangzhou University (approval number: 2024ky098). Adhered to the ethical precepts delineated in the Declaration of Helsinki as well as other relevant regulations. Owing to the retrospective nature of the investigation, our institutional review board waived the need for informed consent.

Data collection

We collected data on basic characteristics such as the patients' age, sex, smoking status (yes/no), previous medical history, medication use, and anthropometric measurements (height and weight). In the morning, 5 mL of fasting venous blood samples were collected. Laboratory measurements comprised fasting blood glucose and fasting blood lipids. Blood pressure was measured on the right brachial artery by using an electronic sphygmomanometer. The patients rested in a seated position with their feet naturally flat on the ground for at least 5 min.

Carotid artery color Doppler ultrasonography was performed with the patient in the supine position. Experienced ultrasound physicians conducted the examinations, commencing with a transverse scan from the neck root toward the head. They particularly evaluated the proximal, middle, and distal segments of the carotid artery, including the carotid bifurcation, and both the internal and external carotid arteries. This was followed by a longitudinal scan along the long axis of the carotid artery; finally, the blood flow velocity of the arterial lumen was determined through color Doppler flow imaging.

Definitions and diagnostic criteria

NAFLD was diagnosed on the basis of the following criteria: the presence of hepatic steatosis, the absence of excessive alcohol consumption (alcohol consumption <20 g/day in women and<30 g/day in men), and the absence of other liver diseases (20). Criteria for ultrasonic diagnosis of fatty liver (two or more of the subsequent conditions must be met): enhanced echogenicity in the anterior segment of the liver, exhibiting a 'bright liver' characteristic; attenuation of far-field echoes; obscured visualization of intrahepatic duct structures (21).

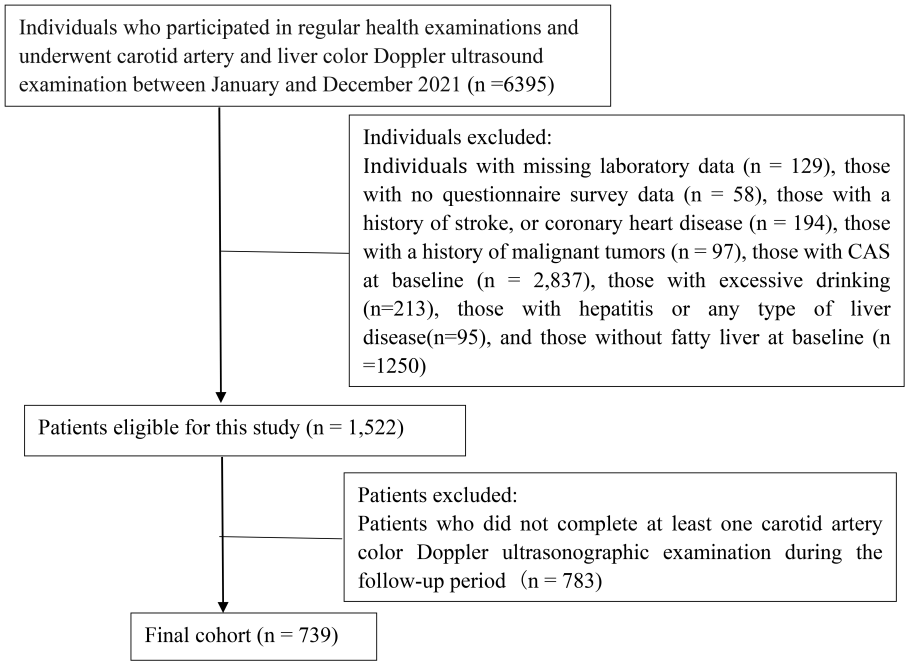

FIGURE 1
The flowchart depicting the process of patient selection.

The criteria for ultrasonic diagnosis of carotid atherosclerosis are intima-media thickness (IMT) > 1.0mm, or the detection of plaque formation. Carotid plaques were identified by IMT ≥1.5 mm, or IMT value that exceeded the surrounding area by ≥50% (22, 23).

Hypertension was defined as systolic blood pressure ≥18.7Kpa (140 mmHg), or diastolic blood pressure ≥12.0Kpa (90 mmHg). Patients who have been definitively diagnosed and are undergoing antihypertensive treatment, even if their blood pressure is below 140/90 mmHg, are still considered to have hypertension (24). Diabetes was defined by FPG ≥7.0 mmol/L, diagnosed diabetes, a hemoglobin A1c level of ≥6.5%, or existing use of oral or subcutaneous antidiabetic medications (25). TyG index =ln [TG × FBG/2]. TG and FBG were presented in terms of milligrams per deciliter.

Statistical analysis

We performed statistical analyses utilizing SPSS (version 25.0), R (version 4.1.3), and EmpowerStats software. Normally distributed data are typically presented in terms of M ± SD, whereas nonnormally distributed data are presented in terms of median (25th percentile and 75th percentile) values. Between-group comparisons were conducted utilizing either the *t*-test or the Mann–Whitney U test., and multigroup comparisons were performed using ANOVA or Kruskal–Wallis test. Categorical data were analyzed using χ^2 test.

Kaplan–Meier curves, plotted based on TyG index tertiles, depicted the cumulative incidence rates of CAS events. We utilized the log-rank test for between-group comparisons. Cox proportional hazards regression was performed to calculate HR and 95% CI values for the correlation between the TyG index and CAS incidence. When Omnibus test P < 0.05, it indicated the constructed COX regression model was significant. The adjustment of covariates is determined by the results of inter-group comparisons, common clinical risk factors and multicollinearity tests. When the variance inflation factor (VIF) was greater than 5, it indicated the presence of multicollinearity, which necessitates its exclusion. Additionally, both the TyG ×BMI and TyG index were indicators used to assess insulin resistance, and TyG ×BMI was the product of TyG and BMI. In the multivariate COX regression, TyG×BMI was not included. Three statistical models were used for data analysis. Model 1 had no control variables. Model 2 had controls for age, sex, smoking, history of hypertension and diabetes. Model 3 had controls for sex, age, smoking, history of hypertension, diabetes, SBP, anti-hypertension medication, antidiabetic agents, lipid-lowering medication, FBG, TC. TG was screened out because of covariance. A four-knot RCS analysis was conducted to examine the nonlinear correlation between the TyG index and the incidence of CAS in NAFLD patients. Using the 5th percentile as a benchmark, knots were established at 5th, 35th, 65th, and 95th percentiles of TyG measures.

Subgroup analyses were performed to test interactions among age groups (<50 or ≥50 years), sex groups, and BMI-based groups (<24 or ≥24 kg/m^2). P for interaction >0.05 indicated that there was no significant difference between groups. Sensitivity analyses (using TyG quartile grouping and excluding subjects with a follow-up time of less than 9 months) were conducted to confirm the consistency of the findings. Missing values, including 31 cases of blood pressure values and 23 cases of height and weight values, were addressed using multiple imputation methods.

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Results

The demographic characteristics and clinical data comparison of the study population

This study included 739 patients (mean age: 51.53 ± 11.46 years). The follow-up duration was 708 (568, 730) days (minimum: 200 days; maximum: 1045 days). The mean ± standard deviation of TyG was 7.52 ± 0.64. The patients were stratified into three groups by TyG index tertiles: Q1 (TyG index value ≤ 7.21), Q2 (TyG index value: 7.21–7.70) and Q3 (TyG index value > 7.70) groups. No significant between-group difference was noted in age, sex, smoking, BMI, anti-hypertension medication, antidiabetic agents, lipid-lowering medication or follow-up duration (P = 0.178, 0.418, 0.076, 0.429, 0.032, 0.160, 0.788 and 0.816, respectively). Compared to Group Q1, Groups Q2 and Q3 exhibited higher prevalence rates of hypertension and diabetes, as well as higher levels of FBG, TG, TC, LDL-C, and metabolic indexes (including TyG×BMI and TyG). However, their HDL-C levels were lower (Table 1).

Incidence of CAS in patients With NAFLD

Of the 739 patients with NAFLD who were monitored for 3 years, 199 developed CAS (cumulative incidence rate: 26.93%).

TABLE 1 General characteristics of the study population (n = 739).

TyG group	N	Q1 ≤7.21	Q2 7.21-7.70	Q3 >7.70	*P*-value
Sample Size (n)	739	244	248	247	
Age(years)	51.53 ± 11.46	50.69 ± 11.79	52.57 ± 11.48	51.31 ± 11.06	0.178
Gender(n, %)					0.418
male	436 (59.00%)	139 (56.97%)	143 (57.66%)	154 (62.35%)	
female	303 (41.00%)	105 (43.03%)	105 (42.34%)	93 (37.65%)	
Smoking(n, %)	107 (14.48%)	30 (12.30%)	31 (12.50%)	46 (18.62%)	0.076
Hypertension(n, %)					**0.009**
yes	160 (21.65%)	41 (16.80%)	50 (20.16%)	69 (27.94%)	
no	579 (78.35%)	203 (83.20%)	198 (79.84%)	178 (72.06%)	
Diabetes(n, %)					**< 0.001**
yes	105 (14.21%)	4 (1.64%)	21 (8.47%)	80 (32.39%)	
no	634 (85.79%)	240 (98.36%)	227 (91.53%)	167 (67.61%)	
Systolic Blood Pressure (SBP, mmHg)	132.47 ± 17.74	128.36 ± 17.46	132.39 ± 16.06	136.61 ± 18.71	**< 0.001**
Diastolic Blood Pressure (DBP, mmHg)	79.20 ± 10.85	77.62 ± 10.89	78.87 ± 10.19	81.09 ± 11.21	**0.002**
Body Mass Index(BMI, kg/m^2)	26.04 ± 2.78	25.97 ± 2.66	26.22 ± 2.85	25.92 ± 2.83	0.429
Fasting Blood Glucose(FBG, mmol/L)	5.32 (4.87-6.01)	5.01 (4.63-5.36)	5.30 (4.87-5.87)	5.87 (5.25-7.59)	**< 0.001**
Triglycerides(TG, mmol/L)	1.85 (1.40-2.77)	1.27 (1.10-1.45)	1.87 (1.69-2.16)	3.32 (2.71-4.64)	**< 0.001**
High-Density Lipoprotein Cholesterol (HDL-C, mmol/L)	1.13 ± 0.26	1.23 ± 0.26	1.15 ± 0.23	1.01 ± 0.23	**< 0.001**
Low-Density Lipoprotein Cholesterol (LDL-C, mmol/L)	3.02 ± 0.82	3.03 ± 0.71	3.17 ± 0.80	2.85 ± 0.91	**< 0.001**
Total Cholesterol (TC, mmol/L)	4.87 ± 0.92	4.61 ± 0.81	4.87 ± 0.89	5.13 ± 0.98	**< 0.001**
Anti-hypertension medication (n, %)	62 (8.39%)	15 (6.15%)	17 (6.85%)	30 (12.15%)	**0.032**
Antidiabetic agents (n, %)	37 (5.01%)	7 (2.87%)	16 (6.45%)	14 (5.67%)	0.160
Lipid-lowering medication (n, %)	12 (1.62%)	3 (1.23%)	5 (2.02%)	4 (1.62%)	0.788
Follow-up Time (days)	708.00 (568.00-730.00)	707.00 (566.00-729.25)	708.50 (533.25-734.00)	708.00 (614.50-729.00)	0.816
TyG ×BMI	195.85 ± 26.62	179.25 ± 19.81	194.58 ± 21.35	213.52 ± 26.31	**< 0.001**
TyG	7.52± 0.64	6.90 ± 0.24	7.42 ± 0.14	8.24 ± 0.48	**< 0.001**

BMI, body mass index; TyG, triglycerides- glucose index; the bold values, P<0.05.

The annual incidence rate was 1,238/10,000 person-years or 12.38% person-years (95% CI: 10.34-14.70%). The incidence rate of CAS was higher in the Q2 and Q3 groups than in the Q1 group (8.44% vs. 23.23% [$P < 0.001$] and 8.44% vs. 42.91% [$P < 0.001$], Figure 2).

Clinical and biochemical characteristics of individuals with or without CAS

Our individuals with NAFLD were sorted into two groups based on the occurrence of CAS throughout the follow-up period: those with CAS and those without CAS. Regrading general characteristics, no significant between-group difference was noted in sex distribution ($P = 0.212$). Patients with CAS had higher SBP compared to those without CAS ($P < 0.001$). There are differences in the use of antihypertensive drugs and hypoglycemic drugs between the two groups, and the difference is statistically significant (P = 0.005, 0.007, respectively). Furthermore, the values of IR indicators, such as TyG×BMI value, TyG index, were notably elevated in patients with CAS compared to those without ($P < 0.05$), and the difference between groups in TyG index was greater, with higher levels of TyG in CAS patients. There were no notable differences observed in HDL-C, LDL-C, or lipid-lowering medication between the groups ($P > 0.05$; Table 2).

Association between the TyG index and CAS incidence among individuals with NAFLD

Kaplan–Meier curves for CAS incidence indicated that a heightened baseline TyG was linked to an elevated likelihood of CAS (Q1 vs. Q2 and Q1 vs. Q3, log-rank $P < 0.001$; Q1 vs. Q3, log-rank $P < 0.001$; Figure 3).

Cox regression was performed to investigate the relationship between the TyG index and CAS incidence among individuals diagnosed with NAFLD (Table 3). Omnibus test P were <0.001 in all constructed COX regression models. The TyG value, when treated as a continuous variable, was found to be linked with the incidence of CAS. This association remained significant even after covariate adjustment (adjusted HR 1.39; 95% CI: 1.10 - 1.76; $P = 0.006$). When the TyG index was assigned as a qualitative variable, with Q1 as the reference group, Model 1 revealed that the HR for CAS incidence in the Q3 group was 5.23 (95% CI: 3.28 - 8.36; $P < 0.001$). Model 3 showed a positive relationship between the TyG index and the occurrence of CAS in the Q2 and Q3 groups.; notably, this association was the strongest in the highest tertile group of TyG group (HR: 4.51; 95% CI: 2.69 - 7.56; $P < 0.001$). The univariate Cox regression analysis showed that there was a correlation between TyG × BMI and CAS, but the correlation was relatively low (HR = 1.009, 95% CI: 1.004 - 1.013, $P < 0.001$). Furthermore, the RCS analysis unveiled a dose–response correlation between the TyG index and CAS incidence in individuals diagnosed with NAFLD. The nonlinear correlation between TyG and CAS risk was consistent when BMI was divided into whether ≥ 24 kg/m^2 or not (P non-linear < 0.05; Figure 4).

Subgroup analysis

Further analyses consistently revealed a positive relationship between the TyG and CAS incidence across patients stratified by age, sex, BMI, or hypertension history (P for interaction = 0.397, 0.620, 0.101, and 0.686, respectively; Table 4). Notably, the TyG

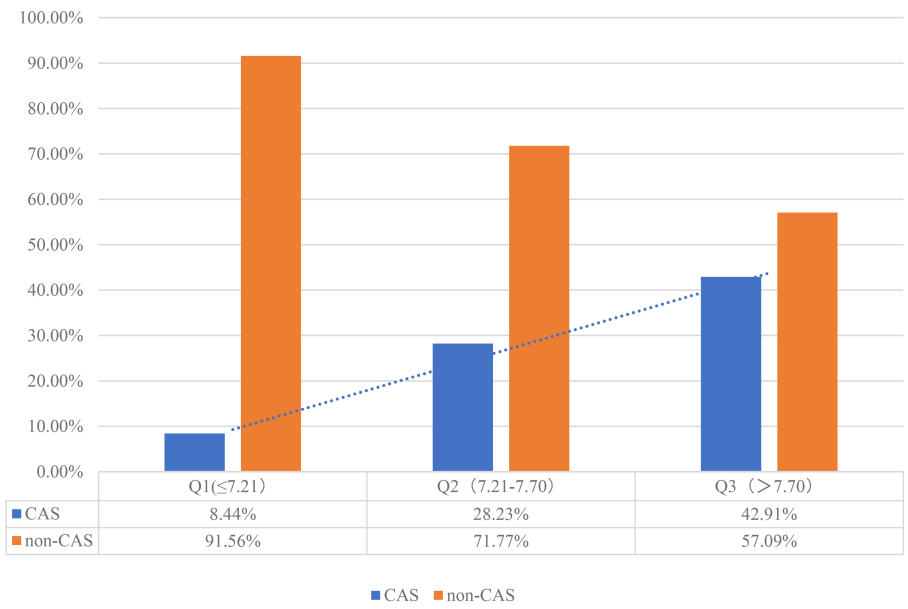

FIGURE 2
The incidence of CAS in NAFLD patients across different TyG groups.

TABLE 2 Clinical and biochemical characteristics of patients with or without CAS.

	NAFLD	NAFLD-CAS	Standardize diff.	*P*-value
Cases(n)	540	199		
Age(years)	50.46 ± 11.38	54.43 ± 11.21	0.35 (0.19, 0.51)	< **0.001**
Gender(n, %)			0.10 (-0.06, 0.27)	0.212
male	326 (60.37%)	110 (55.28%)		
female	214 (39.63%)	89 (44.72%)		
Smoking(n, %)	79 (14.63%)	28 (14.07%)	0.02 (-0.15, 0.18)	0.848
Hypertension(n, %)			0.20(0.04,0.36)	**0.005**
yes	103 (19.07%)	57 (28.64%)		
no	423 (75.13%)	137 (65.87%)		
Diabetes(n, %)			0.51 (0.34, 0.67)	< **0.001**
yes	49 (9.07%)	56 (28.14%)		
no	491 (90.93%)	143 (71.86%)		
Systolic Blood Pressure (SBP, mmHg)	130.64 ± 17.20	137.44 ± 18.25	0.38 (0.22, 0.55)	< **0.001**
Diastolic Blood Pressure (DBP, mmHg)	78.86 ± 10.74	80.11 ± 11.12	0.11 (-0.05, 0.28)	0.166
Body Mass Index(BMI, kg/m^2)	26.04 ± 2.80	26.04 ± 2.73	0.00 (-0.16, 0.16)	1.000
Fasting Blood Glucose(FBG, mmol/L)	5.19 (4.80, 5.75)	5.72 (5.19, 7.09)	0.51 (0.34, 0.67)	< **0.001**
Triglycerides(TG, mmol/L)	1.72 (1.32, 2.48)	2.23 (1.79, 3.16)	0.28 (0.12, 0.44)	< **0.001**
High-Density Lipoprotein Cholesterol (HDL-C, mmol/L)	1.13 ± 0.26	1.13 ± 0.25	0.01 (-0.15, 0.17)	0.884
Low-Density Lipoprotein Cholesterol (LDL-C, mmol/L)	2.99 ± 0.79	3.10 ± 0.88	0.14 (-0.02, 0.30)	0.082
Total Cholesterol (TC, mmol/L)	4.78 ± 0.90	5.10 ± 0.94	0.35 (0.18, 0.51)	**<0.001**
Anti-hypertension medication (n, %)	103 (19.07%)	57 (28.64%)	0.23 (0.06, 0.39)	**0.005**
Antidiabetic agents (n, %)	20 (3.70%)	17 (8.54%)	0.20 (0.04, 0.37)	**0.007**
Lipid-lowering medication (n, %)	10 (1.85%)	2 (1.01%)	0.07 (-0.09, 0.23)	0.419
TyG ×BMI	193.09 ± 26.11	203.32 ± 26.61	0.39 (0.22, 0.55)	**<0.001**
TyG	7.42 ± 0.62	7.81 ± 0.59	0.65 (0.48, 0.81)	**<0.001**

BMI, body mass index; TyG, triglycerides- glucose index; the bold values, P<0.05.

index exhibited superior predictive performance in patients with NAFLD without diabetes (HR: 1.82; 95% CI: 1.44–2.31) than diabetic patients (HR: 0.93; 95% CI: 0.65–1.32); the *P* value for interaction was 0.013.

Results of sensitivity analysis

The TyG index remained significantly associated with CAS after patient stratification by TyG index tertiles (Supplementary Table S1). After adjusting for all covariates, the HR (95% CI) was 4.34 (2.44 - 7.69), *P* <0.001. Even after the exclusion of patients who developed CAS within the first 9 months of follow-up, no notable change was detected in the aforementioned association (Supplementary Table S2). After adjusting for all relevant covariates, the HR (95% CI) was found to be 4.55 (2.74 - 7.56), with a p-value <0.001.

Discussion

This longitudinal cohort study unveiled a robust positive correlation between the TyG and the CAS incidence in NAFLD individuals. The correlation remained consistent even after covariate adjustment, indicating that a heightened TyG value indicates an elevated risk of CAS. Thus, a high TyG value appears to independently contribute to CAS in patients with NAFLD. This study might represent the initial exploration into unveiling the predictive capability of the TyG index concerning CAS risk within this demographic.

Previous studies have shown that there is an association between the TyG index and carotid atherosclerosis (such as carotid plaque formation, carotid stenosis, and arterial stiffness) (23, 26, 27). However, the relationship between TyG and CAS in specific populations remains unclear and requires further assessment, as the

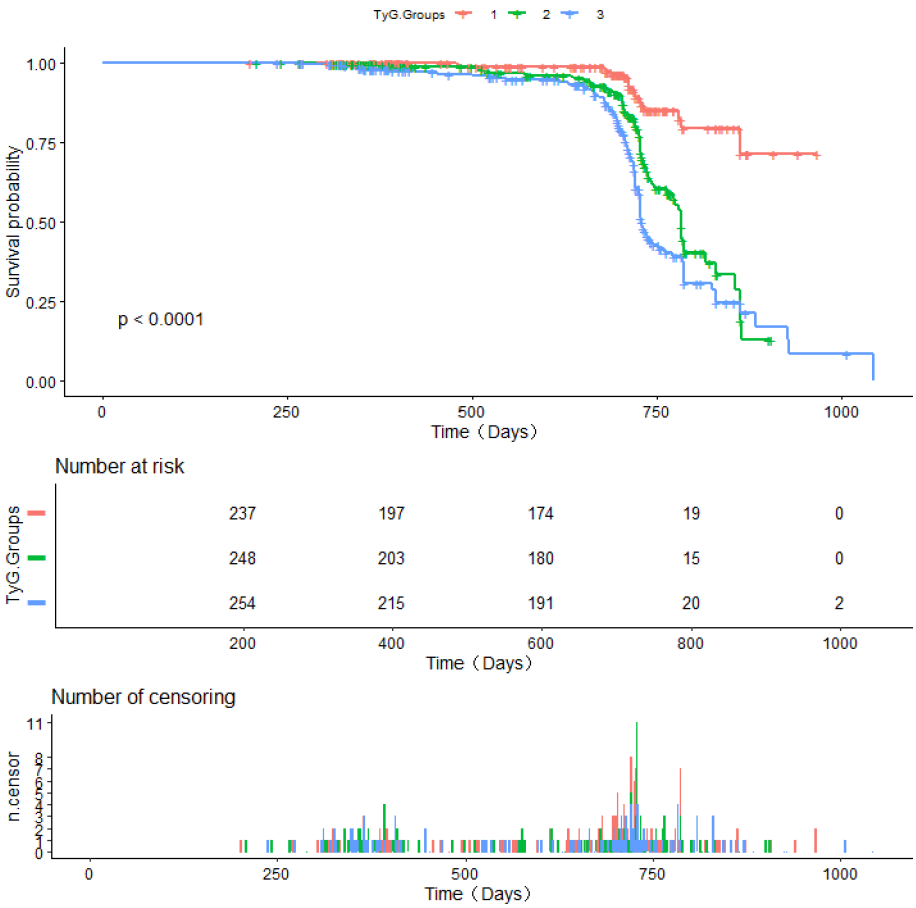

FIGURE 3
Survival curves derived from Kaplan-Meier analysis for the incidence of CAS in patients with NAFLD.

TyG index is largely determined by the state of glucose and lipid metabolism. Individuals with familial hypercholesterolemia (FH), TyG was positively correlated with the incidence of atherosclerotic cardiovascular disease (ASCVD)[OR = 1.74(95%CI: 1.15–2.63, p <0.05)] (13). In patients with symptomatic coronary artery disease, the incidence of CAS was significantly higher in those with the highest quartile of the TyG index compared to those with the lowest quartile [OR = 2.31 (95% CI 1.27, 4.20), P < 0.05] (27). Our study revealed that in patients with metabolic-specific conditions (NAFLD), each unit increase in the TyG index was associated with a 39% increased risk of CAS (95% CI: 1.10 - 1.76; P = 0.006). In a study involving 26,765 subjects with BMI less than 25, an increase in the TyG index was observed to be associated with an increased prevalence of CAS. However, after adjusting for confounding factors, the statistical association between them became insignificant (28). In the subgroup analysis of this study, no significant impact of varying BMI levels on the relationship between the TyG index and CAS was observed. The I-Lan Longitudinal Aging Study (ILAS) unveiled compelling evidence suggesting that the TyG index holds significance in forecasting atherosclerosis in patients without diabetes, particularly women, but not in those with diabetes (29). The findings of Anxin Wang (30) and Yawen Lu et al. (29) are consistent with our research results. In diabetic patients, no relationship was found between TyG and CAS, which may be related to the use of hypoglycemic medications. Although the documented correlation between the TyG index and NAFLD is well-established (31–33). the potential role of TyG in predicting the possibility of cervical vascular diseases in these patients has not yet been fully explored and confirmed (34, 35).

Changes in TyG index values, determined on the metabolic status of glucose and lipid, suggest the potential of this index in predicting CAS in individuals with specific metabolic characteristics, such as those with NAFLD (36–38). However, further research is necessary to comprehensively understand the biological mechanisms that connect the TyG with the emergence of CAS in individuals with NAFLD. Beyond its association with IR, the TyG index may be influenced by factors such as inflammation, oxidative stress, gut function, and gut microbial dysbiosis.

IR is a major driver of both NAFLD and CAS. An excessively high intrahepatic TG level, a characteristic of NAFLD, and the occurrence of *de novo* lipogenesis (DNL) within the liver promote hepatic steatosis in individuals afflicted by NAFLD (39). Insulin resistance improves the plasma levels of insulin and glucose, further promoting DNL. DNL may produce toxic metabolites, such as ceramides, which can exacerbate IR (40, 41). IR also significantly contributes to the onset of atherosclerosis (9, 10). Insulin signaling is essential for activating nitric oxide (NO), and IR inhibits NO production. NO is a key vasodilator and antiatherosclerotic agent. A

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TABLE 3 Association between the baseline TyG and CAS incidence in individuals with NAFLD.

Models	Model1 HR (95% CI)	*P*-value	Model2 HR (95% CI)	*P*-value	Model3 HR (95% CI)	*P*-value
Continuous TyG	1.60(1.35-1.90)	***P* < 0.001**	1.50(1.22-1.83)	***P* < 0.001**	1.39(1.10-1.76)	***P* = 0.006**
Q1 ≤7.21	1.00		1.00		1.00	
Q2 7.21-7.70	3.48(2.13-5.67)	***P* < 0.001**	3.34(2.04-5.47)	***P* < 0.001**	3.11(1.87-5.17)	***P* < 0.001**
Q3 >7.70	5.23(3.28-8.36)	***P* < 0.001**	4.77(2.92-7.78)	***P* < 0.001**	4.51(2.69-7.56)	***P* < 0.001**

Model1: Crude model.
Model2: Adjusted for sex, age, smoking, history of hypertension, diabetes.
Model3: Adjusted for sex, age, smoking, history of hypertension, diabetes, SBP, anti-hypertension medication, antidiabetic agents, lipid-lowering medication, FBG, TC.
The bold values, P<0.05.

reduction in NO level impairs the phosphoinositide 3-kinase/NO pathway. Furthermore, an IR-induced increase in insulin level can activate the mitogen-activated protein kinase pathway. The imbalance between these two pathways can lead to endothelial dysfunction (38, 39) (. Furthermore, IR upregulates the production of endothelin-1, thus promoting vasoconstriction and atherosclerosis progression (42). Elevated TyG index values in NAFLD patients may reflect underlying IR, which may contribute to the progression of CAS.

NAFLD is a systemic chronic inflammatory condition. Adipose tissue plays a momentous role in the chronic inflammatory reaction associated with NAFLD (43). This tissue is not merely a passive storage site for excess energy but actively participates in the metabolic and inflammatory processes that characterize NAFLD. An imbalance between adipokine and cytokine levels can explain this association (37, 44). This imbalance manifests as reductions in the levels of anti-inflammatory adipokines (e.g., adiponectin) and increases in those of proinflammatory cytokines, including interleukin (IL)-8, IL-6, IL-1β, interferon (IFN)-γ, and so on. Hyperplasia and dysfunction of adipose tissue, particularly visceral adipose tissue, downregulate the synthesis of anti-inflammatory adipokines, while concurrently upregulating the synthesis of proinflammatory cytokines. This proinflammatory milieu in NAFLD promotes atherosclerosis, as demonstrated by the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (45).Insulin resistance (IR) leads to a chronic, low-grade inflammatory state in adipose tissue and other metabolically active tissues such as the liver. These tissues release a multitude of inflammatory mediators, including cytokines, chemokines, and adhesion molecules. These mediators are capable of attracting and activating inflammatory cells, such as monocytes and macrophages, towards the vascular wall. Once infiltrated into the vascular wall, these inflammatory cells release additional inflammatory mediators and growth factors, which stimulate the proliferation, migration, and phenotypic transformation of vascular smooth muscle cells (VSMCs) (46). Furthermore, they promote the synthesis and deposition of extracellular matrix (ECM) components. Collectively, these changes contribute to the formation and progression of atherosclerotic plaques. The TyG index, as a comprehensive indicator of lipid and glucose metabolism, may simultaneously reflect these two aspects of change. By integrating information on triglyceride levels and fasting glucose, the TyG index offers a glimpse into the underlying metabolic disturbances that precede and accompany atherosclerosis, including those driven by IR, lipid dysregulation, and chronic inflammation.

Furthermore, the onset and progression of NAFLD are associated with microbial flora (43, 47). NAFLD often features gut dysbiosis characterized by an increased abundance of *Escherichia coli* and a reduced abundance of *Prevotella* sp. These gut microbes convert dietary choline or carnitine to trimethylamine, which the liver converts to trimethylamine N-oxide. The metabolized form alters calcium signaling in platelets,

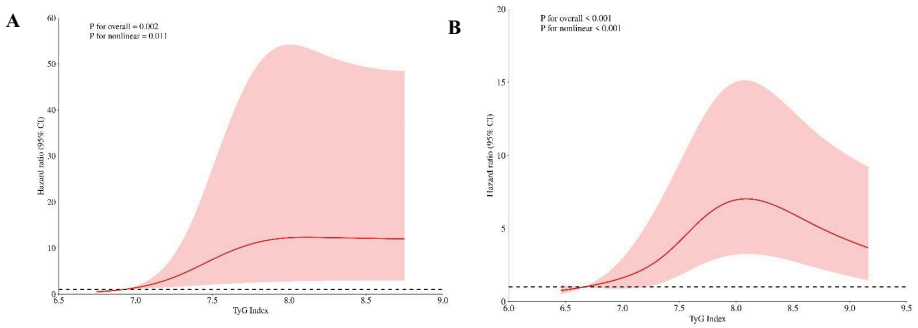

FIGURE 4
RCS plots depicting the risk ratio of the TyG in different BMI groups. **(A)** BMI<24kg/m^2. **(B)** BMI≥24kg/m^2. **(A)** shows TyG index 6.71 and **(B)** shows TyG index 6.65 as the references. The vertical axis illustrates the hazard ratio (HR), while the red shaded region depicts the 95% confidence interval (CI) value. The horizontal dashed line signifies an HR of 1.

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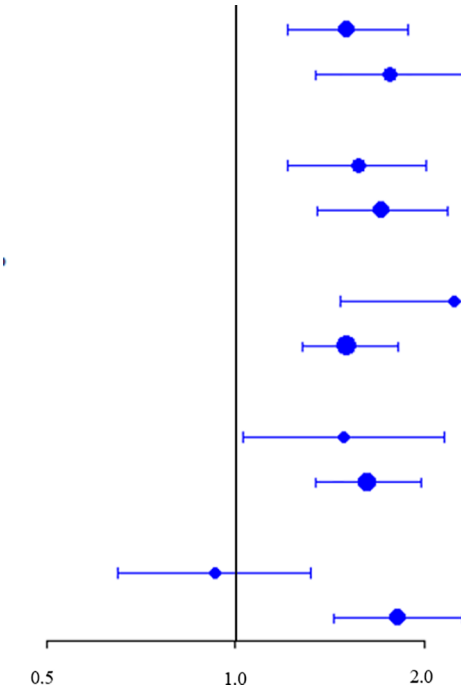
TABLE 4 Forest plot depicting the risk ratio of CAS across the subgroups.

Subgroups	HR	95%CI	*P*-value	*P*-interaction
Sex				0.397
Male	1.51	(1.21, 1.89)	<0.001	
Female	1.76	(1.34, 2.32)	<0.001	
Age(years)				0.620
≤50	1.57	(1.21, 2.02)	<0.001	
>50	1.71	(1.35, 2.18)	<0.001	
BMI(kg/m2)				0.101
<24	2.23	(1.47, 3.39)	<0.001	
≥24	1.51	(1.28, 1.82)	<0.001	
Hypertension				0.686
Yes	1.49	(1.03, 2.16)	0.034	
No	1.62	(1.34, 1.98)	<0.001	
Diabetes				**0.013**
Yes	0.93	(0.65, 1.32)	0.669	
No	1.82	(1.44, 2.31)	<0.001	



The bold values, P<0.05.

leading to increased platelet reactivity and thrombosis, thus promoting atherosclerosis (37, 48). Studies have shown a link between insulin resistance and gut microflora (49). The TyG index may also be influenced by the state of the gut microbiota.

In recent years, the TyG index has gained increasing popularity and recognition in clinical practice due to its remarkable cost-effectiveness. This index has significantly broadened its application beyond merely assessing cardiovascular diseases, now encompassing the prediction of acute kidney injury risk (50). Furthermore, the TyG index has been firmly established as a crucial factor in evaluating the incidence of chest pain (51), offering a novel perspective for stratified management of patients experiencing this condition. Notably, the index has also demonstrated potential in the field of mental health, exhibiting a significant correlation with the risk of depression onset, thereby providing a new biomarker reference for early screening and the formulation of preventive strategies for depression (52).

The strength of this study lies in its 3-year longitudinal cohort design, which gave it an advantage over cross-sectional studies in causal inference. Our findings indicate that the prognostic capacity of the TyG for carotid atherosclerosis (CAS) rate is more pronounced in patients with NAFLD who do not have diabetes compared to those who do. Furthermore, we performed covariate adjustment and risk stratification analyses across various subgroups.

This study is subject to certain limitations. Firstly, due to the study's single-center, retrospective cohort design, our findings may be subject to selection bias. Secondly, we used ultrasonography instead of the gold standard liver biopsy for diagnosing NAFLD. While liver biopsy provides the most definitive assessment by directly examining liver tissue, it is an invasive procedure with associated risks and discomfort for patients. Ultrasonography offers a non-invasive, safe, and widely accessible alternative. Despite its limitations compared to liver biopsy, ultrasonography is still an effective diagnostic tool for NAFLD, with a high sensitivity and specificity (20). Thirdly, despite performing multivariate Cox regression as well as subgroup and sensitivity analyses, we could not fully exclude potential confounders, such as diet and exercise. Fourthly, the patients were not stratified by the severity of NAFLD. We are unable to determine whether the correlation between Tyg and CAS varies across different levels of NAFLD. Finally, the RCS analysis indicated that the HR for CAS incidence in patients with NAFLD exhibited an upward trend with increasing TyG index values, until a threshold was reached; thereafter, a downward trend was noted. However, it is important to note that we cannot definitively conclude that the prognostic capacity of the TyG for the risk of carotid atherosclerosis (CAS) diminishes after reaching a certain threshold. This drawback arises due to the relatively limited sample size of individuals with high TyG index values in our study. Currently, our research is confined solely to NAFLD patients and cannot be generalized to the general population. Further research with larger cohorts is essential to confirm and extend these findings, facilitating a broader comprehension of the prognostic capability of the TyG across diverse stages among NAFLD patients.

Conclusion

We noted that patients with elevated TyG demonstrated a notably increased possibility of developing CAS among those diagnosed with NAFLD. This association underscores the TyG as a crucial indicator in

assessing the risk of atherosclerotic complications. It can be utilized for the early prevention and intervention of CAS, thereby improving patient outcomes and overall cerebrovascular health.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Ethics Committee of Northern Jiangsu People's Hospital Affiliated to Yangzhou University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the retrospective nature of the investigation, our institutional review board waived the need for informed consent. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because of the retrospective nature of the investigation.

Author contributions

XW: Funding acquisition, Supervision, Visualization, Writing – review & editing. WH: Conceptualization, Data curation, Project administration, Writing – original draft. HW: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. ZS: Visualization, Writing – review & editing. XY: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1448359/full#supplementary-material

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Differential association of abdominal, liver, and epicardial adiposity with anthropometry, diabetes, and cardiac remodeling in Asians

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Background: Heterogenous deposition and homeostasis roles of physiologic and ectopic adipose tissues underscore the impact of fat compartmentalization on cardiometabolic risk. We aimed to characterize the distribution of abdominal visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), epicardial adipose tissue (EAT), and liver fat on magnetic resonance imaging (MRI), and evaluate their associations with anthropometric indices and adverse cardiac remodeling.

Methods: In this cross-sectional observational study, 149 Asian adults (57.0 ± 12.8 years; 65% males) with at least one cardiometabolic risk factor underwent multiparametric fat and cardiovascular MRI. Anthropometric indices included body mass index (BMI), waist circumference (WC), waist-hip ratio (WHR), and bioimpedance body fat mass (BFM). Associations between fat depots and anthropometric measures as well as cardiac remodeling features were examined as a single cohort and stratified by type 2 diabetes mellitus (T2DM) status.

Results: VAT and SAT had opposing associations with liver fat and EAT. Therefore the VAT/SAT ratio was explored as an integrated marker of visceral adiposity. VAT/SAT was positively associated with EAT (β=0.35, P<0.001) and liver fat (β=0.32, P=0.003) independent of confounders. Of the anthropometric measurements assessed, only WHR was independently associated with VAT/SAT (β=0.17, P=0.021). Individuals with T2DM had higher VAT and lower SAT compared to those without T2DM, translating to a significantly higher VAT/SAT ratio. EAT volume was independently associated with adverse features of cardiac remodeling: increased left ventricular (LV) mass (β=0.24, P=0.005), larger myocyte volume (β=0.26, P=0.001), increased myocardial fibrosis (β=0.19, P=0.023), higher concentricity (β=0.18, P=0.035), and elevated wall stress (β=−0.18, P=0.023).

Conclusion: Multiparametric MRI revealed abdominal VAT and SAT have differential associations with anthropometric indices and ectopic fats in a single cohort of Asians at risk of cardiometabolic disease. People with T2DM have expanded VAT and diminished SAT, endorsing the VAT/SAT ratio beyond

usual anthropometric measurements as a marker for multiorgan visceral fat composition. Among the fat depots examined, EAT is uniquely associated with adverse cardiac remodeling, suggesting its distinctive cardiometabolic properties and implications.

KEYWORDS

cardiometabolic disease, fat distribution, visceral adiposity, diabetes, anthropometric indices, epicardial fat, cardiac remodeling, magnetic resonance imaging

1 Introduction

Disequilibrium or dysfunctional adipose tissue leads to obesity and metabolic disorders which in turn are risk factors for cardiovascular complications, described as cardiometabolic disease (1). As major fat depots, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are believed to have distinct metabolic roles. Ectopically, abnormal expansion of epicardial adipose tissue (EAT) is associated with coronary artery disease (CAD), heart failure (HF), and atrial fibrillation (AF) (2) whereas excessive liver fat accompanying metabolic dysregulation in metabolic dysfunction-associated fatty liver disease (MAFLD) is implicated in elevated cardiometabolic risk (3).

The metabolic heterogeneity of adipose tissues in type, size, function, and distribution as well as their modifiable potential indicate the need for fat phenotyping, enabled by advances in imaging-based quantification. However, the utility of conventional anthropometric indices for accurate assessment of adiposity is often challenged by the inability to account for the anatomical composition of fat and the multifactorial variation of body habitus. Alternative measures have been proposed but have yet to become mainstays of obesity diagnosis and stratification.

Current data suggest that Asians have a higher propensity for visceral fat storage and develop metabolic syndrome at a lower body mass index (BMI) (4). We aim to characterize the distribution of abdominal VAT and SAT, liver fat, and EAT in Asians at risk of cardiometabolic disease using multiparametric MRI. Associations of fat composition with anthropometric indices and features of cardiac remodeling were examined. We hypothesized heterogeneous associations among these fat depots with anthropometric indices and cardiac remodeling characteristics, which are distinguished by glycemic status.

2 Materials and methods

2.1 Study population

This observational study consisted of participants selected from the National Heart Centre Singapore Biobank, who had at least one of the following cardiometabolic risk factors: hypertension, type 2 diabetes mellitus (T2DM), hyperlipidemia, fatty liver, increased BMI, and abdominal obesity. Individuals with inherited cardiomyopathies (hypertrophic, dilated and infiltrative cardiomyopathies) were excluded from the study.

Parameters evaluated included anthropometric measurements, body fat mass by bioimpedance analysis, MRI-quantified adipose tissue (abdominal VAT and SAT areas, liver fat fraction, EAT volume), and cardiac metrics (mass, volumes, myocardial fibrosis markers, wall stress) using cardiovascular magnetic resonance (CMR).

Ethics approval was granted by the SingHealth Biobank Research Scientific Advisory Committee (SBRSA 2019/001). The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki. All study participants provided written informed consent.

2.2 Anthropometric indices and bioimpedance body fat analysis

Anthropometric measurements acquired with standard methods included BMI, waist circumference (WC), and waist-hip ratio (WHR). BMI was calculated as weight (kg)/height $(m)^2$. WC was measured at just above the navel. Hip circumference was taken at the widest portion of the hip area. The ratio between waist and hip circumferences was calculated as WHR. All measurements were taken in a standing position. Bioimpedance analysis (InBody, Cerritos, California, USA) was used to measure body fat mass (BFM), calculated as the difference between total body mass and fat-free mass that was made up of water, protein, and minerals.

Local BMI thresholds guided by the recommendations made by the WHO Expert Consultation Panel were used to define normal (<23.0 kg/m^2), overweight (23.0-30.0 kg/m^2), and obese (>30.0 kg/m^2) (5). Abdominal obesity was defined as WHR >0.90 and >0.85 or WC >90 cm and >80 cm for males and females, respectively (6).

2.3 Abdominal and cardiac MRI acquisition

MRI was performed for all participants using the 1.5T Siemens Aera (Siemens Healthineers, Erlangen, Germany). Abdominal VAT and SAT were examined from a series of contiguous cross-sectional

abdominal water- and fat-separated images obtained from the two-point Dixon method (TEs: 2.39 and 4.77 ms; TR: 6.5 ms; flip angle: 10 degrees; matrix size: 260 × 320 mm^2; FOV: 325-366 × 400-450 mm^2; slice thickness: 4 mm, slice gap: 0.8 mm) (7). Liver proton density fat fraction (PDFF) was acquired according to Liver*MultiScan*-Iterative Decomposition of water and fat with the Echo Asymmetry and Least Squares estimation method (*LMS IDEAL*; Perspectum Ltd, Oxford, London), which has been implemented across MRI platforms (8). The sequence parameters were as follows: TEs: 1.30, 3.30, 5,30, 7.30, 9.30, and 11.30 ms; TR: 14 ms; flip angle: 5 degrees; matrix size: 232 × 256 mm^2; FOV: 398 × 440 mm^2; slice thickness:10 mm; number of slices: 5; slice gap: 5 mm.

For CMR, balanced steady-state free precession cine images were acquired in the long-axis 2, 3, 4 chamber views, and short-axis view extending from the mitral valve annulus to the apex (acquired voxel size: 1.6 × 1.3 × 8.0 mm^3; slice gap: 2mm; 30 phases per cardiac cycle). Late gadolinium enhancement (LGE) imaging denoting replacement myocardial fibrosis was performed 8 minutes after 0.1 mmol/kg of gadobutrol administration (Gadovist; Bayer Pharma AG, Germany). A breath-held inversion-recovery fast gradient echo sequence was used, and the inversion time was optimized to achieve appropriate nulling of the myocardium. The native and 15-minute postcontrast myocardial T1 maps were acquired with a modified Look-Locker inversion-recovery sequence, applying a heartbeat acquisition scheme of 5(3)3 and 4(1)3(1)2, respectively.

2.4 MRI-based fat and cardiac analysis

De-identified abdominal and cardiac images were analyzed at Perspectum and the National Heart Research Institute (NHRIS) Core Laboratory, respectively, by trained individuals who were blinded to clinical data. Abdominal VAT, SAT, and liver PDFF were analyzed by Perspectum's expertly trained image analysts who were blinded to the clinical data.

Cross-sectional areas of VAT and SAT were segmented from the abdominal Dixon MRI image at the L3 vertebral level using ITK-SNAP software version 3.8 (PICLS, University of Pennsylvania, USA) (Figure 1A). This single-slice approach of quantifying VAT and SAT has been shown to correlate strongly with total SAT and VAT volumes (r>0.9 in men and women) (9, 10). Liver fat was quantified as PDFF, expressed as a percentage, and computed as fat/(fat+water) based on MRI-visible fat and water signals in the regions of interest placed on the PDFF parametric map, avoiding image artifacts and vessels (11, 12) (Figure 1B). Fatty liver was defined as PDFF >5.6% (13, 14). Liver*MultiScan* reports IDEAL-acquired PDFF with an accuracy within 3% of lab-analyzed fat samples (15).

EAT volume on the left and right ventricles was quantified at the end systole on short-axis cines extending from the mitral valve annulus to the apex using CVI42 (Circle Cardiovascular Imaging, Calgary, Canada). The bright layer between the myo-epicardial border and the pericardium constituted the EAT. EAT was carefully delineated along the pericardium to exclude the paracardial fat which sits outside the margin of the pericardium (Figure 1C).

LV mass and cardiac volumes were analyzed according to standardized protocols (16). LV concentricity was defined as the ratio of LV mass over end-diastolic volume (EDV) (17). The Remodeling Index (RI) is a surrogate marker of global myocardial wall stress, calculated as $RI = \sqrt[3]{EDV}/t$, where EDV is the LV end-diastolic volume (mL) and t is the maximal wall thickness (cm) across the 16 myocardial segments (18). A lower RI denotes increased global myocardial wall stress and predicts worse cardiovascular outcomes in individuals with hypertension (19).

Interstitial volume (mL), as a measure of diffuse interstitial myocardial fibrosis, was calculated as the extracellular volume (ECV) fraction × myocardial volume (mL), where extracellular volume (ECV) was quantified from native and post-contrast T1 maps, and myocardial volume was calculated by dividing the myocardial mass by the specific gravity of the myocardium (1.05 g/mL). Myocyte volume (mL) = myocardial volume – interstitial volume (20).

2.5 Statistical analysis

The normality of data distribution was assessed with the Shapiro-Wilk test. Continuous variables were presented as mean ± standard

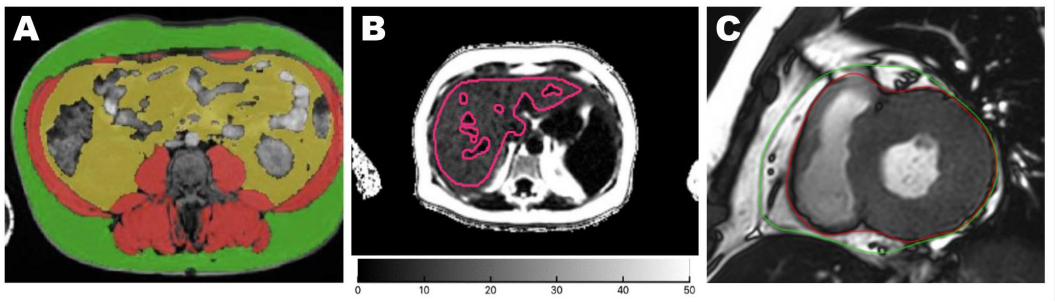

FIGURE 1
Quantification of adipose tissue from MRI axial images. Areas of abdominal adipose tissues were acquired at the vertebral L3 level. Green: SAT; yellow: VAT **(A)**. Liver PDFF was quantified from the whole liver region of interest marked in red lines on a parametric map, avoiding image artifacts and major vessels **(B)**. EAT was segmented between the epicardium (red line) and the pericardium (green line) on both ventricles at end-systole from the basal to apical short-axis cines. The paracardial fat outside the pericardium was not included in the EAT contour **(C)**. EAT, epicardial adipose tissue; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

deviation (SD) if normally distributed or median (interquartile range) if otherwise. Categorical variables were expressed as frequency (percentage) and were analyzed using the χ^2 test.

Depending on the continuous or categorical nature of the dependent variable, multivariable linear or logistic regression analyses with adjustment for potential confounders were performed to evaluate the associations between (i) anthropometric indices and adipose tissues; (ii) abdominal, epicardial, and liver adipose tissues; and (iii) adipose tissues and cardiac remodeling markers. Clinically important potential confounders, including age, sex, ethnicity, BMI, systolic blood pressure (SBP), hyperlipidemia, and T2DM status, were adjusted for where applicable.

Mean differences in adipose tissues between categorical groups (WHR categories, BMI categories, T2DM status) were adjusted for confounders and compared using a one-way analysis of covariance (ANCOVA). *Post hoc* Bonferroni was performed for pairwise comparison between BMI categories (normal, overweight, and obese). Adjusted mean differences with a 95% confidence interval (CI) were reported. We compared the ability of VAT, SAT, and VAT/SAT ratio to differentiate individuals with and without T2DM using the area under the receiver operating characteristic curve (AUC).

Statistical significance was defined as $P<0.05$. Statistical analyses were performed using IBM SPSS Statistics Version 26 (IBM Corp, Armonk, NY, USA) and GraphPad Prism Version 7.05 (GraphPad Software, Inc, La Jolla, CA, USA).

3 Results

A total of 149 participants (57.0 ± 12.8 years old; 65% males; 83% Chinese) with cardiometabolic risk factors had MRI assessment of compartmental fat and cardiac remodeling (Table 1). Mean BMI was 26.9 ± 4.2 kg/m^2 and mean WHR was 0.93 ± 0.08 (males: 0.96 ± 0.06, females: 0.87 ± 0.09; $P<0.001$). The prevalence of normal, overweight, and obese status defined by BMI was 22%, 58%, and 20%, respectively. These participants had other cardiometabolic risk factors including hypertension (n=120, 81%), T2DM (n=56, 38%), hyperlipidemia (n=75, 50%), and fatty liver (PDFF=6.7 [3.3-14.3] %). A greater proportion of T2DM participants were men (n=43, 77%; $P=0.020$ for sex difference) but the proportion of hyperlipidemia and fatty liver was not significantly different between sexes ($P=0.275$ and $P=0.913$, respectively).

3.1 Association between anthropometric indices and fat depots

All anthropometric measurements were independently associated with VAT and SAT, with modest differences in the strength of associations: WHR was associated more strongly with VAT, whereas WC, BMI, and BFM were associated more with SAT (Table 2).

VAT and SAT were significantly higher in individuals with abnormal WHR and BMI (Figures 2A–D). We explored the VAT/SAT ratio as an integrated variable to examine the relative

TABLE 1 Baseline characteristics.

Demographics and Clinical Characteristics	
Age, years	57.0 ± 12.8
Male, n (%)	97 (65.1)
Chinese, n (%)	124 (83.2)
24-hour mean SBP, mmHg	131 ± 13
24-hour mean DBP, mmHg	80 ± 11
Hypertension, n (%)	120 (80.5)
Hyperlipidemia, n (%)	75 (50.3)
T2DM, n (%)	56 (37.5)
Fatty liver, n (%)	84 (56.4)
Ischemic heart disease, n (%)	4 (2.7)
HbA1c, %[Π]	7.0 (6.5-7.5)
Anthropometric and Bioimpedance Indices	
Body surface area, m^2	1.79 ± 0.21
Weight, kg	73.1 ± 14.6
Height, m	1.64 ± 0.09
BMI, kg/m^2	26.9 ± 4.2
Waist circumference, cm	93 ± 12
Hip circumference, cm	100 ± 8
WHR	0.93 ± 0.18
Bioimpedance BFM, kg	24.4 ± 8.3
Skeletal muscle mass, kg	27.5 ± 8.7
Adipose Tissue Characteristics	
VAT area, cm^2	170.8 ± 82.7
SAT area, cm^2	180.5 ± 87.3
VAT/SAT ratio	1.10 ± 0.68
EAT volume, cm^3	113.2 ± 38.5
Liver PDFF, %	6.7 (3.3-14.3)
Cardiovascular Magnetic Resonance Characteristics	
Indexed LV mass, g/m^{2*}	50 ± 11
Indexed LV EDV, mL/m^{2*}	70 ± 12
Indexed LV ESV, mL/m^{2*}	29 ± 8
Indexed LV SV, mL/m^{2*}	41 ± 7
LV EF, %	59 ± 6
LV mass/EDV ratio	0.71 ± 0.15
Indexed RV EDV, mL/m^{2*}	71 ± 13
Indexed RV ESV, mL/m^{2*}	30 ± 10
Indexed RV SV, mL/m^{2*}	41 ± 7
RV EF, %	58 ± 9
Late gadolinium enhancement, n (%)	28 (18.8)

(Continued)

TABLE 1 Continued

Cardiovascular Magnetic Resonance Characteristics	
Extracellular volume fraction, %	25.1 ± 2.5
Indexed interstitial volume, mL/m^{2*}	11.9 ± 2.6
Indexed myocyte volume, mL/m^{2*}	35.6 ± 7.9
Remodeling index	5.9 ± 1.1
Global longitudinal strain, %	-16.6 ± 2.3
Global circumferential strain, %	-19.4 ± 2.6
Global radial strain, %	33.9 ± 7.7

[1] Only in individuals with T2DM. *Indexed to body surface area calculated using the DuBois formula = 0.007184 × height (m)$^{0.725}$ × weight (kg)$^{0.425}$.
BFM, body fat mass; DBP, diastolic blood pressure; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LA, left atrial; LV, left ventricular; PDFF, proton density fat fraction; RA; right atrial; RV, right ventricular; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure; SV, stroke volume; T2DM, type 2 diabetes mellitus; VAT, visceral adipose tissue; WHR, waist-hip ratio.

distribution of VAT and SAT by anthropometry. VAT/SAT ratio was strongly associated with male sex (β=0.27, P<0.001), increasing age (β=0.35, P<0.001), and T2DM status (OR=4.071, P=0.001; Supplementary Table S1). Of all the anthropometric measures assessed, only WHR was independently associated with VAT/SAT ratio (β=0.17, P=0.021).

VAT/SAT ratio was significantly increased in those with abnormal WHR but not across BMI categories (Figures 2E, F). EAT volume was greater with abnormal WHR, and across BMI (Figures 2G, H); liver PDFF was increased in those with abnormal WHR, but not significantly different between overweight and obese individuals (Figures 2I, J). All findings were adjusted for age, sex, ethnicity, SBP, hyperlipidemia, and T2DM (Supplementary Tables S2, S3).

3.2 Association between fat depots

Abdominal VAT and SAT were weakly correlated with each other (r=0.19, P=0.024) and had opposing associations with EAT and liver PDFF. While an increase in VAT was associated with an increase in EAT (β=0.48; P<0.001), an increase in SAT was associated with a smaller EAT volume (β=−0.42; P=0.001). Similarly, greater VAT area was associated with higher liver PDFF (β=0.48; P<0.001) but no association was observed between SAT and liver PDFF (β=0; P=0.999) (Figure 3).

Using the VAT/SAT ratio to examine the contrasting effects between VAT and SAT, we observed that an increase in VAT/SAT ratio was significantly associated with an increase in both EAT (β=0.35, P<0.001) and liver PDFF (β=0.32, P=0.003) (Figure 3). All analyses were adjusted for age, sex, ethnicity, BMI, SBP, hyperlipidemia, and T2DM status.

Despite similar anthropometric measures (WC, WHR, BMI, and bioimpedance BFM) between individuals with and without T2DM (Supplementary Figure S1), individuals with T2DM had an increased propensity for visceral fat accumulation. Compared to non-diabetic participants, those with T2DM had significantly increased VAT (193.0 ± 7.2 versus 157.4 ± 5.4 cm^2, P<0.001), less SAT (164.3 ± 7.0 versus 190.3 ± 5.3 cm^2, P=0.006), a larger EAT volume (124.5 ± 4.5 versus 106.4 ± 3.4 cm^3, P=0.003), and a higher liver PDFF (11.7 ± 1.1 versus 7.9 ± 0.8%, P=0.007) after adjustment for potential confounders (Figure 3; Supplementary Table S4).

The higher VAT and lower SAT in T2DM translated to a significantly higher VAT/SAT ratio in individuals with T2DM than those without (adjusted mean difference=0.37, 95% CI=0.18-0.56, P<0.001) (Figure 4; Supplementary Table S4). Indeed, VAT/SAT ratio demonstrated the highest discrimination for the presence of T2DM (AUC=0.79, 95% CI=0.72-0.86, P<0.001) compared to VAT (AUC=0.71, 95% CI=0.63-0.80, P<0.001) and SAT (AUC=0.62, 95% CI=0.53-0.71, P=0.019) alone (Supplementary Table S5).

TABLE 2 Multivariable linear regression demonstrating independent associations between anthropometric indices and abdominal fat.

	VAT, cm^2	SAT, cm^2	VAT/SAT ratio
WC, cm	0.75, P<0.001	0.81, P<0.001	0.071, P=0.311
WHR	0.53, P<0.001	0.39, P<0.001	0.172, P=0.021
BMI, kg/m^2	0.61, P<0.001	0.78, P<0.001	0.007, P=0.909
BFM, kg	0.62, P<0.001	0.78, P<0.001	0.045, P=0.470

All analyses were adjusted for age, sex, ethnicity, SBP, hyperlipidemia, and T2DM. Data presented as standardized β coefficients and corresponding P values. BFM, body fat mass on bioimpedance; BMI, body mass index; WC, waist circumference; WHR, waist hip ratio; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

3.3 Association between fat depots and CMR markers of cardiac remodeling

Among all the fat depots assessed in the study, EAT demonstrated consistent and independent associations with adverse features of cardiac remodeling on CMR, which remained significant after adjustment for age, sex, SBP, hyperlipidemia, and T2DM status (Figure 3). Specifically, an increase in EAT volume was independently associated with increased LV mass (β=0.24, P=0.004), expanded interstitial volume denoting diffuse interstitial myocardial fibrosis (β=0.19, P=0.023), larger myocyte volume (β=0.26, P=0.001), increased concentricity (LV mass/EDV ratio: β=0.18, P=0.035), and reduced RI denoting increased myocardial wall stress (β=−0.18, P=0.023). A higher VAT/SAT ratio demonstrated independent association only with increased concentricity (β=0.23, P=0.035) (Figure 5; Supplementary Table S6).

A total of 28 individuals (18.8%) had LGE on CMR (ischemic pattern consistent with infarction, n=4; non-ischemic pattern, n=24). Individuals with LGE had similar EAT volumes compared to those without (125.7 ± 33.9 versus 110.8 ± 38.8 cm^3, P=0.064), although this should be interpreted with caution because only a small proportion of individuals had LGE.

4 Discussion

Our results showed that abdominal VAT and SAT were both increased in central and systemic obesity, with WHR (but not BMI

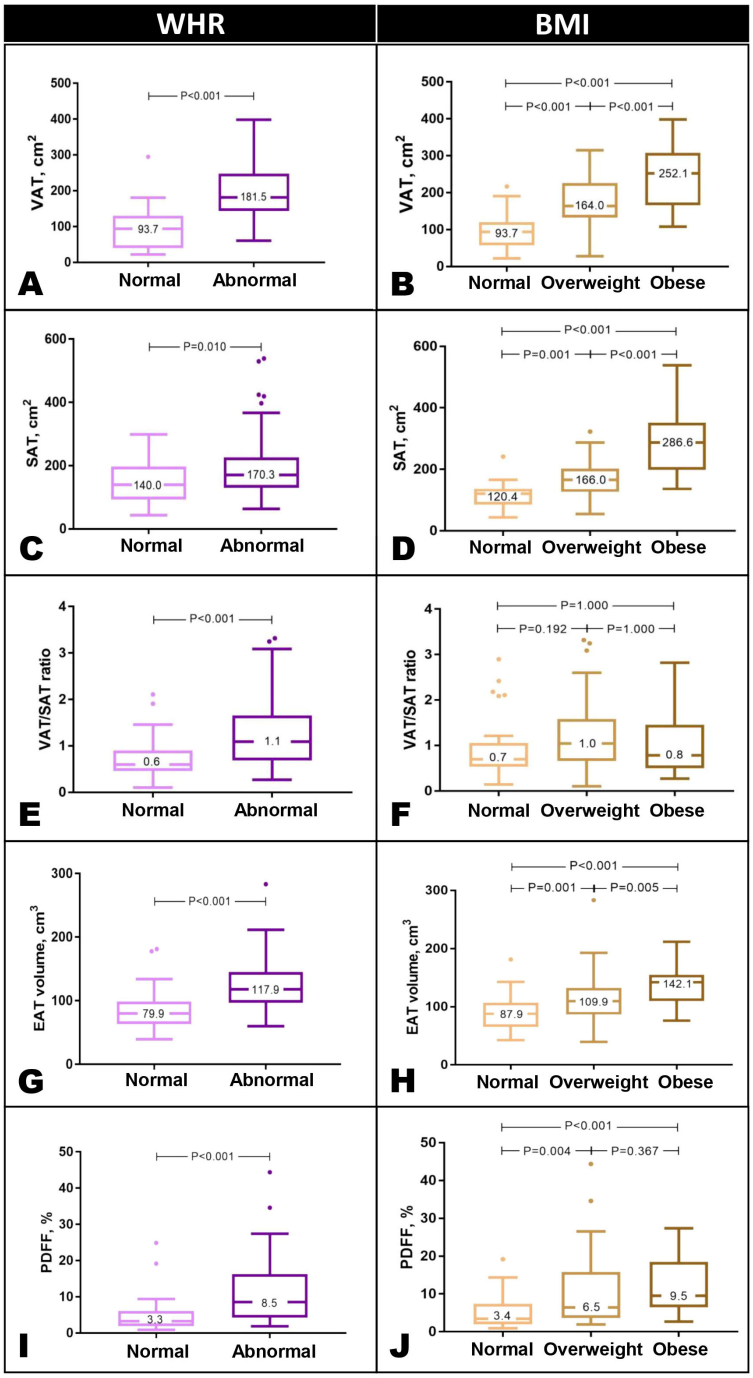

FIGURE 2
Abdominal VAT and SAT were significantly higher in individuals with abnormal WHR and across BMI categories **(A–D)**. VAT/SAT ratio was significantly increased in individuals with elevated WHR but not across BMI categories **(E, F)**. EAT was increased in those with abnormal WHR and across BMI categories **(G, H)**. Liver PDFF was greater in those with abnormal WHR. Across BMI categories, PDFF was higher than normal but not significantly different between overweight and obese individuals **(G–J)**. Results are presented in Tukey box and whisker plots. WHR thresholds: males, 0.90, females, 0.85. Asian BMI thresholds: normal <23 kg/m^2, overweight 23-30 kg/m^2, obese >30 kg/m^2. BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WHR, waist-hip ratio.

classification) as a better indicator of visceral adiposity. To the best of our knowledge, this study is the first to report that VAT and SAT have inverse associations with ectopic fats and T2DM, endorsing the potential value of the VAT/SAT ratio as an indication of relative visceral adiposity. The amounts of EAT and liver fat were associated with VAT, all of which were distinctively increased in the presence of T2DM while SAT was diminished. Among the fat depots assessed, the accumulation of EAT was associated with adverse features of cardiac remodeling on CMR.

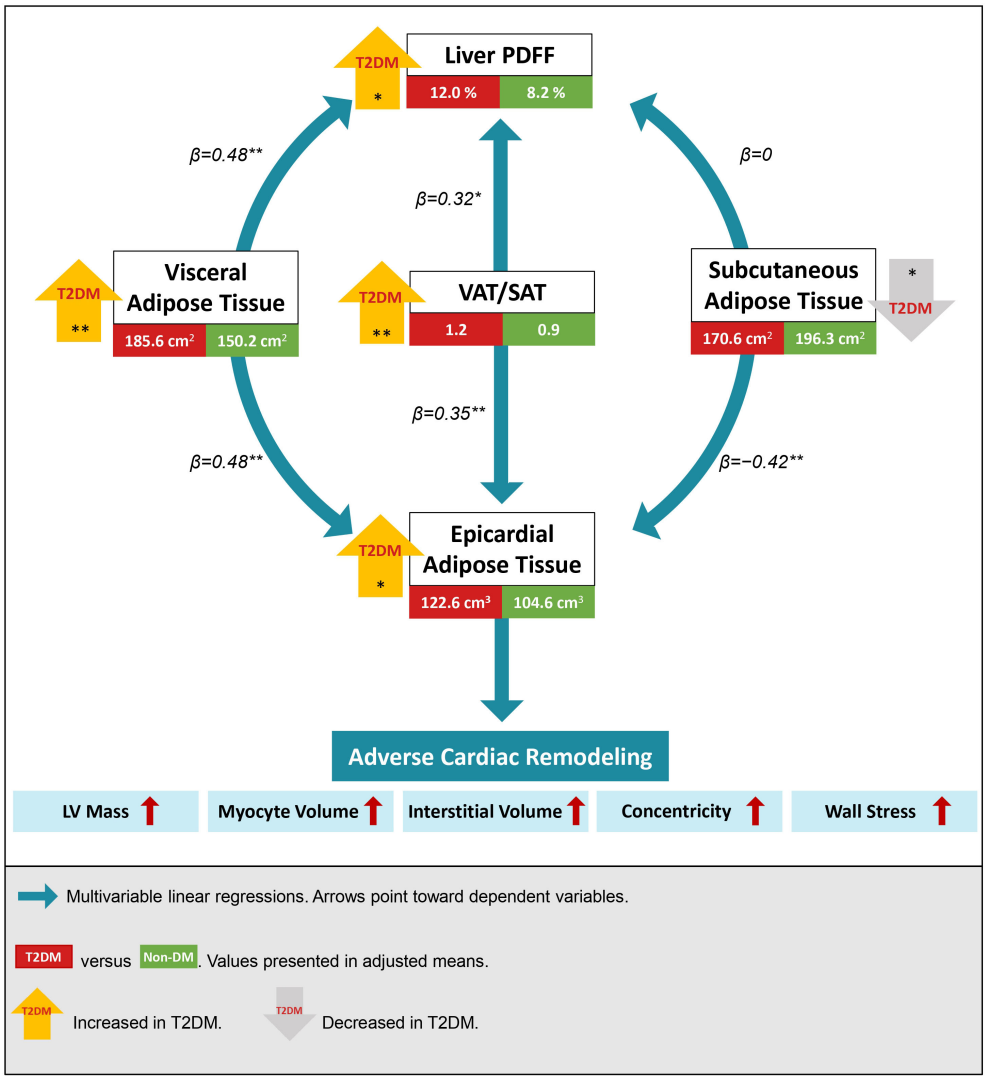

FIGURE 3
Visceral and subcutaneous adipose tissue (VAT and SAT) had inverse associations with epicardial adipose tissue (EAT) and liver proton density fat fraction (PDFF). An increase in the integrated VAT/SAT index was associated with an increase in both EAT and liver PDFF. Individuals with type 2 diabetes mellitus (T2DM) had increased visceral and ectopic fat depots. Regardless of diabetes status, adverse cardiac remodeling was observed with the accumulation of ectopic EAT. Multivariable regressions were adjusted for age, sex, ethnicity, systolic blood pressure, hyperlipidemia, body mass index, and T2DM. Mean differences in fat depots between T2DM and non-DM were analyzed using one-way ANCOVA adjusted for all confounders except T2DM status. *P<0.05; **P<0.001.

4.1 Relative visceral adiposity

VAT, being a metabolically active endocrine organ, confers higher cardiometabolic risks over SAT (21, 22). A cross-sectional study of 3,197 Japanese healthy adults demonstrated a greater association between VAT and metabolic diseases. SAT, by contrast, demonstrated an inverse association with impaired glucose metabolism in men and no significant association in women (23). In another study involving biopsy-proven non-alcoholic fatty liver disease (NAFLD) patients, MRI-quantified VAT was associated with insulin resistance, glucose, triglyceride, and WHR whilst SAT was negatively associated with these same indices (24). Inflammatory mediators were also differentially associated with VAT and SAT. Pro-inflammatory factors were expressed in a greater amount by VAT than SAT (25, 26). Conversely, adiponectin, which has a putative anti-inflammatory effect, was less abundant in the VAT (27). Lower levels of adiponectin were associated with a higher prevalence and increased risk of cardiovascular diseases (28, 29). These differences supported our observations of the opposite associations of VAT and SAT with T2DM, liver fat, and EAT.

Different treatments had different effects on adiposity. For instance, an improvement in glycemic profile with troglitazone therapy was accompanied by increased SAT (30) whereas glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy decreased VAT and not SAT (31, 32). Furthermore, surgical removal of VAT ameliorated metabolic syndrome while the effects of SAT removal have been inconsistent, with some demonstrating an improved (33, 34) or neutral (35, 36) effect on insulin sensitivity. For these reasons, the absolute amount of either

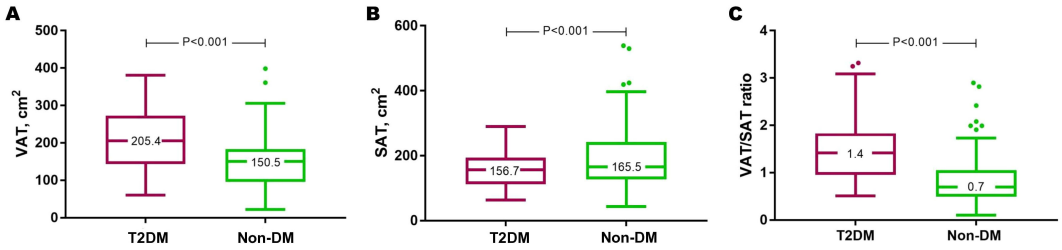

FIGURE 4
Individuals with T2DM had increased VAT **(A)**, reduced SAT **(B)**, and this translated to a higher VAT/SAT ratio **(C)**. Results are presented in Tukey box and whisker plots. DM, diabetes mellitus; SAT, subcutaneous adipose tissue; T2DM, type 2 diabetes mellitus; VAT, visceral adipose tissue.

of these fat depots may not fully reflect obesity-related cardiometabolic risk. Visceral adiposity, which has an established link with insulin resistance (37, 38), is therefore an appealing option that may be represented by the VAT/SAT ratio. Our findings corroborated this postulation, demonstrating the superior ability of the VAT/SAT ratio to discriminate diabetes status over VAT and SAT alone. This integrated index, interpreted in the context of the absolute amount of SAT and VAT, will likely inform a more complete metabolic profile of an individual.

4.2 Anthropometric indices and fat depots

In our study, BMI correlated weakly with VAT, EAT, and liver PDFF compared with waist-derived measurements. The advantage of WHR in estimating visceral adiposity is substantiated by the ability of abnormal sex-specific WHR to indicate an increased VAT/SAT ratio. In contrast, the Asian-specific BMI classification showed no difference in the VAT/SAT ratio between normal, overweight, and obese status. BMI's inference on obesity as a function of weight and height lacked the sensitivity to delineate body fat composition. Such inadequacy in reflecting true adiposity and the associated cardiometabolic risk has given rise to phenomena such as normal-weight obesity (39, 40) and metabolically healthy obesity (41). Despite accounting for muscle, water, and bone mass, bioimpedance BFM is a measure of generalized fat storage and does not differentiate anatomical fat distribution. The predominant localization of VAT around the intra-abdominal organs and SAT in the gluteal-femoral region (42, 43) may suggest WHR as the preferred surrogate measure for abdominal visceral adiposity.

4.3 Abdominal, epicardial, and liver fat depots

Parallel with predominant visceral adiposity at the abdominal level, we observed greater EAT volume and liver fat in patients with T2DM. EAT is considered the true visceral fat of the heart as it originates from the same embryonic layer as VAT and is in direct contact with the myocardium (44). Our finding is in line with this

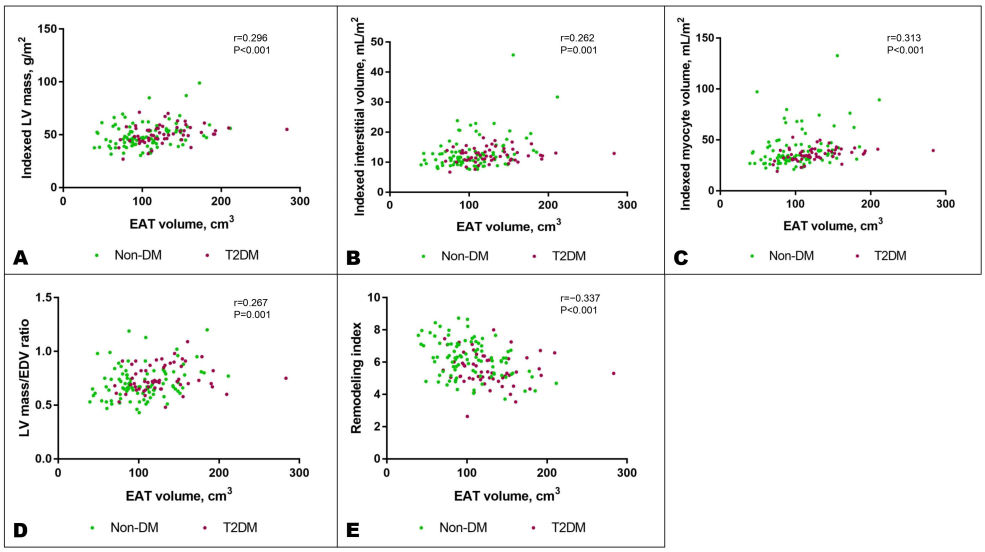

FIGURE 5
Increased EAT volume was associated with features of adverse cardiac remodeling: increased indexed LV mass **(A)**, indexed interstitial volume **(B)**, indexed myocyte volume **(C)**, LV mass/EDV ratio denoting concentricity **(D)**, and reduced remodeling index, a marker of elevated myocardial wall stress **(E)**. These associations remained significant after adjusting for potential confounders as listed in the text. DM, diabetes mellitus; EDV, end-diastolic volume; LV, left ventricular; T2DM, type 2 diabetes mellitus.

theory such that EAT was positively associated with VAT but negatively with SAT. Notably, in non-diabetic patients, although they had relatively more abdominal SAT, there was a good correlation between their VAT/SAT ratio and EAT volume, implying that EAT size could be approximated by relative abdominal visceral adiposity regardless of their diabetes status.

On a similar note, the liver PDFF was significantly higher with more abdominal VAT but not SAT. This differential association between abdominal fat with PDFF could be explained by insulin resistance exacerbated by visceral adiposity. The free fatty acids of VAT are drained by the portal vein (45) which when increased in metabolic disorders would lead to hepatic steatosis (46, 47). Whilst NAFLD increases the risk of cardiac complications (48), NAFLD patients with expanded EAT are at risk of more severe liver fibrosis (49), suggesting a bidirectional pathophysiological cross-talk between the heart and the liver. Trials with GLP-1RAs and sodium-glucose co-transporter 2 (SGLT2) inhibitors have reported reductions in EAT thickness, liver fat, and abdominal fat, often without significant BMI changes or correlation (50–55), highlighting the interrelation of these fat depots as well as their modifiable potential independent of body weight, hence the value of their quantification for risk prevention and treatment monitoring.

4.4 Epicardial adipose tissue and CMR markers of cardiac remodeling

Of the fat depots we assessed, a greater EAT volume was associated with adverse cardiac remodeling: expanded myocyte and interstitial volumes, increased LV mass, a more concentric LV, and higher global myocardial wall stress. The anatomic proximity of EAT to the myocardium facilitates infiltration of lipids, vasocrine and paracrine factors into the myocardium (56), rendering it susceptible to a cascade of metabolic, inflammatory, and immune activity alterations. It has been reported that paracrine exertion of EAT-derived adipokines was associated with LV systolic and diastolic functions (57). Such paracrine effects could have modulated the structural LV remodeling observed with increased EAT in the present cohort of relatively well individuals prior to discernable functional deterioration.

In insulin resistance, glucose utilization and lipolysis are reduced in EAT. Such metabolic remodeling along with the hemodynamic changes due to mechanical impediment imposed by an excessive fat pad could increase the cardiac output and energy demands of the heart, leading to elevated myocardial wall stress. The left and right filling pressures are elevated with greater EAT volume in patients with obesity and concomitant heart failure with preserved ejection fraction (HFpEF) (58). To compensate for pressure overload, cardiomyocytes undergo hypertrophic growth, manifested as increased myocyte volume and LV mass, to reduce wall stress. The disproportionate growth of wall thickness was accompanied by increased wall stress and concentricity, reflected in lower RI and mass/volume ratio, respectively. One study reported that even in patients with no HF or other cardiovascular risk factors, increased visceral adiposity was associated with myocardial steatosis, impaired myocardial energetics, increased LV mass, concentric remodeling, and diastolic dysfunction (59).

We have previously determined that increased myocardial wall stress was associated with myocardial fibrosis, possibly mediated by inflammation and immune activation (18, 60). Considering the implications of inflammation on EAT (61), we observed that a greater EAT volume was associated with an expansion of interstitial volume, a marker of diffuse interstitial myocardial fibrosis. While diabetic patients had worse cardiac remodeling (60), the present study demonstrated that the association between features of adverse cardiac remodeling and EAT amount appeared to be independent of T2DM status, hinting at a complex interplay between glucose metabolism, epicardial adiposity, and cardiac remodeling, which calls for further investigations.

4.5 Strengths and limitations

A strength of this study lies in the multiparametric MRI quantification of fat depots in the abdomen, liver, and heart that are metabolically important in the regulation of cardiometabolic health, providing insights into the implications of fat distribution for myocardial remodeling. Along with imaging data, comprehensive anthropometric indices offered a surrogate indication of fat composition for easy and quick measurement. Our cohort predominantly consisted of Chinese participants. Investigations on ethnic differences in fat composition, anthropometry, and implications in cardiac remodeling are warranted in future studies.

The quantification of PDFF did not account for T1 and T2* and thus estimation of liver fat may be affected by the presence or extent of inflammation, fibrosis, and iron. However, calculating PDFF using this approach was shown to provide excellent diagnostic accuracy for liver fat similar to biopsy-confirmed non-alcoholic steatohepatitis (11). Furthermore, assessing PDFF using the *LMS IDEAL* approach has been validated against lab-analyzed fat samples (15). The *LMS IDEAL* method is also robust against the fat/water swapping error. These factors increased the confidence of our PDFF analyses while acknowledging that correction for T1 and T2* should be considered for future studies involving fibrotic and inflammatory liver pathologies.

5 Conclusion

In Asian adults with cardiometabolic risk factors, our study, using multiparametric MRI, demonstrated that abdominal VAT and SAT have differential associations with anthropometric indices and ectopic fats. Distinctive abdominal visceral adiposity indicated by an increased VAT/SAT ratio was more prominently implicated in T2DM and was associated with increased liver and epicardial fat, the latter of which was uniquely associated with adverse cardiac remodeling. With the current data suggesting a close link between epicardial, liver, and abdominal visceral adiposity, further investigations are needed to validate the utility and reliability of measuring these fat depots using anthropometric measures such as WHR for assessment and monitoring of cardiometabolic health and remodeling.

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 SingHealth Biobank Research Scientific Advisory 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

VL: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. YH: Data curation, Formal analysis, Investigation, Writing – review & editing. D-FT: Data curation, Project administration, Writing – review & editing. JB: Methodology, Supervision, Validation, Writing – review & editing. RB: Methodology, Validation, Writing – review & editing. T-TL: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. CC: Conceptualization, Funding acquisition, Investigation, 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/fendo.2024.1439691/full#supplementary-material

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The serum uric acid-to-high-density lipoprotein cholesterol ratio is a predictor for all-cause and cardiovascular disease mortality: a cross-sectional study

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Objective: The exact relationship between the serum uric acid-to-HDL cholesterol ratio (UHR) and mortality rates remains enigmatic among American adults. This study aims to clarify the association between UHR and both all-cause and cardiovascular disease (CVD) mortality in US adults.

Methods: This study enrolled 48054 patients from the National Health and Nutrition Examination Survey (NHANES). Mortality outcomes were determined by linking to National Death Index (NDI) records up to December 31,2019. Multivariate Cox proportional hazards models were constructed to analyze explore the associations between UHR and mortality. Dose-response relationships were explored using restricted cubic splines, and stratified analyses were conducted based on gender, age, race, education, PIR, smoking status, alcohol intake, physical activity, BMI, diabetes and hypertension.

Results: During the follow-up period, the overall mortality for all-cause and CVD was 10.9% and 2.7%, respectively. The adjusted HRs in the highest quintile were 1.16 (95% CI: 1.05, 1.29) for all-cause mortality and 1.2 (95% CI: 1, 1.45) for CVD mortality. In diabetes, obese, and CVD subgroups, significantly elevated adjusted HRs were observed for both all-cause and CVD mortality. Specifically, diabetes patients had adjusted HRs of 1.32 (95% CI: 1.11, 1.57) and 1.38 (95% CI: 1.01, 1.90), obese individuals had HRs of 1.32 (95% CI: 1.10, 1.58) and 1.55 (95% CI: 1.06, 2.28), and CVD patients had HRs of 1.29 (95% CI: 1.10, 1.50) and 1.38 (95% CI: 1.06, 1.79), respectively. A non-linear relationship between UHR and mortality was identified, with critical thresholds of 12.4 for all-cause mortality and 10.7 for CVD mortality in the general population. Significant interactions were observed between UHR and stratified variables, including gender, BMI, education, smoking, alcohol use, and hypertension for all-cause mortality, while significant interactions were observed based on gender, smoking, and alcohol intake for CVD mortality. Comparable trends were also observed in patient with diabetes, obese and CVD.

Conclusions: In this cohort study, we provide novel insights into the association between serum UHR concentrations and mortality in the general population. UHR is a strong predictor of all-cause and cardiovascular mortality in the general population.

KEYWORDS

the serum uric acid-to-high-density lipoprotein cholesterol ratio, mortality, cardiovascular disease, obese, diabetes, NHANES

Background

Cardiovascular disease (CVD), the foremost cause of mortality globally, remains a formidable barrier to public health (1, 2). Despite remarkable treatment breakthroughs, patients with CVD still grapple with persistent recurrences (3), maintaining a stubbornly high mortality rate (1). Unraveling the prognostic factors for CVD patients offers a promising avenue to significantly reduce the global mortality burden, particularly cardiovascular mortality. Ideally, prognostic factors should be independently identifiable, cost-effective, and seamlessly integrated into clinical practice for enhanced prognostic precision and patient care.

In clinical practice, serum uric acid (UA) (4–9) and high-density lipoprotein cholesterol (HDL-C) (10–12) have been linked to cardiovascular disease (CVD) and adverse events. However, comorbidities affecting renal excretion and lipid metabolism limit their predictive accuracy (13–15). This underscores the importance of a more comprehensive, multifaceted evaluation. In this context, the serum uric acid-to-HDL-cholesterol ratio (UHR) emerges as a promising marker. Studies show a strong correlation between UHR and CVD, including atherosclerosis (16), ischemic heart disease (17–20), hypertension (21), acute myocardial infarction (22), coronary artery disease (CAD) (23, 24) and acute coronary syndrome (18). More importantly, studies have shown that the UHR predicts the onset of coronary artery disease better than UA or HDL-C alone in patients with chronic kidney disease (23). Additionally, UHR is correlated with CVD risk factors, including insulin resistance (25, 26), visceral fat accumulation (27, 28), and is also associated with metabolic diseases such as diabetes (29–31), metabolic syndrome (32), metabolism dysfunction-associated fatty liver disease (33–36), chronic kidney disease (37), Hashimoto's thyroiditis (38). UHR's broad correlation with these factors and conditions underscores its value in CVD risk assessment, integrating several key risk indicators.

Despite the remarkable potential of the UHR in forecasting CVD, investigations into its correlation with adverse cardiovascular outcomes, notably CVD mortality, are still limited. To date, there is only one study that has identified UHR as a predictive factor for cardiovascular mortality in patients undergoing peritoneal dialysis (39). The question of whether UHR can similarly predict cardiovascular mortality in the general population and among specific subgroups remains elusive. Therefore, our study endeavors to bridge this knowledge gap by examining the influence of UHR on mortality and elucidating the dose-response relationship, utilizing data from the National Health and Nutrition Examination Survey (NHANES) across diverse American populations.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; BUN, Blood urea nitrogen; CHD, Coronary heart disease; CHF, Congestive heart failure; CI, Confidence interval; CV, Cardiovascular; CVD, Cardiovascular disease; DBP, Diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, Fasting blood glucose; GGT, gamma-glutamyltransferase; HbA1c, Glycosylated hemoglobin A1c; HDL-C, High-density lipoprotein cholesterol; HR, Hazard ratio; IR, Insulin resistance; LDH, Lactate dehydrogenase; LDL-C, Low-density lipoprotein cholesterol; MI, Myocardial infarction; MNCHS, National Center for Health Statistics; NDI, National Death Index; NHANES, National Health and Nutrition Examination Survey; PIR, Family income to poverty ratios; SBP, Systolic blood pressure; Scr, Serum creatinine; SD, Standard deviation; T2DM, Type 2 diabetes mellitus; Tbil, Total bilirubin; TC, Total cholesterol; TG, Triglyceride; UA, Uric acid; UHR, Uric acid-to-high-density lipoprotein cholesterol ratio.

Methods

Study population and design

NHANES, a comprehensive, multistage survey conducted by the U.S. Centers for Disease Control and Prevention's National Center for Health Statistics, collects demographic, socioeconomic, dietary, physiological, and laboratory data through interviews and medical exams. NHANES has received ethical approval from the CDC's research ethics review board [NHANES 1999-2004: Protocol #98-12; NHANES 2005-2010; Protocol #2005-06; NHANES 2011-2018: Protocol #2011-17, #2018-01 (Effective beginning October 26, 2017)7]. NHANES ensures participant rights protection through informed written consent. Datasets from NHANES, including those used in our study, are publicly accessible on the official NHANES website (https://www.cdc.gov/nchs/nhanes/index.html).

Criteria for subgroup division are as follows: diabetes, defined by the American Diabetes Association (ADA), includes self-reported diagnosis, insulin/oral hypoglycemic use, fasting blood glucose ≥ 126 mg/dL, or HbA1c ≥ 6.5% (40). BMI is calculated as weight divided by height squared, with obesity defined as BMI ≥ 30 kg/m² (41), and CVD diagnosis is determined through self-reported physician diagnoses during interviews using a standardized questionnaire on CHF/CHD/angina pectoris/MI/stroke, with affirmative answers indicating the presence of CVD.

Patients were excluded if they met any of the following criteria: 1) age < 20 years; 2) missing death status information; 3) incomplete data on UA levels and HDL-C values; or 4) missing covariant data. A final cohort of 48,054 patients from NHANES 1999–2018 was included in the study (Figure 1).

Assessment of UHR

The exposure variable was the UHR, calculated as serum UA divided by HDL- C. UA measurements were performed using various multichannel analyzers across NHANES cycles (Hitachi Model 704, Beckman Synchron LX20, Beckman UniCel DxC800 Synchron, and Roche Cobas 6000). Fasting serum HDL- C concentrations were measured using the ARCHITECT auto-analyzer and Abbott reagent kits. Participants were categorized into four groups (Q1-Q4) based on UHR quartiles, with Q1 serving as the reference group.

Outcome ascertainment

The primary endpoint was all-cause mortality, with CVD-specific mortality as a secondary outcome. Mortality status was determined using the NHANES Public-Use Linked Mortality File, updated until December 31, 2019 (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm), which linked to the NDI data with a probabilistic matching algorithm to determine mortality status (42). The disease-specific mortality data in the NDI have been identified according to the International Statistical Classification of Diseases, 10th Revision (ICD-10), with only a relatively slight possibility of misclassification. Specific mortality was defined as death due to heart diseases (054–064), malignant neoplasms (019–043), and all

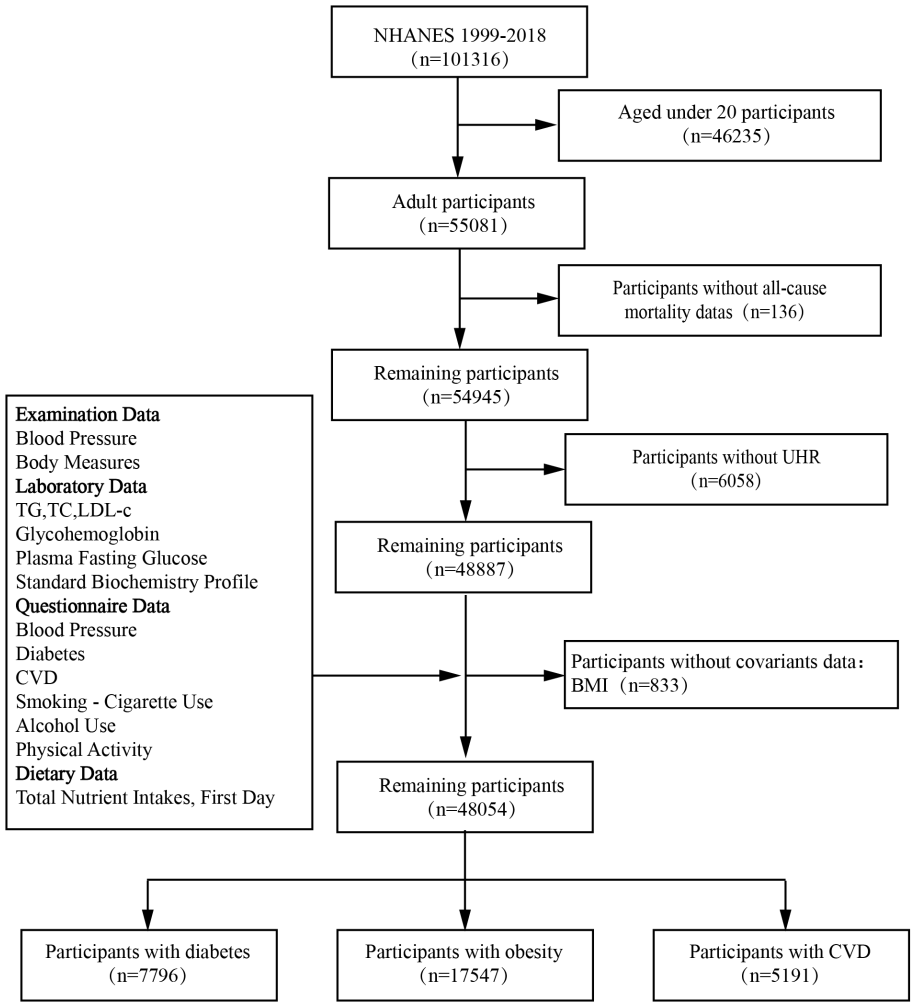

FIGURE 1
The selection flowchart of the participants.

other causes (010) for our study (43). Follow-up time for each person was calculated as the difference between the baseline examination date and the last known date alive or censored from the mortality file.

Assessment of covariates

Confounding factors potentially associated with mortality were enrolled in this analysis. Information on age, sex, race or ethnicity, education level, and family income was collected from the demographic data. Race was categorized as Mexican American, non-Hispanic White, non-Hispanic Black, or other race, while education level was grouped as less than high school, high school or equivalent, or college or above. Family economic status was determined by income to poverty ratio (PIR), with three categories: < 1.30, 1.31 to 3.50, and ≥ 3.50 (44).

Smoking status, alcoholic intake, and physical activity were assessed via standardized questionnaires. Participants were categorized into nonsmokers, former smokers, and current smokers based on smoking history and habits. Alcohol consumption was determined using a 24-hour dietary recall, classifying individuals as nondrinkers, moderate drinkers (0.1-27.9 g/day for men, 0.1-13.9 g/day for women), or heavy drinkers (≥ 28 g/day for men, ≥ 14 g/day for women). Physical activity was divided into inactive, active (meeting recommended levels), and insufficiently active categories based on previous literature (45).

Clinical indicators such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (Scr), gamma-glutamyltransferase(GGT), lactate dehydrogenase (LDH), total bilirubin (Tbil), fasting blood glucose (FBG), glycosylated hemoglobin A1c (HbA1c), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and HDL-C were measured in the NHANES laboratory following the relevant standardized protocols. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation (46).

Hypertension was defined as having a history of hypertension, systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 80 mmHg, according to the 2017 American College of Cardiology and American Heart Association hypertension guidelines.

Statistical analysis

The statistical analysis was performed by using R software (version 4.3.1; https://www.r-project.org). Given the complicated sampling design, NHANES weights and strata variables were considered when calculating statistics (47). Data categorized into continuous (mean ± SD) and categorical (percentages) variables. Statistical analysis of continuous variables employed Student's t-test or Mann–Whitney U test, depending on data distribution. Categorical variables were compared using chi-square test. Obesity phenotype stratified, baseline characteristics compared using one-way ANOVA.

Study participants were divided into four quartiles (Q1-Q4) of UHR. Baseline characteristics were compared across quartiles using ANOVA and chi-square tests. Incidence rates of all-cause and CVD mortality were computed for each quartile during follow-up.

To evaluate the independent predictive value of the UHR, we developed multivariate weighted Cox proportional hazards regression models with three models to control for confounding factors. Model 1 was unadjusted, Model 2 was adjusted for age, race, and gender, and Model 3 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes and hypertension. We utilized the restricted cubic spline (RCS) model to graphically represent the dose-response relationship between UHR levels and both all-cause and CVD mortality.

Stratified analyses were performed in the strata of age (< 30,30-40,40-50 or ≥ 50 years old), sex (male or female), race or ethnicity (White, Black, Mexican, or Other), education level (less than high school, high school or equivalent, or college or above), family income level(<1.30, 1.31 to 3.50, and ≥ 3.50), smoking status (current smoker, former smoker or nonsmoker), alcohol intake (heavy drinking, moderate drinking or nondrinking), physical activity(active, insufficiently or active), BMI (< 25 or 25-30, ≥ 30 kg/m^2), diabetes and hypertension. A *P*-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of study participants

Table 1 outlines the baseline characteristics of 48,054 participants stratified by UHR quartiles. The average age of the participants was 46.99 ± 16.85 years, and 51.8% of them were women. During a mean follow-up of 8.05 ± 5.17 years, the mortality of all-cause, CVD and malignant neoplasms were 10.9%, 2.7% and 2.5%, respectively. Average UHR in the enrolled patients was 5.4 ± 1.42. Participants with higher UHR level tended to be older, male, obese, and had a higher prevalence of comorbidities. They exhibited significantly higher all-cause and CVD mortality rates. Among all subjects, there were 7796 patients with diabetes, 17547 patients with obesity, and 5191 patients with CVD. Detailed characteristics of patients with diabetes, obesity and CVD are provided in Supplementary Tables 1–3 of the Supplementary Material.

Relationships of UHR level with mortality

Table 2 presents the results of Cox regression analysis, revealing a positive association between UHR levels and all-cause and CVD

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TABLE 1 Baseline characteristics of participants.

	Overal	The UHR quartiles[a]				*P*
		≤7.54	7.54-10.43	10.43-14.19	>14.19	
n (cases)	202156431.6	51971562.8	49440178.08	50561106.09	50183584.61	
Gender [Female (%)]	104687265.4 (51.8)	44827046.3 (86.3)	30468895.3 (61.6)	19284634.1 (38.1)	10106689.7 (20.1)	<0.001
Age (years)	46.99 ± 16.85	46.6 ± 16.63	47 ± 17.2	47.38 ± 16.85	47.01 ± 16.73	0.058
Race (%)						<0.001
Mexican American	16644088.2 (8.2)	3648695.5 (7.0)	4225619.2 (8.5)	4453138.1 (8.8)	4316635.5 (8.6)	
Other race	25192744.8 (12.5)	6153615.3 (11.8)	6162769.6 (12.5)	6312241.4 (12.5)	6564118.4 (13.1)	
Non-Hispanic White	138834120.3 (68.7)	36185001.0 (69.6)	33174168.3 (67.1)	34545745.2 (68.3)	34929205.8 (69.6)	
Non-Hispanic Black	21485478.2 (10.6)	5984251.0 (11.5)	5877621.0 (11.9)	5249981.4 (10.4)	4373624.9 (8.7)	
Education (%)						<0.001
Less than high school	34697307.6 (17.2)	7111915.3 (13.7)	8815042.1 (17.8)	9027755.4 (17.9)	9742594.9 (19.4)	
High school	48371833.5 (23.9)	10445913.6 (20.1)	11806768.0 (23.9)	12589035.8 (24.9)	13530116.1 (27.0)	
College or above	118912435.0 (58.8)	34378002.7 (66.1)	28762629.0 (58.2)	28916889.7 (57.2)	26854913.6 (53.5)	
Missing data [c]	174855.5 (0.1)	35731.3 (0.1)	55739.0 (0.1)	27425.2 (0.1)	55960.0 (0.1)	
PIR (%)						<0.001
<1.30	39612722.5 (19.6)	8877508.5 (17.1)	10163751.9 (20.6)	10237321.0 (20.2)	10334141.1 (20.6)	
1.31-3.50	67367994.0 (33.3)	16429692.4 (31.6)	16536231.6 (33.4)	17063335.8 (33.7)	17338734.2 (34.6)	
≥3.50	80861327.2 (40.0)	22748699.6 (43.8)	19273129.9 (39.0)	19840101.9 (39.2)	18999395.8 (37.9)	
Missing data [c]	14314387.8 (7.1)	3915662.3 (7.5)	3467064.7 (7.0)	3420347.4 (6.8)	3511313.4 (7.0)	
All-cause mortality (%)	22059155.3 (10.9)	4571034.2 (8.8)	5048167.8 (10.2)	5501256.1 (10.9)	6938697.3 (13.8)	<0.001
CVD mortality (%)	5407837.3 (2.7)	999293.2 (1.9)	1110675.9 (2.2)	1400666.7 (2.8)	1897201.4 (3.8)	<0.001
Malignant neoplasms mortality (%)	5107016.4 (2.5)	1059275.7 (2.0)	1168394.9 (2.4)	1360012.7 (2.7)	1519333.1 (3.0)	<0.001
Time(years)	9.95 ± 5.65	9.95 ± 5.65	9.93 ± 5.66	9.97 ± 5.6	9.93 ± 5.67	0.946
UHR (%)	11.32 ± 5.23	5.82 ± 1.17	8.96 ± 0.83	12.15 ± 1.06	18.5 ± 4.25	<0.001
ALB(g/L)	42.77 ± 3.48	42.41 ± 3.65	42.63 ± 3.47	43 ± 3.42	43.03 ± 3.34	<0.001
ALT (U/L)	25.47 ± 22.57	20.28 ± 13.84	22.81 ± 18.97	26.54 ± 17.61	32.41 ± 33.21	<0.001
AST (U/L)	25.13 ± 16.04	23.45 ± 13.13	23.99 ± 15.93	25.45 ± 16.08	27.64 ± 18.36	<0.001
Tbil (umol/L)	11.53 ± 5.39	10.77 ± 4.9	11.22 ± 5.18	11.89 ± 5.59	12.29 ± 5.73	<0.001
GGT (IU/L)	28.54 ± 41.59	22.09 ± 33.71	25.77 ± 39.67	30.7 ± 49.34	35.78 ± 40.98	<0.001
LDH(IU/L)	133.41 ± 30.74	131.11 ± 29.48	132.86 ± 30.8	133.5 ± 29.8	136.22 ± 32.62	<0.001
BUN (mmol/L)	4.84 ± 1.93	4.41 ± 1.63	4.7 ± 1.71	4.96 ± 1.91	5.28 ± 2.3	<0.001
Scr (umol/L)	77.66 ± 32.71	67.22 ± 25.1	74.49 ± 29.33	80.94 ± 30.8	88.3 ± 40.09	<0.001
eGFR (mL/min/1.73 m2)	101.79 ± 30.86	110.8 ± 34.6	103.59 ± 29.8	98.63 ± 28.03	93.88 ± 27.76	<0.001
TC (mmol/L) [b]	5.08 ± 1.08	5.16 ± 1	5.06 ± 1.06	5.05 ± 1.11	5.05 ± 1.16	<0.001
TG (mmol/L) [b]	1.5 ± 1.33	1 ± 0.54	1.24 ± 0.99	1.55 ± 1.08	2.22 ± 1.96	<0.001
LDL-C (mmol/L) [b]	3 ± 0.92	2.86 ± 0.87	3.01 ± 0.9	3.08 ± 0.95	3.04 ± 0.95	<0.001
BMI (kg/m2)	28.77 ± 6.72	25.49 ± 5.4	28.15 ± 6.33	29.76 ± 6.7	31.79 ± 6.74	<0.001

(Continued)

TABLE 1 Continued

	Overal	The UHR quartiles[a]				*P*
		≤7.54	7.54-10.43	10.43-14.19	>14.19	
HbA1c (%)	5.57 ± 0.92	5.4 ± 0.8	5.54 ± 0.89	5.63 ± 0.94	5.72 ± 0.99	<0.001
FPG (mmol/L) [b]	5.84 ± 1.72	5.47 ± 1.44	5.75 ± 1.65	5.99 ± 1.85	6.16 ± 1.84	<0.001
Diabetes (%)						<0.001
No	178002180.0 (88.1)	48762598.4 (93.8)	44370413.9 (89.7)	43636421.7 (86.3)	41232746.0 (82.2)	
Yes	24154251.6 (11.9)	3208964.4 (6.2)	5069764.2 (10.3)	6924684.4 (13.7)	8950838.7 (17.8)	
Hypertension (%)						<0.001
No	103046265.1 (51.0)	32637494.8 (62.8)	26753863.4 (54.1)	23683920.8 (46.8)	19970986.1 (39.8)	
Yes	99074121.1 (49.0)	19327299.7 (37.2)	22670648.8 (45.9)	26866702.6 (53.1)	30209470.0 (60.2)	
Missing data [c]	36045.4 (0.0)	6768.3 (0.0)	15666.0 (0.0)	10482.7 (0.0)	3128.5 (0.0)	
Smoking status (%)						<0.001
Current smokers	43201648.6 (21.4)	9264230.9 (17.8)	10637060.8 (21.5)	11508643.9 (22.8)	11791713.0 (23.5)	
Former smokers	50238986.9 (24.9)	11417592.6 (22.0)	11043733.2 (22.3)	13493747.9 (26.7)	14283913.2 (28.5)	
Non-smokers	108606961.8 (53.7)	31262680.8 (60.2)	27749339.5 (56.1)	25517851.2 (50.5)	24077090.4 (48.0)	
Missing data [c]	108834.1 (0.1)	27058.4 (0.1)	10044.6 (0.0)	40863.1 (0.1)	30868.0 (0.1)	
Alcohol consumption (%)						<0.001
Heavy drinking	35474457.6 (17.5)	10779188.1 (20.7)	9093401.0 (18.4)	8312898.3 (16.4)	7288970.0 (14.5)	
Moderate drinking	17278527.1 (8.5)	3599253.4 (6.9)	4072538.6 (8.2)	4835566.2 (9.6)	4771168.9 (9.5)	
Non-drinkers	139969963.9 (69.2)	34922824.2 (67.2)	33785477.7 (68.3)	35244158.6 (69.7)	36017503.4 (71.8)	
Missing data [c]	9433483.1 (4.7)	2670297.1 (5.1)	2488760.8 (5.0)	2168482.9 (4.3)	2105942.2 (4.2)	
Physical activity (%)						<0.001
Active	58358328.6 (28.9)	17493954.7 (33.7)	14669261.3 (29.7)	13802646.8 (27.3)	12392465.7 (24.7)	
Insufficiently	46854957.4 (23.2)	11901223.9 (22.9)	11127554.4 (22.5)	12120485.6 (24.0)	11705693.5 (23.3)	
Inactive	83188212.5 (41.2)	18905683.3 (36.4)	20173830.4 (40.8)	21334164.5 (42.2)	22774534.3 (45.4)	
Missing data [c]	13754933.0 (6.8)	3670700.8 (7.1)	3469531.9 (7.0)	3303809.2 (6.5)	3310891.1 (6.6)	
CVD (%)						<0.001
No	184957521.7 (91.5)	49261629.1 (94.8)	45836575.0 (92.7)	45831107.8 (90.6)	44028209.8 (87.7)	
Yes	17184657.3 (8.5)	2709251.1 (5.2)	3600701.2 (7.3)	4725269.7 (9.3)	6149435.2 (12.3)	
Missing data [c]	14252.6 (0.0)	682.6 (0.0)	2901.9 (0.0)	4728.6 (0.0)	5939.5 (0.0)	

[a]Values are mean (standard deviation) for continuous variables and percentages for categorical variables.
[b]Numbers may not sum to the total number of participants due to missing data.
[c]The total did not sum to 100% because small proportions of participants chose "prefer not to answer" or "do not know".

mortality, adjusting for covariates. No significant association was found between UHR and malignant neoplasms mortality. The hazard ratios (HRs) and 95% confidence intervals (CIs) in the highest quintile were 1.16 (95% CI: 1.05, 1.29) for all-cause mortality and 1.2 (95% CI: 1.00, 1.45) for CVD mortality, indicating increasing risk with higher UHR quartiles. Interestingly, not all the quadratic term for UHR was not statistically significant, suggesting a non-linear association between UHR and mortality.

Patients in the highest quintile of diabetes, obesity, and CVD exhibited significantly elevated risks for both all-cause and CVD mortality compared to those in the lowest quintile. Specifically, HRs were 1.32 (95% CI: 1.11, 1.57) for all-cause mortality and 1.38 (95% CI: 1.01, 1.9) for CVD mortality in diabetes patients (Supplementary Table 4); 1.32 (95% CI: 1.10, 1.58) and 1.55 (95% CI: 1.06, 2.28) in obesity patients (Supplementary Table 5); and 1.29 (95% CI: 1.10, 1.50) and 1.38 (95% CI: 1.06, 1.79) in CVD patients (Supplementary Table 6), respectively.

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The dose-response association of UHR level with mortality

Due to Cox regression analysis indicated a non-linear relationship between UHR and the risk of all-cause and CVD mortality, we employed a restricted cubic splines models to further investigate the correlation. After adjusting for multiple potential confounders, we found a non-linear relationship between UHR and all-cause (*P*-nonlinearity < 0.0001) (Figure 2A) and CVD (*P*-nonlinearity = 0.018) (Figure 2B) in general population and different subgroup (Supplementary Figure 1).

Using Kaplan-Meier analysis, we identified critical thresholds of 12.4 for all-cause mortality and 10.7 for CVD mortality. Analysis of adjusted Cox-regression survival estimates across UHR groups, stratified by these thresholds, demonstrated significant dose-dependent increases in both all-cause (adjusted HR: 1.16, 95% CI: 1.09, 1.24, $P < 0.0011$) and CVD mortality (adjusted HR: 1.2, 95% CI: 1.05, 1.37, $P = 0.0064$). Notably, survival rates were notably lower in the high UHR group, as summarized in Table 3.

In the subgroup analysis, adjusted Cox-regression survival analysis demonstrated significant and dose-dependent increases in both all-cause and CVD mortality among UHR groups stratified by individual thresholds. Specifically, for the diabetes subgroup, the HRs were 1.32 (95% CI: 1.15, 1.51) for all-cause mortality and 1.5 (95% CI: 1.18, 1.89) for CVD mortality compared to the low group (Supplementary Table 7). Comparable trends were observed in the obese and CVD subgroups, with adjusted HRs of 1.22 (95% CI: 1.08, 1.37) for all-cause mortality and 1.49 (95% CI: 1.17, 1.9) for CVD mortality in obese patients (Supplementary Table 8), and 1.37 (95% CI: 1.16, 1.62) for all-cause mortality and 1.46 (95% CI: 1.21, 1.77) for CVD mortality in CVD patients (Supplementary Table 9).

Stratified analyses

Stratified analyses demonstrated the disadvantage of higher UHR (≥ 12.4 for all-cause mortality) versus lower UHR (< 12.4) was consistent across subgroups in the general population (Figure 3).

TABLE 2 Associations of serum UHR with mortality in US adults.

All-cause mortality	Mode 1			Mode 2			Mode 3		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
UHR	1.03	1.03,1.04	<0.001	1.03	1.02,1.04	<0.001	1.02	1.01,1.02	<0.001
Q1	Reference								
Q2	1.16	1.07,1.26	0.0002	0.99	0.91,1.08	0.895	0.91	0.83,0.99	0.0366
Q3	1.24	1.14,1.34	<0.001	1.03	0.95,1.13	0.478	0.93	0.84,1.02	0.1182
Q4	1.57	1.45,1.71	<0.001	1.39	1.26,1.54	<0.001	1.16	1.05,1.29	0.0052
P for trend			<0.001			<0.001			0.0007
CVD mortality									
UHR	1.05	1.03,1.06	<0.001	1.05	1.04,1.06	<0.001	1.03	1.02,1.04	<0.001
Q1	Reference								
Q2	1.17	1,1.37	0.0525	0.99	0.84,1.16	0.8633	0.82	0.69,0.98	0.026
Q3	1.44	1.23,1.68	<0.001	1.2	1.02,1.41	0.0301	0.94	0.79,1.12	0.4795
Q4	1.97	1.68,2.31	<0.001	1.76	1.48,2.08	<0.001	1.2	1,1.45	0.0463
P for trend			<0.001			<0.001			0.0038
Malignant neoplasms mortality									
UHR	1.03	1.02,1.04	<0.001	1.01	1,1.03	0.0299	1.01	1,1.02	0.169
Q1	Reference								
Q2	1.16	0.95,1.42	0.1446	0.94	0.77,1.15	0.563	0.9	0.74,1.09	0.27
Q3	1.32	1.11,1.57	0.0018	0.97	0.81,1.17	0.771	0.92	0.76,1.12	0.424
Q4	1.49	1.23,1.8	<0.001	1.1	0.91,1.34	0.319	1.01	0.82,1.24	0.94
P for trend			<0.001			0.247			0.746

multivariate weighted Cox proportional hazards regression models with three models to control for confounding factors.
Model 1 was unadjusted;
Model 2 was adjusted for age, gender and race;
Model 3 was adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes and hypertension.

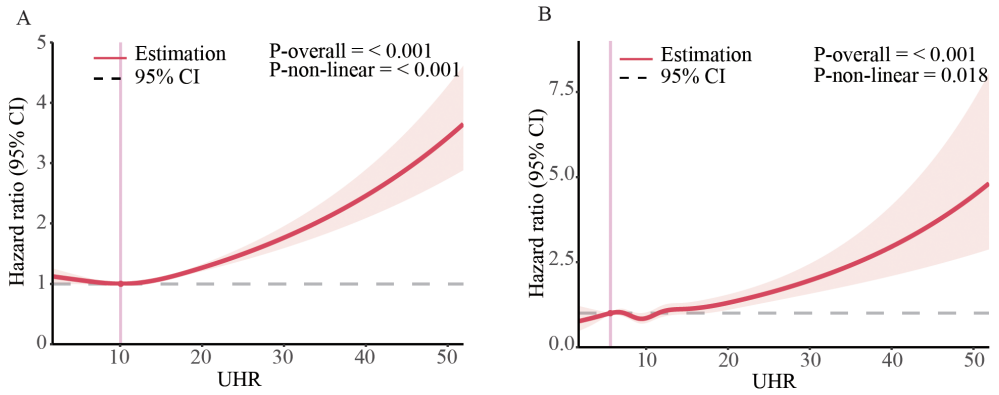

FIGURE 2
Dose-response associations of UHR with all-cause, and CVD mortality in US adults. Association between UHR and all-cause **(A)** and CVD mortality **(B)** in general population. The associations were examined by multivariable Cox regression models with restricted cubic splines. HRs adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes and hypertension except the corresponding stratification variable. Solid lines represent estimates of HRs and dashed lines represent 95% CIs.

Significant interactions were observed between UHR and stratified variables, particularly gender, BMI, education, smoking, alcohol use, and hypertension. subgroup analysis revealed a strong association between UHR and all-cause mortality among female patients aged over 50. Similarly, the disadvantage of higher UHR (≥ 10.7 for CVD mortality) compared to lower UHR (< 10.7) was consistent across subgroups (Figure 4), with significant interactions based on gender, smoking, and alcohol intake. These findings underscore the importance of considering multiple factors when assessing the impact of UHR on mortality outcomes.

The stratified analyses on diabetes subgroup model revealed significant interactions between sex groups for all-cause mortality, and age categories, education level, and smoking status for CVD mortality (Supplementary Figures 2, 3). The stratified analyses on obesity subgroup model revealed significant interactions between sex groups, education level, and smoking status for all-cause mortality, and sex groups, education level, and diabetes status for CVD mortality (Supplementary Figures 4, 5). The stratified analyses on CVD subgroup model revealed significant interactions between sex groups and education level for all-cause mortality, and education level for CVD mortality (Supplementary Figures 6, 7).

Discussion

To our knowledge, this is the first study to investigate the relationship between the UHR with all-cause and CVD mortality among US general population, the current study demonstrated that higher UHR levels are associated with increased risks of both types of mortality. Kaplan-Meier analysis identified thresholds of 12.4 and 10.7 for all-cause and CVD mortality, respectively. Our results underscore the predictive power of UHR for cardiovascular and overall mortality.

Studies conducted by Yu et al. have investigated the association between UHR and all-cause/CVD mortality among peritoneal dialysis (PD) patients. Their findings revealed that patients with

TABLE 3 Threshold effect analysis of UHR on mortality in US patients.

General population			
All-cause mortality	HR	95% CI	*P* value
UHR	1.02	1.02,1.03	<0.001
Low group: UHR<12.4	Reference		
High group: UHR ≥12.4	1.16	1.09,1.24	<0.001
CVD mortality			
UHR	1.03	1.02,1.04	<0.001
Low group:UHR<10.7	Reference		
High group: UHR ≥10.7	1.2	1.05,1.37	0.0064

Cox proportional hazards models were used to estimate HR and 95% CI. Adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes and hypertension.

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Variable	Count	Percent	HR (95% CI)	*P* value	*P* for interaction
Overall	48054	100	1.35 (1.27 to 1.43)	<0.001	
sex					<0.001
Male	23160	48.2	0.98 (0.90 to 1.06)	0.623	
Female	24894	51.8	2.07 (1.87 to 2.29)	<0.001	
Age					0.28
<30	8369	17.4	2.13 (1.33 to 3.42)	0.002	
30-40	8196	17.1	1.43 (1.01 to 2.03)	0.043	
40-50	8133	16.9	1.43 (1.08 to 1.90)	0.013	
≥50	23356	48.6	1.32 (1.23 to 1.42)	<0.001	
Race					0.103
Mexican American	8556	17.8	1.27 (1.06 to 1.52)	0.011	
Non–Hispanic White	21425	44.6	1.36 (1.27 to 1.45)	<0.001	
Non-Hispanic Black	9682	20.1	1.52 (1.34 to 1.72)	<0.001	
Other Race	8391	17.5	1.17 (0.98 to 1.40)	0.088	
BMI					0.003
<25	14186	29.5	1.63 (1.45 to 1.82)	<0.001	
25-30	16321	34	1.26 (1.14 to 1.40)	<0.001	
≥30	17547	36.5	1.29 (1.16 to 1.43)	<0.001	
Education					0.016
Less than high school	12881	26.8	1.31 (1.21 to 1.42)	<0.001	
High school	11087	23.1	1.12 (0.98 to 1.29)	0.098	
College or above	24029	50	1.42 (1.30 to 1.56)	<0.001	
Missing data	57	0.1			
Family income level					0.205
<1.30	13451	28	1.24 (1.10 to 1.40)	<0.001	
1.31-3.50	16714	34.8	1.40 (1.28 to 1.54)	<0.001	
≥3.50	13747	28.6	1.35 (1.18 to 1.53)	<0.001	
Missing data	4142	8.6	1.19 (1.03 to 1.38)	0.017	
Diabetes					0.582
No	40258	83.8	1.20 (1.11 to 1.29)	<0.001	
Yes	7796	16.2	1.25 (1.12 to 1.40)	<0.001	
Hypertension					<0.001
No	22558	47	1.44 (1.27 to 1.63)	<0.001	
Yes	25485	53	1.07 (1.00 to 1.15)	0.058	
CVD					0.055
No	42858	89.2	1.21 (1.13 to 1.30)	<0.001	
Yes	5191	10.8	1.06 (0.94 to 1.18)	0.342	
Alcohol intake					0.003
Heavy drinking	6836	14.2	0.98 (0.81 to 1.18)	0.845	
Moderate drinking	3843	8	1.19 (0.96 to 1.46)	0.108	
Non drinkers	34684	72.2	1.42 (1.32 to 1.53)	<0.001	
Missing data	2691	5.6	1.41 (1.07 to 1.86)	0.014	
Smoking status					0.049
Current smokers	9998	20.8	1.12 (0.97 to 1.30)	0.128	
Former smokers	11915	24.8	1.42 (1.28 to 1.56)	<0.001	
Non smokers	26103	54.3	1.29 (1.17 to 1.42)	<0.001	

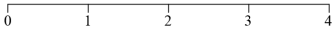

FIGURE 3
Forest plot of Stratified analyses of UHA and all-cause mortality in general population. HRs adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes and hypertension except the corresponding stratification variable.

higher UHR exhibited an elevated risk of both all-cause and cardiovascular mortality, particularly among those aged 65 and older (39). Our study aligns with this evidence, further validating the predictive value of UHR for mortality. Meanwhile, previous studies have shown that UHR is a reliable marker for CVD risk across patient groups. Elevated UHR predicts increased risk of adverse cardiovascular events and CVD mortality, as demonstrated by studies on acute myocardial infarction (22), coronary chronic total occlusion (19), and ischemic heart disease (17). Our study further confirms the correlation between UHR and risk of CVD mortality across diverse patient groups, emphasizing the significance of UHR as a predictor of cardiovascular disease outcomes.

Although the precise biological mechanisms linking UHR index to mortality remain elusive, insulin resistance (IR) is a potential key pathway. IR, characterized by reduced insulin sensitivity and responsiveness, can trigger oxidative stress, exacerbate inflammation, promote foam cell formation, impair endothelial function, and encourage smooth muscle cell proliferation (48). Persistent IR can also increase sympathetic nervous system activity, renal sodium retention, and blood pressure, leading to vascular and renal damage (49). These pathological changes contribute to CVD development, progression, and poor prognosis. Multiple studies suggest a correlation between UHR and IR, with Xu et al. (26) finding a positive association between UHR and HOMA-IR in type 2 diabetes patients, and Dağ et al. (50) observing a link between high UHR levels and obesity/IR in adolescents. This suggests that UHR may influence all-cause and cardiovascular mortality through IR. Meanwhile, our study, in alignment with numerous previous investigations (21, 26–28, 30, 31, 50, 51), further confirms that an increase in UHR corresponds to a gradual elevation in multiple risk factors for CVD and IR, including BMI, FBG, HbA1c, TG, TC and LDL. Additionally, UHR has been associated with a spectrum of metabolic-inflammatory diseases, ranging from diabetes mellitus (31, 52), metabolic syndrome (53), and NAFLD (35, 36, 38, 54). Collectively, these findings suggest that the association between UHR and adverse outcomes is primarily explained by the presence of traditional CVD and IR risk factors.

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Variable	Count	Percent	HR (95% CI)	*P* value	*P* for interaction
Overall	48054	100	1.56 (1.40 to 1.74)	<0.001	
sex					<0.001
Male	23160	48.2	1.10 (0.95 to 1.28)	0.211	
Female	24894	51.8	2.46 (2.07 to 2.92)	<0.001	
Age					0.58
<30	8369	17.4	3.41 (0.98 to 11.81)	0.053	
30-40	8196	17.1	1.26 (0.53 to 3.01)	0.601	
40-50	8133	16.9	1.91 (1.11 to 3.28)	0.019	
≥50	23356	48.6	1.54 (1.35 to 1.75)	<0.001	
Race					0.385
Mexican American	8556	17.8	1.71 (1.12 to 2.59)	0.012	
Non–Hispanic White	21425	44.6	1.60 (1.40 to 1.83)	<0.001	
Non-Hispanic Black	9682	20.1	1.66 (1.31 to 2.11)	<0.001	
Other Race	8391	17.5	1.04 (0.65 to 1.69)	0.861	
BMI					0.621
<25	14186	29.5	1.57 (1.22 to 2.02)	<0.001	
25-30	16321	34	1.35 (1.11 to 1.64)	0.003	
≥30	17547	36.5	1.52 (1.24 to 1.86)	<0.001	
Education					0.287
Less than high school	12881	26.8	1.44 (1.21 to 1.71)	<0.001	
High school	11087	23.1	1.34 (1.05 to 1.70)	0.017	
College or above	24029	50	1.67 (1.38 to 2.04)	<0.001	
Missing data	57	0.1			
Family income level					0.365
<1.30	13451	28	1.31 (1.05 to 1.63)	0.015	
1.31-3.50	16714	34.8	1.55 (1.31 to 1.83)	<0.001	
≥3.50	13747	28.6	1.82 (1.39 to 2.38)	<0.001	
Missing data	4142	8.6	1.51 (1.07 to 2.13)	0.018	
Diabetes					0.469
No	40258	83.8	1.33 (1.16 to 1.53)	<0.001	
Yes	7796	16.2	1.47 (1.20 to 1.80)	<0.001	
Hypertension					0.106
No	22558	47	1.62 (1.22 to 2.16)	0.001	
Yes	25485	53	1.22 (1.07 to 1.40)	0.003	
CVD					0.166
No	42858	89.2	1.35 (1.15 to 1.58)	<0.001	
Yes	5191	10.8	1.13 (0.95 to 1.35)	0.17	
Alcohol intake					0.03
Heavy drinking	6836	14.2	1.18 (0.77 to 1.82)	0.445	
Moderate drinking	3843	8	0.99 (0.70 to 1.40)	0.954	
Non drinkers	34684	72.2	1.69 (1.47 to 1.94)	<0.001	
Missing data	2691	5.6	1.21 (0.72 to 2.05)	0.476	
Smoking status					0.037
Current smokers	9998	20.8	1.16 (0.86 to 1.57)	0.329	
Former smokers	11915	24.8	1.97 (1.60 to 2.42)	<0.001	
Non smokers	26103	54.3	1.38 (1.16 to 1.63)	<0.001	

FIGURE 4
Forest plot of Stratified analyses of UHA and CVD mortality in general population. HRs adjusted for age, gender, race, education level, family income level, BMI, smoking status, alcohol intake, diabetes and hypertension except the corresponding stratification variable.

We further studied the population with diabetes, obesity, and CVD separately, and the results showed that there was still a nonlinear relationship between the UHR index and the all-cause mortality and CVD mortality of the population with diabetes, obesity, and CVD. Among these different populations, the diagnostic predictive value of UHR is higher than that of the general population. Taken together, our findings support the utility of the UHR as a reliable and accurate indicator of all-cause and CVD mortality in the real world.

To fully appreciate the research findings, acknowledging the limitations of this cross-sectional study is paramount. Firstly, causality cannot be definitively established, necessitating further cohort studies to confirm the results. Secondly, cross-sectional studies, although valuable, are susceptible to confounding variables that could potentially bias the results, thereby affecting the interpretation of the findings. Although attempts were made to account for these factors, unknown variables or biases may still exist, leading to inaccurate results. Therefore, a cautious approach is warranted when interpreting the findings, requiring further validation under different conditions. At last, this analysis only examines the prognostic value of the UHR, and it is unclear whether changes in the UHR during follow-up also predict mortality, which requires further investigation.

In conclusion, our study highlights the UHR as a key predictor of all-cause and CVD mortality across different populations. Measuring UHR could aid risk assessment and prognosis. Future research should explore interventions targeting UHR for improved outcomes.

Data availability statement

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

Ethics statement

The studies involving humans were approved by The Centers for Disease Control and Prevention (CDC) and the National Center

for Health Statistics (NCHS) research Ethics Review 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

ZL: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. QL: Data curation, Formal analysis, Funding acquisition, Writing – original draft. ZY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1417485/full#supplementary-material

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Gender-specific correlations between remnant cholesterol and severe abdominal aortic calcification in American adults

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Background: Remnant cholesterol (RC) predicts cardiovascular risk and is associated with a range of diseases, including asthma, hypertension, depression, periodontitis, and alcoholic fatty liver disease. However, its correlation with abdominal aortic calcification (AAC) has not been reported.

Methods: Using a cross-sectional approach, this study examined data from the 2013-2014 National Health and Nutrition Examination Survey (NHANES) cycle. Multiple logistic regression, generalized summation models, and subgroup analyses were used in examining the correlation between RC and the prevalence of severe AAC.

Results: The mean age of participants in this study was 57.70 ± 11.73 years, with 142 individuals (9.67%) suffering from severe AAC. The median RC was 0.52 mmol/L (Q1-Q3, 0.36-0.75 mmol/L). Among female participants, a significant positive correlation was observed between RC and severe AAC (per natural log [RC] increment: 2.14; 95% CI, 1.07-4.27). Smooth curve fitting and threshold effect analysis revealed a saturation effect at an RC level of 0.57 mmol/L. Conversely, in male participants, no significant correlation was found between RC and the prevalence of severe AAC (per natural log [RC] increment: 0.88; 95% CI, 0.43-1.78). Our findings suggest a significant interaction between gender and RC in relation to severe AAC (*P* for interaction = 0.0042).

Conclusions: Higher RC levels were significantly associated with an increased prevalence of severe AAC in women.

KEYWORDS

remnant cholesterol, cholesterol, gender differences, NHANES, abdominal aortic calcification

Background

Calcification typically first manifests in the aorta, and its prevalence increases with age (1). The Framingham Heart Study revealed that fewer than one-sixth of participants aged 45 displayed detectable signs of abdominal aortic calcification (AAC). By the age of 65, the prevalence of AAC increased to approximately 90% (2). The MESA (Multi-Ethnic Study of Atherosclerosis) study further showed that AAC prevalence varied from 34% in the 45-54 age group to 94% in those aged 75-84 (3). AAC serves as a potential indicator of subclinical atherosclerosis and is associated with a heightened relative risk of various outcomes, including coronary and cerebrovascular events, overall cardiovascular incidents, and cardiovascular-related mortality (4, 5). Its association with overall mortality is more pronounced than its association with coronary artery calcification (CAC) (6). Patients with severe AAC exhibit significantly higher absolute and relative risks for cardiovascular events, fatal cardiovascular incidents, and all-cause mortality compared to those with no or minimal AAC (7).

Remnant cholesterol (RC) encompasses the cholesterol found in triglyceride-rich lipoproteins such as chylomicron remnants, as well as in very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins (IDL) (8). Its potential value in predicting cardiovascular risk is garnering attention, positioning it as a new therapeutic target in the era of "beyond low-density lipoprotein cholesterol (LDL-C)" (9). Moreover, RC is linked to a variety of diseases, including asthma, hypertension, depression, periodontitis, and non-alcoholic fatty liver disease (NAFLD) (10–15). However, its correlation with AAC remains unreported.

Data from the 2013 to 2014 National Health and Nutrition Examination Survey (NHANES), encompassing a wide range of American adults, were analyzed to study the relationship between RC and severe AAC. This analysis also includes an exploration of potential modifying factors that may influence the relationship between RC and severe AAC.

Methods

Study population

The NHANES serves as a comprehensive database that captures the health and nutritional status of both children and adults in the United States. All participants provided informed consent, and the program was approved by an ethical review board. The present study analyzed data from the 2013-2014 cycle, including a total of 10,175 participants. Initially, subjects younger than 20 years of age were excluded from the study. In addition, participants lacking data on high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and LDL-C, or without AAC score measurements, were also excluded. Consequently, 1,469 subjects remained eligible for analysis. Figure 1 outlines the study's inclusion and exclusion criteria.

Study variables

The variable of interest, RC, is calculated using the formula RC = TC - LDL-C - HDL-C.

Severe AAC was defined as the outcome variable. Individuals aged 40 and above underwent dual-energy X-ray absorptiometry (DXA) scans. Participants were excluded based on the following criteria (1): pregnancy (2); recent exposure to radiographic contrast agents (barium) within the preceding 7 days (3); weight greater than 450 pounds; or (4) scoliosis with Harrington rods in the spine. Severe AAC was diagnosed when the Kauppila score exceeded 6.

Covariates were included in the final multivariate logistic regression models as potential confounders if they altered the RC estimates for severe AAC by more than 10% or were recognized as traditional risk factors for AAC. The included covariates encompassed various demographic, health, and biochemical indicators, including sex, age, race, education level, body mass index (BMI), presence of hypertension or diabetes mellitus, alcohol use, smoking status, and levels of creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), HDL-C, 25-hydroxyvitamin D (25[OH]D), and uric acid (UA). Hypertension status was determined by questionnaire. Diabetes mellitus diagnosis was based on one or more of the following criteria: determination through a questionnaire, fasting plasma glucose (FPG) levels of 7.0 mmol/L or higher, random glucose levels exceeding 11.1 mmol/L, HbA1c above 6.5%, or a 2-hour oral glucose tolerance test (OGTT) showing glucose levels of 11.1 mmol/L or more. BMI was classified into three categories: under 25 kg/m^2 as normal weight, 25-29.9 kg/m^2 as overweight, and 30 kg/m^2 or higher as obese. Smoking was defined as having smoked more than 100 cigarettes in a lifetime, and alcohol consumption was defined as consuming more than 12 drinks per year.

Statistical analysis

Statistical analyses followed CDC guidelines. Sample weights were applied to account for the complex probability sampling of NHANES and to ensure representative adequacy, especially considering the oversampling in survey cycles.

The data were transformed to natural logarithms due to the non-normal distribution of RC. Descriptive analyses employed weighted t-tests and chi-square tests to evaluate differences among participants stratified by RC tertiles. Multiple logistic regression analyses were conducted to investigate the association between RC and severe AAC. We developed three analytical models: Model 1, which remained unadjusted; Model 2, which included adjustments for gender (only for the total population), age, and race; and Model 3, which incorporated corrections for all the previously mentioned covariates. To improve the robustness of the analysis, a sensitivity analysis was conducted by converting RC into categorical variables. The median value of each category of the independent variable was included in the model as a continuous variable to determine linear trends, and subsequent subgroup

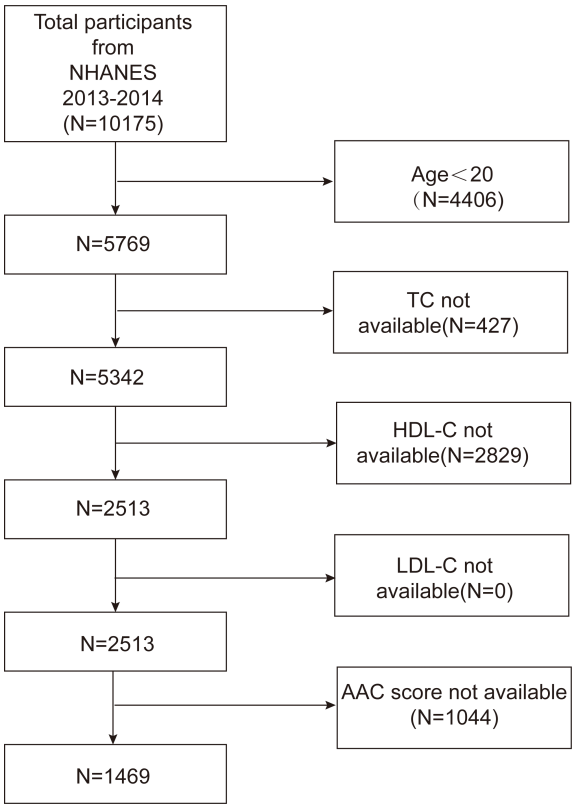

FIGURE 1
Flowchart of participant selection. TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AAC, abdominal aortic calcification.

analyses were conducted. To detect any potential nonlinear associations, a generalized additive model was used, supplemented by smoothed curve fitting. Significant trend deviations were identified at inflection points using a two-stage linear regression approach. Statistical significance was defined as $P < 0.05$. All analyses and visualizations were performed using R (version 4.2.0) and EmpowerStats (version 4.0).

Results

Subject characteristics

The demographic and main clinical characteristics of the study population are summarized as follows. The mean age of participants was 57.70 ± 11.73 years. Among the participants, 142 individuals (9.67%) had a diagnosis of severe AAC. The overall sample consisted of 707 males (48.22%) and 762 females (51.78%). Of the participants, 6.88% were Mexican American, 4.62% were other Hispanic, 71.75% were non-Hispanic White, 9.58% were non-Hispanic Black, and 7.18% were from other racial groups. The mean age and prevalence of severe AAC in male participants were 57.37 ± 11.62 years and 9.48%, respectively. In female participants, the mean age and prevalence of severe AAC were 58.02 ± 11.82 years and 9.84%, respectively.

Table 1 presents the demographic data of the study population according to tertiles of RC among male and female participants in the 2013-2014 NHANES. In males, higher RC was more common in younger adults, smokers, individuals with hypertension, diabetes, higher education levels, and Mexican Americans; BMI, UA, and ALT levels were also higher. Female participants with moderate to high RC were more likely to be older, have hypertension, diabetes, severe AAC, to be smokers, and to be Mexican Americans. They also had higher levels of BMI, UA, AST, and ALT compared to participants with low RC.

No significant differences were observed in alcohol intake, Cr, or 25(OH)D levels across the three RC tertiles in both male and female participants. Additionally, there were no statistically significant differences in AST levels or severe AAC among the three groups of male participants, nor in education levels among the three groups of female participants.

Association between RC and severe AAC

The detailed outcomes of the multivariate analysis are presented in Table 2. In female patients, there was a significant positive correlation between RC and severe AAC (per natural log [RC] increment: OR, 2.14; 95% CI 1.07-4.27). Upon categorizing continuous RC into tertiles, the adjusted ORs for the second and

TABLE 1 Baseline characteristics of study participants.

Characteristics	Males			*P* value	Females			*P* value
	RC (mmol/L) tertiles				RC (mmol/L) tertiles			
	Tertiles 1	Tertile 2	Tertile 3		Tertiles 1	Tertile 2	Tertile 3	
RC range	< 0.42	0.42–0.65	> 0.65		< 0.39	0.39–0.63	> 0.63	
N	235	236	236		252	256	254	
Age, years	58.64 ± 11.62	57.73 ± 11.56	55.88 ± 11.51	0.0266	56.01 ± 11.95	58.22 ± 11.97	59.87 ± 11.21	0.0010
Race				0.0010				0.0112
Mexican American, %	2.86	10.56	7.40		5.32	7.27	8.28	
Other Hispanic, %	2.51	5.69	3.69		3.97	5.28	6.65	
Non-Hispanic White, %	75.58	67.29	74.80		68.41	69.63	74.27	
Non-Hispanic Black, %	14.21	9.05	5.67		14.16	10.88	3.65	
Other races, %	4.84	7.41	8.45		8.14	6.94	7.14	
Education level				0.0118				0.0600
Less than 9th grade, %	4	7.03	5.46		3.91	4.42	5.67	
9-11th grade, %	11.62	8.45	12.22		8.88	13.05	15.90	
High school graduate, %	25.62	18.65	18.10		17.15	22.69	20.97	
Some college or Associate of Arts degree, %	18.81	32.34	31.55		34.36	34.68	32.54	
College graduate or above, %	39.96	33.54	32.67		35.69	25.17	24.93	
BMI, kg/m^2	26.09 ± 3.82	27.55 ± 3.80	29.78 ± 4.53	< 0.0001	27.11 ± 6.70	28.61 ± 5.87	30.60 ± 6.02	< 0.0001
HDL-C, mmol/L	1.55 ± 0.51	1.29 ± 0.27	1.08 ± 0.24	< 0.0001	1.85 ± 0.47	1.58 ± 0.39	1.31 ± 0.30	< 0.0001
TC, mmol/L	4.52 ± 0.82	4.93 ± 1.06	5.19 ± 1.08	< 0.0001	4.86 ± 0.93	5.12 ± 0.99	5.63 ± 1.07	< 0.0001
LDL-C, mmol/L	2.66 ± 0.74	3.10 ± 0.97	3.10 ± 0.97	< 0.0001	2.72 ± 0.76	3.03 ± 0.86	3.37 ± 1.06	< 0.0001
TG, mmol/L	0.67 ± 0.16	1.17 ± 0.15	2.33 ± 0.73	< 0.0001	0.63 ± 0.15	1.11 ± 0.14	2.07 ± 0.63	< 0.0001
Cr, mmol/L	91.78 ± 73.79	92.76 ± 37.96	91.87± 30.17	0.9757	70.60 ± 31.06	70.10 ± 17.13	68.41 ± 17.31	0.5299
UA, umol/L	341.01 ± 78.08	358.88 ± 68.35	383.30 ± 79.72	< 0.0001	269.54 ± 68.48	286.64 ± 65.82	318.09 ± 80.33	< 0.0001
AST, U/L	27.16 ± 14.81	24.83 ± 8.52	26.29 ± 10.71	0.1083	22.83 ± 9.74	22.52 ± 8.14	27.22 ± 30.72	0.0189
ALT, U/L	24.98 ± 15.67	25.71 ± 11.16	29.59 ± 16.37	0.0011	20.75 ± 12.00	20.82 ± 10.38	24.20 ± 15.47	0.0028
25(OH)D, nmol/L	58.86 ± 24.98	70.70 ± 24.14	68.51 ± 20.06	0.5585	84.58 ± 36.00	81.26 ± 32.31	77.72 ± 29.72	0.0621
Diabetes, %	16.72	17.21	30.15	0.0002	7.07	19.13	23.82	< 0.0001
Hypertension, %	33.42	34.12	47.36	0.0017	39.26	49.46	60.96	< 0.0001
Drinkers, %	86.02	90.15	85.85	0.3195	70.61	61.89	64.83	0.1199
Smokers, %	48.36	57.67	58.56	0.0461	33.27	38.20	46.12	< 0.0001
Severe AAC, %	8.31	8.25	5.68	0.4433	3.11	11.68	13.50	< 0.0001

RC, remnant cholesterol; BMI, body mass index; UA, uric acid; AAC, abdominal aortic calcification; Cr, creatinine; 25(OH)D, 25-hydroxyvitamin D; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol.

third tertiles were 3.14 (95% CI: 1.32-7.46) and 3.17 (95% CI: 1.25-8.04), respectively, compared to the first tertile (*P* for trend <0.05). However, no association between RC and severe AAC was found in the overall population (OR: 1.33; 95% CI: 0.83-2.13) or in male participants (OR: 0.88; 95% CI: 0.43-1.78). Gender influenced the association between RC and severe AAC (*P* for interaction = 0.0042).

Stratified analyses for male and female participants were separately conducted to evaluate the association between RC and the prevalence of severe AAC across different subgroups (Figure 2). In both female (Figure 2A) and male (Figure 2B) participants, no significant modification of the association between RC and the prevalence of severe AAC was observed with variables such as BMI,

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TABLE 2 Association between RC and severe AAC.

RC, mmol/L	Severe AAC OR (95% CI), *P* value		
	Model 1	Model 2	Model 3
Continuous (ln RC)	1.17 (0.85, 1.62), 0.3305	1.30 (0.90, 1.89), 0.1629	1.33 (0.83, 2.13), 0.2387
Tertile 1	Reference	Reference	Reference
Tertile 2	1.26 (0.81, 1.96), 0.3128	1.33 (0.82, 2.15), 0.2421	1.37 (0.80, 2.35) 0.2552
Tertile 3	1.45 (0.94, 2.22), 0.0936	1.56 (0.97, 2.50), 0.0657	1.55 (0.86, 2.79), 0.1430
P for trend	0.0944	0.0670	0.1498
Male			
Continuous (ln RC)	0.63 (0.39, 1.01), 0.0526	0.70 (0.40, 1.21), 0.1965	0.88 (0.43, 1.78), 0.7158
Tertile 1	Reference	Reference	Reference
Tertile 2	0.65 (0.35, 1.19), 0.1643	0.69 (0.35, 1.35), 0.2771	0.77 (0.36, 1.69) 0.5216
Tertile 3	0.68 (0.37, 1.25), 0.2192	0.81 (0.41, 1.58), 0.0129	0.95 (0.40, 2.24) 0.9002
P for trend	0.2041	0.5091	0.8943
Female			
Continuous (ln RC)	2.17 (1.36, 3.46), 0.0011	2.37 (1.38, 4.07), 0.0018	2.14 (1.07, 4.27), 0.0304
Tertile 1	Reference	Reference	Reference
Tertile 2	3.33 (1.60, 6.96), 0.0013	3.40 (1.56, 7.43), 0.0021	3.14 (1.32, 7.46), 0.0094
Tertile 3	3.74 (1.81, 7.75), 0.0004	3.67 (1.68, 8.01), 0.0011	3.17 (1.25, 8.04), 0.0151
P for trend	0.0005	0.0087	0.0260
P for interaction	0.0002	0.0036	0.0042

The analytical models were defined as follows Model 1: unadjusted; Model 2: adjusted for sex, age, and race; and Model 3: sex, age, race, education, BMI, hypertension, diabetes mellitus, smoking status, drinking status, Cr, UC, HDL-C, 25(OH)D, AST, ALT.

smoking status, drinking status, hypertension, and diabetes (*P* for all interactions > 0.05). However, age was found to modify the association between RC and the prevalence of severe AAC in male subjects, a trend not observed in female subjects.

Curve fitting techniques were utilized to explore the nonlinear relationship between ln RC and severe AAC, with analyses stratified by gender, as illustrated in Figure 3. In female participants, a positive association between ln RC and the prevalence of severe AAC was observed, a pattern not evident in male participants. According to the threshold effect analysis in Table 3, this nonlinear relationship was identified exclusively in female subjects (log-likelihood ratio < 0.05). The analysis revealed a saturation effect, indicating a significant 8.19-fold increase in the prevalence of severe AAC for each unit increase in ln RC at values less than -0.56, corresponding to an RC < 0.57mmol/L (OR 8.19, 95% CI 2.06-32.53). However, at ln RC values greater than -0.56 (RC > 0.57 mmol/L), no significant correlation between ln RC and severe AAC was observed (OR 0.61, 95% CI 0.17-2.18).

Discussion

This study is the first to explore the correlation between RC and severe AAC, revealing that gender may play a modifying role in this relationship. A positive correlation between RC and the prevalence of severe AAC was observed in female participants, remaining significant even after adjusting for confounding factors such as race, age, education level, and BMI (per natural log [RC] increment: OR, 2.14; 95% CI 1.07-4.27). However, this relationship was not observed in male participants. In females, smooth curve fitting and threshold effect analysis revealed a non-linear relationship. When ln RC is less than -0.56 (equivalent to RC being less than 0.57mmol/L), each unit increase in ln RC was associated with an 8.19-fold increase in the odds of severe AAC (OR 8.19, 95% CI 2.06-32.53). Conversely, when ln RC is greater than -0.56, no correlation was found between ln RC and severe AAC (OR 0.61, 95% CI 0.17-2.18).

Prior studies have investigated the correlation between AAC and lipid profiles. One such study in a blood dialysis population found no significant link between AAC severity and levels of LDL-C, HDL-C, triglycerides, or lipoprotein (a) (16). However, different results have emerged from other research. For example, the MESA study demonstrated a significant association between elevated TC, reduced HDL-C, and an increased risk of AAC (3). Furthermore, an analysis of 1078 patients without cardiovascular disease revealed correlations between AAC and levels of HDL-C and non-HDL-C, as well as the TC to HDL-C ratio (17).

Despite these findings, the role of lipids in the progression of AAC remains uncertain. Terry JG et al. noted that, despite significant reductions in TC, triglycerides, and LDL-C, simvastatin treatment did not slow the progression of CAC or AAC (18). Similarly, a study involving 16 patients with familial hypercholesterolemia treated with high-dose statins/ezetimibe found little impact of baseline or treatment-level TC or LDL-C on AAC progression (19).

Global guidelines consistently emphasize that LDL-C is a central factor in the development of atherosclerotic cardiovascular disease (ASCVD), positioning it as a central target for prevention and treatment (20, 21). However, even after significant LDL-C reduction to recommended targets with statin therapy, the risk of recurrent cardiovascular events in patients remains higher than expected (9). This suggests the presence of other risk factors beyond LDL-C, HDL-C, hypertriglyceridemia, and lipoprotein (a). RC, including chylomicron remnants produced by the intestines and VLDL and IDL cholesterol from the liver, is transformed into triglyceride-rich remnants in circulation (22). Multiple studies have confirmed the link between RC and cardiovascular risk. For every 1 mmol/L increase in non-fasting RC, the risk of ischemic heart disease increased 2.8-fold, regardless of HDL cholesterol levels (23). In overweight or obese individuals at high risk for heart disease, triglyceride and RC levels, rather than LDL-C, are linked to

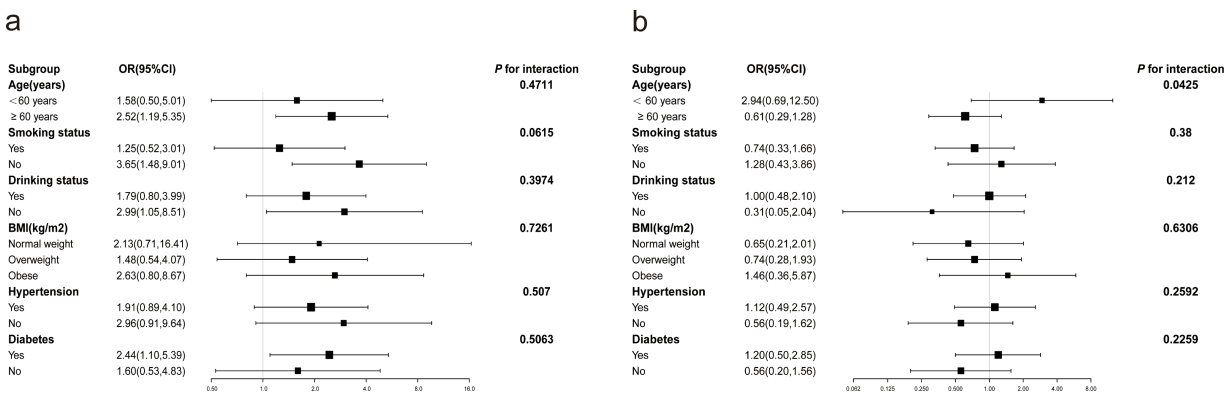

FIGURE 2
Subgroup analysis of the correlation between RC and severe AAC. Potential moderators of the association between RC and the prevalence of severe abdominal aortic calcification were stratified by sex. **(A)** Females; **(B)** Males. In addition to stratification variables, each subgroup analysis was adjusted for age, race, education, BMI, hypertension, diabetes mellitus, smoking status, drinking status, Cr, UC, HDL-C, 25(OH)D, AST, ALT.

cardiovascular outcomes, regardless of other risk factors (24). A cohort study in Denmark involving 109,574 individuals found that reducing RC to 0.8 mmol/L in individuals diagnosed with myocardial infarction/ischemic stroke could reduce recurrent major cardiovascular events by 20% in secondary prevention (9). The concentration of RC is an important predictor of cardiovascular disease risk, potentially surpassing that of LDL-C (25). However, the relationship between RC and AAC has not been investigated in prior studies.

This study revealed a significant association between elevated RC levels and increased severe AAC incidence in females, with a noted saturation effect. Subgroup analyses confirmed this stable relationship in the female subgroup. One possible explanation for the positive correlation between RC and severe AAC is that RC, similar to LDL cholesterol, infiltrates and remains in the intima-media layer of the arterial wall, leading to cholesterol accumulation, atherosclerosis, and ultimately severe calcification. Experimental studies have also identified potential mechanisms by which RC are associated with endothelial dysfunction, such as impaired vasodilatation and enhanced inflammatory response, leading to plaque rupture and thrombosis (26).

The results of the interaction test showed that there was a significant gender difference in the risk of severe AAC associated with RC, with female participants having a higher risk. Similarly, this gender difference is observed in the association between RC and conditions such as NAFLD and metabolic syndrome (15, 27). This difference is also reflected in the higher association between RC and mortality in the female subgroup compared to the male subgroup (28). The NHANES study only screened for AAC in people over the age of 40; therefore, this study focused on the middle-aged and older population. Among the baseline characteristics of the study participants, it was found that men with higher RC were younger, whereas women with higher RC were older. Thus, the increased risk of severe AAC in women with high RC may be due to estrogen deficiency in postmenopausal women. Estrogen is closely linked to

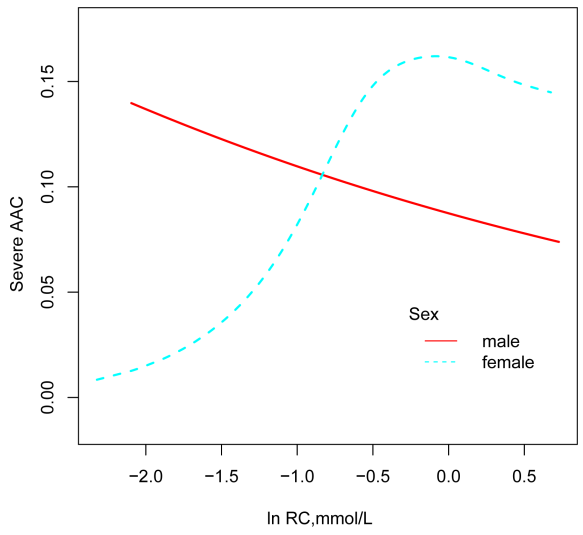

FIGURE 3
Association between RC and prevalence of severe AAC (by sex). All models were adjusted for sex, age, race, education, BMI, hypertension, diabetes mellitus, smoking status, drinking status, Cr, UC, HDL-C, 25(OH)D, AST, ALT.

TABLE 3 Threshold analysis of the effect of ln RC on severe AAC using two-piece linear regression models.

Severe AAC	OR (95%) *P* value	
	male	female
ln RC		
Inflection point	-0.67	-0.56
<Inflection point	0.55 (0.16, 1.93) 0.3493	8.19 (2.06, 32.53) 0.0028
>Inflection point	1.32 (0.42, 4.11) 0.6364	0.61(0.17, 2.18) 0.4472
Log likelihood ratio	0.384	0.014

All models were adjusted for age, race, education, hypertension, diabetes mellitus, smoking status, drinking status, Cr, UC, BMI, HDL-C, 25(OH)D, AST, ALT.

cholesterol metabolism and plays a cardioprotective role by inhibiting inflammation and atherosclerosis, ameliorating vascular damage, and reducing vascular calcification (29). Studies have found that women who have undergone bilateral salpingo-oophorectomy have a five-fold increased risk of calcification of the abdominal aorta (30). Estrogen replacement therapy greatly reduces the risk of coronary artery or aortic calcification in women (31–33). Given the lack of established normal ranges or measurement standards for RC and the need for further research to clarify its mechanisms, additional studies are urgently needed to confirm our findings and better understand the underlying processes (34, 35). As research on the relationship between RC and AAC advances, therapeutic strategies targeting RC regulation may emerge as a new area of focus.

Study strengths and limitations

This study has two significant advantages that bolster the credibility and validity of its results. First, the large sample size and the consistency between preliminary and sensitivity analysis findings underscore the robustness of the results. Secondly, RC is easily calculable and obtainable, making it particularly suitable for chronic disease risk assessment and epidemiological surveys in the general population.

However, there are limitations. First, the cross-sectional nature precludes inferences about causality. Second, despite adjustments for a wide range of previously selected confounding factors due to the observational nature of this study, other confounding factors may still exist. Considering these limitations, a carefully designed prospective cohort trial is required to validate our findings.

Conclusion

This cross-sectional study indicates a positive correlation between RC and severe AAC among American women. RC can be utilized to identify the female population at risk for severe AAC. This highlights the importance of considering gender differences in cardiovascular risk assessments and may guide future research into targeted prevention strategies.

Data availability statement

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

Ethics statement

The studies involving humans were approved by NCHS Research Ethics Review 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

LY: Writing – review & editing. XH: Writing – review & editing. SW: Writing – review & editing. SZ: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Association between a body shape index and cognitive impairment among US older adults aged 40 years and above from a cross-sectional survey of the NHANES 2011-2014

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Purpose: This research aimed to assess the correlation between the Adjusted Body Shape Index (ABSI) and the presence of abdominal aortic calcification (AAC) among middle-aged and older American adults.

Methods: Employing a cross-sectional design, this study analyzed data from the 2013-2014 National Health and Nutrition Examination Survey (NHANES), focusing on 3077 participants aged 40 and above. AAC detection was conducted using dual-energy X-ray absorptiometry (DXA). ABSI was determined based on waist circumference (WC), weight, and height data. The association between ABSI and AAC was examined through multiple linear regression, smoothed curve analysis, threshold effect evaluation, subgroup analysis, and interaction testing.

Results: The study encompassed 3077 individuals aged 40 and above. Findings indicated a noteworthy positive relationship between ABSI and AAC when adjusting various covariates. Analysis of threshold effects identified a K-point at 0.0908, showing no significant effect to its left but a significant effect to its right. Further, subgroup and interaction analyses highlighted the ABSI-AAC connection specifically within different age groups and among individuals with diabetes.

Conclusion: Higher ABSI was correlated with higher AAC score.

KEYWORDS

adjusted body size index, cognitive function, cross-sectional survey, elderly, NHANES

1 Introduction

Vascular calcification is characterized by the accumulation of calcium salts in the blood vessel walls, leading to stiffness and loss of elasticity. It is established that the calcification of coronary arteries is a predictor for the risk of cardiovascular diseases and mortality (1). Despite the commonality of calcification in vascular areas beyond the coronary arteries, the prognostic value of such calcifications has been less explored. Notably, the abdominal aorta is among the first vessels to experience calcification, typically before the coronary arteries (2, 3). The incidence of AAC is around one-third in individuals between 45 to 54 years of age and escalates to as much as 90% in those 75 years and older. For elderly patients with type 2 diabetes(T2DM) or chronic kidney disease (CKD) requiring dialysis, prevalence figures range from 84% to 97%. The link between AAC and cardiovascular events is well-documented. In individuals aged 45 to 84 years, AAC has been shown to independently correlate with cardiovascular disease mortality and is more strongly related to total mortality compared to coronary artery calcification (4). Severe AAC in older white women has been closely linked to an increased risk of atherosclerotic disease events and decreased long-term survival (5). Furthermore, AAC has been identified as an independent predictor for myocardial infarction and cardiovascular events (6). Particularly in populations with a high prevalence of AAC, such as older adults and individuals with chronic kidney disease, the presence of AAC significantly heightens the risk of future cardiovascular events and suggests a poorer prognosis. Highlighting the importance of AAC is crucial for clinicians to effectively assess and manage the cardiovascular risk of their patients (7).

Obesity has escalated into a widespread chronic condition worldwide. Data from 2015 indicate that around 603.7 million adults worldwide are classified as obese. Since 1980, obesity rates have doubled in over 70 countries and continue to rise elsewhere. A high BMI is linked to over 4 million deaths annually on a global scale, with cardiovascular diseases accounting for the majority of these fatalities (8). The global healthcare cost of obesity is estimated at $2 trillion (9). Notably, the location of body fat accumulation is variably linked to obesity-related health outcomes, with metabolic complications of obesity showing a direct association with the extent of abdominal fat (10). Although the World Health Organization (WHO) uses BMI to assess general obesity, there is no consensus on how to assess the distribution of body fat. ABSI is independent of BMI (11), and complements the optimal BMI by effectively risk stratifying between underweight, obese, and normal-weight and overweight BMI categories (12). The ABSI estimates both visceral abdominal fat and general overall adiposity and is a better predictor of premature mortality (13).

While the link between Body Mass Index (BMI) and the risk of cardiovascular disease has been the subject of considerable research, studies focusing on the ABSI are notably less common. The relationship between ABSI and AAC particularly lacks emphasis in existing research. This investigation seeks to delve into the possible correlation between ABSI and AAC, drawing upon data from NHANES. It aims to enrich the framework for evaluating cardiovascular disease risk by incorporating insights into the intricate interplay between body fat distribution and cardiovascular health. Moreover, by uncovering the potential connection between ABSI and AAC, this study contributes to a deeper comprehension of obesity's impact on the cardiovascular system. Such insights are crucial for informing the development of future clinical practices and public health initiatives.

2 Methods

2.1 Study population

NHANES is a cross-sectional analysis aimed at gathering essential health status data and information, employing a stratified, multi-stage probability sampling method within the non-institutionalized demographic. The National Center for Health Statistics (NCHS) is responsible for executing the survey. NCHS's ethical review committee has approved the study protocol, and all involved participants provided written informed consent. For this research, the 2013 to 2014 NHANES dataset was utilized, selected specifically because it was the only survey period to AAC measurements. Initially, 10,175 individuals were screened in this survey. The study excluded 1514 participants due to the absence of waist circumference data, 21 participants for lacking BMI data, and 5563 participants for missing AAC data. Consequently, 3077 participants were ultimately included in this analysis (Figure 1).

2.2 ABSI

ABSI is designed to be a dimensionless index. Although the absolute value of the ABSI is not a direct measure of obesity, it can be used in statistical analyses to compare the relative risk of abdominal obesity between different individuals or groups. ABSI was calculated by the following equal:

$$ABSI = WC / (BMI^{2/3} * Height^{1/2}).$$

2.3 Measurement of AAC

AAC was assessed using dual-energy X-ray absorptiometry (DXA). During the 2013-2014 NHANES cycle, lateral DXA scans of the thoracolumbar spine were conducted on participants aged 40 and above at the Mobile Examination Center (MEC). Individuals were excluded from DXA scanning if they were pregnant, had used a radiographic contrast agent (e.g., barium) within the last seven days, reported a weight over 450 pounds, or had scoliosis treated with Harrington rods. The scans utilized a Hologic Discovery Model A densitometer, produced by Hologic, Inc., based in Marlborough, Massachusetts, operating on Apex 3.2 software. For evaluating AAC, the AAC24 rating system was employed, dividing the anterior and posterior aorta walls into four segments each, located in front of the lumbar vertebrae from L1 to L4. These eight

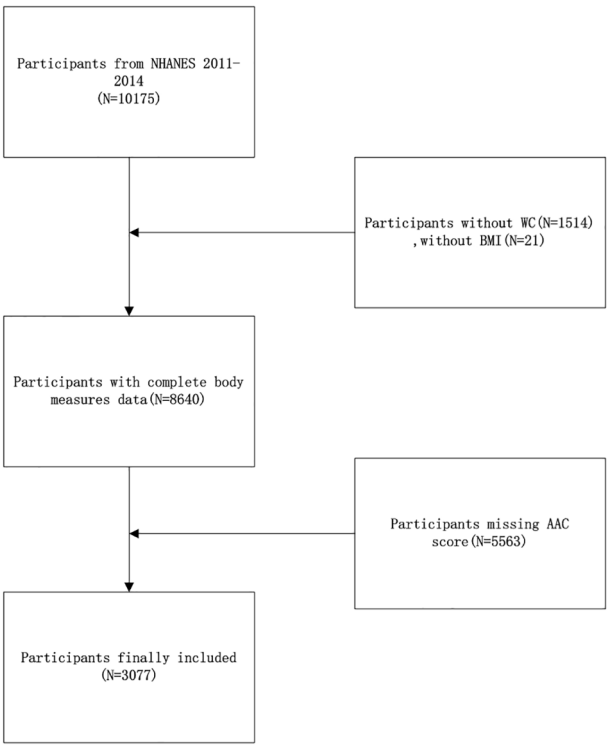

FIGURE 1
Flow chart showing the NHANES participants' selection.

segments allow for the visual identification of aortic calcification as white spots or lines across the aorta's walls. Calcification scoring is detailed as follows: a score of 0 indicates no calcification; 1 signifies calcification occupying a third or less of the segment's aortic wall; 2 denotes calcification extending over a third but under two-thirds of the wall; and 3 reflects more than two-thirds coverage. Each anterior and posterior aortic wall is scored independently, leading to a potential range of 0 to 6 per lumbar vertebra and a cumulative possible score ranging from 0 to 24. Additionally, the AAC8 scale was applied to quantify the total calcification length along the anterior and posterior walls of the aorta across vertebrae L1 to L4. The scoring criteria are as follows: 0 for no observable calcification; 1 if total calcification length is up to one vertebral bone height; 2 for length surpassing one but not two vertebral heights; 3 for calcification extending beyond two but under three vertebral heights; and a score of 4 is assigned if the calcification length exceeds three vertebral bone heights.

2.4 Covariates

In this study, we included multiple characteristics as covariates for analysis, including age, gender, race, education level, income level (measured by the Poverty Income Ratio, PIR), smoking history, frequency of alcohol intake, diabetes, and the presence of hypertension. Diabetes and hypertension were based on participants' self-reported responses to the questions, "Doctor told you have diabetes" and "Ever told you had high blood pressure" These data, along with the analytical methods, were obtained from the publicly available NHANES database, which is widely used for research purposes.

2.5 Statistical analysis

In this research, the application of NHANES sampling weights was meticulously adhered to for all statistical analyses, aligning with the CDC's guidelines and acknowledging the intricacies of the survey's multi-stage, complex sampling design. Statistical evaluations were conducted utilizing EmpowerStats software (version 4.2) and the R statistical package (version 4.2), ensuring rigorous analysis. Participants were divided into three groups of equal size based on their ABSI scores, and disparities in demographic attributes were examined using chi-square tests for categorical variables and t-tests for continuous variables. To assess the link between ABSI and AAC, a multivariate linear regression model was employed. Additionally, a weighted smoothing curve-fitting method alongside a threshold effect analysis was utilized to investigate the non-linear dynamics of the ABSI-AAC relationship. Subgroup analyses and interaction tests were further implemented to delve into the specifics of this association across different demographics. The threshold for deeming results statistically significant was established at a two-tailed p-value of less than 0.05.

3 Results

3.1 Baseline characteristics

Table 1 outlines the demographic characteristics of the study participants, who were segmented into three groups based on tertiles of their ABSI. The study included 3077 adults aged 40 years and above. The mean age of the participants was 57.36 ± 11.50 years, with a gender distribution of 48.20% male and 51.80% female. The thresholds for the ABSI tertiles were identified as 0.08102 and 0.08489. Comparing the higher to the lower ABSI group reveals several notable differences: the high ABSI group had an older average age, a greater percentage of male participants, a higher likelihood of being non-Hispanic white, a lower Poverty Income Ratio (PIR), a lower educational attainment level, a higher proportion of current smokers, and a higher prevalence of individuals with diabetes and hypertension.

3.2 Relationship between ABSI and AAC

Table 2 presents the findings from the multifactor regression analysis, illustrating the relationship between the ABSI and AAC scores. In the unadjusted model, ABSI exhibited a strong positive correlation with AAC24, with a coefficient [β=154.34, (confidence interval: 129.66, 179.02)], indicating a significant association. This significant positive correlation persisted in Model 2, even after adjusting for gender, age, and race [β=48.01, (22.06, 73.96)]. In

TABLE 1 Weighted characteristics of the study population based on ABSI tertiles.

Characteristics	Adjusted body size index			P value
	T1 (ABSI ≤ 0.08102)	T2 (0.081021 < ABSI ≤ 0.08489)	T3 (ABSI > 0.08489)	
Age (years)	52.72 ± 9.90	56.63 ± 11.10	63.11 ± 11.04	<0.0001
Gender (%)				<0.0001
Male	36.49	51.69	57.15	
Female	63.51	48.31	42.85	
PIR	3.34 ± 1.59	3.16 ± 1.59	2.99 ± 1.61	<0.0001
Race (%)				<0.0001
Mexican American	7.03	7.91	5.84	
Other Hispanic	4.56	5.91	3.61	
Non-Hispanic White	66.14	69	78.18	
Non-Hispanic Black	14.66	9.29	6.27	
Non-Hispanic Asian	5.16	5.61	4.57	
Other Race	2.46	2.27	1.53	
Education (%)				0.001
< high school	4.04	5.13	6.23	
9-11th grade	8.75	9.87	12.22	
High school graduate	20.34	22.64	22.1	
Some college or AA degree	27.85	30.55	30.61	
College graduate or above	39.02	31.81	28.84	
Don't Know			0.05	
Smoked ≥ 100 cigarettes (%)				<0.0001
Yes	36.76	46.59	55.24	
No	63.24	53.41	44.76	
Alcohol intakes ≥12drinks/year (%)				0.6075
Yes	78.75	78.47	77.04	
No	63.24	53.41	44.76	
HBP (%)				<0.0001
Yes	39.35	37.57	54.83	
No	60.65	62.43	45.17	
Diabetes (%)				<0.0001
Yes	6.91	13.11	19.27	
No	90.77	83.07	75.71	
Broadline	2.31	3.82	5.03	
AAC24	0.78 ± 2.24	1.33 ± 3.00	2.32 ± 4.14	<0.0001
AAC8	0.38 ± 0.91	0.58 ± 1.12	0.94 ± 1.47	<0.0001

Mean ± SD for continuous variables: the P value was calculated by the weighted linear regression model; (%) for categorical variables: the P value was calculated by the weighted chi-square test. T tertiles, PIR Ratio of family income to poverty, BMI Body mass index, HBP High blood pressure, AAC abdominal aortic calcification.

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TABLE 2 Associations between ABSI and AAC.

ABSI	Model1 β (95%CI) P value	Model2 β (95%CI) P value	Model3 β (95%CI) P value
AAC24	154.34 (129.66, 179.02) <0.0001	48.01 (22.06, 73.96) 0.0003	26.62 (0.42, 52.82) 0.0465
T1	Ref	Ref	Ref
T2	0.56 (0.28, 0.83) <0.0001	0.13 (-0.13, 0.40) 0.3179	0.05 (-0.21, 0.31) 0.7238
T3	1.54 (1.27, 1.82) <0.0001	0.42 (0.13, 0.70) 0.0043	0.18 (-0.10, 0.47) 0.2074
P for trend	<0.0001	0.0044	0.2086
AAC8	56.46 (47.33, 65.58) <0.0001	19.51 (9.83, 29.19) <0.0001	11.69 (1.93, 21.46) 0.0190
T1	Ref	Ref	Ref
T2	0.20 (0.10, 0.30) <0.0001	0.05 (-0.04, 0.15) 0.2722	0.02 (-0.07, 0.12) 0.6527
T3	0.56 (0.46, 0.66) <0.0001	0.16 (0.06, 0.27) 0.0024	0.08 (-0.03, 0.19) 0.1429
P for trend	<0.0001	0.0024	0.1438

Model 1: variables were not adjusted. Model 2: adjustments were made to age, gender, and race. Model 3: Age, gender, race, PIR, hypertension, diabetes, smoking status, and alcohol intake were adjusted.T, tertiles, PIR Ratio of family income to poverty, BMI Body mass index, AAC abdominal aortic calcification.

Model 3, which accounted for all covariates, each unit increase in ABSI corresponded to a 26.62point increase in the AAC24 score [β=26.62, (0.42, 52.82), p=0.0465]. Moreover, a positive correlation between ABSI and AAC8 scores was consistently observed across all models. Specifically, in Model 1, the correlation coefficient was β=56.46 (47.33, 65.58); in Model 2, it was β=19.51 (9.83, 29.19); and in Model 3, it was β=11.69 (1.93, 21.46) with a p-value of 0.0190, indicating statistical significance. Despite dividing ABSI into tertiles and testing for trends with AAC, no significant trend emerged. However, further exploration through smoothed curve fitting and threshold effect analysis revealed a nonlinear relationship between ABSI and AAC, identifying a critical threshold (K-point) at 0.0908

TABLE 3 Threshold effect analysis of WWI on severe AAC.

Outcome	AAC24	AAC8
Model3		
β (95%CI) P value	26.62 (0.42, 52.82) 0.0465	11.69 (1.93, 21.46) 0.0190
Model3^{+}		
K-point	0.0908	0.0908
β1 (<0.0908)	5.71 (-22.14, 33.56) 0.6877	4.68 (-5.71, 15.07) 0.3770
β2 (> 0.0908)	380.92 (215.38, 546.46) <0.0001	130.4667 (68.71, 192.23) <0.0001
β2-β1	375.21(202.09, 548.32) <0.0001	125.78 (61.20, 190.37) 0.0001
AAC at K-point	2.50 (2.26, 2.75)	1.01 (0.92, 1.10)
Logarithmic likelihood ratio test P value	<0.001	<0.001

Age, gender, race, PIR, HBP, diabetes, smoking status, and alcohol intake were adjusted. PIR Ratio of family income to poverty, HBP High blood pressure, AAC abdominal aortic calcification.

(Figure 2). This analysis underscores the complexity of the relationship between ABSI and AAC. The left and right side effects of AAC24 at the K-points were 5.42 (-23.08, 33.93) 0.7093, and 289.22 (146.25, 432.18) < 0.0001, respectively; AAC8 had 4.59 (-6.04, 15.22) 0.3976 and 99.68 (46.35, 153.01) 0.0003 left- and right-side effects at the K-points, respectively, with log-likelihood-ratio tests of less than 0.001 (Table 3).

We conducted subgroup analyses by subgroups of age, sex, race, smoking, alcohol consumption, HBP, and diabetes mellitus to explore the relationship between ABSI and AAC in different populations (Table 4). After adjusting for covariates, significant differences in the relationship between ABSI and AAC were found in subgroups with different ages and diabetes status.

4 Discussion

This research examined the correlation between ABSI and AAC among 3077 middle-aged and elderly individuals in the United States. The results of the study showed that both AAC24 and AAC8

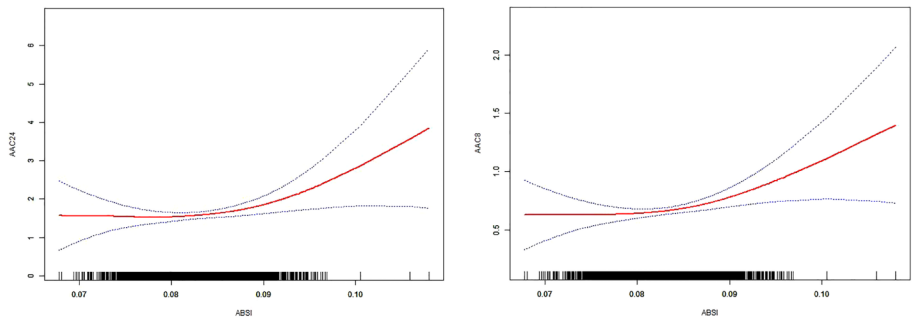

FIGURE 2
The solid red line represents the smooth curve fit between the variables. The 95% confidence interval derived from the fit is shown by blue bands.

TABLE 4 Subgroup analysis of the associations between ABSI and cognitive function.

Subgroup	AAC24 β(95%CI) P value	P for interaction	AAC8 β (95%CI) P value	P for interaction
Age		<0.0001		<0.0001
<60	10.63 (-25.06, 46.31) 0.5595		2.87 (-10.44, 16.18) 0.6726	
≥60	128.47 (90.19, 166.76) <0.0001		50.42 (36.14, 64.70) <0.0001	
Gender		0.2472		0.3656
Male	43.10 (1.59, 84.61) 0.0419		16.35 (0.86, 31.83) 0.0386	
Female	11.95 (-21.56, 45.46) 0.4847		7.27 (-5.23, 19.77) 0.2547	
Race		0.8965		0.7429
Mexican American	-18.21 (-122.53, 86.11) 0.7322		-9.36 (-48.25, 29.54) 0.6372	
Other Hispanic	-2.44 (-141.57, 136.69) 0.9725		5.15 (-46.73, 57.02) 0.8458	
Non-Hispanic White	36.07 (5.43, 66.71) 0.0211		14.79 (3.37, 26.22) 0.0112	
Non-Hispanic Black	1.78 (-80.80, 84.36) 0.9663		-1.95 (-32.74, 28.84) 0.9014	
Non-Hispanic Asian	26.15 (-98.26, 150.56) 0.6804		26.79 (-19.60, 73.18) 0.2577	
Other Race	36.85 (-193.07, 266.78) 0.7534		5.86 (-79.87, 91.59) 0.8934	
Alcohol intakes ≥12drinks/year		0.2205		0.3626
Yes	35.90 (5.61, 66.19) 0.0203		14.12 (2.81, 25.44) 0.0145	
No	-1.65 (-54.11, 50.81) 0.9509		3.59 (-16.20, 23.39) 0.7220	
Smoked ≥ 100 cigarettes		0.5986		0.406
Yes	35.23 (-4.81, 75.27) 0.0847		16.17 (1.23, 31.11) 0.0340	
No	21.09 (-13.63, 55.81) 0.2339		7.84 (-5.12, 20.79) 0.2358	
HBP		0.2223		0.2928
Yes	42.42 (5.24, 79.59) 0.0254		16.96 (2.95, 30.97) 0.0177	
No	10.78 (-24.86, 46.42) 0.5534		6.61 (-6.84, 20.06) 0.3357	
Diabetes		<0.0001		<0.0001
Yes	-18.51 (-91.30, 54.27) 0.6182		0.53 (-26.69, 27.74) 0.9697	
No	12.83 (-15.66, 41.31) 0.3775		6.67 (-3.98, 17.32) 0.2196	
Broadline	355.79 (229.56, 482.03) <0.0001		118.23 (71.03, 165.43) <0.0001	

Age, gender, race, education level, PIR, smoking, alcohol intake, HBP, and diabetes are adjusted.
T, tertiles, PIR Ratio of family income to poverty, HBP High blood pressure, AAC abdominal aortic calcification.

maintained a significant positive correlation with ABSI, and the two were nonlinearly correlated with a K-point of 0.0908, with a non-significant correlation to the left of the K-point and a significant positive correlation to the right of the K-point. This positive correlation suggests that as the ABSI increases, the AAC also increases, especially after the K-point, which may suggest the potential value of the ABSI in assessing the risk of cardiovascular disease.

This investigation marks a pioneering effort to probe the relationship between ABSI and AAC. Traditional reliance on BMI for obesity assessment has been challenged by BMI's limited capacity to distinguish between different types of body fat and its strong correlation with waist circumference, underscoring BMI's inadequacies in obesity diagnosis. The recognition of central obesity as a crucial element in cardiovascular risk evaluation led to the creation of ABSI. Since its introduction in 2012, ABSI has been linked to a range of diseases and metabolic disorders, with elevated ABSI values signaling a heightened risk of premature mortality in the broader population (11). ABSI's effectiveness in detecting visceral and muscle-reducing obesity in overweight or obese adults with Type 2 Diabetes Mellitus (T2DM) underscores its superiority over BMI in predicting diabetes and chronic kidney disease (CKD) in certain populations (14, 15). The direct relationship between ABSI and cardiovascular risk, as well as its stronger correlation with mortality (overall, cardiovascular, and cancer), highlights its potential as a predictor of cardiovascular events (16–18). Our results suggest that individuals with a higher

ABSI may have more abdominal fat accumulation, which is associated with increased AAC scores. Abdominal fat is considered a metabolically active tissue that secretes a variety of inflammatory factors and hormones, which may be one of the mechanisms that promote atherosclerosis (19). Thus, ABSI could offer a straightforward and accessible measure for clinicians to identify middle-aged and older adults at elevated risk of developing AAC and subsequent cardiovascular diseases. Furthermore, the determination of K-points offers a clinical benchmark, suggesting potential thresholds for intensified monitoring and intervention efforts.

The positive correlation between ABSI and AAC may involve complex biological mechanisms. The systemic inflammatory state induced by obesity is a key factor in the promotion of atherosclerosis and vascular calcification (20, 21). Inflammatory mediators released from adipose tissue, such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), exacerbate inflammatory responses in the vascular wall, which further contribute to the calcification process (20, 22). At the same time, obesity is closely related to insulin resistance and T2DM (23), and these pathological states raise the risk of vascular calcification by increasing calcium salt deposition in vascular smooth muscle cells (24–26). In addition, obesity is strongly associated with abnormalities of lipid metabolism, such as hypertriacylglycerolemia and high low-density lipoprotein (LDL) cholesterol levels (27, 28). These abnormalities have been suggested to be the major contributing factors to both atherosclerosis and vascular calcification (29). Obesity also leads to an increase in oxidative stress (30), which may disrupt vascular endothelial function and promote inflammatory responses as well as the migration and proliferation of vascular smooth muscle cells, all of which are critical aspects of the calcification process (31). Hormonal imbalances induced by obesity, such as altered levels of lipofuscin and leptin, also have a direct or indirect effect on vascular calcification. Of these, leptin may promote calcification due to its proinflammatory properties (32–34). Whereas lipocalin, which has anti-inflammatory effects, is reduced in obese individuals and may increase the risk of calcification (35–37). Vitamin D deficiency is more common in obese individuals (38, 39), and vitamin D is essential for calcium and phosphorus metabolism and maintenance of vascular health. Its deficiency may promote vascular calcification through various mechanisms (40–42). In summary, inflammation, insulin resistance and diabetes mellitus, abnormal lipid metabolism, oxidative stress, adipose-related hormone imbalances, and vitamin D deficiency constitute a complex network of interactions that together drive the progression of vascular calcification.

Subgroup analyses and interaction tests revealed significant modifications in the relationship between the ABSI and AAC by age and diabetes status. Specifically, a more pronounced positive correlation between ABSI and AAC was evident among participants aged 60 years and older. This finding implies that central obesity's impact on cardiovascular disease (CVD) risk escalates with advancing age. Such a trend could be attributed to a blend of age-associated biological changes, including genetic and potentially epigenetic factors, environmental influences like diabetes mellitus and chronic kidney disease, and the propensity of vascular smooth muscle cells to adopt an osteogenic phenotype — key contributors to age-dependent vascular calcification (43). Furthermore, processes inherent to the aging phenomenon, such as cellular senescence, autophagy, the emission of extracellular vesicles, and oxidative stress, play pivotal roles in facilitating vascular calcification (44). Additionally, within the diabetes subgroups, a notable correlation between ABSI and AAC was observed among patients with borderline blood glucose levels. However, this association might indicate statistical variance arising from the smaller sample sizes of the subgroups under examination.

This study utilized data collected by NHANES between 2013 and 2014 and included 3,077 adults aged 40 years and older as study participants. This large and diverse sample makes our findings more representative and generalizable. Methodologically, we employed sophisticated statistical analysis techniques, such as multivariate linear regression, smooth curve fitting, threshold effect analysis, subgroup analysis, and interaction test, to delve into the interactions between ABSI and AAC. This methodology was utilized to ensure the accuracy and reliability of the study results. This study pays special attention to the potential association between ABSI and AAC that has not been fully explored, providing a new perspective for understanding the link between obesity and cardiovascular disease risk.

However, this study also has some limitations. As a cross-sectional study, it failed to establish a causal relationship between ABSI and AAC, although it revealed a correlation between the two. Future studies may need to employ prospective or interventional designs to explore this relationship in depth. Additionally, the data sources relied upon for this study were limited to NHANES data from 2013 to 2014, which may not fully reflect current population health status and trends. Finally, although this study considered multiple covariates, it may have still missed other potential variables, such as lifestyle and dietary habits, which may also influence the relationship between ABSI and AAC.

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

Author contributions

YC: Investigation, Validation, Formal analysis, Software, Resources, Supervision, Methodology, Writing – review & editing. YZ: Writing – original draft, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. YD: Writing – original draft, Software, Resources, Project

administration, Methodology, Investigation, Funding acquisition, Formal analysis. SJ: Writing – review & editing, Visualization, Validation, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Mendelian randomization studies of lifestyle-related risk factors for stroke: a systematic review and meta-analysis

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Objective: Stroke risk factors often exert long-term effects, and Mendelian randomization (MR) offers significant advantages over traditional observational studies in evaluating the causal impact of these factors on stroke. This study aims to consolidate and evaluate the relationships between potential causal factors and stroke risk, drawing upon existing MR research.

Methods: A comprehensive search for MR studies related to stroke was conducted up to August 2023 using databases such as PubMed, Web of Science, Embase, and Scopus. This meta-analysis examines the relationships between potential causative factors and stroke risk. Both random-effects and fixed-effects models were utilized to compile the dominance ratios of various causative elements linked to stroke. The reliability of the included studies was assessed according to the Strengthening the Reporting of Observational Studies in Epidemiology incorporating Mendelian Randomization (STROBE-MR) guidelines.

Results: The analysis identified several risk factors for stroke, including obesity, hypertension, low-density lipoprotein cholesterol (LDL-C), chronic kidney disease (CKD), and smoking. Protective factors included high-density lipoprotein cholesterol (HDL-C), estimated glomerular filtration rate (eGFR), and educational attainment. Subgroup analysis revealed that type 2 diabetes mellitus (T2DM), diastolic blood pressure (DBP) are risk factors for ischemic stroke (IS).

Conclusion: This study confirms that variables such as obesity, hypertension, elevated LDL-C levels, CKD, and smoking are significantly linked to the development of stroke. Our findings provide new insights into genetic susceptibility and potential biological pathways involved in stroke development.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO, identifier CRD42024503049.

KEYWORDS

stroke, ischemic stroke, small vessel stroke, mendelian randomization analysis, genetic epidemiology

1 Introduction

Stroke, a severe neurological condition, is often triggered by decreased blood flow or breakdown of vascular structures, leading to irreversible damage to neurons in the cerebrum (1). Stroke is the second most common cause of death worldwide and a significant contributor to severe disability, impacting more than 150,000 individuals each year. According to the Global Burden of Disease (GBD) study, the annual number of strokes and stroke-related deaths increased substantially between 1990 and 2019, with incident strokes rising by 70% and stroke-related deaths by 43%. Notably, it is anticipated that by 2030, the incidence of ischemic stroke (IS), one of the two major subtypes of stroke, will escalate to 4.90 million globally (2–5). Especially in low-income countries, the disease burden of stroke is even higher (6–11). In recent years, studies on the etiology of stroke have gradually revealed connections between numerous life-style and physiologic factors and their likelihood of leading to the disease (12–15). Lower educational attainment is linked to an increased risk of stroke. Obesity, especially increased body mass index (BMI) and waist circumference (WC), is an independent predictor of stroke occurrence (16). Furthermore, smoking may result in the emergence of additional cardiovascular risk factors such as dyslipidemia, and hypertension through metabolic and hemodynamic changes (17). Importantly, the presence of chronic kidney disease (CKD) dramatically increases death risk in individuals suffering from a stroke (18). However, establishing a direct causal connection between a particular cause and its associated disease is difficult due to inherent limitations in observation-based studies, like potential confounding factors and skewed information. These hindrances make proving causality a tricky task. Mendelian Randomization (MR) is a method in human genetics, using single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) in genome-wide association study (GWAS) focus on exposure events (19). It is specifically aimed at elucidating the causal connections between exposure and outcomes (20). Recent research undertaking MR has turned its attention towards identifying how specific risk factors could potentially contribute to a stroke. Given the diverse nature of these studies, it becomes overwhelmingly essential to carry out comprehensive systematic reviews coupled with meta-analysis. Such evaluations are vital in bolstering the evidence that supports effective strategies in both the prevention and treatment of stroke.

This paper presents a systematic review and meta-analysis of MR studies related to stroke. We evaluate a spectrum of stroke-related risk factors, including obesity, lipid profiles, blood pressure (BP), renal function, and environmental factors. The primary outcome of this study is total stroke. Additionally, we focus on ischemic stroke (IS), defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or vascular infarction, assessed in subgroup analysis (21, 22).

2 Materials and method

2.1 Literature search

The configuration and documentation of this systematic evaluation were conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (23, 100) and pre-registered with PROSPERO(CRD42024503049).

In pursuit of a comprehensive scholarly investigation, a thorough search was carried out through four databases: PubMed, Web of Science, Embase, and Scopus. The databases were searched for relevant citations published from their inception to August 20, 2023, using the search terms “Mendelian randomization analysis” combined with “stroke.” The strategies used to search the databases are described in Supplementary Table 1. To ensure a comprehensive literature review, we carefully reviewed the references in the selected studies to identify relevant articles potentially missed in the preliminary search. Each of these articles was manually verified for relevance. When discrepancies arose among the reviewers, they engaged in deliberative discussions until a unanimous consensus was reached. Prior to the assessment using the predefined inclusion and exclusion criteria, articles were initially screened to ensure relevance and de-emphasize any irrelevant ones.

The following criteria guided the selection of studies for inclusion in the screening process:

1. International studies published up to August 2023 that utilized the MR method to investigate causal links between stroke or related phenotypes and various risk factors;

2. All studies using genetic variation to establish causal relationships regarding the impact of exposure factors on stroke outcomes;

3. All studies that includes MR in their analysis using GWAS or phenotype-wide association studies (PheWAS);

4. Studies reporting outcomes as 95% confidence intervals (CI), odds ratios (OR), and relative risks (RR), or providing raw data that can be converted to these metrics;

5. Original research articles.

The following criteria guide the exclusion of studies in the screening process:

1. Diagnosis of other types of cerebrovascular disease, such as cerebral atherosclerosis, cerebral arteritis, cerebral aneurysm, cerebral artery injury, intracranial vascular malformation, thrombosis, and cerebral arteriovenous fistula;

2. Relevant outcome indicators were not reported or data were incomplete (101);

3. Repeatedly published studies;

4. Editorials, letters to the editor, review articles, conference coverage, systematic reviews, case reports, and experimental animal studies.

2.2 Literature screening and data extraction

All identified literature was imported into EndNote 20 for systematic review. Two researchers independently conducted the screening process, initially reviewing titles and abstracts, followed by full-text assessments in accordance with predefined inclusion and exclusion criteria. Articles selected during this initial phase underwent a more detailed full-text review. In cases of disagreement about eligibility, a third researcher was consulted to make the final decision.

Data extraction involved several key parameters, including the first author's name, publication year, study ethnicity, consortium responsible for stroke genomics research, exposure variables, outcome sample size, and major findings. Additionally, OR and 95% CI were extracted using various MR methods, including inverse variance weighted (IVW), weighted median estimator (WME), MR-Egger regression, simple mode, and weighted mode (see Supplementary Table 2).

2.3 Assessment of methodological quality

The methodological quality of the studies included in the meta-analysis was evaluated using a modified version of the Strengthening the Reporting of Observational Studies in Epidemiology for Mendelian Randomization (STROBE-MR) guidelines (24). We converted quality scores into percentages: studies scoring below 75% were classified as poor quality, those scoring between 75% and 85% were considered moderate quality, and studies scoring above 85% were regarded as high quality (25, 26). Two researchers independently conducted the quality assessment, and any discrepancies were resolved through consultation with a third researcher.

2.4 Statistical analysis

To qualify for the meta-analysis, each study had to meet specific criteria. It needed to be among at least two independent investigations focusing on the etiology of stroke or examining the causal relationships between stroke and various genetic or contributing factors. Statistical analysis was conducted using Stata 17.0 software. Outcome measures included OR values and 95% CI as effect size metrics, with a significance threshold of α=0.05. Inter-study heterogeneity was assessed using the χ^2 test, with the p-value and I^2 as indicators. For I^2< 50% and $p > 0.1$, a fixed-effects model was applied. For $I^2 \geq 50\%$, indicating substantial heterogeneity, sensitivity and subgroup analyses were conducted to identify sources of heterogeneity. If sources of heterogeneity could not be resolved, a random-effects model was employed (27, 28). Sensitivity analysis was performed to assess the stability of the results by comparing the combined effect estimates from both random-effects and fixed-effects models. Significant differences indicated high sensitivity and potential instability in the outcomes of the meta-analysis. Egger's test was utilized for funnel plot analysis to evaluate publication bias, with a p-value < 0.05 considered statistically significant.

3 Results

3.1 Literature screening and selection

The database search initially resulted in 2,089 documents. Following the use of EndNote 20 and manual verification by the researchers, this number was narrowed down to 881 articles. During the preliminary review of titles and abstracts, two researchers identified 30 pertinent articles. Subsequent full-text reviews further reduced the selection down to 11 articles for inclusion. The literature screening process and its outcomes are illustrated in Figure 1.

3.2 Characteristics and quality of included studies

The meta-analysis included 11 MR studies (29–39). All studies were evaluated as high quality (Supplementary Table 3). These studies included subjects from multiple datasets (29–32, 34, 37), covering Europeans (31–36, 38, 39), Africans (29, 37), Asians (29, 30, 37), and Latin Americans (29, 37). Most MR studies used a strict linkage disequilibrium (LD) threshold (R^2 < 0.001) and restricted the genetic distance to a maximum of 10,000 kilobases (kb) to select independent SNPs as IVs for exposure. However, some studies opted to identify all conditionally independent SNPs in GWAS. The number of SNPs used in the studies varied from tens to thousands, with one study failing to report the number of SNPs used in MR (30). One study did not report the sample size for the outcome variable (39). The most frequently utilized cohort was the UK Biobank, which was featured in seven studies (29, 32, 34, 36, 37, 39). Additionally, four of the cohorts focused on stroke outcomes and all utilized the MEGASTROKE consortium (31, 32, 36–38). Two studies considered stratification by arterial gender (39), and population (30) respectively. All studies were statistically analyzed for MR, with one study reporting results based on IVW, MR-Egger regression, WME, simple mode, and weighted mode (34). Due to the limited number of included studies, funnel plots were not generated for all phenotypes.

3.3 Meta-analysis results

A total of four studies on type 2 diabetes mellitus (T2DM) (29, 35–37), two studies on waist-hip ratio (WHR) (29, 32), five studies on BMI (32, 33, 35, 37, 39), five studies on triglycerides (TGs) (six datasets) (29–31, 35, 37), four studies on high-density lipoprotein cholesterol (HDL-C) (five datasets) (30, 31, 35, 37), four studies on low-density lipoprotein cholesterol (LDL-C) (five datasets) (30, 31, 35, 37), four studies on systolic blood pressure (SBP) (29, 32, 35, 36), three studies on diastolic blood pressure (DBP) (29, 35, 36), two studies on hypertension (35–37), two studies on estimated

glomerular filtration rate (eGFR) (three datasets) (34, 38), two studies on CKD (three datasets) (34, 38), two studies on smoking (35, 37), and two studies on educational level (35, 36).

3.3.1 Obesity related indicators

The study demonstrated that genetic tendencies towards two obesity-related measures correlated with an increased stroke risk, although this correlation was not observed for one of the measures (Figure 2). Specifically, T2DM [1.11(1.07-1.14)], WHR [1.14, (0.98-1.33)], BMI [1.08(1.05-1.12)]. There was heterogeneity between T2DM and stroke (I^2 = 62.5%, p=0.046), which we attribute to variations in the demographics of the study populations. Therefore, we utilized a random-effects model. Heterogeneity was also observed in the correlation between WHR and stroke (I^2 = 64.4%, p=0.094). It is possible that differences in the populations used for the exposure factors contributed to this, while the outcome metrics were based on the same population. There was no heterogeneity between BMI and stroke risk when using a fixed-effects model.

3.3.2 Lipid-related Indicators

The IVW method was used to calculate the values, which were then utilized to evaluate the overall causal effect of the three lipid-related indicators on stroke (Figure 2). HDL-C has a protective effect against stroke [0.94, (0.97-0.97)], and there was slight heterogeneity in the results (I^2 = 58.9%, p=0.045). The heterogeneity was possibly due to the fact that HDL-C data was derived from five different populations, necessitating the use of a random-effects model. Elevated levels of LDL-C might correlate with an increased likelihood of stroke [1.08(1.05-1.12)], with slight heterogeneity in the results (I^2 = 51.7%, p = 0.082), possibly due to the inclusion of LDL-C data from five different populations, thus requiring a random-effects model. There was no evidence of a causal relationship between TGs and stroke [1.06 (0.99-1.13)].

3.3.3 Blood pressure-related indicators

Genetic susceptibility to two blood pressure-related indices correlated with a heightened likelihood of developing stroke

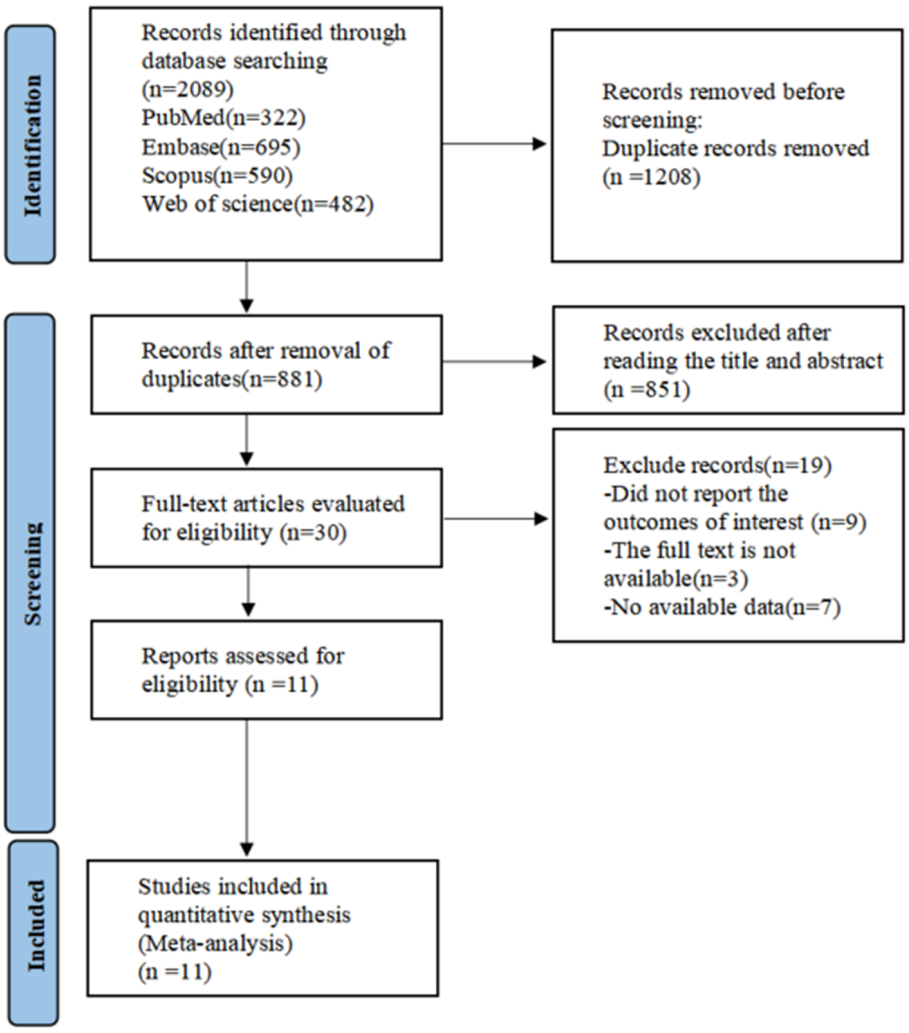

FIGURE 1
PRISMA flow diagram of the study process. PRISMA, Preferred Reporting Items for Systematic review and Meta-analysis.

(Figure 3). Specifically, DBP [1.04 (1.03 -1.05)], SBP [1.03 (1.03 -1.03)], and hypertension [2.25(0.49-10.40)]. There was heterogeneity in the statistical results between DBP(I^2 = 66%), SBP(I^2 = 0%), hypertension(I^2 = 99.7%) and stroke. The heterogeneity in the results was attributed to the use of different populations and strata as exposure factors. All analyses were conducted using a random-effects model.

3.3.4 Renal function related indicators

Values obtained using the IVW method were used to assess the overall causal impact of two renal function-related indicators on stroke: eGFR [0.92 (0.87-0.98)] and CKD [1.07 (1.03-1.10)]. The results suggest a causal effect for both indicators. There was no heterogeneity (I^2 = 0%; I^2 = 0%) in the statistical results for the onset of stroke using fixed-effects models (Figure 4, Supplementary Figure 1).

3.3.5 Living environment-related indicators

A causal link was established between stroke and smoking [1.32 (1.12-1.55)], with slight heterogeneity in the results (I^2 = 60%, p= 0.114), which was attributed to different populations. Therefore, a random-effects model was used. Educational level had a protective effect against stroke [0.68 (0.64-0.72)]. There was no heterogeneity in the results (I^2 = 0%, p= 0.852), so a fixed-effects model was used (Figure 4).

3.3.6 Subgroup analoysis of indicators related to ischemic stroke

The two indicators associated with IS are T2DM [1.10 (1.04-1.15)], DBP [1.04 (1.02-1.06)]. They all exhibit heterogeneity (I^2 = 72.2%, I^2 = 71.8%), attributed to differences in populations and stratification (Figure 5).

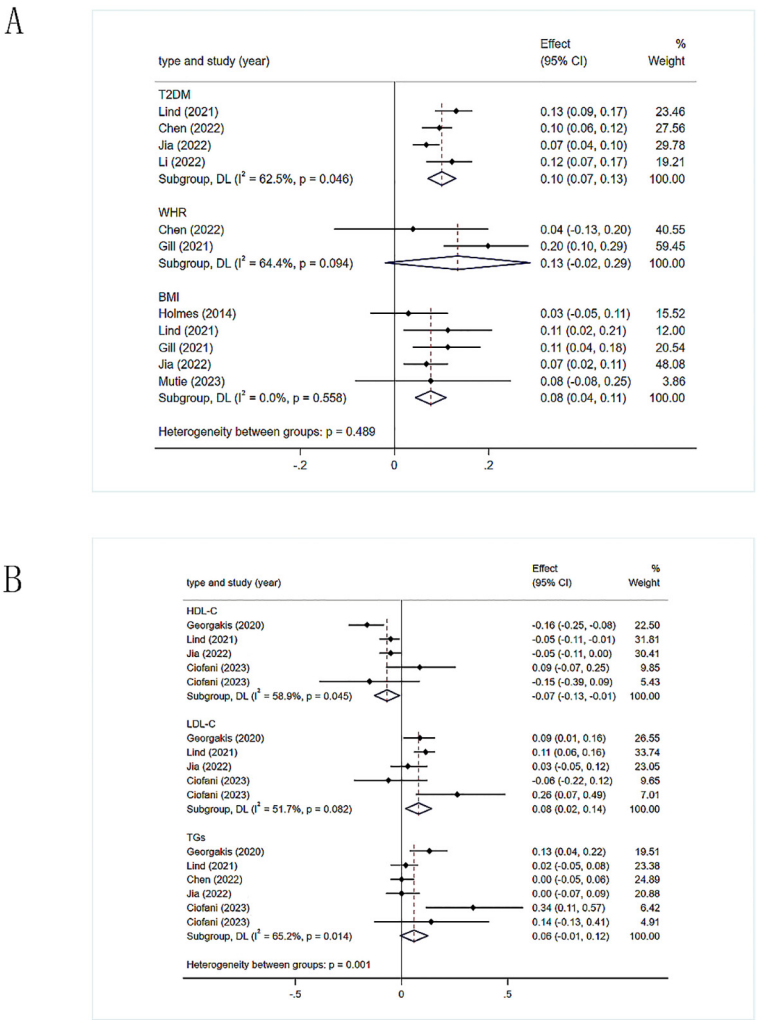

FIGURE 2
(A) Meta-analysis results of the association between genetic liability to obesity-related indicators and risk of stroke. T2DM, type 2 diabetes mellitus; WHR, waist-hip ratio; BMI, body mass index. **(B)** Meta-analysis results of the association between genetic liability to lipid related indicators and risk of stroke. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides.

4 Discussion

This review is a meta-analysis of published MR findings related to stroke. Genetic evidence suggests that T2DM, BMI, LDL-C, SBP, DBP, CKD, and smoking contribute to a higher likelihood of stroke, while HDL-C, eGFR, and educational level are protective factors against stroke. Conversely, no causal link was found between WHR, TGs, and stroke. In subgroup analyses, T2DM and DBP showed a correlation with a higher risk of IS.

4.1 Obesity related indicators

Obesity markedly elevates the likelihood of developing cardiovascular disease by inducing metabolic syndrome, which involves insulin resistance, elevated blood glucose levels, substantial body fat accumulation, irregular cholesterol profiles, and hypertension (40, 41). Specifically, in visceral obesity, the combined effects of adipocyte hypertrophy and proliferation lead to an elevated release of pro-inflammatory cytokines (42), exacerbating the systemic and vascular inflammatory response (43–45). Further supporting this, our meta-analysis revealed that obesity-related indicators, such as BMI and T2DM, are risk factors for stroke, consistent with experimental findings. Notably, a higher BMI was correlated with a heightened overall risk of stroke, with combined RR values of 1.25 (95% CI 1.16-1.34, $I^2 = 84.8\%$, $p = 0.00$) and 1.47 (95% CI 1.02-2.11, $I^2 = 99.4\%$, $p = 0.04$) (46–48). Moreover, T2DM was found to be causal for stroke in Europeans (49) (95% CI 1.06-1.09). While studies have shown that WHR is a risk factor for stroke (50–52), intriguingly, our meta-analysis indicated no direct causal relationship between WHR and stroke. This might be due to gender differences in how visceral fat relates to calcified atherosclerosis (53–57). The differing findings between our study and Riaz H et al. may be due to differences in study populations and genetic instruments used (58). Our analysis includes a broader population and more recent studies, which may provide updated data. Methodological variations, such as inclusion criteria and statistical approaches, could also contribute to the discrepancies. Therefore, we propose that for a more comprehensive anthropometric assessment of cardiovascular disease(CVD) risk, a combination of measurements including WHR, WC, and Waist-to-Height Ratio (WHtR) should be utilized (59–61).

4.2 Lipid-related indicators

According to our systematic meta-analysis and comprehensive observational studies, elevated levels of HDL-C are significantly associated with the prevention of IS. Concurrently, LDL-C has been identified as the most useful biomarker for predicting the risk of stroke (62–65). HDL-C facilitates the uptake of cholesterol from peripheral tissues through the reverse cholesterol transport (RCT) pathway. It influences macrophage activity and function, triggers

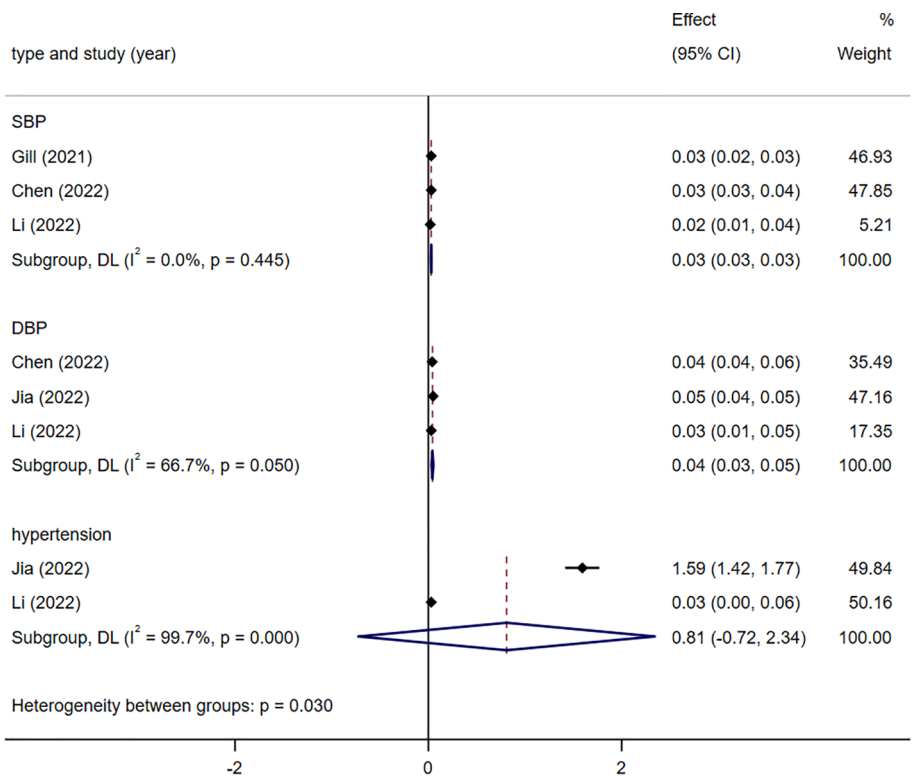

FIGURE 3
Meta-analysis results of the association between genetic liability to blood pressure-related indicators and risk of stroke. SBP, systolic blood pressure; DBP, diastolic blood pressure.

local aggregation of pro-inflammatory cells (66–68), and its antioxidant properties prevent the oxidation of LDL into ox-LDL, thus inhibiting the process of atherosclerosis formation (69). However, our meta-analysis indicates no definitive evidence supporting a causal relationship between TGs and stroke. Research indicates arteriosclerosis-inducing dyslipidemia is attributed to other lipid components (70, 71), notably triglyceride-rich lipoproteins (TRLs) and remnant cholesterol (72), which are crucial in atherosclerotic processes (70, 73). Therefore, further investigation into the collective influence of TGs, TRLs, and remnant cholesterol on atherosclerotic cardiovascular disease (ASCVD) is warranted.

4.3 Blood pressure-related indicators

Studies have confirmed that SBP, DBP, and hypertension are risk factors for stroke, a finding supported by our meta-analysis (74–77). In endothelial cells, a deficiency in Piezo1 can impair flow-mediated vasodilation and elevate SBP (78). Additionally, endothelial damage (79), proliferation of vascular smooth muscle cells (VSMCs) (80, 81), and infiltration of immune cells (82), may induce hypertension (83). Reduced expression of transmembrane member 16A (TMEM16A) may promote cellular proliferation and brain vascular remodeling induced by hypertension (84). Furthermore, the China Stroke Primary Prevention Trial (CSPPT) demonstrated that the risk of stroke was lowest in patients with an average SBP of 120-130 mm Hg, increasing in those with SBP <120 mm Hg and SBP 130-140 mmHg (85). Therefore, we suggest enhancing awareness and improving treatment compliance for hypertension to effectively prevent stroke.

4.4 Renal function related indicators

Our meta-analysis and systematic review indicate CKD as a significant risk factor for stroke (86–89). This is further supported by studies demonstrating CKD's independent impact on the risk of

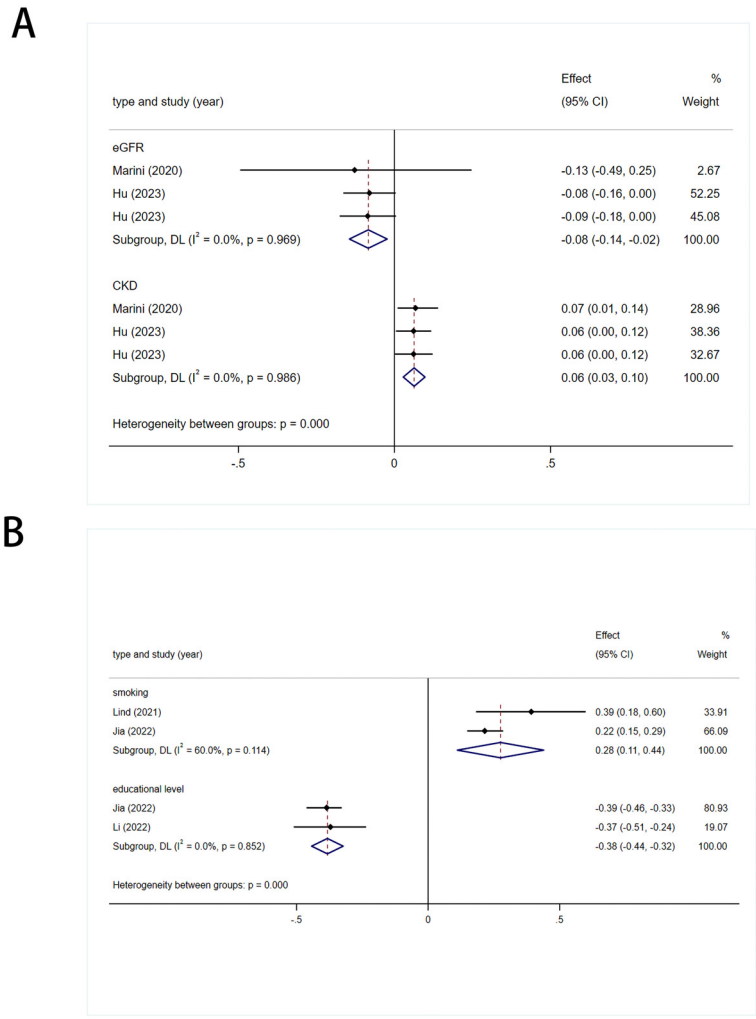

FIGURE 4
(A) Meta analysis results of the association between genetic liability to renal function related indicators and risk of stroke. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease. **(B)** Meta analysis results of the association between genetic liability to living environment related indicators and risk of stroke.

stroke, especially when characterized by reduced eGFR (34, 89). Moreover, eGFR is crucial for assessing renal function, with levels < 15, 15-29, and 30-44 mL/min/1.73m^2 closely linked to increased likelihoods of adverse clinical outcomes in stroke patients (90–93). However, research on the categorization of eGFR in relation to stroke prognosis (90). Therefore, our study emphasizes the importance of monitoring renal function in these patients (93). We advocate for further research to investigate the temporal relationship between eGFR and stroke over time, and we recommend eGFR as the preferred marker for assessing stroke risk.

4.5 Living environment-related indicators

Previous observational studies, along with our meta-analysis, indicate that smoking and lower educational levels increase the risk of stroke (74, 94, 95). Delgado et al. discovered elevated levels of soluble Intercellular Adhesion Molecule-1 (sICAM-1), soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1), as well as sE-selectin, sP-selectin, and sL-selectin in smokers. These elements are produced by both endothelial cells and leukocytes (96). Consequently, we believe that smoking cessation should be a primary intervention. Additionally, since higher educational attainment is linked to a decreased risk of stroke (97, 98), we recommend improving the overall education and cultural literacy of the general population.

4.6 Indicators related to ischemic stroke

Subgroup analysis of IS indicated that T2DM, DBP significantly elevate IS risk, consistent with clinical observations. However, our analysis did not find evidence of a causal relationship between SBP and IS, this result we view with caution. Considering clinical studies affirming the association of IS with SBP (74), we still advise IS patients to diligently monitor both SBP and DBP, engage in moderate exercise, and actively manage blood glucose and BP. Although limited clinical studies exist in this area, some research does support a causal relationship between BP and SV-Stroke (36, 99). Therefore, we recommend observational studies analyzing risk factors for stroke subtypes (large artery, cardioembolic, SV-Stroke) to further understand these associations.

5 Clinical implications and future research

Given the heightened risk of stroke associated with obesity, abnormal BP, and smoking, it is crucial to prioritize the promotion of healthy dietary habits, regular physical activity, and stress reduction. Additionally, the implementation of smoking cessation programs is essential for primary prevention and non-pharmacological interventions. Enhancing educational and literacy levels is also key in reducing the occurrence of strokes. While our findings show no clear association between WHR and stroke, we remain skeptical of these results. Therefore, it is still recommended to maintain a healthy body weight and closely monitor metrics such as WHR, WC, and WHtR.

This paper summarizes current MR research on risk factors for stroke but identifies several issues that need further study. Specifically, it emphasizes the importance of incorporating novel SNPs as IVs in stroke etiology research through MR studies. This method leverages recent genetic markers to more precisely determine the influence of diverse risk factors on stroke. Further research should expand to encompass diverse cohorts, especially those exposed to different environmental factors, for a more comprehensive understanding of stroke risk factors. The MR method is crucial in providing new insights into epidemiological studies and elucidating complex diseases such as

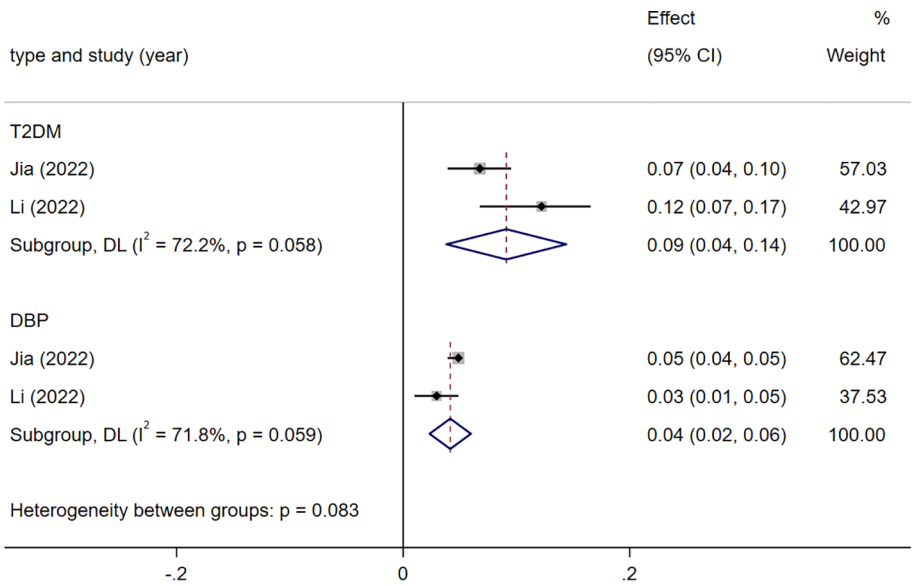

FIGURE 5
Meta analysis results of indicators related to ischemic stroke(IS). T2DM, type 2 diabetes mellitus; DBP, diastolic blood pressure.

stroke, including their pathophysiology and pharmacological treatments. Future efforts should focus on integrating MR into clinical settings to improve treatment protocols and reduce medication side effects. This advancement could significantly enhance stroke prevention and therapy.

This meta-analysis has several limitations. Firstly, the limited number of existing MR studies on stroke restricts our ability to assess publication bias through funnel plot symmetry analysis and the application of Egger's and Begg's tests. Additionally, we were unable to perform subgroup analyses based on region, age, and sex, limiting our exploration of the potential effects of these variables on the consolidated results. Secondly, the significant heterogeneity observed across studies necessitates careful interpretation of the results. This heterogeneity is somewhat expected given the variations in study methods, participant characteristics, and locations. In summary, although MR methods offer advantages over traditional meta-analysis and provide strong evidence linking stroke with its risk factors, they still have limitations. MR studies may be affected by measurement errors in exposure and outcomes, as well as limited ability to capture longitudinal causal relationships.

6 Conclusion

In conclusion, risk factors for stroke include obesity, dyslipidemia, abnormal BP, CKD, and smoking. Conversely, HDL-C, eGFR, and higher levels of education serve as protective factors against stroke. Therefore, the likelihood of stroke can be significantly reduced by quitting smoking, maintaining a healthy body weight, addressing CKD treatment, and improving educational attainment, particularly in individuals predisposed to stroke, such as hereditary susceptibility.

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

YT: Writing – original draft, Writing – review & editing. XT: Data curation, Methodology, Writing – review & editing. YL: Formal analysis, Methodology, Writing – review & editing. SL: Writing – review & editing, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1379516/full#supplementary-material

SUPPLEMENTARY FIGURE 1
(A) Meta-analysis results of the association between genetic liability to chronic kidney disease (CKD) and risk of stroke. CKD: chronic kidney disease; IVW: inverse variance weighted, MR-Egger: MR-Egger regression; simple mode; weighted mode; WME: weighted median estimator. **(B)** Meta-analysis results of the association between genetic liability to estimated glomerular filtration rate (eGFR) and risk of stroke. CKD: chronic kidney disease; IVW: inverse variance weighted, MR-Egger: MR-Egger regression; simple mode; weighted mode; WME: weighted median estimator.

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Triglycerides to apolipoprotein A1 ratio: an effective insulin resistance-associated index in identifying metabolic dysfunction-associated fatty liver disease in type 2 diabetes mellitus

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Background: The triglycerides to Apolipoprotein A1 ratio (TG/APOA1) holds promise to be a more valuable index of insulin resistance for the diagnosis of metabolic dysfunction-associated fatty liver disease (MAFLD) in type 2 diabetes mellitus (T2DM). This study aims to evaluate the correlation between TG/APOA1 and MAFLD, as well as compare the efficacy of TG/APOA1 with triglycerides to high-density lipoprotein cholesterol ratio (TG/HDL-c) and triglyceride-glucose (TyG) index in identifying MAFLD among individuals with T2DM.

Method: This study consecutively recruited 779 individuals with T2DM for the investigation. The unenhanced abdominal CT scans were conducted to measure CT liver-spleen attenuation measurement (CT_{L-S}). The CT_{L-S} less than 1.0 and without other liver comorbidities were considered to be MAFLD. The binomial logistic regression analysis and restricted cubic spines (RCS) were employed to evaluate the association between TG/APOA1 and MAFLD. The receiver operating characteristic (ROC) curve analysis was performed to compare the efficacy of TG/APOA1 with TG/HDL-c and TyG index identifying MAFLD.

Results: The TG/APOA1 exhibited a substantial increase in the MAFLD group ($P<0.05$). Even after adjustments for potential confounding factors, TG/APOA1 exhibited significant associations with nonalcoholic fatty liver disease fibrosis score ($\beta=0.266$, $P<0.001$), fibrosis-4 index ($\beta=0.123$, $P=0.029$), aspartate aminotransferase-to-platelet ratio index ($\beta=0.113$, $P=0.037$), and CT_{L-S} ($\beta=-0.225$, $P<0.001$). Meanwhile, TG/APOA1 contributed to an independent variable for MAFLD, the odds ratio with a 95% CI was 2.092 (1.840-2.380) in the total population, 2.123 (1.810-2.511) in men, and 2.162 (1.824-2.587) in women. Additionally, the results also revealed a nonlinear association between elevated TG/APOA1 and higher MAFLD risk according to the RCS analysis whether in the total population, men, or women (P for nonlinearity and overall <0.001).

Furthermore, TG/APOA1 had higher AUC level compared to TG/HDL-c and TyG index in the total population (0.769 vs 0.742, P=0.025; 0.769 vs 0.694, $P < 0.001$), men (0.776 vs 0.744, P=0.044; 0.776 vs 0.709, $P < 0.001$), and women (0.762 vs 0.728, P=0.041; 0.762 vs 0.674, $P < 0.001$).

Conclusion: TG/APOA1 serves as an effective index of insulin resistance in identifying MAFLD, offering advantages in the screening of MAFLD in T2DM.

KEYWORDS

triglycerides to apolipoprotein A1 ratio, triglycerides to high-density lipoprotein cholesterol ratio, triglyceride glucose index, insulin resistance, metabolic dysfunction-associated fatty liver disease, type 2 diabetes mellitus

Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) represents a novel classification of nonalcoholic fatty liver disease (NAFLD), emphasizing the role of metabolic risk factors in the development and progression of NAFLD-related pathology. MAFLD is characterized by hepatic triglycerides (1) accumulation and can advance to more severe manifestations like non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and even hepatocellular carcinoma, posing a significant public health concern in the obese population (2). Notably, MAFLD demonstrates a close association with type 2 diabetes mellitus (T2DM) and obesity (3), as they share common pathophysiological mechanisms involving insulin resistance, heightened oxidative stress, perturbed hepatic glucose regulation, and impaired lipid metabolism (4–6). Furthermore, accumulating evidence has demonstrated that the impact of MAFLD extends beyond hepatic implications and profoundly influences T2DM (7). MAFLD amplifies the risk of diabetes-related complications in individuals with T2DM, including cardiovascular diseases (8) and progressive chronic kidney disease (9). Given the prevalence and detrimental effects of MAFLD in T2DM, timely identification of MAFLD and effective intervention strategies are imperative to either achieve remission or delay the progression to advanced stages.

Insulin resistance constitutes a pivotal factor in the pathogenesis of MAFLD and exacerbates its progression to nonalcoholic steatohepatitis and fibrosis (10, 11). Recent advances in MAFLD have unveiled several insulin resistance indexes that exhibit diagnostic and prognostic potential by combining lipid profiles and blood glucose parameters. Among these indexes, the TG to high-density lipoprotein cholesterol ratio (TG/HDL-c) and triglyceride-glucose (TyG) index have gained wide recognition as surrogate indicators of insulin resistance (12, 13), offering diagnostic value for MAFLD (14, 15). Apolipoprotein A1 (APOA1), the primary protein constituent of high-density lipoprotein cholesterol (HDL-c), appears to establish a potential link between MAFLD and cardiovascular disease (16). Mounting evidence suggests that APOA1 plays multifaceted roles in anti-inflammation, anti-insulin resistance, anti-atherosclerosis, and the inhibition of oxidative stress and nitric oxide production, surpassing the effects of HDL-c itself (17, 18). Additionally, an observational study revealed that the monocyte-to-APOA1 ratio outperforms the monocyte-to-HDL-c ratio in identifying metabolic syndrome (19). Given the biological properties of APOA1 and the supporting clinical evidence, it is plausible to suggest that APOA1 could serve as a more valuable lipid marker for diagnosing MAFLD. As of today, the knowledge regarding the ability of the TG to APOA1 ratio (TG/APOA1) in identifying MAFLD remains uncertain. Consequently, this study aims to evaluate the correlation between TG/APOA1 and MAFLD, as well as compare the efficacy of TG/APOA1 with other insulin resistance indexes, such as TG/HDL-c and TyG index, in identifying MAFLD among individuals with T2DM.

Methods

Participants

This cross-sectional study consecutively recruited individuals with T2DM who were admitted to the national metabolic management center at Longyan First Affiliated Hospital of Fujian Medical University from June 2022 to September 2023. Exclusion criteria were applied to eliminate individuals with the following specific conditions: (1) a history of excessive alcohol consumption (daily alcohol intake ≥ 30 g for men and ≥ 20 g for women), (2) a history of other liver comorbidities such as liver malignancy, viral hepatitis, or autoimmune hepatitis, and (3) treatment with medications that can interfere with lipid metabolism or induce liver steatosis and insulin resistance (e.g., estrogens, tamoxifen, and glucocorticoids), (4) presence of severe hyperglycemia or hypertriglyceridemia, including conditions such as diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, and hyperlipidemic pancreatitis. Before enrollment, all participants

provided written informed consent, and ethical approval was obtained from the Ethical Committee of Longyan First Affiliated Hospital of Fujian Medical University (IC-2022-009). All procedures adhered to the principles outlined in the Declaration of Helsinki. Based on the requirement of a multiple binomial logistic regression model with 10-15 variables (20), following the principle of 5-10 events per variable, and considering the prevalence of MAFLD ranging from 40% to 50.0%, a sample size of 600-800 patients was planned for this study. Figure 1 visually represents the flow chart illustrating participant recruitment in this study. Ultimately, a total of 779 participants were included in the final analysis.

Data collection and laboratory assessments

Demographic information, encompassing sex, age, diabetic duration, smoking status, alcohol intake, medication usage, and medical history, was collected by trained research personnel using a standardized questionnaire. Additionally, anthropometric measurements, including weight, height, waist circumference (WC), and blood pressure (BP), were recorded by trained nurses upon admission. Following an overnight fast, venous blood samples were carefully obtained by the trained nurses and subsequently analyzed in the key laboratory of Longyan First Hospital. The laboratory assessments encompassed a comprehensive set of measurements comprising creatinine, alanine aminotransferase, albumin, aspartate aminotransferase (AST), uric acid (UA), FBG, serum insulin, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), APOA1, HDL-c, hemoglobin A1c (HbA1c), and platelets. The auto-biochemical analyzer (Roche Diagnostics Corporation) was used to determine the biochemical indexes. The polyethylene glycol-enhanced immunoturbidimetric assay (Maker, Chengdu, China) was used to calculate serum ApoA1 levels. HbA1c was evaluated by high-performance liquid chromatography with a D10 set (Bio-RAD).

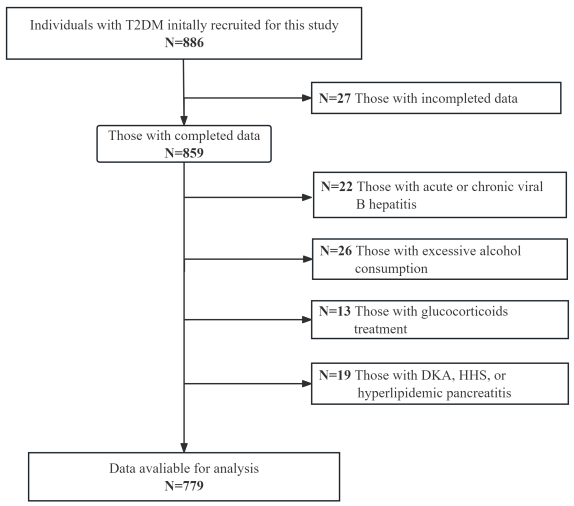

FIGURE 1
The flowchart visually depicts the process of enrolling the study population.

Definition

Insulin resistance indexes, including HOMA-IR, TG/APOA1, TG/HDL-c, and TyG index, were computed using the following equations. HOMA-IR was calculated as fasting serum insulin (μU/ml) x FBG (mmol/l)/22.5 (21). TG/APOA1 and TG/HDL-c were calculated as TG (mmol/l)/APOA1 (mmol/l) and TG (mmol/l)/HDL-c (mmol/l). TyG index was calculated as ln (TG (mg/dl) x FBG (mg/dl)/2) (22). Metabolic dysfunctions, as defined by established criteria (23), encompassed the following conditions: (1) Abdominal obesity indicated by a WC ≥90 cm in men or WC ≥ 80 cm in women. (2) Increased BP characterized by BP ≥ 130/85 mmHg or specific antihypertensive medication. (3) Elevated plasma TG levels characterized by TG≥1.70 mmol/L, or the use of specific lipid-lowering medication. (4) Low levels of HDL-c characterized by HDL-c<1.0 mmol/L in men or HDL-c<1.3 mmol/L in women, or the use of specific lipid-modifying medication. (5) Presence of prediabetes or diabetes. (6) Hyperuricemia characterized by UA ≥ 420 μmol/L or the use of specific medication targeting UA management. (7) Evidence of insulin resistance characterized by HOMA-IR ≥2.5.

Assessment of MAFLD and liver fibrosis risk

The diagnosis of MAFLD in T2DM was established according to the latest international expert consensus statement (23), which stipulated the identification of hepatic steatosis through imaging techniques, blood biomarkers, or liver histology. In this study, the detection of fatty liver was based on the utilization of CT liver-spleen attenuation measurement ($CT_{L\text{-}S}$), a highly accurate CT index specifically designed for evaluating fatty liver. To minimize inter-operator variability, two radiologists were involved in the assessment. $CT_{L\text{-}S}$ was computed by dividing the mean liver attenuation by the mean spleen attenuation. According to the Guidelines for the prevention and treatment of nonalcoholic fatty liver disease (2018, China). The diagnostic criterion for fatty liver was set at $CT_{L\text{-}S}$ <1.0. Further categorization of fatty liver severity was conducted using cut-off points of 0.7 and 0.5, resulting in the classification of mild, moderate, or severe fatty liver (24).

To estimate the probability of liver fibrosis, this study utilized validated indexes known as the nonalcoholic fatty liver disease fibrosis score (NFS), the aspartate aminotransferase-to-platelet ratio index (APRI), and the fibrosis-4 (FIB-4) index, which have shown efficacy in predicting advanced liver fibrosis risk in T2DM with MAFLD (25). The NFS was calculated using the formula: -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 + 0.99 × AST/ALT ratio - 0.013 × platelet count (10^9/L) - 0.66 × albumin (g/dL). The FIB-4 index was determined as age (years) × AST (IU/L)/(platelet count (10^9/L) × ALT (IU/L)$^{1/2}$). Additionally, the APRI was computed as AST (IU/L)/AST (IU/L)/platelet count (10^9/L) × 100. Classification of MAFLD participants into low, intermediate, or high-risk groups for advanced fibrosis was based on specific cut-off points: NFS (-1.455 and 0.676), APRI (0.25 and 0.5), and FIB-4 (1.30 and 2.67).

Statistical analysis

Statistical analysis was conducted using SPSS 26.0 software (SPSS Inc., IBM). To compare baseline characteristics between the MAFLD and Non-MAFLD groups, independent samples T-tests or Kruskal-Wallis tests were performed for continuous variables, while chi-squared (χ^2) tests or Fisher's exact tests were used for categorical variables. Correlation analyses, employing either Pearson's correlation coefficient or Spearman's rank-order correlation coefficient, were performed to assess associations between TG/APOA1 and liver fibrosis-related indexes, as well as $CT_{L\text{-}S}$ in the MAFLD population. Multiple regression analysis was subsequently utilized to further analyze these correlations, with adjustments made for potential confounding variables. The influence of TG/APOA1 on the presence of MAFLD was assessed using binomial logistic regression analysis and Restricted cubic splines (RCS), controlling for relevant confounders across different models. The receiver operating characteristic (ROC) curves analysis was used to compare the identifying value of TG/APOA1 with TG/HDL-c and TyG index for MAFLD. Statistical significance was defined as a two-tailed P-value of less than 0.05, indicating a significant association or difference.

Result

Comparison of clinical characteristics between MAFLD and non-MAFLD group

A total of 779 participants were included in this study, with 401 (52.8%) being men. The mean age of the participants was 53.5 ± 8.0 years old. The overall prevalence of MAFLD was 51.5%. Table 1 summarizes an overview of the comparison of clinical characteristics between the MAFLD and non-MAFLD groups. In

TABLE 1 Comparison of clinical characteristics between the MAFLD and non-MAFLD groups.

Variable	Total (n=779)	MAFLD (n=401)	Non-MAFLD (n=378)	*P*
Age(year)	53.5 ± 8.0	53.0 ± 7.5	54.0 ± 8.6	0.063
Men, n(%)	411 (52.8)	220 (55.1)	189 (49.7)	0.173
Smoking, n(%)	249 (32.0)	130 (34.4)	119 (29.7)	0.158
Drinking, n(%)	291 (37.4)	185(46.1)	106 (28.0)	<0.001
BMI(kg/m^2)	24.4 ± 3.2	25.4 ± 3.2	23.3 ± 2.6	<0.001
WC (cm)	85.8 ± 7.0	88.3 ± 7.4	83.2 ± 5.8	<0.001
SBP (mmHg)	133.4 ± 18.1	139.2 ± 18.4	127.3 ± 15.6	<0.001
DBP (mmHg)	81.5 ± 9.3	83.4 ± 8.5	77.9 ± 8.7	<0.001
HbA1c(%)	8.8 ± 1.1	8.9 ± 1.1	8.8 ± 1.0	0.330
TG(mmol/L)	2.22 ± 1.36	2.64 ± 1.47	1.79 ± 1.13	<0.001
TC(mmol/L)	5.29 ± 1.22	5.20 ± 1.26	5.24 ± 1.17	0.487
HDL-c(mmol/L)	1.09 ± 0.24	0.99 ± 0.21	1.18 ± 0.24	<0.001
LDL-c(mmol/L)	3.52 ± 0.94	3.55 ± 0.98	3.49 ± 0.92	0.299
APOA1(g/L)	0.99 ± 0.19	0.70 ± 0.20	0.97 ± 0.18	<0.001
UA(umol/L)	346.3 ± 86.8	364.7 ± 91.3	326.7 ± 77.2	<0.001
Creatinine(umol/L)	69.2 ± 13.3	68.4 ± 13.3	70.1 ± 13.4	0.086
ALT (IU/L)	37.7 ± 9.0	38.6 ± 9.3	36.7 ± 8.5	0.004
AST (IU/L)	31.2 ± 7.0	32.2 ± 7.7	30.2 ± 6.1	<0.001
Albumin(g/L)	40.1 ± 4.3	39.9 ± 5.1	40.3 ± 4.1	0.783
Platelets(10^9/L)	188.8 ± 51.6	187.8 ± 54.3	190.1 ± 49.3	0.689
HOMA-IR	3.18 ± 1.76	3.71 ± 1.81	2.62 ± 1.51	<0.001
TG/APOA1	3.00 ± 2.39	4.04 ± 2.67	1.89 ± 1.37	<0.001
TG/HDL-c	2.34 ± 1.91	2.90 ± 2.0	1.73 ± 1.59	<0.001
TyG index	9.44 ± 0.68	9.66 ± 0.64	9.21 ± 0.65	<0.001

BMI, body mass index; WC, waist circumference; HbA1c, Glycated hemoglobin; UA, uric acid; TG, triglycerides; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMR-IR, homeostasis model assessment insulin resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APOA1, apolipoprotein A1; TG/APOA1, triglycerides to apolipoprotein A1 ratio; TG/HDL-c, triglycerides to high-density lipoprotein cholesterol ratio; TyG, triglyceride glucose index.

comparison to the non-MAFLD group, various parameters exhibited significant differences in the MAFLD group. Specifically, BMI, WC, SBP, DBP, TG, UA, ALT, AST, and insulin resistance indexes such as HOMA-IR, TG/APOA1, TG/HDL-c, and TyG index. In contrast, HDL-c and APOA1 levels were decreased in the MAFLD group.

Metabolic dysfunctions and liver fibrosis risk across TG/APOA1 quartiles

The prevalence of MAFLD and metabolic dysfunctions across TG/APOA1quartiles (Q1: <1.37; Q2: 1.37-2.31; Q3: 2.32-3.83; Q4: >3.83) in individuals with T2DM are depicted in Figure 2. The prevalence of MAFLD ranged from 15.7% in Q1 to 84.1% in Q4, indicating a significant increase with higher TG/APOA1 quartiles (Figure 2A). Furthermore, the distribution of metabolic dysfunctions differed significantly across the four quartiles (Figure 2B). The proportion of participants with more than three metabolic dysfunctions decreased significantly from 95.4% in the higher quartiles to 4.0% in the lower quartiles ($P < 0.05$). Figure 3 illustrates advanced liver fibrosis risk and fatty liver severity across TG/APOA1 quartiles (Q1:<2.24; Q2:2.24-3.33; Q3:3.34-4.95; Q4: >4.95) in participants with MAFLD. The results demonstrate a significant increase in the proportion of participants with intermediate or high-risk advanced liver fibrosis in the higher quartiles compared to the lower quartiles based on NFS (Figure 3A), FIB-4 (Figure 3B), and APRI (Figure 3C). Additionally, higher TG/APOA1 quartiles were associated with a higher prevalence of moderate or severe fatty liver (Figure 3D).

Correlations of TG/APOA1 with $CT_{L\text{-}S}$ and advanced liver fibrosis risk

Figure 4 illustrates the univariate correlations between TG/APOA1 and NFS (Figure 4A), FIB-4 (Figure 4B), APRI (Figure 4C), and $CT_{L\text{-}S}$ (Figure 4D) in the MAFLD population. The findings indicate positive correlations of TG/APOA1 with NFS (r=0.401, P<0.001), FIB-4 (r=0.197, P<0.001), and APRI (r=0.193, P<0.001). Conversely, a negative correlation was observed between TG/APOA1 with $CT_{L\text{-}S}$ (r=-0.352, P<0.001). To further evaluate these correlations while accounting for potential confounding factors, multiple linear regression analyses were conducted. The results are presented in Table 2, demonstrating that TG/APOA1 maintained positive associations with NFS, FIB-4, and APRI while exhibiting a negative association with $CT_{L\text{-}S}$ in Model 1 (adjustments for age, sex, diabetic duration, smoking, and drinking) and Model 2 (further adjustments for BMI, SBP, DBP, HbA1c, and UA based on Model 1). Furthermore, even after adjusting for lipid profiles such as TC, LDL, and HDL-c based on Model 2 (Model 3), TG/APOA1 continued to exhibit significant associations with NFS (β=0.266, P<0.001), FIB-4 (β=0.123, P=0.029), APRI (β=0.113, P=0.037), and $CT_{L\text{-}S}$ (β=-0.225, P<0.001).

Correlations of TG/APOA1 with MAFLD

Figure 5 illustrates the correlation between TG/APOA1 and MAFLD following adjustments for confounding factors using binomial logistic regression analysis. The findings reveal that TG/APOA1 demonstrated an independent correlation with MAFLD in model 1(adjustments for age, sex, diabetic duration, smoking, and drinking) and model 2(further adjustments for metabolic dysfunctional indicators like BMI, WC, SBP, DBP, HbA1c, UA, TC, LDL, and HDL-c based on model 1) whether in the total population, men, or women. Notably, even after further adjusting for liver functional indicators like ALT, AST, albumin, and platelets based on model 2 (model 3), TG/APOA1 remained significantly associated with MAFLD. The OR with a 95% CI was calculated as 2.092 (1.840-2.380) in the total population, 2.123 (1.810-2.511) in men, and 2.162 (1.824-2.587) in women. Figure 6 illustrates the relationship between TG/APOA1 and MAFLD analyzed using RCS. The results indicate a nonlinear increasing association between TG/APOA1 and MAFLD even after adjustments for model 3 whether in the total population (Figure 6A), men (Figure 6B), or women (Figure 6C). Crucially, both the statistical values for nonlinearity and overall association are below the threshold of significance ($P < 0.001$).

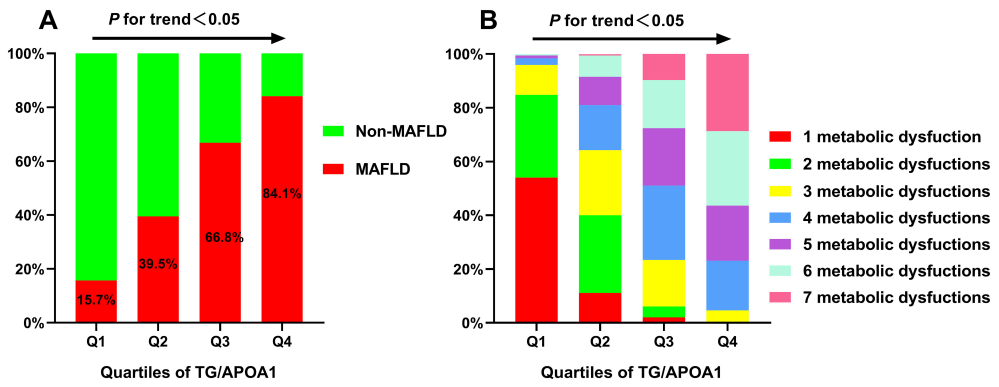

FIGURE 2
The increased prevalence of MAFLD across TG/APOA1 quartiles **(A)**. The distribution of 1 metabolic dysfunction to 7 metabolic dysfunctions in the TG/APOA quartile groups **(B)**. MAFLD, metabolic dysfunction-associated fatty liver disease; TG/APOA1, triglycerides to Apolipoprotein A1 ratio.

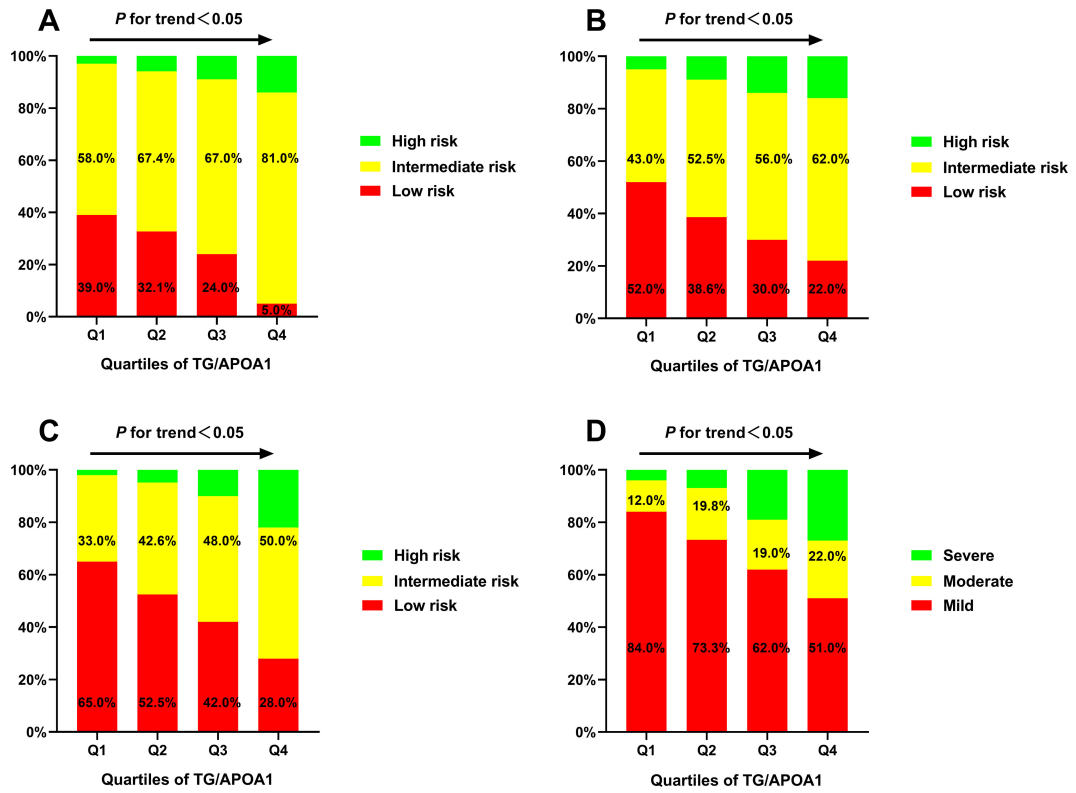

FIGURE 3
The advanced liver fibrosis risk based on the nonalcoholic fatty liver disease fibrosis score **(A)**, the fibrosis-4 index **(B)**, and the aspartate aminotransferase-to-platelet ratio index **(C)** index and the severity of fatty liver based on CT liver-spleen attenuation measurement **(D)**.

Comparison of MAFLD identifying value between TG/APOA1 and TG/HDL-c, TyG index

Figure 7 illustrates the comparative efficacy of TG/APOA1, TG/HDL-c, and the TyG index in identifying MAFLD. In the total population (Figure 7A), TG/APOA1 demonstrated a superior AUC compared to TG/HDL-c (0.769 vs 0.742, P=0.025) and the TyG index (0.769 vs 0.694, $P < 0.001$). Among men (Figure 7B), TG/APOA1 also exhibited a higher AUC than TG/HDL-c (0.776 vs 0.744, P=0.044), and the TyG index (0.776 vs 0.709, $P < 0.001$). Similarly, in women (Figure 7C), TG/APOA1 displayed a higher AUC level than TG/HDL-c (0.762 vs 0.728, P=0.041), and the TyG index (0.762 vs 0.674, $P < 0.001$).

Discussion

MAFLD has emerged as a prevalent cardiometabolic disorder with far-reaching effects beyond the liver, including its impact on T2DM. Consequently, early identification of high-risk MAFLD cases in T2DM becomes imperative for timely intervention. Notably, recent evidence suggests that APOA1 plays a pivotal role in linking MAFLD to cardiovascular disease and possesses multifaceted functions in anti-inflammation and anti-insulin resistance, surpassing the influence of HDL-c alone. Therefore, the TG/APOA1 holds promise to be a more valuable insulin resistance marker for diagnosing MAFLD. This study evaluated the correlation between TG/APOA1 and MAFLD and compared the efficacy of TG/APOA1 with TG/HDL-c and TyG index in identifying MAFLD among individuals with T2DM. The results revealed that TG/APOA1 exhibited significant associations with NFS, FIB-4, APRI, and CT_{L-S}. Meanwhile, TG/APOA1 contributed to an independent variable for MAFLD. This study also uncovered a notable association between elevated TG/APOA1 and higher MAFLD risk. Notably, TG/APOA1 outperformed both TG/HDL-c and the TyG index in identifying MAFLD among individuals with T2DM.

The intricate relationship between metabolic dysfunctions and the complex mechanisms underlying the development of NAFLD has prompted the consideration of renaming it as MAFLD (26). Aside from liver damage, MAFLD is frequently accompanied by various metabolic dysfunctions, including obesity, hypertension, dyslipidemia, hyperuricemia, and increased insulin resistance (27). Hence, this study observed that participants in the MAFLD group exhibited higher levels of WC, SBP, DBP, TG, UA, and HOMA-IR. Conversely, participants in the MAFLD group exhibited lower levels of HDL-c and APOA1 compared to the non-MAFLD group. Insulin resistance, a central contributor to MAFLD, disrupts glucose and lipid metabolism, thereby driving the onset and progression of the disease (10). Excessive hepatic triglyceride accumulation characterizes MAFLD, and hepatic insulin resistance contributes to impaired inhibition of hepatic gluconeogenesis and

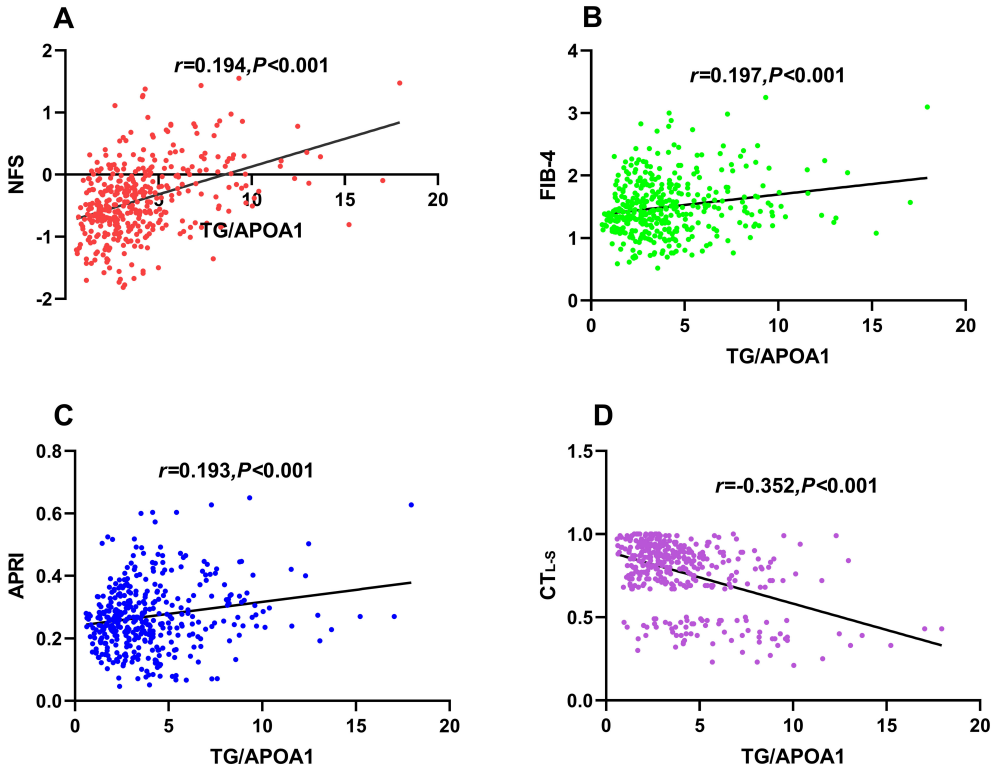

FIGURE 4
Univariate correlations between TG/APOA1 and NFS **(A)**, FIB-4 **(B)**, APRI **(C)**, and CT_{L-S} **(D)**. TG/APOA1, triglycerides to Apolipoprotein A1 ratio; NFS, nonalcoholic fatty liver disease fibrosis score; FIB-4, fibrosis-4 index **(B)**. APRI, AST-to-platelet ratio index; CT_{L-S}, CT liver-spleen attenuation measurement.

increased *de novo* lipogenesis, triggering hepatic lipogenesis and impaired glucose metabolism (1, 28), the combination of TG with HDL-c or FBG as insulin resistance indexes of MAFLD in T2DM has been explored in previous studies. Zhu. et al. identified a robust association between TG/HDL-c and the risk of NAFLD in a cohort of 1913 participants with T2DM (29). Additionally, Malek M. et al. delineated independent correlations between the TyG index and NAFLD in a study involving 175 individuals with T2DM (30).

TABLE 2 Multivariate linear regression analysis of the association between TG/APOA1 and NFS, FIB-4, APRI, and CT_{L-S} in participants with MAFLD.

Variable	Model 1		Model 2		Model 3	
	β	*P*	*β*	*P*	*β*	*P*
NFS	0.388	<0.001	0.323	<0.001	0.266	<0.001
FIB-4	0.193	<0.001	0.147	0.005	0.123	0.029
APRI	0.191	<0.001	0.132	0.012	0.113	0.037
CT_{L-S}	-0.329	<0.001	-0.253	<0.001	-0.225	<0.001

Model 1: adjusted for age, gender, diabetic duration, drinking, and smoking.
Model 2: further adjustment for body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, glycated hemoglobin A1c, and uric acid.
Model 3: additional adjustment for lipid profiles like total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.
TG/APOA1, triglycerides to Apolipoprotein A1 ratio; NFS, nonalcoholic fatty liver disease fibrosis score; FIB-4, fibrosis-4 index; APRI, AST-to-platelet ratio index; MAFLD, metabolic dysfunction-associated fatty liver disease.

Consistent with the aforementioned studies, this study revealed that TG/APOA1 contributed to an independent variable for MAFLD even after adjusting for metabolic and liver functional profiles. This study also uncovered a notable association between elevated TG/APOA1 and higher MAFLD risk from the RCS analysis. The findings indicated that TG/APOA1 contributed to being an independent risk factor for MAFLD and holds promise to be a valuable insulin resistance marker for identifying MAFLD.

Liver biopsy was conventionally regarded as the gold standard for diagnosing NAFLD and liver fibrosis, representing a primary endpoint in clinical studies. However, its invasive nature and significant variability have restricted its widespread clinical application (31). Consequently, several non-invasive methods, including advanced imaging techniques and blood biomarkers, have emerged in recent decades as alternatives to liver biopsy. Notably, NFS, FIB-4, and APRI have been validated and recommended as indexes to assess the risk of advanced liver fibrosis in MAFLD (25). Previous studies have reported a positive correlation between the TG/HDL-c and NFS, as well as FIB-4, among 265 participants with NAFLD (32). Similarly, Ting et al. identified TG/HDL-c as an independent predictor of liver fibrosis evaluated through controlled attenuation parameters and liver stiffness measurements in pediatric NAFLD (33). This study aligns with these observations regarding TG/HDL-c, demonstrating a positive and independent association between TG/APOA1 and NFS, FIB-4, and APRI. Consequently, it can be speculated that TG/HDL-c may

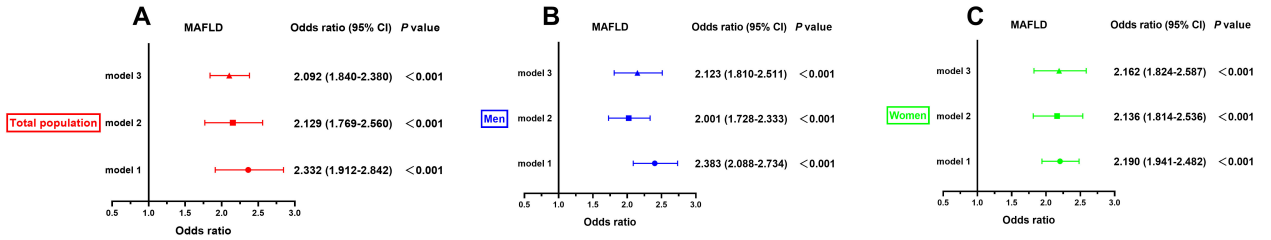

FIGURE 5
The correlation of TG/APOA1 with MAFLD after adjusting for different models in the total population **(A)**, men **(B)**, and women **(C)**. model 1: adjustments for age, sex, diabetic duration, smoking, and drinking. model 2: further adjustments for metabolic dysfunctional indicators like body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, glycated hemoglobin A1c, uric acid, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol based on model 1. model 3: further adjusting for liver functional indicators like aminotransferase, aspartate aminotransferase albumin, albumin, and platelets based on model 2. MAFLD, metabolic dysfunction-associated fatty liver disease; TG/APOA1, triglycerides to Apolipoprotein A1 ratio.

play a role in the development and progression of MAFLD. However, further follow-up studies incorporating liver biopsies are warranted to confirm this hypothesis. Additional investigations are necessary to gather more evidence through longitudinal examination, ultimately strengthening the relationship between TG/APOA1 and liver biopsies. This comprehensive approach will facilitate validating the potential of TG/APOA1 as a reliable marker in assessing the risk of advanced liver fibrosis in MAFLD.

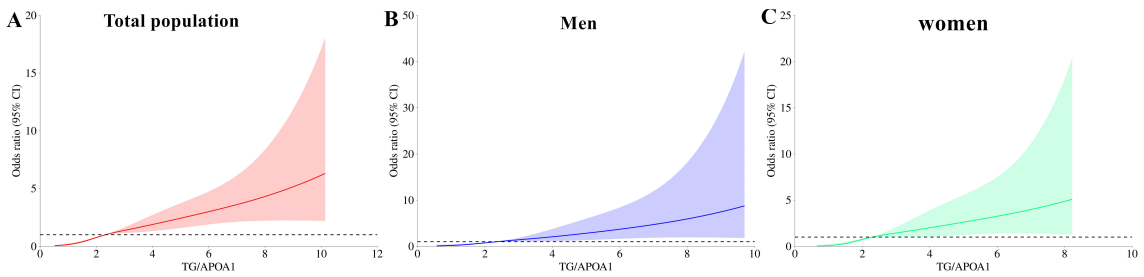

FIGURE 6
Restricted cubic spines analysis of the correlation between TG/APOA1 and MAFLD after adjusting for model 3 in the total population **(A)**, men **(B)**, and women **(C)**. model 3: adjustments for age, sex, diabetic duration, smoking, drinking, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, glycated hemoglobin A1c, uric acid, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and liver functional indicators like aminotransferase, aspartate aminotransferase albumin, albumin, and platelets MAFLD, metabolic dysfunction-associated fatty liver disease; TG/APOA1, triglycerides to Apolipoprotein A1 ratio.

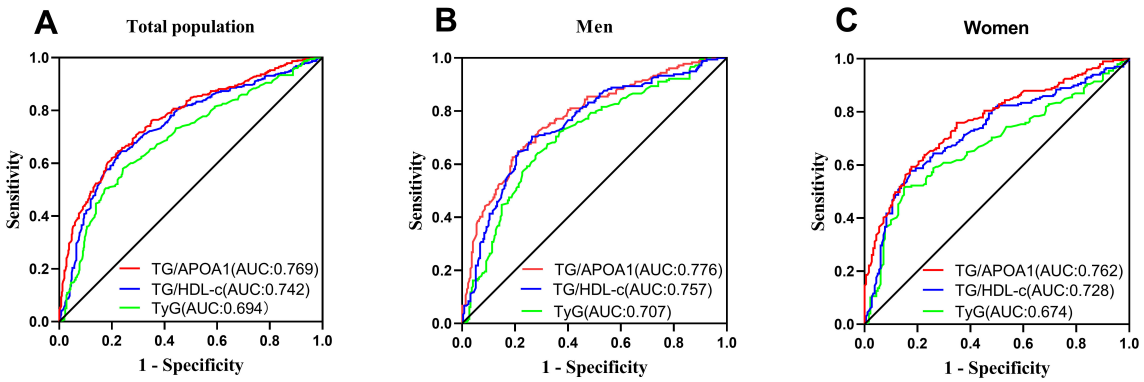

FIGURE 7
Comparison of MAFLD identifying value between TG/APOA1 and TG/HDL-c, TyG index in the total population **(A)**, men **(B)**, and women **(C)**. MAFLD, metabolic dysfunction-associated fatty liver disease; TG/APOA1, triglycerides to Apolipoprotein A1 ratio; TG/HDL-c, triglycerides to high-density lipoprotein cholesterol ratio; TyG index, triglyceride-glucose index.

Emerging evidence has suggested that the TG/HDL-c and TyG index hold diagnostic value for MAFLD in individuals with T2DM (34, 35). However, compared to TG/APOA1 and TG/HDL-c, the TyG index has certain limitations in diagnosing cardiometabolic diseases. Some studies have not definitively confirmed the close association between the TyG index and cardiovascular events, particularly in diabetic patients who may experience extreme FBG levels (36). This study compared the efficacy of TG/APOA1 with TG/HDL-c and TyG index in identifying MAFLD among individuals with T2DM. The results demonstrated that TG/APOA1 and TG/HDL-c outperformed the TyG index in identifying MAFLD. Additionally, TG/APOA1 exhibited superior identification capability for MAFLD compared to TG/HDL-c. Notably, the superiority of TG/APOA1 over TG/HDL-c in identifying MAFLD may be attributed to the biological properties of APOA1. Beyond its well-documented cardioprotective function, recent research has shown that APOA1 also plays novel roles in mitigating inflammation and insulin resistance in the pathogenesis of NAFLD. Among the transcription factors involved in fatty acid metabolism, inflammation, and fibrosis in MAFLD, peroxisome proliferator-activated receptors (PPARs) play crucial roles, exhibiting high oxidative rates in the liver (37). Chen et al. identified APOA1 as a central protein linking PPARs and NAFLD, as it beneficially regulates 16 out of 21 upstream regulators involved in NAFLD (38). Additionally, the anti-inflammatory function of HDL-c has been demonstrated to depend on its functionality rather than serum level, particularly in individuals with T2DM (39). Considering that APOA1 is the functional protein component of HDL-c, serum levels of APOA1 may better reflect the anti-insulin properties of HDL-c.

Strength and limitation

This study possesses noteworthy strengths, primarily contributing to a novel insulin resistance index for diagnosing MAFLD in T2DM. In addition, this study also conducted the RCS analysis and adjusted the potential confounders to evaluate the association between TG/APOA1 and MAFLD. However, it is important to acknowledge several limitations associated with this investigation. Firstly, hepatic steatosis assessment was conducted through unenhanced CT scans, rather than utilizing liver biopsy, which is considered the gold standard criteria. This methodological variation may introduce potential discrepancies in the accuracy of the diagnosis. Secondly, the study design was cross-sectional, lacking a longitudinal follow-up, limiting the ability to establish a direct correlation between TG/APOA1 and MAFLD over time. Future studies with a prospective approach allowing for longitudinal evaluations are warranted to explore the dynamic relationship between TG/APOA1 and the progression of MAFLD. Lastly, it is worth noting that the data for this study were collected exclusively from a single center within the Chinese population. Consequently, caution should be exercised when generalizing the findings to other populations due to potential variations related to race and ethnicity.

Conclusion

In conclusion, this study demonstrated significant associations between TG/APOA1 and NFS, FIB-4, APRI, and MAFLD. Importantly, TG/APOA1 exhibited superior diagnostic capability for identifying MAFLD compared to TG/HDL-c and the TyG index. These findings suggest that TG/APOA1 may be an effective index in identifying MAFLD. Overall, these results highlight the potential of TG/APOA1 as a promising index for efficient screening of MAFLD.

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 Ethical Committee of Longyan First Affiliated Hospital of Fujian Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WW: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. YC: Data curation, Investigation, Software, Writing – original draft. MT: Data curation, Investigation, Writing – original draft. HC: Data curation, Investigation, Methodology, 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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Lipid metabolism indicators provide tools for the diagnosis of non-alcoholic fatty liver disease: results of a nationwide survey

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Background: Cardiometabolic index (CMI), visceral adiposity index (VAI), and lipid accumulation product (LAP) are lipid-related parameters that reflect central obesity, which is closely associated with the development of non-alcoholic fatty liver disease (NAFLD). The aim of this study is to investigate the effectiveness of these lipid-related parameters in diagnosing NAFLD and to compare their predictive abilities.

Methods: This population-based study extracted datasets from the National Health and Nutrition Examination Survey (NHANES) 2017–2020. CMI, VAI, and LAP were included in the multivariate logistic model as both continuous and categorical variables to assess the relationship between different lipid-related parameters and NAFLD. To further elucidate this connection, we utilized restricted cubic splines and conducted subgroup analysis. Additionally, the receiver operating characteristics (ROC) curve was employed to evaluate the predictive effectiveness of CMI, VAI, and LAP for NAFLD.

Results: The study included 2,878 adults as the study population, of whom 1,263 participants were diagnosed with NAFLD. When lipid-related parameters were analyzed as continuous variables, they showed a positive correlation with NAFLD. The OR(95%CI) were 2.29(1.81,2.89) for CMI (per 1-unit), 1.40(1.28,1.52) for VAI (per 1-unit) and 1.15(1.11,1.20) for LAP (per 10-units). This correlation remains statistically significant when the lipid-related parameters are analyzed as categorical variables. In descending order of diagnostic capability for NAFLD, the AUC values are as follows: LAP (0.794), CMI (0.752), and VAI (0.719).

Conclusion: CMI, VAI, and LAP may be important clinical indicators for identifying NAFLD, with LAP demonstrating the best predictive ability among them.

KEYWORDS

visceral adiposity index, cardiometabolic index, lipid accumulation product, non-alcoholic fatty liver disease, cardiometabolic disease, NHANES

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver condition marked by excessive lipid accumulation in hepatocytes except alcohol and other definite liver injury factors. NAFLD can progress from hepatic steatosis to non-alcoholic steatohepatitis (NASH) and, in more severe cases, advance to liver fibrosis and cirrhosis, ultimately leading to hepatocellular carcinoma (HCC) (1). As the most prevalent chronic liver disease, the number of NAFLD patients in America is projected to reach 100.9 million by 2030 (2). The overall prevalence of NAFLD was estimated to be 32.4% worldwide, and its incidence and liver-related mortality are increasing significantly (3, 4). NAFLD is a metabolic disease closely related to obesity, dyslipidemia, diabetes, hypertension and other metabolic disorders, and its etiology is still unclear (5, 6). To accurately reflect the primary drivers of the disease, the concept of metabolic dysfunction-associated fatty liver disease (MAFLD) has been proposed in recent years (7). NAFLD has greatly increased the burden of human health and social health care, so it is important to find effective clinical indicators to identify NAFLD as early as possible and reduce its risk.

Previous studies have indicated that visceral fat and dyslipidemia are significant risk factors for the development of NAFLD (8–12). As a composite index of waist circumference (WC), body mass index (BMI), triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C), visceral adiposity index (VAI) can effectively reflect visceral fat accumulation and dysfunction (13). Xu et al.'s prospective cohort study based on the Chinese population and Okamura et al.'s longitudinal study based on the Japanese population both found that VAI can serve as a predictive indicator for NAFLD (14, 15). Cardiometabolic index (CMI) is a novel index that combines waist-to-height ratio and TG/HDL-C, and it is considered an effective measure for assessing visceral adipose tissue (16, 17). A study involving 14,251 Japanese individuals found that elevated CMI is independently linked to a higher risk of NAFLD (18). The lipid accumulation product (LAP), calculated using WC and TG, can more accurately reflect the degree of lipid accumulation (19). Although studies have shown that CMI, VAI, and LAP are associated with the risk of NAFLD, the predictive abilities of these lipid-related parameters for NAFLD have not yet been clarified.

Using the latest data from the nationally representative National Health and Nutrition Examination Survey (NHANES) database, this study aimed to compare the potential value of lipid-related parameters in predicting NAFLD among the adults in the U.S.

Materials and methods

Study design

NHANES formed representative population data in the United States by surveying different populations, which adopted a stratified multi-stage sampling design and was approved by the National Center for Health Statistics Ethics Review Board. The study followed the Declaration of Helsinki and obtained written informed consent from the study population.

In this research, we focused on the NHANES 2017-March 2020 cycle, which included 15,560 participants. The exclusion criteria for the study population were as follows (1): individuals aged< 20 years old; (2) individuals without controlled attenuation parameter (CAP) values; (3) individuals without WC, BMI, TG or HDL-C; (4) individuals who were positive for Hepatitis B virus (HBV) surface antigen or Hepatitis C virus (HCV) RNA; (5) individuals who drank more than 2 alcoholic beverages per day for females and more than 3 alcoholic beverages per day for males. Consequently, the final study population consisted of 2,878 participants (Figure 1).

Study variables

CMI, VAI and LAP were calculated as follows:

$$CMI = \frac{WC}{Height} \times \frac{TG}{HDL-C}$$

$$VAI = \{WC/[39.68 + (1.88 \times BMI)]\} \times (TG/1.03) \times (1.31/HDL-C)$$

for males;

$$VAI = \{WC/[36.58 + (1.89 \times BMI)]\} \times (TG/0.81) \times (1.52/HDL-C)$$

for females;

$$LAP = (WC - 65) \times TG$$

for males;

$$LAP = (WC - 58) \times TG$$

for females

WC and height were measured in cm, BMI was reported in kg/m^2, TG and HDL-C were measured in mmol/L. The diagnosis of NAFLD was based on the CAP value obtained by liver ultrasound transient elastography, and the diagnostic criterion was CAP≥274 dB/m (20).

Covariates included age, gender, race, BMI, education level, marital status, poverty income ratio (PIR), WC, HDL-C, TG, diabetes, hypertension, smoking and drinking status. Education level was categorized into three groups: below high school, high school, and above high school. Smoking status was determined by asking participants if they had smoked at least 100 cigarettes in their lifetime. Drinking status was assessed by asking participants if they had consumed at least 12 alcoholic drinks in one year.

All study variables were obtained from the publicly available NHANES dataset. These variables were selected based on their relevance to the study objectives.

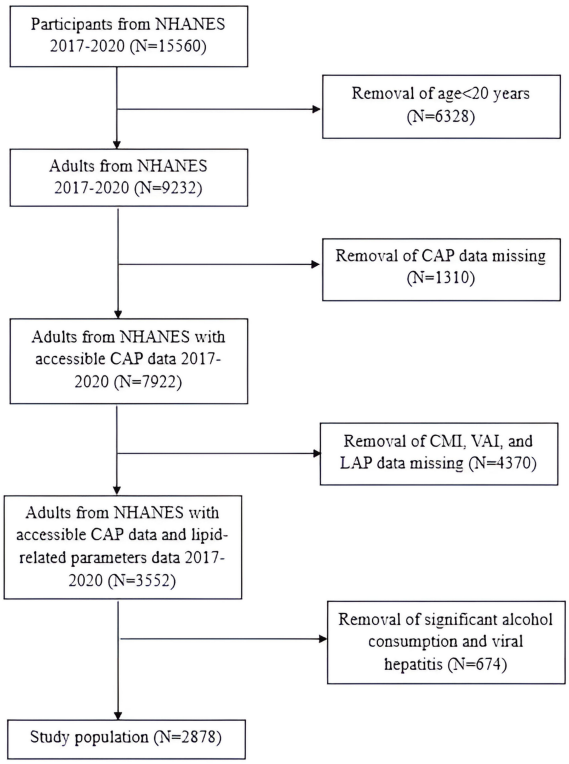

FIGURE 1
Flowchart of the study population.

Statistical analysis

Continuous variables conforming to a normal distribution were presented as mean ± standard deviation (SD). Conversely, those not following a normal distribution were depicted by the median along with the interquartile range (IQR). Categorical variables were reported as frequencies (n) and proportions (%). To analyze continuous variables, ANOVA and Kruskal-Wallis H tests were employed, while chi-square tests were used to compare categorical variables. This analysis aimed to investigate the characteristics of the participants with and without NAFLD. Study population was categorized into quartiles according to their CMI, VAI, and LAP values, designated as Q1, Q2, Q3, and Q4. To assess the correlation between lipid-related parameters and NAFLD, multivariate logistic regression was applied across three models. The strength of these associations was expressed using odds ratios (OR) and 95% confidence intervals (CI). Model 1 made no adjustments for covariates. Model 2 adjusted for gender, age, and race, while Model 3 accounted for all covariates. At first, lipid-related parameters were included in logistic models as continuous variables and then categorized into quartiles. The potential nonlinear dose-response relationships between these lipid-related parameters and NAFLD were investigated by restricted cubic splines (RCS). Additionally, we conducted a subgroup analysis to assess whether this association varies among different populations. To compare the predictive performance of the lipid-related parameters for NAFLD, we calculated the area under the curve (AUC) for each parameter and explored their respective cutoff values. All analyses were performed using SAS version 9.4, with a two-sided P-value of less than 0.05 considered statistically significant.

Results

Characteristics of the study population

The study included 2,878 participants, comprising 1,374 males and 1,504 females. According to CAP, 1,263 participants were diagnosed with NAFLD, resulting in a prevalence rate of 43.9%. The mean ± SD values for the lipid-related parameters (CMI, VAI, and LAP) were 0.7 ± 1.0, 1.8 ± 2.2 and 51.7 ± 56.8. We described the characteristics of the study population based on the presence or absence of NAFLD (Table 1). Generally, individuals with NAFLD tend to be older, more frequently male, and show a higher prevalence of diabetes and hypertension. As components of lipid-related parameters, BMI, WC and TG were significantly increased in participants with NAFLD, while HDL-C was significantly decreased. Furthermore, participants with NAFLD demonstrated significantly higher levels of CMI, VAI, and LAP compared to those without the disease (P<0.0001).

Table 2 presents the characteristics of the participants grouped according to the quartiles of CMI, VAI, and LAP. In the groups based on different indicators, it was found that the subgroups with higher lipid-related parameters had a higher proportion of people with NAFLD, diabetes, and hypertension. Additionally, BMI, WC,

TABLE 1 Comparison of characteristics between participants with and without NAFLD.

Characteristics	Total (N=2878)	Without NAFLD (N=1615)	With NAFLD (N=1263)	P Value
Age (year), mean ± SD	52.3 ± 16.9	50.1 ± 17.8	55.1 ± 15.3	<0.0001
Gender, n (%)				<0.0001
Male	1374 (47.7)	718 (44.5)	656 (51.9)	
Female	1504 (52.3)	897 (55.5)	607 (48.1)	
Race, n (%)				<0.0001
Mexican American	333 (11.6)	145 (9.0)	188 (14.9)	
Other Hispanic	297 (10.3)	166 (10.3)	131 (10.4)	
Non-Hispanic White	971 (33.7)	510 (31.6)	461 (36.5)	
Non-Hispanic Black	732 (25.4)	468 (29.0)	264 (20.9)	
Other Race	545 (18.9)	326 (20.2)	219 (17.3)	
Education level, n (%)				0.1830
Less than high school	526 (18.3)	279 (17.3)	247 (19.6)	
High school	659 (22.9)	364 (22.6)	295 (23.4)	
More than high school	1691 (58.8)	971 (60.2)	720 (57.1)	
Marital status, n (%)				<0.0001
Cohabitation	1758 (61.2)	924 (57.3)	834 (66.1)	
Solitude	1116 (38.8)	689 (42.7)	427 (33.9)	
PIR, mean ± SD	2.7 ± 1.6	2.7 ± 1.6	2.7 ± 1.6	0.4812
Smoking status, n (%)	1127 (39.2)	612 (37.9)	515 (40.8)	0.1223
Drinking status, n (%)	1078 (44.1)	641 (47.0)	437 (40.4)	0.0012
Diabetes, n (%)	477 (16.6)	158 (9.8)	319 (25.3)	<0.0001
Hypertension, n (%)	1138 (39.6)	506 (31.4)	632 (50.1)	<0.0001
BMI (kg/m^2), mean ± SD	29.7 ± 7.1	27.0 ± 5.9	33.2 ± 7.1	<0.0001
Height (cm), mean ± SD	166.4 ± 10.0	166.0 ± 10.0	167.0 ± 10.1	0.0059
WC (cm), mean ± SD	100.5 ± 16.8	93.3 ± 14.2	109.7 ± 15.4	<0.0001
TG (mmol/L), mean ± SD	1.2 ± 1.1	1.0 ± 0.8	1.5 ± 1.4	<0.0001
HDL-C (mmol/L), mean ± SD	1.4 ± 0.4	1.5 ± 0.4	1.3 ± 0.4	<0.0001
CMI, mean ± SD	0.7 ± 1.0	0.5 ± 0.6	0.9 ± 1.2	<0.0001
VAI, mean ± SD	1.8 ± 2.2	1.3 ± 1.4	2.4 ± 2.8	<0.0001
LAP, mean ± SD	51.7 ± 56.8	34.1 ± 32.7	74.1 ± 71.4	<0.0001

*NAFLD, non-alcoholic fatty liver disease; PIR, poverty income ratio; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; WC, waist circumference; TG, triglyceride; CMI, cardiometabolic index; VAI, visceral adiposity index; LAP, lipid accumulation product.

and TG were higher in groups with higher lipid-related parameters, while HDL-C was lower in these groups.

The correlation between lipid-related parameters and NAFLD

Table 3 illustrates the association between lipid-related parameters and NAFLD. Analyzing these parameters as continuous variables, a positive relationship with NAFLD is evident across all three models. In Model 3, each 1-unit increase in CMI is associated with a 1.29-fold increase in the risk of developing NAFLD [OR (95% CI): 2.29 (1.81, 2.89)]. Similarly, each 1-unit increase in VAI corresponds to a 40% higher risk of NAFLD [OR (95% CI): 1.40 (1.28, 1.52)]. Additionally, for every 10-unit rise in LAP, the risk of NAFLD increases by 15% [OR (95% CI): 1.15 (1.11, 1.20)]. The association between lipid-related parameters and NAFLD remains statistically significant when these parameters are included in the model as categorical variables. Participants with higher quartiles of lipid-related parameters have a greater risk of developing NAFLD.

TABLE 2 Comparison of intergroup differences based on grouping by lipid-related parameters.

Characteristics	CMI				VAI				LAP			
	Q1 (<0.26) (N=719)	Q2 (0.26-0.46) (N=720)	Q3 (0.46-0.81) (N=719)	Q4 (>0.81) (N=720)	Q1 (<0.75) (N=719)	Q2 (0.75-1.27) (N=720)	Q3 (1.27-2.15) (N=719)	Q4 (>2.15) (N=720)	Q1 (<0.75) (N=719)	Q2 (20.68-38.76) (N=720)	Q3 (38.76-65.18) (N=719)	Q4 (>65.18) (N=720)
NAFLD, n (%)	122 (17.0)	234 (32.5)	391 (54.4)	516 (71.7)	154 (21.4)	242 (33.6)	387 (53.8)	480 (66.7)	86 (12.0)	228 (31.7)	391 (54.4)	558 (77.5)
Age (year), mean ± SD	47.6 ± 18.0	52.5 ± 17.1	54.4 ± 16.1	54.6 ± 15.5	48.1 ± 18.1	51.9 ± 17.0	54.5 ± 16.3	54.6 ± 15.4	44.6 ± 17.5	53.7 ± 16.9	55.2 ± 15.6	55.6 ± 15.3
Gender, n (%)												
Male	289 (40.2)	337 (46.8)	340 (47.3)	408 (56.7)	376 (52.3)	348 (48.3)	332 (46.2)	318 (44.2)	351 (48.8)	340 (47.2)	341 (47.4)	342 (47.5)
Female	430 (59.8)	383 (53.2)	379 (52.7)	312 (43.3)	343 (47.7)	372 (51.7)	387 (53.8)	402 (55.8)	368 (51.2)	380 (52.8)	378 (52.6)	378 (52.5)
Race, n (%)												
Mexican American	51 (7.1)	87 (12.1)	80 (11.1)	115 (16.0)	55 (7.6)	84 (11.7)	83 (11.5)	111 (15.4)	52 (7.2)	91 (12.6)	85 (11.8)	105 (14.6)
Other Hispanic	48 (6.7)	68 (9.4)	92 (12.8)	89 (12.4)	46 (6.4)	78 (10.8)	78 (10.8)	95 (13.2)	50 (7.0)	74 (10.3)	88 (12.2)	85 (11.8)
Non-Hispanic White	227 (31.6)	225 (31.3)	225 (31.3)	294 (40.8)	219 (30.5)	216 (30.0)	245 (34.1)	291 (40.4)	208 (28.9)	215 (29.9)	231 (32.1)	317 (44.0)
Non-Hispanic Black	253 (35.2)	219 (30.4)	181 (25.2)	79 (11.0)	265 (36.9)	222 (30.8)	171 (23.8)	74 (10.3)	239 (33.2)	196 (27.2)	196 (27.3)	101 (14.0)
Other Race	140 (19.5)	121 (16.8)	141 (19.6)	143 (19.9)	134 (18.6)	120 (16.7)	142 (19.7)	149 (20.7)	170 (23.6)	144 (20.0)	119 (16.6)	112 (15.6)
Education level, n (%)												
Less than high school	81 (11.3)	114 (15.8)	155 (21.6)	176 (24.4)	94 (13.1)	100 (13.9)	155 (21.6)	177 (24.6)	87 (12.1)	130 (18.1)	145 (20.2)	164 (22.8)
High school	167 (23.3)	180 (25.0)	154 (21.4)	158 (21.9)	168 (23.4)	175 (24.3)	165 (22.9)	151 (21.0)	184 (25.6)	164 (22.8)	146 (20.3)	165 (22.9)
More than high school	469 (65.4)	426 (59.2)	410 (57.0)	386 (53.6)	455 (63.5)	445 (61.8)	399 (55.5)	392 (54.4)	447 (62.3)	425 (59.1)	428 (59.5)	391 (54.3)
Marital status, n (%)												
Cohabitation	398 (55.6)	436 (60.6)	454 (63.1)	470 (65.4)	405 (56.5)	439 (61.1)	450 (62.6)	464 (64.5)	402 (56.0)	447 (62.3)	456 (63.4)	453 (63.0)
Solitude	318 (44.4)	284 (39.4)	265 (36.9)	249 (34.6)	312 (43.5)	280 (38.9)	269 (37.4)	255 (35.5)	316 (44.0)	271 (37.7)	263 (36.6)	266 (37.0)
PIR, mean ± SD	2.9 ± 1.6	2.7 ± 1.6	2.6 ± 1.6	2.6 ± 1.6	2.9 ± 1.6	2.8 ± 1.6	2.6 ± 1.6	2.6 ± 1.6	2.8 ± 1.6	2.8 ± 1.6	2.7 ± 1.6	2.6 ± 1.6
Smoking, n (%)	251 (34.9)	267 (37.2)	280 (38.9)	329 (45.7)	265 (36.9)	255 (35.5)	298 (41.4)	309 (42.9)	254 (35.4)	263 (36.5)	279 (38.9)	331 (46.0)
Drinking, n (%)	329 (53.8)	273 (45.2)	244 (39.2)	232 (38.2)	337 (54.4)	289 (47.4)	236 (38.2)	216 (36.1)	312 (51.6)	284 (47.2)	258 (41.3)	224 (36.5)
Diabetes, n (%)	45 (6.3)	96 (13.4)	137 (19.1)	199 (27.6)	59 (8.2)	90 (12.5)	135 (18.8)	193 (26.8)	49 (6.8)	79 (11.0)	143 (19.9)	206 (28.6)
Hypertension, n (%)	192 (26.7)	267 (37.1)	321 (44.8)	358 (49.7)	208 (28.9)	254 (35.3)	327 (45.5)	349 (48.6)	149 (20.7)	267 (37.1)	331 (46.2)	391 (54.3)
BMI (kg/m^2), mean ± SD	25.2 ± 5.1	29.0 ± 6.3	31.2 ± 6.9	33.4 ± 7.3	26.3 ± 5.9	29.2 ± 7.1	31.1 ± 7.1	32.2 ± 6.9	23.7 ± 3.9	28.4 ± 4.9	31.2 ± 6.0	35.5 ± 7.4

(Continued)

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TABLE 2 Continued

Characteristics	CMI				VAI				LAP			
	Q1 (<0.26) (N=719)	Q2 (0.26-0.46) (N=720)	Q3 (0.46-0.81) (N=719)	Q4 (>0.81) (N=720)	Q1 (<0.75) (N=719)	Q2 (0.75-1.27) (N=720)	Q3 (1.27-2.15) (N=719)	Q4 (>2.15) (N=720)	Q1 (<0.75) (N=719)	Q2 (20.68-38.76) (N=720)	Q3 (38.76-65.18) (N=719)	Q4 (>65.18) (N=720)
Marital status, n (%)												
Height (cm), mean ± SD	166.6 ± 9.8	167.1 ± 10.2	165.5 ± 10.0	166.5 ± 10.1	168.1 ± 10.0	166.9 ± 9.9	165.6 ± 10.2	165.1 ± 9.9	167.1 ± 9.9	166.2 ± 10.1	166.3 ± 10.1	166.1 ± 10.1
WC (cm), mean ± SD	87.5 ± 12.7	99.3 ± 14.8	104.3 ± 14.7	110.7 ± 15.8	90.5 ± 14.8	99.2 ± 16.0	104.7 ± 15.9	107.5 ± 15.4	83.5 ± 9.6	97.4 ± 10.9	105.5 ± 12.8	115.4 ± 14.7
TG (mmol/L), mean ± SD	0.6 ± 0.2	0.9 ± 0.2	1.2 ± 0.3	2.3 ± 1.8	0.6 ± 0.2	0.9 ± 0.2	1.2 ± 0.3	2.3 ± 1.8	0.6 ± 0.2	0.9 ± 0.3	1.2 ± 0.4	2.2 ± 1.8
HDL-C (mmol/L), mean ± SD	1.8 ± 0.4	1.4 ± 0.3	1.3 ± 0.2	1.1 ± 0.2	1.7 ± 0.4	1.4 ± 0.3	1.3 ± 0.2	1.1 ± 0.2	1.7 ± 0.4	1.4 ± 0.4	1.3 ± 0.3	1.1 ± 0.3
CMI	0.2 ± 0.1	0.4 ± 0.1	0.6 ± 0.1	1.6 ± 1.6	0.2 ± 0.1	0.4 ± 0.1	0.6 ± 0.2	1.5 ± 1.6	0.2 ± 0.1	0.4 ± 0.1	0.6 ± 0.2	1.5 ± 1.6
VAI	0.5 ± 0.2	1.0 ± 0.2	1.7 ± 0.4	3.8 ± 3.6	0.5 ± 0.1	1.0 ± 0.1	1.7 ± 0.2	3.9 ± 3.6	0.6 ± 0.3	1.1 ± 0.4	1.7 ± 0.7	3.7 ± 3.7
LAP	14.8 ± 7.7	31.6 ± 11.9	51.1 ± 16.6	109.1 ± 85.9	16.0 ± 9.3	31.8 ± 13.2	52.3 ± 20.1	106.6 ± 87.0	12.7 ± 5.0	29.6 ± 5.1	50.6 ± 7.5	113.6 ± 83.5

*NAFLD, non-alcoholic fatty liver disease; PIR, poverty income ratio; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; WC, waist circumference; TG, triglyceride; CMI, cardiometabolic index; VAI, visceral adiposity index; LAP, lipid accumulation product.

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TABLE 3 Association between CMI, VAI, LAP and NAFLD.

Exposure	Model 1 OR (95%CI)	Model 2 OR (95%CI)	Model 3 OR (95%CI)
CMI (per 1-unit)	5.43 (4.46,6.62)	4.96 (4.06,6.07)	2.29 (1.81,2.89)
CMI (quartile)			
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	2.36 (1.84,3.02)	2.17 (1.69,2.79)	1.27 (0.92,1.75)
Q3	5.83 (4.57,7.44)	5.41 (4.22,6.93)	2.53 (1.83,3.48)
Q4	12.38 (9.61,15.94)	11.14 (8.58,14.46)	3.85 (2.73,5.43)
VAI (per 1-unit)	1.70 (1.59,1.83)	1.68 (1.56,1.80)	1.40 (1.28,1.52)
VAI (quartile)			
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	1.86 (1.47,2.35)	1.79 (1.41,2.28)	1.36 (1.00,1.86)
Q3	4.28 (3.40,5.39)	4.14 (3.27,5.25)	2.33 (1.71,3.17)
Q4	7.34 (5.79,9.29)	7.13 (5.57,9.13)	3.57 (2.58,4.93)
LAP (per 10-unit)	1.35 (1.32,1.40)	1.34 (1.30,1.39)	1.15 (1.11,1.20)
LAP (quartile)			
Q1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Q2	3.41 (2.59,4.49)	3.20 (2.42,4.24)	2.00 (1.41,2.84)
Q3	8.77 (6.71,11.48)	8.40 (6.37,11.07)	3.59 (2.51,5.14)
Q4	25.35 (19.06,33.72)	24.28 (18.07,32.62)	6.51 (4.32,9.80)

Model 1: no covariates were adjusted;
Model 2: age, gender, and race were adjusted;
Model 3: age, gender, race, BMI, education level, marital status, PIR, diabetes, hypertension, smoking and drinking status were adjusted.

The RCS plot shown in Figure 2 visualizes the association between lipid-related parameters and the prevalence of NAFLD. After adjusting for all confounding factors, an increased risk of NAFLD was observed with higher lipid-related parameters.

Comparison of lipid-related parameters

To assess the predictive performance of lipid-related parameters for NAFLD, receiver operating characteristics (ROC) curve was generated. Among these lipid-related parameters, LAP exhibited the highest predictive capability, with an AUC of 0.794 (95% CI: 0.778, 0.810). CMI came next, showing an AUC (95% CI) of 0.752 (0.735, 0.770). In contrast, VAI had comparatively weaker predictive power for NAFLD, with an AUC (95% CI) of 0.719 (0.700, 0.738). Figure 3 displays the ROC curves. According to the principle of closest proximity to (0,1), the optimal cut-off values for CMI, VAI, and LAP should be set at 0.465, 1.341, and 37.02, respectively. At this point, the sensitivity of CMI, VAI, and LAP were 0.717, 0.671, and 0.781, respectively, while the specificity was 0.674, 0.676, and 0.682, respectively (Table 4).

Subgroup analysis

To verify the robustness of lipid-related parameters in predicting NAFLD risk in different populations, we further performed subgroup analysis. The results of the subgroup analysis demonstrated the robustness of the relationship between lipid-related parameters and NAFLD across different populations, with this association being more pronounced in individuals with diabetes, non-smokers, and non-drinkers (Figure 4).

Discussion

In this large national survey, we confirmed the association between lipid-related parameters and NAFLD, and validated the reliability of the results across different subpopulations. This study also compared the predictive abilities of CMI, VAI, and LAP, with LAP demonstrating superior diagnostic capability.

Previous researches have explored the relationship between CMI, VAI, LAP, and NAFLD. A cross-sectional study of 7,238 participants found a positive association between VAI and the risk of NAFLD [OR (95%CI): 1.291(1.223,1.362)], and NAFLD patients

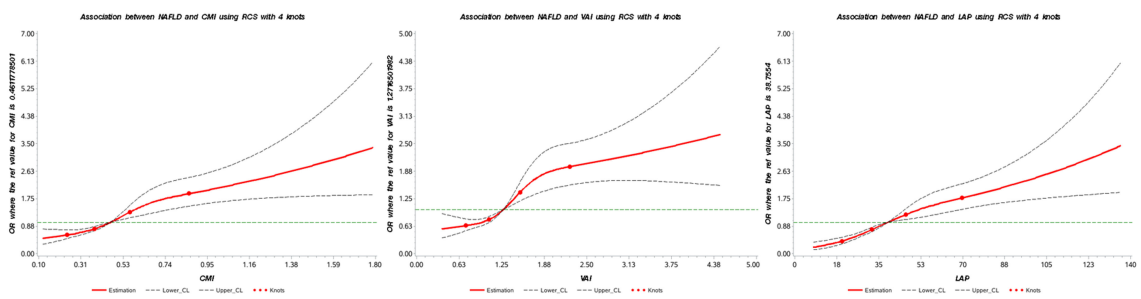

FIGURE 2
Association between lipid-related parameters and NAFLD. The red solid line represents the smoothed curve fit between the variables, while the black dashed lines indicate the 95% confidence interval of the fit. CMI, cardiometabolic index; VAI, visceral adiposity index; LAP, lipid accumulation product.

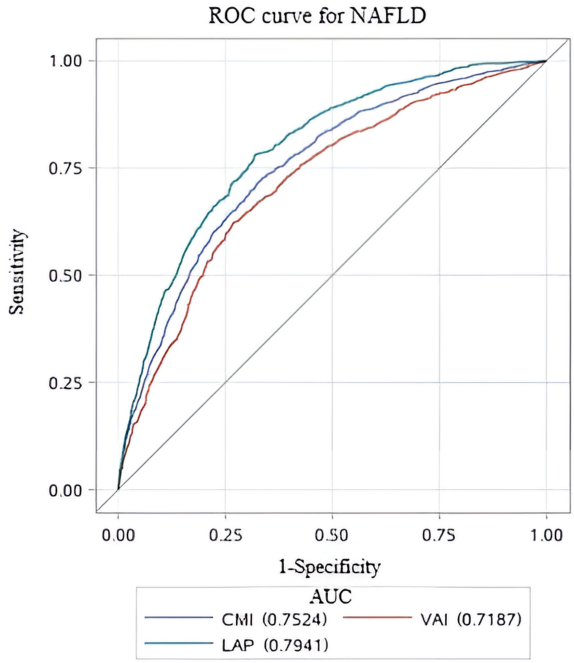

FIGURE 3
ROC curves for different lipid-related parameters to predict NAFLD. ROC, Receiver Operating Characteristic; AUC, area under the curve.

had higher BMI, blood pressure, fasting blood glucose (FBG), TG and WC, and lower HDL-C levels ($p< 0.05$) (21). In addition, a meta-analysis of 24 studies confirmed the reliability of VAI for predicting NAFLD (AUC = 0.767) (22). The study conducted by Li et al., based on NHANES data, also confirmed the association between VAI and NAFLD among U.S. adults (23). A study conducted in the Chinese population suggested that LAP and CMI are convenient indicators for screening and quantifying NAFLD, with a stronger association observed in females (24). A recent study based on the U.S. population found that an increase of one unit in CMI is associated with a 44% increased risk of NAFLD [OR (95%CI): 1.44(1.44,1.45)] (25). Ebrahimi et al. conducted a meta-analysis to assess the diagnostic value of LAP for NAFLD, revealing a sensitivity of 94% and a specificity of 85% (26). Our study utilized the latest NHANES data to confirm the reliability of CMI, VAI, and LAP in predicting the risk of NAFLD among U.S. adults.

CMI, VAI, and LAP, as novel lipid-related parameters, can more effectively reflect the visceral adipose tissue (VAT) than the traditional obesity indicators. VAT may be involved in the pathophysiological mechanism of the occurrence and development of NAFLD through the following ways. Firstly, excessive accumulation of visceral adipose tissue releases free fatty acids (FFA) through lipid interpretation, which reaches the liver through the portal vein and becomes the main source of TG in the liver, and further promotes the development of hepatic steatosis (27–30). Secondly, accumulation of free fatty acids in the liver induces insulin resistance (IR) by inhibiting glucose transport or phosphorylation in muscle (31, 32). IR can not only directly cause NAFLD by enhancing *de novo* lipogenesis in the liver, but also indirectly promote NAFLD by reducing the inhibition of lipolysis in adipose tissue, leading to increased free fatty acid (FFA) delivery to the liver (33, 34). Thirdly, visceral adipose dysfunction disrupts normal metabolic function by increasing inflammatory adipokines, including interleukin-6 (IL-6), macrophage chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α) (35–37). Moreover, oxidative stress resulting from visceral fat accumulation can lead to liver inflammation, NAFLD (38, 39).

The strength of this research lies in the nationally representative study population, which ensures that the predictive value of lipid-related parameters for NAFLD is broadly applicable to the U.S. adult population. In addition, adjustment for potential confounders and the performance of subgroup analyses ensured the reliability of our findings. Several limitations of this study should be acknowledged. In this study, the diagnosis of NAFLD was based on liver ultrasound transient elastography. Although previous

TABLE 4 Evaluation of the performance of lipid-related parameters in predicting NAFLD.

Variables	AUC (95%CI)	Cutoff threshold	Sensitivity	Specificity
CMI	0.752 (0.735, 0.770)	0.465	0.717	0.674
VAI	0.719 (0.700, 0.738)	1.341	0.671	0.676
LAP	0.794 (0.778, 0.810)	37.02	0.781	0.682

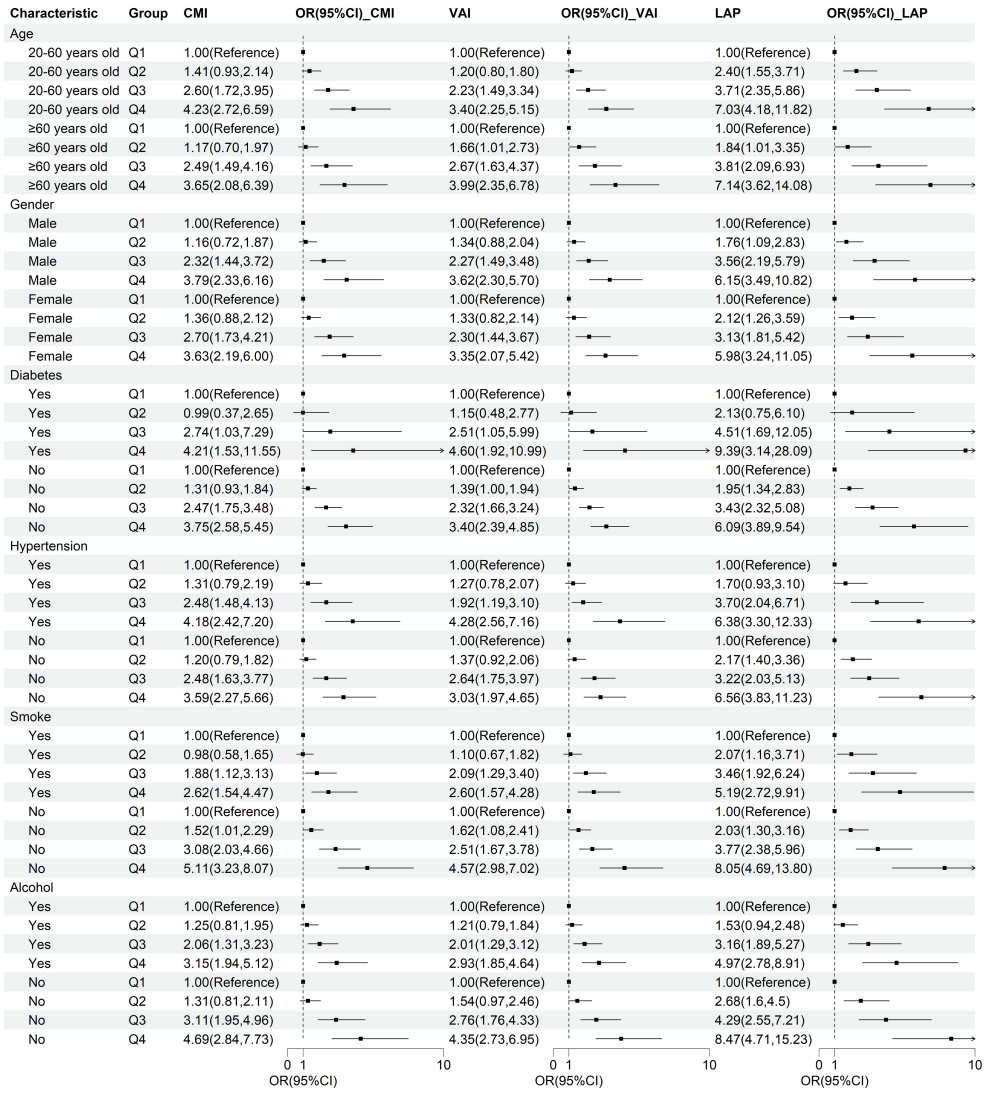

FIGURE 4
Subgroup analysis of the correlation between CMI, VAI, LAP, and NAFLD. Stratification factors include gender, age, smoking and drinking status, diabetes, and hypertension.

studies have shown that its accuracy is very high, there is still a certain gap compared with liver biopsy (40, 41). What's more, because of the design limitations of the survey, the influence of potential confounding factors, including diet and drug use, could not be ruled out.

Conclusions

CMI, VAI, and LAP emerged as useful indicators for identifying NAFLD risk, with LAP showing the highest predictive ability among them in this study. As an easily obtainable clinical indicator, LAP may offer a more practical and cost-effective option for clinical application. However, further research is needed to validate these findings.

Data availability statement

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

Ethics statement

The protocol of NHANES has been approved by the Ethical Review Board of the National Center for Health Statistics, and the participants furnished written informed consent before participation. 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

CF: Conceptualization, Data curation, Methodology, Writing – original draft. HJ: Validation, Visualization, Writing – original draft. YY: Software, Writing – original draft. YW: Data curation, Validation, Project administration, Writing – original draft, Writing – review & editing. XL: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. KL: Investigation, 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.

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Association between LDL/HDL ratio and hypertension in Chinese middle-aged and older adults: a cross-sectional and longitudinal analysis based on CHARLS LDL/HDL ration and hypertension

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Introduction: Hypertension is a global public health issue and major risk factor for cardiovascular disease (CVD). Low-density lipoprotein/high-density lipoprotein ratio (LDL/HDL Ratio, LHR) is an important indicator of lipid metabolism related to CVD. However, the relationship between LHR and the prevalence and incidence of hypertension has not been reported in large populations. This study aims to investigate the association between LHR and hypertension in middle-aged and elderly population.

Methods: This study utilized the China Health and Retirement Longitudinal Study (CHARLS) database from 2011 to 2020. Cross-sectional study was employed to analyze the association between LHR and the prevalence of hypertension; longitudinal analysis was used to examine the association between LHR and the incidence of hypertension. Eligible participants were adults aged 45 years and older with complete LHR and self-reported hypertension records. Multivariate logistic regression, smooth curve fitting, threshold effect analysis was performed.

Results: In the cross-sectional study, we included 13,150 participants. After adjusting for potential confounders, each one-unit increase in LHR was associated with a 22% increase in the prevalence of hypertension (OR = 1.22, 95% CI: 1.15-1.30, $P < 0.0001$). The association between LHR and hypertension was consistent across different subgroups, with higher LHR being more strongly associated with increased hypertension prevalence in females and non-smokers. Our results revealed a linear relationship between LHR and hypertension prevalence. Longitudinal analysis showed that, among participants without hypertension in 2011, after 7 years of follow-up, the association between LHR and hypertension incidence remained robust after adjusting for a wide range of demographic, clinical, and biochemical variables ($P < 0.05$).

Conclusions: These results demonstrated significant positive association between LHR and the prevalence & incidence of hypertension, in a nationwide representative middle-aged and elderly population in China.

KEYWORDS

CHARLS, hypertension, LDL/HDL ratio, prevalence, incidence

Introduction

Hypertension is a public health issue and major risk factor for cardiovascular diseases (CVDs), with atherosclerosis as common mechanism (1). Understanding and managing hypertension involves considering the role of lipid metabolism, particularly the balance between low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). The ratio of LDL-C to HDL-C (LDL/HDL Ratio, LHR) is an important indicator of cardiovascular health and plays a crucial role in the development and progression of hypertension (2, 3).

LHR not only reflects lipid metabolism but also plays a critical role in vascular health. Elevated LHR is associated with atherosclerosis, vascular stiffness, and endothelial dysfunction, all of which contribute to the pathogenesis of hypertension (4). For instance, higher LDL-C levels promote cholesterol deposition in the arterial wall, leading to arterial rigidity and increased vascular resistance, ultimately resulting in elevated blood pressure (5). Meanwhile, lower HDL-C levels impair the body's ability to clear cholesterol, exacerbating the harmful effects of LDL-C and increasing the risk of hypertension.

Recent studies have demonstrated that LHR is an effective predictor of cardiovascular events (6), manifesting greater predictive value than measuring LDL-C or HDL-C levels alone (7). Specifically, LHR was significantly associated with all-cause mortality in hypertensive patients ≥ 65 years old in China (8). Previous studies have also established a potential mechanism why LHR could impact hypertension, with elevated LDL-C levels leading to endothelial dysfunction, inflammation and oxidative stress, arterial narrowing and hardening, consequently hypertension (9). Meanwhile, lower HDL-C levels attenuated protective effect against these processes (10). However, despite multiple studies establishing the predictive value of LHR in cardiovascular health, there is still a lack of large-scale epidemiological data directly evaluating the relationship between LHR and the prevalence/incidence of hypertension. Given the increasing trend of hypertension in the aging population of China, it is particularly important to further investigate this association.

The aim of this study is to investigate the association between the LHR and the prevalence & incidence of hypertension in middle-aged and older populations. Thus, we conducted a cross-sectional and longitudinal analysis on data from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative study in 45 years and above population in China. These data allow for an effective assessment of the relationship between LHR and the risk of hypertension in middle-aged and older population, a high-risk population for hypertension.

Methods

Study design and population

This study utilized data from the CHARLS, gathered from 150 counties or districts and 450 villages across 28 provinces in China, containing demographic, economic, health status, blood tests and functional information. Baseline survey was performed in 2011 (Wave 1), follow-ups were conducted every two years, Wave 2 in 2013, Wave 3 in 2015, Wave 4 in 2018, Wave 5 in 2020, blood tests were only performed in 2011 and 2015. Access to the CHARLS dataset is available via its official website at charls.ccer.edu.cn/en.

In the cross-sectional analysis, we combined data from Wave 1 and Wave 3. Inclusion criteria were aged 45 years and older; and complete hypertension diagnostic data, DBP, SBP, LDL-C, HDL-C; and complete sociodemographic information. Exclusion criteria were age < 45 years; or incomplete hypertension diagnostic data, DBP, SBP, LDL-C, HDL-C; or incomplete sociodemographic information; or history of lipid-lowering medication use. After rigorous screening, 13,150 participants qualified for the cross-sectional analysis, with flowchart shown in Figure 1.

For the longitudinal analysis, we selected participants without hypertension in 2011, focusing on the incidence of hypertension during follow-up. Inclusion criteria were complete LHR value in 2011; and complete hypertension diagnostic data during at least one follow-up. Exclusion criteria were age < 45 years; or incomplete hypertension diagnostic data, DBP, SBP, LDL-C, HDL-C; or

Abbreviations: HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; LHR, Low-Density Lipoprotein to High-Density Lipoprotein Ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, Blood urea nitrogen; SUA, Serum uric acid; Scr, Serum creatinine; CRP, C-Reactive Protein; FBG, Fasting Blood Glucose; HbA1c, Hemoglobin A1c; TG, Triglyceride; TC, Total Cholesterol; BMI, Body mass index; CI, Confidence Interval; OR, Odds Ratio; HTN, Hypertension; CVD, Cardiovascular disease; CHARLS, China Health and Retirement Longitudinal Study.

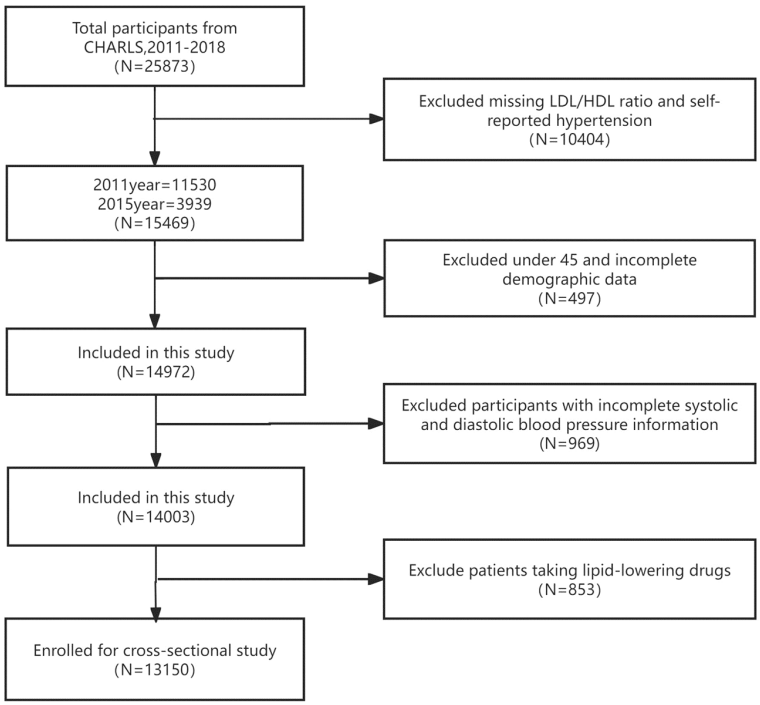

FIGURE 1
Flowchart of participant selection.

incomplete sociodemographic information; or history of lipid-lowering medication use. After rigorous screening, 7,508 participants qualified for the longitudinal analysis, with flowchart shown in Figure 2.

Ethical approval

The CHARLS project and the protocol for biomarker sample collection were approved by the Biomedical Ethics Review Committee of Peking University (IRB00001052-11014) and the Institutional Review Board of the National School of Development at Peking University (IRB00001052-11015), with informed consent obtained from all participants.

Data collection and potential covariates

Data collection was performed by professionally trained personnel via structured questionnaires to gather sociodemographic information. Health-related behaviors such as smoking and drinking status, medical history (diabetes, heart disease, and stroke), and medication used for diabetes, dyslipidemia or hypertension were also recorded. Trained professionals conducted physical measurements, including height, weight, and blood pressure. Blood pressure was measured using Omron HEM-7200 sphygmomanometer, the average of three readings was recorded.

Fasting venous blood samples were collected in the morning to measure fasting blood glucose (FBG), HbA1c, triglyceride (TG), total cholesterol (TC), HDL-C, LDL-C, serum creatinine (Scr), blood urea nitrogen (BUN), and serum uric acid (SUA) levels.

The covariates included gender, age, education level, smoking status, drinking status, SBP, DBP, BMI, TC, TG, FBG, CRP, HbA1c, Scr, BUN and SUA levels.

Measurement of LHR

The LHR was calculated (11) by LDL-C/HDL-C, both of which are expressed in mg/dL. In subsequent analysis, we examined LHR as both a continuous variable and categorized it into two distinct groups based on the ROC threshold value (high LHR group: LHR > 2.14; low LHR group: LHR ≤ 2.14) to enhance the analytical strength.

Definition of hypertension

Hypertension was defined by one of the following criteria (12): ① positive answer to question "Have you ever been diagnosed with hypertension by a doctor?" or ② positive answer to question "Are you currently taking any treatments to manage or control your hypertension, such as Traditional Chinese Medicine or Western modern medicine?"

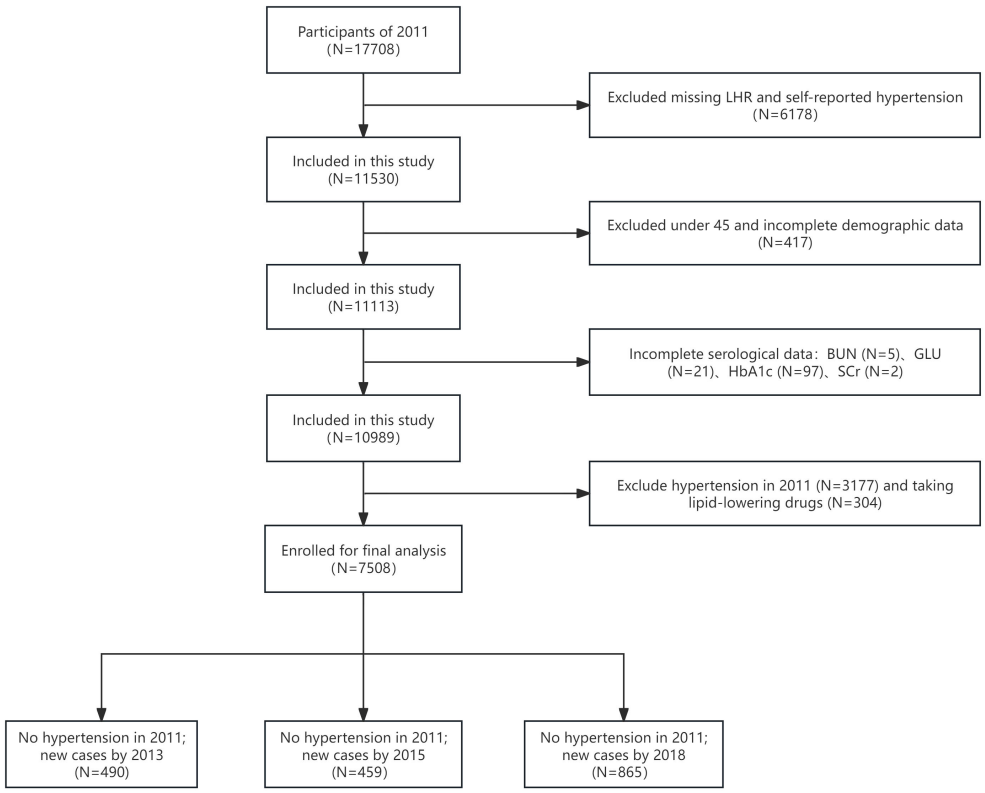

FIGURE 2
Flowchart of participant selection for longitudinal analysis.

Statistical analysis

Statistical analysis was performed via R software (version 4.3.1) and Empower (version 6.0). Continuous variables are expressed as the means ± standard deviations, and categorical variables are expressed as numbers and percentages. Differences in variables across different LHR groups were compared via one-way ANOVA, Kruskal–Wallis H test, or chi–square test. Three models were employed: Model 1 was unadjusted; Model 2 adjusted for gender, age, education level, smoking status, drinking status, SBP, DBP and BMI; Model 3 adjusted for TC, TG, Scr, BUN, CRP, HbA1c, SUA and FBG on basis of Model 2. The association between the LHR and hypertension prevalence/incidence was evaluated, the results were presented as odds ratios (ORs) and 95% confidence intervals (CIs).

A generalized additive model (GAM) was used to explore the nonlinear relationship between LHR and hypertension prevalence, and a segmented regression model was used for threshold effect analysis. Subgroup analyses were conducted on the basis of gender, age, smoking status, drinking status, HbA1c, FBG, BMI, with interactions tested via multivariate logistic regression models. Statistical significance was set at $p < 0.05$.

In the longitudinal analysis, we utilized the 7-year follow-up data from the CHARLS database (2011-2018) to track participants over time. Similar to the cross-sectional study, participants were categorized into two groups based on the ROC of LHR: the low LHR group (LHR ≤ 2.36) and the high LHR group (LHR > 2.36). To assess the long-term impact of LHR on hypertension incidence, we employed a stepwise multivariable logistic regression model and made appropriate adjustments following the principles of cohort studies. This approach allowed us to thoroughly examine the relationship between LHR and hypertension incidence, while accounting for temporal dynamics. The results are presented as ORs with their corresponding 95% CIs, highlighting the long-term effects of LHR on hypertension risk.

Results

Baseline characteristics

There were 25,873 participants enrolled in the CHARLS cohort initially. After excluding missing data and lipid-lowering medication use, 13,150 participants were included in the cross-sectional analysis. Participants were divided into two groups based on LHR: Low LHR group (LHR ≤ 2.14, N=6281) and High LHR group (LHR > 2.14, N=6869). The prevalence of hypertension, diabetes, and stroke was significantly higher in High LHR group than in Low LHR group ($p < 0.001$). Additionally, SBP and DBP, and biochemical indicators such as TC, TG, BUN, SUA, CRP, FBG, and HbA1c were significantly higher in High LHR group ($p < 0.001$). The High LHR group had lower rates of smoking and drinking ($p < 0.001$) (Table 1).

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TABLE 1 Baseline characteristics of participants LHR in cross-sectional study.

Variable	Total	Q1 ≤2.14	Q2 >2.14	*P* value
Participants, sample size (N)	13150	6281	6869	***NA***
Age,years	59.47 ± 9.48	59.53 ± 9.71	59.40 ± 9.25	0.432
Gender (%)				0.002
Male	6222 (47.38)	3059 (48.70)	3163 (46.05)	
Female	6928 (52.62)	3222 (51.30)	3706 (53.95)	
Education level (%)				<0.001
Below high school or vocational school	11818 (89.92)	5708 (90.89)	6110 (88.95)	
High school or vocational school	1160 (8.79)	510 (8.12)	650 (9.46)	
Above high school or vocational school	171 (1.29)	62 (0.99)	109 (1.59)	
Marital status (%)				<0.001
Married	7620 (79.77)	3680 (78.73)	3940 (80.80)	
Married separation	655 (6.88)	362 (7.74)	293 (6.01)	
Separated	41 (0.44)	28 (0.60)	13 (0.27)	
Divorced	90 (0.94)	44 (0.94)	46 (0.94)	
Widowed	1047 (10.96)	504 (10.78)	543 (11.14)	
Never married	97 (1.02)	56 (1.20)	41 (0.84)	
Hypertension (%)				<0.001
yes	3625 (27.41)	1507 (23.99)	2118 (30.83)	
no	9525 (72.59)	4774 (76.01)	4751 (69.17)	
Diabetes (%)				<0.001
yes	593 (5.00)	209 (3.83)	384 (6.17)	
no	11085 (95.00)	5244 (96.17)	5841 (93.83)	
Dyslipidemia (%)				<0.001
yes	991 (7.46)	356 (5.67)	635 (9.24)	
no	12159 (92.54)	5925 (94.33)	6234 (90.76)	
Stroke (%)				<0.001
yes	257 (2.16)	93 (1.70)	164 (2.62)	
no	11484 (97.84)	5380 (98.30)	6104 (97.38)	
SBP,mmHg	128.54 ± 20.85	126.75 ± 20.62	130.33 ± 21.08	<0.001
DBP,mmHg	75.11 ± 12.00	74.09 ± 12.11	76.13 ± 11.88	<0.001
Antihypertensive medication (%)				<0.001
yes	2538 (19.41)	1025 (16.58)	1513 (22.23)	
no	10451 (80.60)	5158 (83.42)	5293 (77.77)	
Antidiabetic medication (%)				<0.001
yes	482 (3.64)	186 (2.96)	296 (4.31)	
no	12668 (96.36)	6095 (97.04)	6573 (95.69)	
Drinking (%)				<0.001
yes	4896 (41.85)	2491 (45.39)	2405 (38.31)	

(Continued)

TABLE 1 Continued

Variable	Total	Q1 ≤2.14	Q2 >2.14	*P* value
Drinking (%)				<0.001
no	6870 (58.15)	2997 (54.61)	3873 (61.69)	
Smoking (%)				<0.001
yes	4726 (40.27)	2292 (41.77)	2434 (38.76)	
no	7040 (59.74)	3195 (58.23)	3845 (61.24)	
BMI (%)				<0.001
<18.5	870 (6.84)	606 (9.77)	264 (3.90)	
18.5-23	5354 (41.62)	3073 (49.56)	2281 (33.67)	
23-25	2668 (20.48)	1153 (18.59)	1515 (22.36)	
≥25	4084 (31.08)	1369 (22.08)	2715 (40.07)	
TC ,mg/dL	189.17 ± 34.32	174.68 ± 31.71	203.65 ± 36.93	<0.001
TG ,mg/dL	131.89 ± 91.10	116.24 ± 98.59	147.53 ± 83.61	<0.001
BUN ,mg/dL	15.67 ± 4.63	15.81 ± 4.79	15.52 ± 4.46	0.002
SUA ,mg/dL	4.62 ± 1.33	4.53 ± 1.32	4.70 ± 1.33	<0.001
Scr ,mg/dL	0.79 ± 0.25	0.78 ± 0.27	0.80 ± 0.23	<0.001
CRP ,mg/dL	2.75 ± 7.21	2.45 ± 6.90	3.04 ± 7.51	<0.001
FBG ,mmol/L	5.88 ± 1.73	5.69 ± 1.51	6.06 ± 1.95	<0.001
HbA1c (%)	5.48 ± 0.90	5.42 ± 0.80	5.54 ± 1.00	<0.001

Data are presented as mean ± standard deviation or number (%).
NA stands for "Not Applicable".

Association between LHR and hypertension prevalence

Multivariate regression analysis revealed a significant association between LHR and hypertension prevalence. Each unit increase in LHR was associated with 22% (OR = 1.22, 95% CI: 1.15-1.30, $p < 0.0001$) increase in hypertension prevalence, after adjusting for potential covariates. Specifically, High LHR group was associated with 32% (OR=1.32, 95% CI: 1.18-1.47, $p < 0.0001$) increase in hypertension prevalence, compared with Low LHR group. These results indicate a significant association between higher LHR and increased hypertension prevalence (Table 2).

Linear relationship between LHR and hypertension

Using smooth curve fitting analysis, we assessed the association between LHR and hypertension prevalence, as shown in Figure 3. The analysis revealed a linear relationship between LHR and hypertension (p for non-linearity = 0.062).

Subgroup analysis

To ensure the reliability of our findings, we conducted a series of subgroup analysis to test the consistency of results across different

TABLE 2 Multivariate regression analysis of the association between LHR and hypertension prevalence.

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
LHR	1.25 (1.20, 1.30)	<0.0001	1.19 (1.13, 1.25)	<0.0001	1.22 (1.15, 1.30)	<0.0001
Low LHR (LHR ≤ 2.14)	**Ref.**		**Ref.**		**Ref.**	
High LHR (LHR > 2.14)	1.41 (1.31, 1.53)	<0.0001	1.31 (1.20, 1.44)	<0.0001	1.32 (1.18, 1.47)	<0.0001

Model 1 adjusted for none. Model 2 adjusted for gender, age,education level, smoking status, drinking status, SBP, DBP, and BMI. Model 3 adjusted for FBG, Scr, BUN, SUA, CRP, HbA1c, TC, TG on the basis of Model 2. LHR as a continuous variable and grouped by ROC threshold.

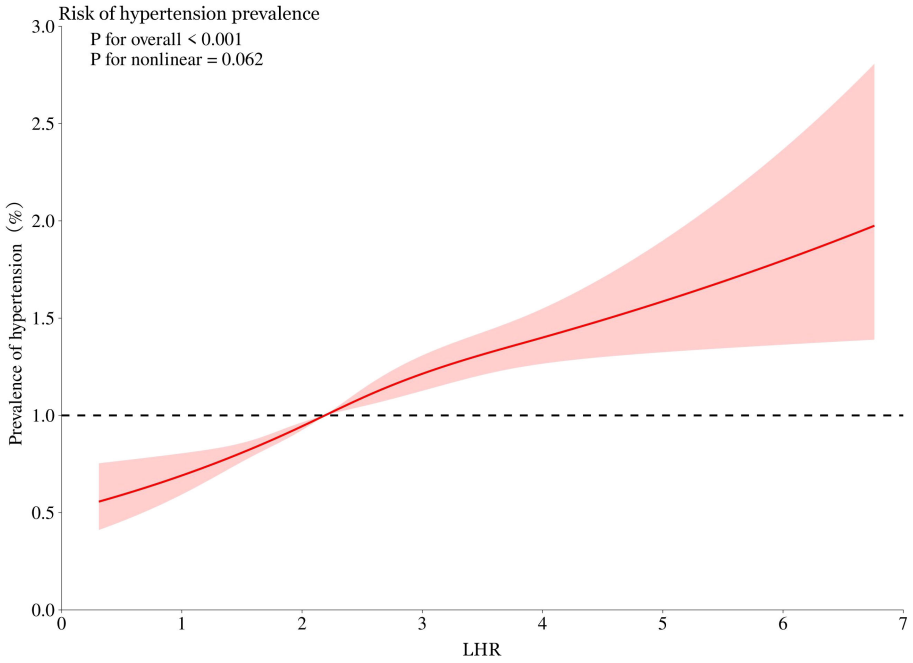

FIGURE 3
Smooth curve fitting was used to evaluate the linear relationship between LHR and hypertension prevalence. The red solid line represents the probability of hypertension prevalence, and the blue dotted line represents the 95% confidence interval curve. LHR, Low-Density Lipoprotein to High-Density Lipoprotein Ratio.

subgroups. As shown in Figure 4, except for the subgroups with HbA1c level > 7.0%, or BMI level < 18.5, all other subgroups demonstrated significant association between LHR and the prevalence of hypertension ($p < 0.05$), which could be attributed to limited sample size of these subgroups.

We identified significant interaction between gender and LHR (p for interaction 0.0018), suggesting female participants were more sensitive to LHR for the prevalence of hypertension than male. We also found significant interaction between smoking status and LHR (p for interaction 0.0038), where never smoked participants were more sensitive to LHR than those ever smoked. Further analysis ruled out interactions between LHR and age, drinking status, HbA1c, FBG, BMI, diabetes and dyslipidemia, indicating that these variables did not significantly alter the association between LHR and hypertension prevalence (all p for interaction > 0.05).

Association between LHR and hypertension incidence

A longitudinal analysis was conducted to explore the relationship between LHR and hypertension incidence over 2-, 4-, and 7-year follow-up periods. When LHR was analyzed as a continuous variable, after adjusting for potential covariates, each one-unit increase in LHR was associated with a 12% increase in hypertension incidence (OR = 1.12, 95% CI: 1.03-1.20, p = 0.0045). These results indicate that LHR is an independent and significant predictor of hypertension incidence. Even after adjusting for a wide range of demographic, clinical, and biochemical variables, the association between LHR and hypertension remained robust (Table 3).

Discussion

This study, which is based on nationally representative data, explored the association between the LHR and hypertension in the Chinese population aged 45 years and above. Our analysis of 13,150 middle-aged and elderly participants revealed a significant association between elevated LHR and hypertension prevalence. Subgroup analysis further confirmed the stability of this positive association. Previous studies have demonstrated that an imbalance in LDL-C and HDL-C levels is a significant risk factor for CVDs (13–15). Our study provides direct evidence of the association between elevated LHR and hypertension prevalence: each unit increase in the LHR was associated with 22% increase in hypertension prevalence.

Subgroup analysis further revealed the variability in the association between the LHR and hypertension risk across gender, age, and lifestyle factors. The association between the LHR and hypertension risk was more pronounced in females and non-smokers, suggesting that special attention should be given to these high-risk subgroups in clinical practice (16). Possible mechanisms may relate to physiological characteristics of lipid metabolism, hormone levels in women (17), as well as non-smoking individuals may have better vascular elasticity and are more sensitive to changes in lipid metabolism (18).

Based on our investigation, no studies to date have specifically examined the relationship between LHR and hypertension incidence. Previous studies have focused primarily on the TG/HDL or TC/HDL Ratios (19, 20). Grover's (21) model identified LHR as a potential lipid marker for predicting cardiovascular events, with hypertension incidence being indirectly linked to cardiovascular events.

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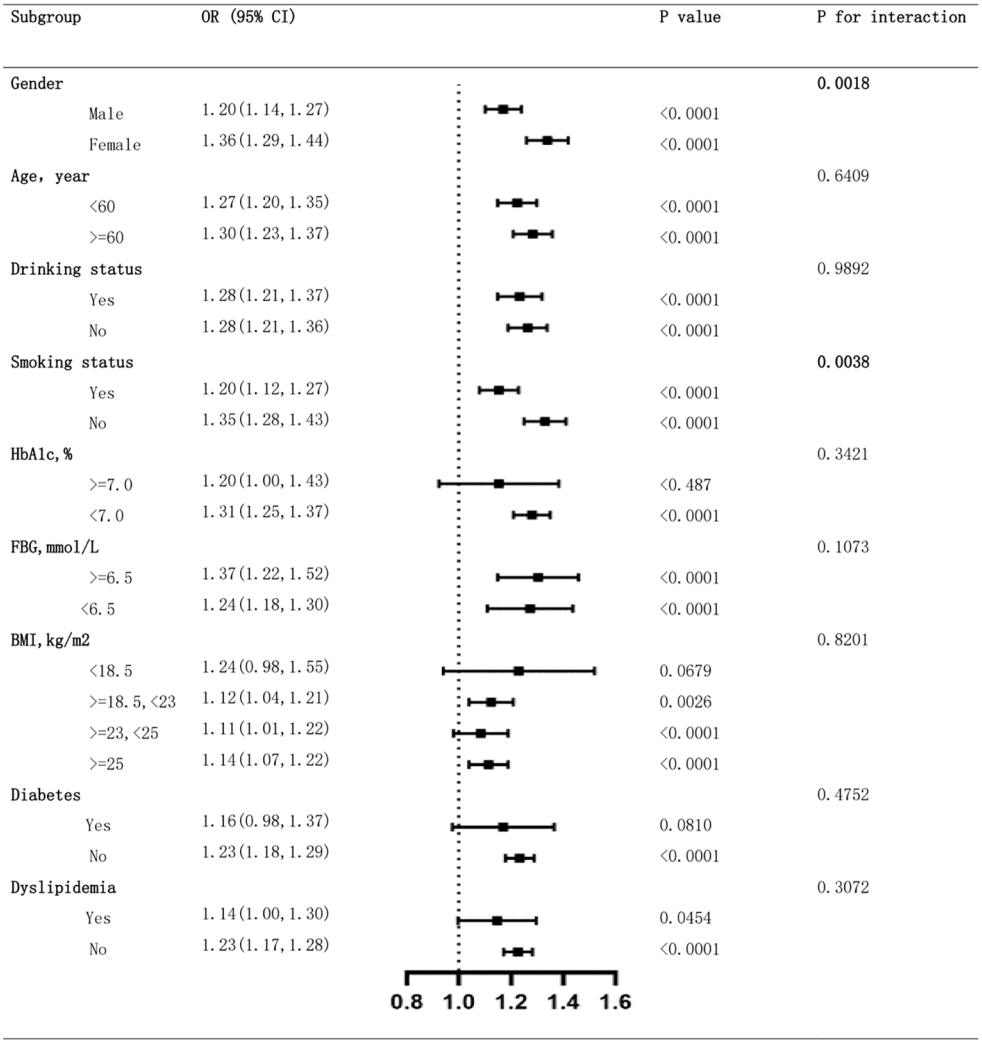

FIGURE 4
Subgroup analysis of the association between LHR and hypertension prevalence. LHR, Low-Density Lipoprotein to High-Density Lipoprotein Ratio.

The longitudinal analysis further supported the value of the LHR as a predictor of hypertension incidence. Following individuals without hypertension at baseline in 2011, we found that the LHR serves as a stable and continuous predictor of future hypertension development, especially in the middle-aged and elderly population. Timely intervention and adjustment of lipid metabolism may effectively reduce the incidence of hypertension (22).

Our smooth curve fitting analysis indicates a linear relationship between LHR and hypertension prevalence, as shown in Figure 3. The non-linearity test yielded a p-value of 0.062, suggesting that the

TABLE 3 Multivariate regression analysis of the association between LHR and hypertension incidence.

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
LHR	1.14 (1.08, 1.20)	<0.0001	1.13 (1.06, 1.21)	0.0002	1.12 (1.03, 1.20)	0.0045
Low LHR (LHR ≤ 2.36)	**Ref.**		**Ref.**		**Ref.**	
High LHR (LHR > 2.36)	1.22 (1.10, 1.36)	0.0002	1.21 (1.07, 1.37)	0.0025	1.15 (1.01, 1.32)	0.0408

Model 1 adjusted for none. Model 2 adjusted for gender, age,education level, smoking status, drinking status, SBP, DBP, and BMI. Model 3 adjusted for FBG, Scr, BUN, SUA, CRP, HbA1c, TC, TG on the basis of Model 2. LDL/HDL Ratio as a continuous variable and grouped by ROC threshold.

relationship is primarily linear. The clinical significance of this linear relationship is that an increase in LHR is proportionally related to an increase in hypertension risk, highlighting the importance of monitoring and managing LHR levels in high-risk patients (23). While LHR showed strong predictive power in this study, its interactions with traditional cardiovascular risk factors, such as BMI, diabetes status, and family history, warrant further investigation. Future studies should also account for dynamic changes in LHR over time by incorporating repeated measurements, allowing for a more nuanced assessment of its relationship with hypertension prevalence and incidence. This approach would offer a deeper understanding of LHR's clinical significance.

The strengths of this study include the use of the nationally representative CHARLS database, which covers various sociodemographic and health-related factors, enhancing the generalizability and credibility of the findings. However, this study also has several limitations. Firstly, although we adjusted for several confounding factors, the observational study design cannot eliminate the influence of residual confounders. Secondly, the study sample was based on middle-aged and elderly Chinese individuals, and the results may not be fully applicable to other races and age groups. Finally, LDL-C and HDL-C levels were measured only at baseline, preventing the assessment of their dynamic changes during follow-up with respect to hypertension risk.

Conclusion

In conclusion, this study revealed a significant association between LHR and hypertension risk, which was particularly evident in specific subgroups and at different follow-up time points. Our findings emphasize the importance of monitoring and managing the LHR in middle-aged and elderly individuals for the prevention and control of hypertension. These findings provide a scientific basis for formulating personalized hypertension prevention strategies. Further research on the impact of different intervention measures on the LHR and hypertension risk is of significant public health importance.

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 Biomedical Ethics Review Committee of Peking University (IRB00001052-11014), and the Institutional Review Board of the National School of Development at Peking University (IRB00001052-11015). 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

WL: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. XC: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. LRW: Conceptualization, Data curation, Methodology, Validation, Writing – original draft, Writing – review & editing. LXW: Conceptualization, Formal analysis, Methodology, Writing – review & editing. XL: Funding acquisition, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. BZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Association of surrogate adiposity markers with prevalence, all-cause mortality and long-term survival of heart failure: a retrospective study from NHANES database

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Introduction: Obesity, especially abdominal obesity, is more common in patients with heart failure (HF), but body mass index (BMI) cannot accurately describe fat distribution. Several surrogate adiposity markers are available to reflect fat distribution and quantity. The objective of this study was to explore which adiposity marker is most highly correlated with HF prevalence, all-cause mortality and patients' long-term survival.

Methods: The National Health and Nutrition Examination Survey (NHANES) database provided all the data for this study. Logistic regression analyses were adopted to compare the association of each surrogate adiposity marker with the prevalence of HF. Cox proportional hazards models and restricted cubic spline (RCS) analysis were employed to assess the association between surrogate adiposity markers and all-cause mortality in HF patients. The ability of surrogate adiposity markers to predict long-term survival in HF patients was assessed using time-dependent receiver operating characteristic (ROC) curves.

Results: 46,257 participants (1,366 HF patients) were encompassed in this retrospective study. An area under the receiver operating characteristic curve (AUC) for the prevalence of HF assessed by weight-adjusted-waist index (WWI) was 0.70 (95% CI: 0.69-0.72). During a median follow-up of 70 months, 700 of 1366 HF patients' death were recorded. The hazard ratio (HR) for HF patients' all-cause mortality was 1.33 (95% CI: 1.06-1.66) in the a body shape index (ABSI) quartile 4 group and 1.43 (95% CI: 1.13-1.82) in the WWI quartile 4 group, compared with the lowest quartile group. The AUC for predicting 5-year survival of HF patients using the ABSI was 0.647 (95% CI: 0.61-0.68).

Conclusions: WWI is strongly correlated with the prevalence of HF. In HF patients, those with higher WWI and ABSI tend to higher all-cause mortality. ABSI can predict patients' long-term survival. We recommend the use of WWI and ABSI for assessing obesity in HF patients.

KEYWORDS

surrogate adiposity markers, heart failure, abdominal obesity, NHANES, retrospective study

1 Introduction

Heart failure (HF) is considered the terminal stage of cardiovascular diseases (1), with its prevalence and disease burden increasing annually, affecting approximately 64 million individuals worldwide (2–4). Similar to malignancies, HF patients' long-term survival is not optimistic (5). Data from Get With The Guidelines-Heart Failure (GWTG-HF) and Medicare shows the median survival for inpatients with HF is 2.1 years (6). In spite of the advent of new pharmaceuticals for HF treatment, the 5-year survival rate of inpatients is only 25% (4). Consequently, early diagnosis and long-term prognosis prediction are more crucial for HF patients.

Obesity, notably abdominal obesity, is globally recognized as a significant health concern and the predominant independent risk factors for the development and progression of HF (7–9). Obesity is strongly linked to HF and HF-related disorders, such as hypertension and diabetes mellitus (DM) (10, 11). Although body mass index (BMI) is a common anthropometric index used to describe obesity, it fails to accurately describe fat distribution (12, 13). Paradoxically, a higher BMI is related to a longer survival time when used to predict HF patients prognosis, and this manifestation has been referred to "obesity paradox" (14). Although waist circumference (WC) as well as waist-to-height ratio (WHtR) are currently crucial markers for abdominal obesity (15), they do not offer significant advantages over BMI in predicting the risk and prognosis of cardiovascular diseases (16).

To enhance accuracy in describing body size and fat distribution, several surrogate adiposity markers have been proposed (17–21). The weight-adjusted waist index (WWI) offers a comprehensive evaluation of adiposity, muscle mass, and bone mass (22). Recent research indicates a potential link between higher WWI and increased risk of cardiovascular events in both American and Asian populations (18, 23). A Body Shape Index (ABSI), another index according to waist circumference, height and weight, provides a better evaluation of fat distribution and is positively correlated with adult mortality (17, 24). Visceral adiposity index (VAI) and lipid accumulation product (LAP) describe lipid accumulation and fat distribution, are strongly linked to cardiovascular metabolism and are more effective than BMI in identifying cardiovascular disease risk (20, 21). Relative fat mass (RFM) is also an emergent index with high predictability for metabolic syndrome (MetS) (19). However, limited studies exist comparing these markers in terms of HF prevalence and prognosis.

The aims of this study were to explore which adiposity marker is most strongly associated with HF prevalence and patients' all-cause mortality and long-term survival. The findings could lead to the adoption of surrogate adiposity markers for obesity assessment and survival prediction in HF patients.

2 Materials and methods

2.1 Study participants

Data from 1999-2018 of the National Health and Nutrition Examination Survey (NHANES), which was approved by the National Center for Health Statistics (NCHS), were used in this study. All participants signed written informed consent. Within adults aged 20 years and above, we excluded those who (1) had missing information on WC, weight, or BMI (2); did not provide a self-reported history of HF (3); lacked linked mortality data (4); had missing laboratory data. This study ultimately included 46,257 participants, of whom 1,366 had HF (Figure 1 in Supplementary Data Sheet 1). This study constituted a quadratic analysis of publicly available NHANES data, thus not requiring ethical review.

Abbreviations: ABSI, A body shape index; AUC, An area under the receiver operating characteristic curve; ANOVA, Analysis of variance; BMI, Body mass index; CHD, Coronary heart disease; CI, Confidence interval; DM, Diabetes mellitus; GED, General equivalency diploma; GWTG-HF, Get With The Guidelines-Heart Failure; HbA1c, Hemoglobin A1c; HDL-C, High-density lipoprotein cholesterol; HF, Heart failure; HFrEF, HF with reduced ejection Fraction; HR, Hazard ratio; K-M, Kaplan-Meier; LAP, Lipid accumulation product; MetS, Metabolic syndrome; MI, Myocardial infarction; NHANES, the National Health and Nutrition Examination Survey; NCHS, the National Center for Health Statistics; OR, Odds ratio; RAAS, Renin-angiotensin-aldosterone system; RFM, Relative fat mass; ROC, Receiver operating characteristic; RCS, Restricted cubic spline; SI, the International System of Units; TC, Total cholesterol; TG, Triglyceride; VAI, Visceral adiposity index; WC, Waist circumference; WHtR, Waist-to-height ratio; WWI, Weight-adjusted-waist index.

2.2 Definition of surrogate adiposity markers, outcomes

The study variables included eight surrogate adiposity markers: BMI, WC, WHtR, WWI, ABSI, LAP, VAI, and RFM. During the survey, professional investigators measured the height, weight, and WC of participants. The formulas for other surrogate adiposity markers are reported in Table 1 in Supplementary Data Sheet 1 (17–21).

The main outcomes were whether the participants had a diagnosis of HF and HF patients' all-cause mortality. Participants' self-reported history of HF was used to define HF patients. We linked the data from this study to the National Death Index to obtain survival information for participants. Survival time is from when the participant took the survey until either the end of follow-up (December 31, 2019) or death.

2.3 Covariates

NHANES categorized race and ethnicity of participants as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, or Other Race based on individual choice. Demographics covariates included sex (female and male), age, marital status (married, widowed, divorced, single, or others), and educational attainment (below high school, high school or general equivalency diploma [GED], above high school, or others). Smoking status was classified into three categories: never smoker (< 100 cigarettes smoked in a lifetime), ever smoker (≥ 100 cigarettes smoked in a lifetime but now quit) and current smoker(≥ 100 cigarettes smoked in a lifetime and not quit). Alcohol consumption was divided into drinking and non-drinking according to the participant's answer to question, "Do you consume at least 12 drinks per year?". The 'others' category for both demographic covariates and alcohol consumption indicated participants who did not answer the corresponding questions. DM was recognized as the presence of at least one of the following (1): hemoglobin A1c (HbA1c) ≥ 6.5% (2), random blood glucose ≥ 200mg/dL (3), self-reported doctor-diagnosed DM (4), use of insulin or hypoglycemic drugs. Hypertension was characterized by a doctor-reported history of hypertension, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg. The laboratory examination data were extracted directly from NHANES.

2.4 Statistical analysis

Sampling weights were calculated for this study considering the intricate sampling design of NHANES spanning a 20-year period. Participants were divided into two categories to compare their baseline characteristics based on whether they had HF. Continuous variables were portrayed as weighted means or medians, while categorical variables were depicted as unweighted frequencies (weighted percentages). Continuous variables were analyzed by analysis of variance (ANOVA) or Kruskal-Wallis test and χ^2 test for categorical variables. Risk factors for HF were assessed using logistic regression analysis.

Participants were grouped according to the quartiles of each surrogate adiposity marker. Three multivariable logistic regression models were developed to assess the correlation between surrogate adiposity markers and HF, utilizing receiver operating characteristic (ROC) curve and an area under ROC curve (AUC) to gauge the predictive accuracy of different surrogate adiposity markers. Moreover, Kaplan-Meier (K-M) method was utilized to illustrate survival trends in HF patients, with the Log-Rank test employed to compare overall patient survival discrepancies across adiposity marker groups. Three multivariable Cox proportional hazard regression models were developed for estimating the connection between surrogate adiposity marker and all-cause mortality in HF patients, presenting outcomes as hazard ratios (HRs) with 95% confidence intervals (CIs). Additionally, restricted cubic spline (RCS) analysis was used to capture the drain-response relations between surrogate adiposity markers and HF patients' all-cause mortality. Evaluation of the predictive value of surrogate adiposity markers for 1-, 3-, and 5-year survival in HF patients using time-dependent ROC curves. In addition, we performed subgroup analyses to assess the concordance of the prognostic value of BMI, WWI, and ABSI with the primary outcome in HF patients. Subgroup analyses took into account gender, age, race, and the presence of comorbidities. All analyses were performed using R software (version 4.2.2) and SPSS statistical software (version 27.0), with statistical significance set at a two-sided P-value less than 0.05.

3 Results

3.1 Baseline characteristics and risk factors for HF

The baseline characteristics of the 46,257 (of whom 1,366 participants had HF) participants included in this study are summarized in Table 2 in Supplementary Data Sheet 1. Compared to the Non-HF group, the HF group were older, male, higher percentage widowed, less educated, and fewer never smoked. Interestingly, a lower proportion of participants in the HF group consumed alcohol. Levels of glucose, HbA1c, and triglyceride (TG) were higher in the HF group in contrast to the Non-HF group, while the opposite trend was observed for total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C). All surrogate adiposity markers differed significantly between the two groups (all P-value < 0.001). HF patients had higher rates of cardiovascular disease (coronary heart disease (CHD), hypertension, myocardial infarction (MI), angina) and DM.

Risk factors for HF were investigated using multivariate logistic regression analysis, the results of which are presented in Figure 1. Notably, to emphasize the effect of changes in the levels of glucose, TC, HDL-C, and TG on HF, we converted these indices to the International System of Units (SI) in this analysis. Age was a risk factor for HF, with the risk increasing by 7% (95% CI = 1.07-1.08) for each additional year. Compared with Mexican Americans, other Hispanic (OR=1.59, 95% CI = 1.07-2.35), non-Hispanic white (OR=1.63, 95% CI = 1.24-2.15), and non-Hispanic black (OR=2.22, 95% CI = 1.61-3.06) individuals had an elevated risk of

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Characteristics	OR (95% CI)
Gender	
Female	Ref
Male	1.08 (0.91-1.29)
Age, y	
	1.07 (1.07-1.08)
Race	
Mexican American	Ref
Other Hispanic	1.59 (1.07-2.35)
Non-Hispanic White	1.63 (1.24-2.15)
Non-Hispanic Black	2.22 (1.61-3.06)
Other Race	1.31 (0.83-2.05)
Marital	
Married	Ref
Divorced	1.33 (1.09-1.62)
Widowed	1.29 (1.06-1.59)
Single	1.23 (0.89-1.69)
Others	1.54 (0.84-2.84)
Education	
Below high school	Ref
High school or GED	0.72 (0.59-0.88)
Above high school	0.56 (0.46-0.68)
Others	0.37 (0.08-1.72)
Smoke	
Never	Ref
Ever	1.65 (1.37-1.97)
Current	2.01 (1.59-2.52)
Drink	
No	Ref
Yes	0.79 (0.66-0.93)
Others	0.74 (0.51-1.08)
Laboratory	
HbA1c	1.12 (1.02-1.24)
HDL-C	0.55 (0.42-0.73)
Glucose	1.05 (1.01-1.09)
TC	0.72 (0.65-0.79)
TG	1.06 (1.01-1.12)

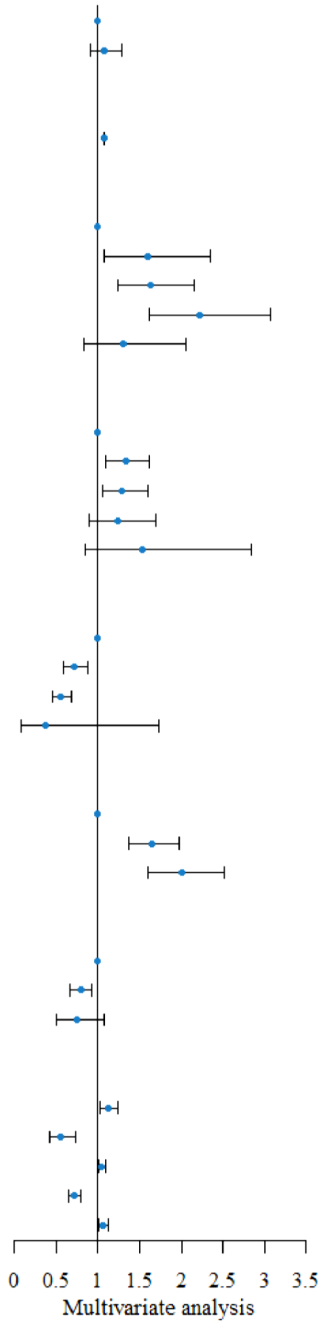

FIGURE 1
The forest plot for assessing risk factors for Heart Failure (HF). HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; Ref, reference; OR, odds ratio. SI conversion factors: To convert HDL-C, glucose, TC, and TG to mmol/L, multiply values by 0.02586, 0.0555, 0.0259, and 0.0113.

HF. Divorced (OR=1.33, 95% CI = 1.09-1.62) and widowed (OR=1.29, 95% CI = 1.06-1.59) participants had an increased risk of HF relative to married respondents. As long as the participant had a history of smoking, the risk of HF increased, regardless of whether they were currently quitting smoking. Higher educational attainment (high school or GED [OR=0.72, 95% CI = 0.59-0.88], above high school [OR=0.56, 95% CI = 0.46-0.68]) was a protective factor for a participant's risk of HF. Interestingly, alcohol consumption appeared to lower the risk of HF (OR=0.79, 95% CI = 0.66-0.93). Each 1% increase in HbA1c was connected with a 12% (95% CI = 1.02-1.24) higher risk of HF. For every 1 mmol/L increase in glucose and TG, the risk of HF increased by 5% (95% CI = 1.01-1.09) and 6% (95% CI = 1.01-1.12), respectively. An increase in HDL-C and TC was correlated with a decreased risk of HF.

3.2 Association of surrogate adiposity markers with HF

Taking the quartiles of surrogate adiposity markers as categorical variables, three models were developed to analyze the relationship between surrogate adiposity markers and HF (Table 3 in Supplementary Data Sheet 1). In model 1, unadjusted for any variables, a rise in each adiposity marker was linked to an enhanced risk of HF development compared to the lowest quadrant. After multivariate adjustment in model 3, all markers, except ABSI and VAI, exhibited an elevated risk of HF prevalence compared to the reference group (P-trend < 0.001). Furthermore, we used ROC curves to assess the risk of HF incidence predicted by different surrogate adiposity markers, the results of which are shown in Figure 2. The WWI had the highest AUC of 0.70 (95% CI = 0.69-0.72) and the cutoff point was 11.15.

3.3 HF patients' all-cause mortality with surrogate adiposity markers

During a median follow-up of 70 months, there were 700 deaths among the 1,366 HF patients. All-cause mortality was compared between quartile groups for each surrogate adiposity marker using K-M survival analysis. Patients with higher WWI and ABSI markers had a significantly greater probability of survival than those with lower markers (all Log-Rank P < 0.0001) (Figures 2B, C in Supplementary Data Sheet 1). In contrast, patients with a lower BMI had a greater probability of survival (Log-Rank P < 0.0001) (Figure 2A in Supplementary Data Sheet 1). No statistically significant differences were noted for the other surrogate adiposity markers (all Log-Rank P > 0.05) (Figure 3 in Supplementary Data Sheet 1).

Taking the quartiles of BMI, WWI and ABSI as categorical variables, three Cox proportional hazard regression models were employed to evaluate the relationship between these three surrogate adiposity markers and HF patients' all-cause mortality (Table 1). In model 1, higher WWI quartiles, ABSI quartiles and lower BMI quartiles were correlated with higher all-cause mortality rates (P -trend < 0.001). In model 3 with multivariate correction, compared to the reference group, the HR in the fourth quartile of WWI was 1.33 (95% CI = 1.06-1.66, P-trend = 0.04) while in the fourth quartile of ABSI was 1.43 (95% CI = 1.13-1.82, P-trend = 0.003). Conversely, no significant correlation was found between the increase of BMI and changes in all-cause mortality of HF patients after multivariable correction (P for trend = 0.22). The RCS model showed an L-shaped correlation of BMI and ABSI with all-cause mortality in HF patients, while the WWI showed a Log-shaped association (Figure 3). The RCS curves were used to identify the inflection points of each of the three markers, and the data were divided into 2 groups for separate regression analyses; the results are shown in Table 4 in Supplementary Data Sheet 1.

The time-dependent ROC curves in Figure 4 show the ability of BMI, WWI, and ABSI to predict HF patients' 1-, 3-, and 5-year survival. In contrast to BMI, the WWI had an improved ability to predict 3- and 5-year survival (3-year, 0.594 vs 0.549; 5-year, 0.594 vs 0.569). ABSI had a moderate ability to predict survival compared to BMI (1-year 0.571 vs 0.541, 3-year 0.631 vs 0.549, 5-year 0.647 vs 0.569).

3.4 Subgroup analysis

Within subgroup analyses, the associations between BMI, WWI, and ABSI and all-cause mortality among HF patients were consistent across most subgroups (Tables 5-7 in Supplementary Data Sheet 1). For patients with HF by race, sex, and marital status, WWI and ABSI correlated better than BMI in assessing risk for primary outcomes. The relationship between WWI, ABSI and all-cause mortality was consistent regardless of whether HF patients had comorbid hypertension, CHD, MI, angina and DM, but the correlations were not entirely consistent for BMI. In addition, the results for most subgroups of interactions with BMI, WWI, and ABSI were not statistically significant, except for BMI with hypertension and BMI, ABSI with TC.

4 Discussion

Within this cohort study, we compared the association of surrogate adiposity markers with HF prevalence and all-cause mortality and explored the ability of surrogate adiposity markers to predict long-term rates in HF patients. Compared to other markers, we observed that the WWI exhibited a notable correlation with an increased risk of prevalent HF and had good predictive value. In survival analyses of the HF population, the BMI-related "obesity paradox" remained after multivariate adjustment but did not recur with the use of WWI and ABSI. Moreover, the ABSI could better predict long-term survival in HF patients.

All surrogate adiposity markers demonstrated that the greater the level of obesity was, the greater the risk of HF, reaffirming obesity's independent role as a risk factor in HF development and progression (25, 26). On the one hand, disorders of lipid metabolism caused by obesity destroy the body's energy homeostasis, resulting in elevated tissue stress and dysfunction (27). Obese patients, especially those with abdominal obesity, often suffer from diabetes, hypertension and other metabolism-related diseases. These chronic diseases are collectively known as MetS (28). Excessive adipocytes lead to a compensatory increase in mitochondrial fatty acid oxidation, leading to increased energy production and generating oxidative stress in adipocytes. This oxidative stress causes adipocytes to express stress markers that are recognized by the body's immune system, ultimately leading to chronic inflammation (29–31). Besides, metabolic disorders can further cause immune cell activation in the liver, spleen and other tissues, further exacerbating the effects of chronic inflammation on the organism (32). The short-term inflammatory reaction leads to increase immune cells infiltration and expression of pro-inflammatory cytokines in the myocardium, resulting in an increased cardiac load. However, prolonged action of inflammatory cells and cytokines on cardiomyocytes causes left ventricular dysfunction and cardiomyocyte remodeling, which

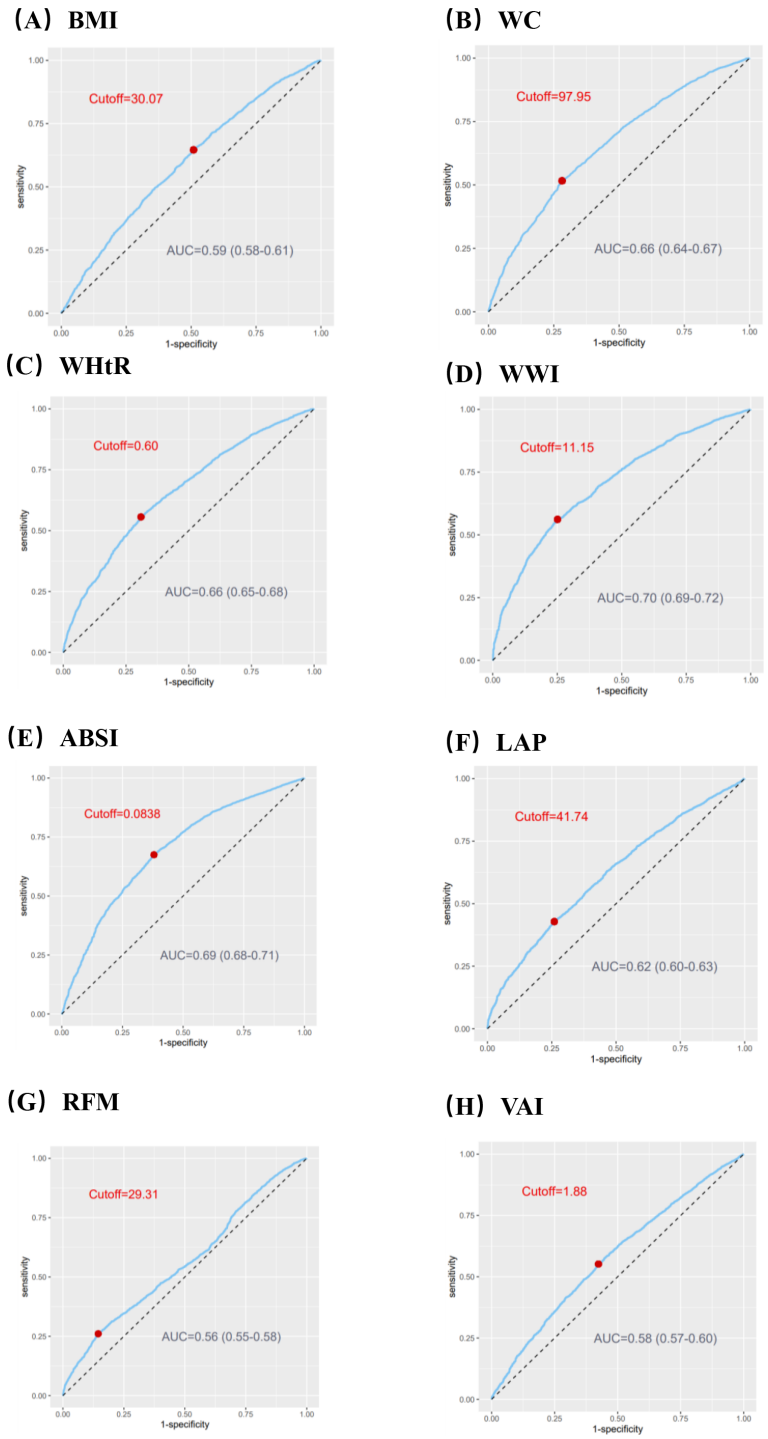

FIGURE 2
ROC curves to assess the capacity of surrogate adiposity markers to predict the Heart Failure (HF) prevalence. **(A)** Body mass index (BMI). **(B)** Waist circumference (WC). **(C)** Waist-to-height ratio (WHtR). **(D)** Weight-adjusted-waist index (WWI). **(E)** A body shape index (ABSI). **(F)** Lipid accumulation product (LAP). **(G)** Relative fat mass (RFM). **(H)** Visceral fat index (VAI). ROC, receiver operating characteristic; AUC, an area under ROC curve.

subsequently induces HF (33). On the other hand, obesity induces hemodynamic alterations characterized by elevated blood volume, cardiac output, and blood pressure, linked to the activation of the renin-angiotensin-aldosterone system (RAAS) and heightened sympathetic nerve activity (34, 35). The increasing blood volume leads to an elevated cardiac preload, the long-term effects of which cause ventricular dilatation and myocardial hypertrophy, facilitating the progression of HF (34).

While there exists a notable relationship between overall obesity and abdominal obesity, certain individuals may solely exhibit overall obesity due to fat distribution uniformity (36). Defining obesity based on BMI may omit patients with abdominal obesity,

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TABLE 1 Association of Heart Failure (HF) patients' all-cause mortality with BMI, WWI, and ABSI.

Characteristics	Model 1[a] HR (95%CI)	Model 2[b] HR (95%CI)	Model 3[c] HR (95%CI)
BMI (quartiles)			
Q1	1 (Ref)	1 (Ref)	1 (Ref)
Q2	0.73 (0.60-0.89) **	0.76 (0.62-0.93) **	0.76 (0.62-0.93) **
Q3	0.76 (0.62-0.93) **	0.88 (0.72-1.08)	0.87 (0.70-1.07)
Q4	0.62 (0.50-0.76) ***	0.87 (0.70-1.09)	0.83 (0.65-1.05)
	C-Index: 0.559	C-Index: 0.679	C-Index: 0.694
	P-trend < 0.001***	P-trend = 0.37	P for trend = 0.22
WWI (quartiles)			
Q1	1 (Ref)	1 (Ref)	1 (Ref)
Q2	1.49 (1.20-1.85) ***	1.23 (0.99-1.53)	1.28 (1.03-1.60) *
Q3	1.57 (1.26-1.96) ***	1.21 (0.97-1.52)	1.18 (0.95-1.48)
Q4	1.85 (1.49-2.29) ***	1.38 (1.11-1.73) **	1.33 (1.06-1.66) *
	C-Index: 0.559	C-Index: 0.678	C-Index: 0.694
	P-trend < 0.001***	P-trend = 0.007**	P-trend = 0.04*
ABSI (quartiles)			
Q1	1 (Ref)	1 (Ref)	1 (Ref)
Q2	1.43 (1.14-1.79) **	1.20 (0.95-1.52)	1.23 (0.97-1.55)
Q3	1.83 (1.46-2.28) ***	1.39 (1.11-1.75) **	1.40 (1.11-1.77) **
Q4	2.43 (1.96-3.02) ***	1.49 (1.18-1.89) ***	1.43 (1.13-1.82) **
	C-Index: 0.598	C-Index: 0.681	C-Index: 0.697
	P-trend < 0.001***	P-trend < 0.001***	P-trend = 0.002**

P-value: *<0.05, **<0.01, ***<0.001
[a]Nothing was adjusted.
[b]Adjusted for age, gender, race.
[c]Adjusted for age, gender, race, marital, education, drink, smoke, hemoglobin A1c, high-density lipoprotein cholesterol, glucose, total cholesterol, triglyceride.
HR, hazard ration; BMI, body mass index; WWI, weight-adjusted-waist index; ABSI, a body shape index.

concealing cardiovascular disease risks within this subgroup (37, 38). With the increasingly research on body composition and fat distribution, more and more scholars believe that BMI cannot be used to represent the true fat content (39). A cohort study from the UK Biobank shows that, regardless of BMI, surrogate adiposity markers have the strongest association with mortality (40). Therefore, this study revealed an increased risk of HF when WC and the WHtR were used to evaluate obesity. This may be explained

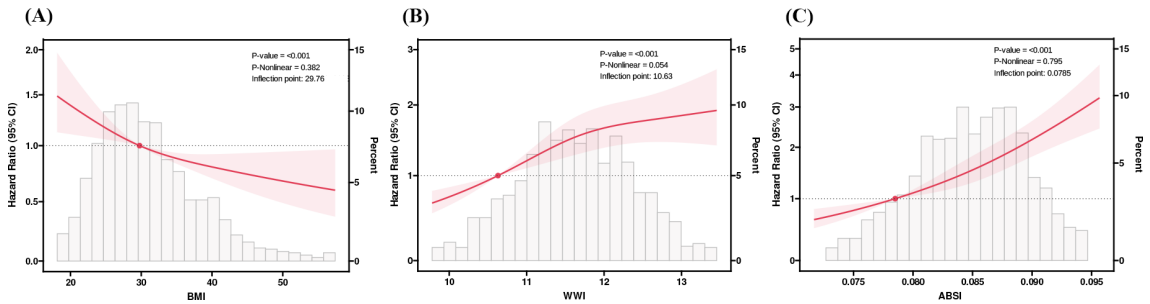

FIGURE 3
RCS analysis of BMI, WWI, and ABSI with Heart Failure (HF) patients' all-cause mortality. **(A)** Body mass index (BMI). **(B)** Weight-adjusted-waist index (WWI). **(C)** A body shape index (ABSI). We used RCS with 3 knots at the 10th, 50th and 90th percentiles of BMI, WWI, and ABSI. Hazard ratios (solid lines), 95%Cis (shaded areas). RCS, restricted cubic spline.

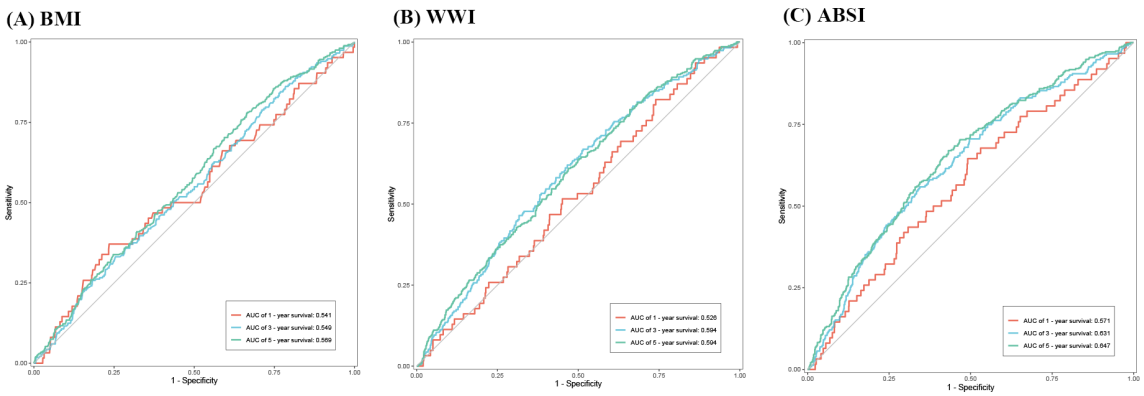

FIGURE 4
Time-dependent ROC curves indicating the capacity of BMI, WWI, and ABSI to predict Heart Failure (HF) patients' long-term survival. **(A)** Body mass index (BMI). **(B)** Weight-adjusted-waist index (WWI). **(C)** A body shape index (ABSI). ROC, receiver operating characteristic; AUC, an area under ROC curve.

by the fact that WC and WHtR can better describe abdominal obesity. Among the other adiposity markers, the WWI and RFM better reflect the association between obesity and HF. The WWI takes into account differences in fat distribution and skeletal muscle mass among individuals and more accurately reflects abdominal obesity, while the RFM takes into account differences in waist circumference by gender and ethnicity (19, 22). In combination with ROC curves to assess the predictive power of adiposity markers for the prevalence of HF, WWI can be considered a replacement to BMI for the assessment of overweight and obesity.

Similar to the results of other studies exploring the correlation between adiposity markers and all-cause mortality in HF patients (41, 42), this study revealed that a higher BMI was associated with reduced mortality, which is considered the BMI-related "obesity paradox". However, other studies have expressed different views (14, 43). Therefore, the use of BMI to define overweight or obesity in HF patients is inappropriate. Abdominal obesity is considered a marker of cardiovascular disease risk, including HF (37, 44–46). In this study, WWI and ABSI, which are more highly correlated with abdominal obesity, were selected for survival analysis and prediction of long-term survival in HF patients, and both were superior to BMI. Controversially, the ABSI showed good performance in predicting long-term survival in HF patients, but was not shown to be significantly different in analyses assessing its association with the risk of prevalent HF using the fully adjusted logistic model. This may be due to the fact that the ABSI was also used to predict risk of death when it was originally proposed (17).

Overall, these data suggest that higher degree of abdominal obesity are associated with a higher risk of HF and poorer long-term survival among HF patients. The use of surrogate adiposity markers that are more strongly correlated with abdominal obesity may be a better predictor of HF prevalence and long-term survival. Other studies have also confirmed the possibility of selecting other adiposity markers in patients with HF with reduced ejection fraction (HFrEF) (43). At the same time, exercise and diet should be used to intervene in abdominal obesity to achieve primary prevention of cardiovascular disease. For HF patients, weight control should be carried out along with cardiac rehabilitation to improve the long-term survival rate (47–49).

This study has the following advantages: first, the research sample is drawn from a representative population in the United States. The inclusion of a large number of participants and the long-term follow-up in the study enhance the reliability of the research results. In this study, we for the first time delved into the feasibility of employing surrogate adiposity markers to prognosticate long-term risks within the heart failure population. In addition, the results of this study also support the use of WWI and ABSI to assess obesity in heart failure patients. These findings highlight the clinical significance and application value of surrogate adiposity markers.

However, there are some limitations in this study. First, the present study is an observational study and it is not possible to specify the exact causal relationship. Although multiple methods have been used to adjust for the effects of potential confounders, it is not possible to rule out influences on the study results due to measurement error and unknown effectors. Second, due to limitations of the NHANES database, information on diseases, including HF, was obtained from respondents' records, and information related to specific medications and hospitalization for HF patients was not available. Therefore, we were unable to base further studies on HF subtypes. Third, as the NHANES survey was exclusively conducted in the US, the generalizability of the results to other populations remains uncertain, warranting future research for validation and broader applicability of the findings. Based on the above issues, more information will be explored in future studies to validate and support our findings.

5 Conclusions

After multivariate adjustment, the risk of prevalent HF was better assessed using the WWI. In HF patients, higher WWI and ABSI were linked to a higher all-cause mortality risk, while eliminating the BMI-related "obesity paradox", highlighting the severe impact of abdominal obesity. Meanwhile, ABSI allow for a better prediction of long-term survival in HF patients. These results suggest that we can redefine overweight and obesity in HF patients with the WWI and ABSI.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

F-SG: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. CG: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing. J-HD: Conceptualization, Investigation, Software, Visualization, Writing – original draft. J-XW: Investigation, Methodology, Supervision, Writing – original draft. R-YW: Formal analysis, Validation, Writing – original draft. S-FS: Formal analysis, Validation, Writing – original draft. X-LS: Conceptualization, Methodology, Validation, Writing – original draft. Y-WH: Conceptualization, Validation, Writing – original draft. JW: Conceptualization, Data curation, 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/fendo.2025.1430277/full#supplementary-material

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Association between the ratio of triglycerides to high-density lipoprotein cholesterol and nocturnal hypertension: a cross-sectional study in a Chinese population

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Background and objective: The ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) serves as a predictive indicator for metabolic syndrome and cardiovascular diseases. Simultaneously, nocturnal hypertension significantly increases the risk of target organ damage and cardiovascular events. However, the relationship between the TG/HDL-C ratio and nocturnal hypertension remains unclear. Therefore, the present study aimed to determine the efficacy of the TG/HDL-C ratio in predicting the occurrence of nocturnal hypertension and reducing related adverse events.

Method: Our rigorous cross-sectional study, which included 749 participants who underwent 24-hour ambulatory blood pressure monitoring at the Cardiology Center of Changchun University of Chinese Medicine Affiliated Hospital, allowed us to determine the association between the TG/HDL-C ratio and nocturnal hypertension. We employed both univariate and multivariate logistic regression analyses to ensure the robustness of our findings. Logistic regression modeling was used to assess the independent predictive ability of TG/HDL-C for nocturnal hypertension while adjusting for confounders such as sex, age, BMI, and smoking status. Model performance was assessed by subject work characteristics (ROC) curves and area under the curve (AUC).

Results: Among the 749 participants included in this study, 566 were identified with nocturnal hypertension. Univariate logistic regression analysis demonstrated that the TG/HDL-C ratio was positively correlated with the occurrence of nocturnal hypertension, with the risk of nocturnal hypertension increasing by 24% (OR 1.24 (1.06-1.45), P=0.006) for every 1-unit increase in the TG/HDL-C ratio. After adjusting for past medical history, medication, and other relevant examinations, a multivariate analysis revealed a significant correlation between the TG/HDL-C ratio and nocturnal hypertension. Logistic regression analysis demonstrated that TG/HDL-C was positively associated with nocturnal hypertension (regression coefficient = 0.115, $P < 0.05$). After adjusting for sex, age, BMI, and smoking status, TG/HDL-C remained a predictor of nocturnal hypertension.

Conclusion: Our study underscores the significant association between an elevated TG/HDL-C ratio and the occurrence of nocturnal hypertension. This finding has the potential to draw the attention of patients and physicians to lipid levels, particularly among males, individuals over 45 years old, those with a BMI greater than 24, smokers, and those with a history of hypertension. An independent positive association between TG/HDL-C and nocturnal hypertension was also determined using logistic regression modeling. The findings suggests that it may have potential application in the early screening of nocturnal hypertension. However, the predictive ability is limited, and further studies are necessary to incorporate larger sample sizes and longitudinal designs. These additional studies would validate the predictive role of TG/HDL-C and explore its biological mechanisms.

KEYWORDS

nocturnal hypertension, TG/HDL-C, ambulatory blood pressure, Asian, cross-sectional studies

Background

In 2023, the World Health Organization released its inaugural *Global Hypertension Report*, which clarified that hypertension affects more than one-third of adults worldwide, with most patients remaining unaware of their condition. If not controlled in a timely manner, hypertension can cause damage to multiple systems throughout the body (1). Recent advancements in hypertension research have led to increased attention to the fluctuations in nocturnal blood pressure. However, large-scale epidemiological studies on nocturnal hypertension remain limited. According to a statement from the American Heart Association, nocturnal hypertension can significantly increase the risk of target organ damage and cardiovascular events (2). A meta-analysis conducted on individual data from 3,468 patients across four prospective European studies revealed that nocturnal blood pressure fluctuations are more predictive of cardiovascular mortality in hypertensive patients than changes in daytime blood pressure (3). Furthermore, an epidemiological study in South Korea indicated that nocturnal hypertension not only affects the diastolic function of the heart in the general population but also increases the risk of white matter hyperintensities (4) in the brain, thereby exacerbating cerebrovascular disease. The incidence rate of nocturnal hypertension in China is considerably higher than that in Europe, which can be attributed to the impact of dietary structure and other factors on diurnal blood pressure (5). Despite the availability of 24-hour ambulatory blood pressure monitoring (ABPM), there is still a lack of predictive indicators for the occurrence of nocturnal hypertension in current clinical practice, particularly in hypertensive patients.

The ratio of TG/HDL-C is a novel clinical indicator commonly used to evaluate insulin resistance due to its relatively simple screening process (6). Recent studies have shown that this indicator is associated with a variety of cardiovascular diseases, which may be attributed to long-term lipid metabolism disorders that lead to and aggravate atherosclerosis (7). However, the correlation between the TG/HDL-C ratio and nocturnal hypertension has been rarely reported. Understanding the prevalence of hypertension among Asian populations and their distinct dietary habits underscores the importance of studying nocturnal hypertension. Moreover, the timely detection of nocturnal hypertension during risk factor screening is essential for adjusting medication appropriately, thereby reducing the risk of nocturnal unconsciousness and cerebrovascular events.

Materials and methods

This study included 749 patients who underwent 24-hour ambulatory blood pressure monitoring at the Cardiology Department of Changchun University of Chinese Medicine Affiliated Hospital between June 2023 and December 2023 (Figure 1). Exclusion criteria for this study were unclear data or missing and incorrect data, and demographic data, such as sex, age, height, weight, and heart rate, collected upon admission. Patients were defined as smokers if they had smoked continuously or cumulatively for 6 months or more in the past. Patients were defined as alcohol drinkers if they had consumed alcohol ≥1 drink per week in the past 12 months. patients with diabetes if their fasting blood glucose concentration was above 6.1mmol/L, their glycosylated hemoglobin level exceeded 6.5%, or if they were currently using insulin or oral hypoglycemic agents. Hypertension was defined as systolic blood pressure ≥ 140mmHg, diastolic blood pressure ≥ 90mmHg, or use of antihypertensive medication. According to the Chinese Guidelines for Blood Lipid Management (8), patients underwent at least two standard fasting

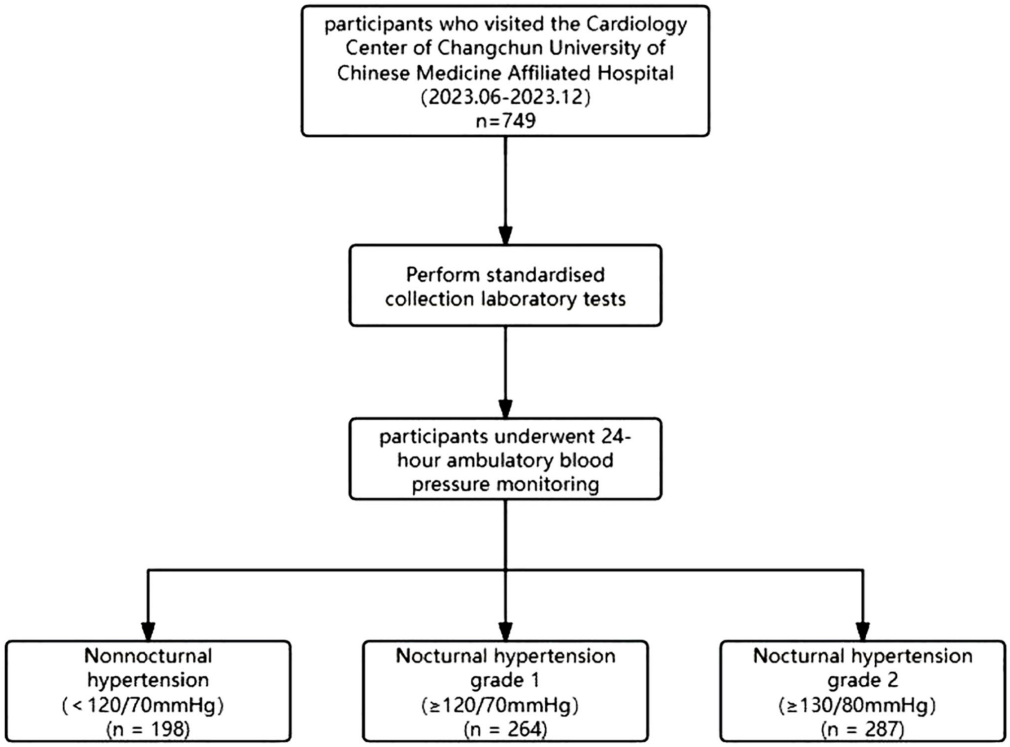

FIGURE 1
Flowchart for selecting participants.

venous blood lipid tests, with a 2-week interval between each test. A diagnosis of abnormal blood lipid levels was made if one or more of the following criteria were met: total serum cholesterol level ≥ 6.2mmol/L, low-density lipoprotein cholesterol ≥ 4.1mmol/L, or triglycerides ≥ 2.3mmol/L. Based on the medications taken within the past 3 months, specific drug information can be determined, including blood pressure medications and statin drugs. The diagnostic thresholds for ambulatory BP were defined according to the ESH hypertension guidelines and the Chinese guidelines for ambulatory BP monitoring (9). The stage 1 threshold for nocturnal BP, corresponding to an office BP of 140/90 mmHg, was 120/70mmHg; the stage 2 threshold for nocturnal hypertension was defined as 130/80 mmHg. This retrospective study was carried out using the opt-out method for the case series of our hospital. To further assess the independent predictive ability of TG/HDL-C for nocturnal hypertension by logistic regression modeling, we identified two datasets that contained the following variables: Outcome Variable: Nocturnal hypertension (0=negative,1= positive).Predictor Variables: TG/HDL-C (ratio of triglycerides to high-density lipoprotein cholesterol), sex, age (years), BMI (kg/m^2), and smoking status (0= non-smoker, 1= smoker).Continuous variables (TG/HDL-C, age, and BMI) were standardized using z-scores to ensure consistency across feature scales. The dataset was randomly divided into training (70%) and testing (30%) sets for model development and validation.

The study was approved by the Ethics Committee of the Affiliated Hospital of Changchun University of Chinese Medicine and was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was waived by our Institutional Review Board because of the retrospective nature of our study.

Measurement of Ambulatory Blood Pressure and Determination of Endpoint

The ambulatory blood pressure recorder used by the Cardiology Center of the Changchun University of Chinese Medicine Affiliated Hospital was sourced from Wuxi Zhongjian Science Instrument Co., Ltd. (model: CB-1805-B, registration number: SXZZ 20142070640). The collected data were analyzed using the ARCS system (Version ABP9.1.1), enabling retrospective analysis of ambulatory blood pressure. We set monitoring intervals from 6:00 to 22:00 during the day, taking blood pressure readings every 30 min. At night, monitoring was continued from 22:00 to 06:00, and measurements were recorded hourly. The reading was considered valid if the number of measurements taken at night was greater than seven. We obtained the average daytime and nocturnal blood pressure values using software analysis. This study was conducted to define nocturnal hypertension according to the ESH Hypertension Guidelines 2023 and Chinese Guidelines for the Prevention and Control of Hypertension. Nocturnal hypertension was defined as an average nighttime systolic blood pressure recorded by ambulatory blood pressure monitoring

(ABPM) of ≥120 and/or diastolic blood pressure of ≥70 mmHg, regardless of their daytime blood pressure status, arytenoid or non-arrytenoid (10, 11).

Laboratory test

We conducted all laboratory tests on fasting participants upon admission, using venous blood collection. The collection process and testing methods were performed under standard conditions, focusing on blood lipid testing, which included total cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B, high-density lipoprotein, low-density lipoprotein, and lipoprotein a. Additionally, we calculated the ratio of apolipoprotein B to apolipoprotein A1 and the ratio of triglycerides to high-density lipoprotein cholesterol based on the results following established standards. We retrospectively collected all the data using a standardized data collection table.

Statistical analysis

All analyses were performed using the statistical software Free Statistics, version 1.9. Bilateral P values < 0.05 were considered statistically significant. Categorical variables are represented by numbers (n) and percentages (%) and were evaluated using chi-square tests. The mean ± standard deviation of a normal distribution represents continuous variables. We included each variable in univariate and multivariate logistic analyses to evaluate the association between the TG/HDL ratio and nocturnal hypertension. We validated the robustness of the results by adjusting for confounding factors. A logistic regression model was employed to assess the independent predictive ability of TG/HDL-C for nocturnal hypertension while adjusting for confounding variables (sex, age, BMI, and smoking status). The model's performance was evaluated using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). The AUC reflects the model's ability to discriminate between positive and negative cases.

Results

Participants were classified based on the presence of nocturnal hypertension and average nocturnal blood pressure. The absence of nocturnal hypertension (n=198) was defined as nighttime mean systolic blood pressure<120mmHg and/or diastolic blood pressure<70mmHg. Nocturnal hypertension level 1 (n=264) was defined as nocturnal mean systolic blood pressure≥120mmHg and/or diastolic blood pressure≥ 70mmHg. Nocturnal hypertension level 2 (n=287) was defined as nocturnal mean systolic blood pressure≥ 130mmHg and/or diastolic blood pressure≥ 80mmHg. We summarized the characteristics of the participants, represented categorical variables by numbers (n) and percentages (%), and evaluated them using the chi-square test. Table 1 details the representation of continuous variables as the mean and standard deviation of the normally distributed data.

We conducted a univariate analysis to investigate the relationship between TG/HDL-C ratio and nocturnal hypertension. Factors with a p-value of < 0.05. Table 1) were identified based on their clinical relevance and prior literature analysis. The results indicated that weight, BMI, TG, HDL-C, and the TG/HDL-C ratio were significantly correlated with nocturnal hypertension. The TG/HDL-C ratio, the main indicator of this study, was found to increase the risk of nocturnal hypertension by 24% (OR 1.24, P=0.006) for every 1 unit increase. Table 2 provides the detailed information.

We performed multivariate analysis to assess the robustness of the results against confounding factors. Model 1 is not adjusted. Model 2 introduced participants' medical histories, including diabetes, hypertension, arrhythmia, CAD, dyslipidemia, smoking, and alcohol drinkers, and recognized their impact on outcomes. Model 3 was further adjusted for past medication information, such as ACEI/ARB, β-blocker, CCB, diuretic, ARNI, and statin, which could affect the changes in blood pressure and lipid levels. The analysis demonstrated that the relationship between TG/HDL-C and nocturnal hypertension remained robust in various models considering past history, medication factors, and other physicochemical indicators (Table 3), further verifying the research results. The logistic regression model achieved an AUC of 0.65 on the test set (Figure 2).

Subgroup analysis

We conducted a subgroup analysis to further investigate the relationship between the TG/HDL-C ratio and nocturnal hypertension across different patient subgroups. We stratified participants based on age (≥45 and <45 years), gender, obesity status (BMI ≥24 kg/m^2 and <24 kg/m^2, according to the Chinese BMI standard) (12), smoking history, and history of hypertension. The analysis revealed a more pronounced association between the TG/HDL-C ratio and nocturnal hypertension among individuals aged 45 or older, males, those with a BMI ≥24 kg/m2, smokers, and those with a history of hypertension (Table 4).

Discussion

Nocturnal hypertension: high prevalence and dangers

Nocturnal hypertension has garnered increased attention from researchers in recent years. However, the prevalence of this condition across different regions and ethnic groups remains unclear due to the lack of large-scale epidemiological studies. In the present study, more than half of the participants exhibited elevated nighttime blood pressure, which is consistent with the findings of de la Sierra et al. in their study, which included 37,096 untreated patients from the Spanish Ambulatory Blood Pressure

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TABLE 1 Baseline characteristics of all participants.

Variables	All participants (n = 749)	Nonnocturnal hypertension (<120/70mmHg) (n = 198)	Nocturnal hypertension grade 1 (≥120/70mmHg) (n = 264)	Nocturnal hypertension grade 2 (≥130/80mmHg) (n = 287)	p	statistic
Sex, n (%)					**0.026**	7.279
female	450 (60.1)	131 (66.2)	163 (61.7)	156 (54.4)		
male	299 (39.9)	67 (33.8)	101 (38.3)	131 (45.6)		
Age Mean ± SD	64.3 ± 11.5	64.3 ± 11.0	63.6 ± 11.4	64.9 ± 11.9	0.453	0.793
High (m) Mean ± SD	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	1.7 ± 0.1	0.244	1.411
Weight (kg) Mean ± SD	67.7 ± 12.7	64.3 ± 11.1	67.0 ± 11.5	70.6 ± 14.2	< **0.001**	15.173
BMI (kg/m2) Mean ± SD	24.8 ± 3.6	23.8 ± 3.5	24.7 ± 3.2	25.7 ± 3.8	< **0.001**	16.466
Heart.rate (bpm) Mean ± SD	77.9 ± 13.7	76.8 ± 13.6	78.6 ± 13.6	78.1 ± 13.9	0.383	0.961
ACEI/ARB n (%)					**0.001**	13.751
No	604 (80.6)	177 (89.4)	208 (78.8)	219 (76.3)		
Yes	145 (19.4)	21 (10.6)	56 (21.2)	68 (23.7)		
β-blocker n (%)					0.369	1.994
No	580 (77.4)	154 (77.8)	211 (79.9)	215 (74.9)		
Yes	169 (22.6)	44 (22.2)	53 (20.1)	72 (25.1)		
CCB, n (%)					< **0.001**	29.427
No	484 (64.6)	157 (79.3)	168 (63.6)	159 (55.4)		
Yes	265 (35.4)	41 (20.7)	96 (36.4)	128 (44.6)		
Diuretic n (%)					0.828	0.377
No	704 (94.0)	185 (93.4)	250 (94.7)	269 (93.7)		
Yes	45 (6.0)	13 (6.6)	14 (5.3)	18 (6.3)		
ARNI n (%)					0.332	2.207
No	709 (94.7)	187 (94.4)	254 (96.2)	268 (93.4)		
Yes	40 (5.3)	11 (5.6)	10 (3.8)	19 (6.6)		
Statin n (%)					0.12	4.235
No		155 (78.3)	211 (79.9)	209 (72.8)		
Yes	174 (23.2)	43 (21.7)	53 (20.1)	78 (27.2)		
Diabetes n (%)					**0.006**	10.292
No	607 (81.0)	172 (86.9)	218 (82.6)	217 (75.6)		
Yes	142 (19.0)	26 (13.1)	46 (17.4)	70 (24.4)		
Hypertension n (%)					< **0.001**	54.722
No	224 (29.9)	97 (49)	76 (28.8)	51 (17.8)		
Yes	525 (70.1)	101 (51)	188 (71.2)	236 (82.2)		

(Continued)

TABLE 1 Continued

Variables	All participants (n = 749)	Nonnocturnal hypertension (<120/70mmHg) (n = 198)	Nocturnal hypertension grade 1 (≥120/70mmHg) (n = 264)	Nocturnal hypertension grade 2 (≥130/80mmHg) (n = 287)	p	statistic
Arrhythmia n (%)					0.147	3.837
No	511 (68.2)	131 (66.2)	192 (72.7)	188 (65.5)		
Yes	238 (31.8)	67 (33.8)	72 (27.3)	99 (34.5)		
CAD n (%)					0.197	3.246
No	352 (47.0)	97 (49)	132 (50)	123 (42.9)		
Yes	397 (53.0)	101 (51)	132 (50)	164 (57.1)		
Dyslipidemia, n (%)					0.129	4.103
No	348 (46.5)	99 (50)	129 (48.9)	120 (41.8)		
Yes	401 (53.5)	99 (50)	135 (51.1)	167 (58.2)		
Smoking n (%)					**0.019**	7.93
No	413 (55.1)	120 (60.6)	153 (58)	140 (48.8)		
Yes	336 (44.9)	78 (39.4)	111 (42)	147 (51.2)		
Drinker, n (%)					**0.007**	9.89
No	507 (67.7)	145 (73.2)	187 (70.8)	175 (61)		
Yes	242 (32.3)	53 (26.8)	77 (29.2)	112 (39)		
TC (mmol/L) Mean ± SD	4.9 ± 1.1	4.9 ± 1.2	4.8 ± 1.1	4.9 ± 1.1	0.522	0.652
TG(mmol/L) Mean ± SD	1.9 ± 1.2	1.7 ± 1.1	1.8 ± 1.2	2.1 ± 1.3	**0.012**	4.471
ApoA1 (g/L) Mean ± SD	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	0.175	1.749
ApoB (g/L) Mean ± SD	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.097	2.336
ApoB/ApoA1 (mmol/L) Mean ± SD	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	**0.047**	3.067
HDL-C (mmol/L) Mean ± SD	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	< **0.001**	7.098
TG/HDL-C (mmol/L) Mean ± SD	1.7 ± 1.4	1.5 ± 1.2	1.7 ± 1.5	1.9 ± 1.4	**0.011**	4.538
LDL-C (mmol/L) Mean ± SD	2.9 ± 0.9	3.0 ± 0.9	2.9 ± 0.9	2.9 ± 0.9	0.344	1.068
LPa (mg/L) Mean ± SD	260.5 ± 240.8	255.2 ± 218.3	273.8 ± 250.8	252.0 ± 246.4	0.533	0.63
Nocturnal hypertension, n (%)					< **0.001**	660.239
no	183 (24.4)	183 (91)	0 (0)	0 (0)		
yes	566 (75.6)	18 (9)	263 (100)	285 (100)		

Data are shown as mean ± standard deviation (SD) for continuous variables and proportions (%)for categorical variables.
Sex, Age, High, Weight, BMI, ACEI/ARB, β-blocker, CCB, Diuretic, ARNI, Statin, Diabetes, Hypertension, Arrhythmia, CAD=Coronary Artery Disease, Dyslipidemia, Smoking, Drink, TC, total cholesterol; TG, triglyceride; ApoA1, apolipoproteinA1; ApoB, apolipoproteinB; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterin; LPa, Lipoprotein a P values in bold are<0.05.

TABLE 2 Univariate analysis for overall population.

Variable	OR_95CI	P_value
Sex=male	1.41 (0.99~1.99)	0.056
Age	1 (0.98~1.01)	0.773
Weight (kg)	1.03 (1.02~1.05)	**<0.001**
BMI (kg/m2)	1.14 (1.08~1.19)	**<0.001**
Heart.rate (bpm)	1.01 (1~1.02)	0.168
Smoking=yes	1.39 (0.99~1.95)	0.058
Drinker=yes	1.37 (0.94~1.97)	0.098
TC (mmol/L)	0.96 (0.83~1.11)	0.606
TG (mmol/L)	1.26 (1.06~1.49)	**0.009**
ApoA1 (mmol/L)	0.75 (0.32~1.78)	0.518
ApoB (mmol/L)	0.87 (0.42~1.82)	0.72
ApoB/ApoA1 (mmol/L)	1.01 (0.44~2.35)	0.981
HDL-C (mmol/L)	0.58 (0.34~0.98)	**0.041**
TG/HDL-C (mmol/L)	1.24 (1.06~1.45)	**0.006**
LDL-C (mmol/L)	0.94 (0.78~1.12)	0.478
LPa (mg/L)	1 (1~1)	0.695

OR, odds ratio; CI, confidence interval; SD, standard deviation.
Abbreviations as in Table 1.
P values in bold are < 0.05.

Monitoring Registry and 62,788 patients receiving anti hypertensive treatment, 40.9% of the untreated group and 49.8% of the treatment group experienced nocturnal hypertension (13). Similarly, JM et al. and Ma et al. conducted ambulatory blood pressure monitoring on hypertensive patients and discovered that more than half of the study population had significant nocturnal hypertension (14, 15).Nocturnal hypertension poses a greater threat compared to daytime fluctuations, primarily due to the difficulty of timely detection and treatment. A substantial body of prior research has centered on identifying predictors of elevated daytime blood pressure. Our study builds upon this research by extending the scope to nocturnal hypertension, a condition that has been demonstrated to exhibit a more robust correlation with target organ damage and cardiovascular events. Elevated nighttime blood pressure demonstrates a stronger correlation with systemic diseases such as cognitive impairment and cerebrovascular conditions. Kario et al. proposed that patients with elevated nighttime blood pressure have a poorer prognosis for both stroke and cardiovascular events compared to those with elevated daytime blood pressure (16). These findings indicate that elevated nighttime blood pressure can cause damage across multiple bodily systems (3, 17). Hoshide et al.'s study also suggested that even in hypertensive patients with well-controlled self-measured home blood pressure, dynamic nocturnal blood pressure elevation may promote target organ damage (18).

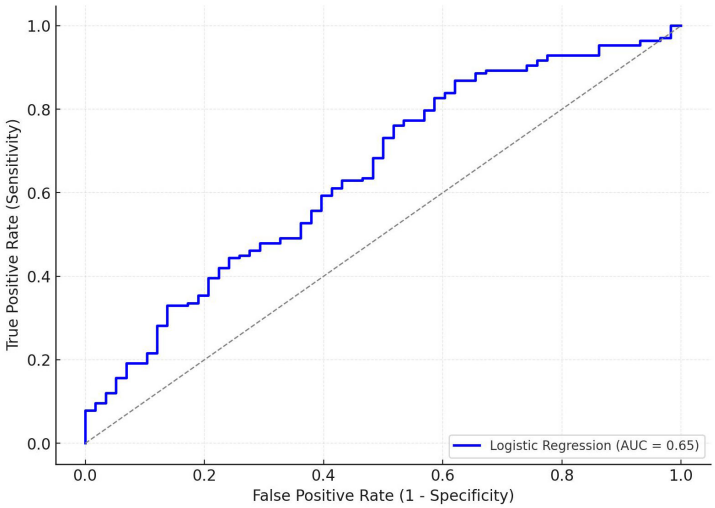
TABLE 3 multivariate analysis for overall population.

Variable	Model 1	Model 2	Model 3
n.total	749	749	749
n.event_%	566 (75.6)	566 (75.6)	566 (75.6)
crude.OR_95CI	1.24 (1.06~1.45)	1.24 (1.06~1.45)	1.24 (1.06~1.45)
crude.P_value	0.006	0.006	0.006
adj.OR_95CI	1.14 (1.02~1.35)	1.18 (1.01~1.38)	1.2 (1.02~1.4)
adj.P_value	0.043	0.036	0.025

Model1-Adj: Basic Information (years, sex, BMI, somking, drink).
Model2-Adj: Past medical history (diabetes, hypertension, arrhythmia, CAD, dyslipidemia).
Model3-Adj: Medications (ACEI/ARB, β-blocker, CCB, diuretic, ARNI, statin).

Relationship between TG/HDL-C ratio and diseases

This study explored the relationship between the ratio of triglycerides to high-density lipoprotein cholesterol (TG/HDL-C) and nocturnal hypertension in a Chinese population. Our findings indicate that the TG/HDL-C ratio is positively associated with the risk of nocturnal hypertension. This suggests that TG/HDL-C, a marker of metabolic dysregulation, may serve as a useful indicator for identifying individuals at risk for nocturnal hypertension, especially in populations with a high prevalence of metabolic disorders. In recent medical studies, an increasing number of researchers have identified metabolic markers as predictors of elevated blood pressure, and a large cohort study in China found that SUA levels were an independent predictor of blood pressure progression and the development of hypertension in the Chinese population (19). A cross-sectional study of an HIV program in Argentina found that INH was highly prevalent in PWH. Metabolic and inflammatory markers predict nocturnal SBP in PWH (20). The ratio of triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) has consistently been recognized as a significant indicator of metabolic syndrome. Extensive research has demonstrated that the TG/HDL-C ratio surpasses individual lipid markers, such as low-density lipoprotein cholesterol (LDL-C), HDL-C, or TG, in predicting the development of type 2 diabetes over a 10-year period (21).The present findings are consistent with the results of other studies that have emphasized the role of TG/HDL-C ratio as a marker of cardiovascular risk, and elevated TG/HDL-C ratio has been associated with insulin resistance, dyslipidemia, and arterial stiffness (22), all of which are associated with hypertension. Furthermore, the TG/HDL-C ratio has been identified as a superior indicator of metabolic syndrome in obese children and adolescents (23). In recent years, a growing body of evidence has highlighted TG/HDL-C ratio as a crucial predictor of various cardiovascular diseases. Azarpazhooh MR et al. reached a similar conclusion, stating that the TG/HDL-C ratio can effectively identify patients with metabolic syndrome, insulin resistance, and severe atherosclerosis (24). These findings underscore the significance of the TG/HDL-C ratio as a vital



Features included: TG/HDL-C, Sex, Age (Years), BMI (kg/m²), Smoking status.
The ROC curve evaluates the discriminative performance of the logistic regression model.

FIGURE 2
ROC curve: logistic regression predicting nocturnal hypertension.

indicator in contemporary clinical diagnosis and expand upon previous research by innovatively proposing the TG/HDL-C ratio as a predictive factor for nocturnal hypertension, addressing the gap in nighttime blood pressure prediction. Logistic regression analysis demonstrated a positive correlation between TG/HDL-C ratio and nocturnal hypertension (regression coefficient of 0.115), indicating that elevated TG/HDL-C ratio is associated with an increased risk of nocturnal hypertension. This observation supports the hypothesis that TG/HDL-C ratio may serve as a potential marker for cardiovascular risk. Despite the relatively modest strength of the observed association, its independent predictive effect remained consistent after controlling for confounding variables, including sex, age, BMI, and smoking status. These findings offer significant insights into the management of hypertension. Daily fluctuations in lipids must be considered in the management of blood pressure in hypertensive patients, leading to timely adjustment of medication strategies. This may necessitate the incorporation of lipid-regulating medications when abnormalities are identified during treatment and the adjustment of medication timing to mitigate the risk of nocturnal hypertension. This integrated approach is expected to address the critical problem of difficulty in detecting and poor control of nocturnal blood pressure elevations in hypertension treatment.

Specificity of the study population

A prior study focusing on hypertension in Asian populations emphasized the importance of addressing drug resistance and nocturnal hypertension in Asia [26]. The participants included in the present study are all Asian. Considering the aging population and unique dietary habits in Asia, the incidence of hypertension is increasing annually. Therefore, the investigation of nocturnal hypertension in Asia provides significant guidance for the prevention, control, management, and treatment of hypertension in this region.

Deficiencies and prospects

Given the cross-sectional design of the study and the lack of long-term follow-up, the findings serve as preliminary evidence based on current research, necessitating further investigation for a comprehensive understanding. Furthermore, the modest sample size, in conjunction with the possibility that other variables were not completely incorporated into the model, yielded an AUC value of 0.65 for the resulting logistic regression model. This finding indicates a modest degree of predictive capability. Consequently, it is imperative that we undertake a large-scale study to substantiate the evidence and enhance the robustness of the model. Furthermore, the study population primarily consists of individuals from northern China, with limited representation from other regions. To address these limitations, future research should aim to conduct multicenter, multiethnic systematic studies to enhance the generalizability of the findings and better inform clinical prevention and treatment strategies.

Conclusion

In conclusion, the present study has definitively established an association between the TG/HDL-C ratio and nocturnal hypertension,

TABLE 4 Subgroup analysis for association between TG/HDL-C and nocturnal hypertension.

Subgroup	n. Total	n. event%	crude. OR_95CI	crude.Pvalue	P.for.interaction1	P.for.interaction2	adj. OR_95CI	adj.P value	P.for.interaction1	P.for.interaction_2
Sex										
sex=female	450	329 (73.1)	1.14 (0.95~1.36)	0.174	0.169	0.182	1.1 (0.91~1.33)	0.306	0.14	0.154
sex=male	299	237 (79.3)	1.43 (1.07~1.91)	**0.014**			1.35 (1.01~1.82)	**0.044**		
Age										
Age<45	40	29 (72.5)	1.51 (0.75~3.04)	0.243	0.554	0.571	1.63 (0.71~3.74)	0.246	0.486	0.505
Age≥45	709	537 (75.7)	1.23 (1.05~1.44)	**0.01**			1.18 (1.01~1.39)	**0.039**		
BMI										
BMI<24kg/m2	298	202 (67.8)	1.05 (0.84~1.32)	0.676	0.205	0.207	0.98 (0.78~1.24)	0.882	0.225	0.228
BMI≥24kg/m2	451	364 (80.7)	1.29 (1.03~1.6)	**0.025**			1.26 (1.01~1.57)	**0.041**		
Hypertension										
hypertension=no	224	133 (59.4)	1.1 (0.89~1.36)	0.395	0.265	0.267	1.1 (0.89~1.37)	0.381	0.318	0.321
hypertension=yes	525	433 (82.5)	1.31 (1.04~1.64)	**0.02**			1.29 (1.02~1.63)	**0.032**		
Smoking										
smoke=no	413	301 (72.9)	1.16 (0.96~1.41)	0.129	0.407	0.411	1.13 (0.92~1.37)	0.238	0.378	0.384
smoke=yes	336	265 (78.9)	1.33 (1.03~1.71)	**0.027**			1.29 (1~1.67)	**0.048**		

Covariates included: medication use, height, weight, history of diabetes.

OR, odds ratio; CI, confidence interval; SD, standard deviation. P values in bold are < 0.05.

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even after adjusting for various confounding variables. This association is particularly pronounced among middle-aged and elderly individuals, males, those who are obese, smokers, and individuals with a history of hypertension. The positive correlation between TG/HDL-C and nocturnal hypertension was confirmed by logistic regression modeling. Despite the limitations of the logistic regression model, the findings provide a foundation for further investigation into the predictive mechanisms of nocturnal hypertension. Subsequent studies should integrate additional clinical and lifestyle characteristics and employ more advanced models to enhance predictive capabilities. Considering the significant risk posed by nocturnal hypertension, the results of blood lipid tests should be emphasized in future clinical practice to screen patients with elevated nighttime blood pressure, guide patients to adhere to medication regimens, and prevent adverse nocturnal events.

Data availability

Data in support of this study were obtained from self-constructed databases and can be obtained from corresponding authors.

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 Ethics Review Committee of the Affiliated Hospital of Changchun University of Traditional Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HD: Conceptualization, Formal Analysis, Writing – original draft. ZL: Conceptualization, Writing – review & editing. JZ: Data curation, Project administration, Writing – original draft. YH: Data curation, Investigation, Writing – original draft. JLZ: Data curation, Software, Writing – original draft. YX: Formal Analysis, Resources, Writing – original draft. LC: Supervision, Validation, Writing – original draft. YD: Methodology, Supervision, Writing – review & editing, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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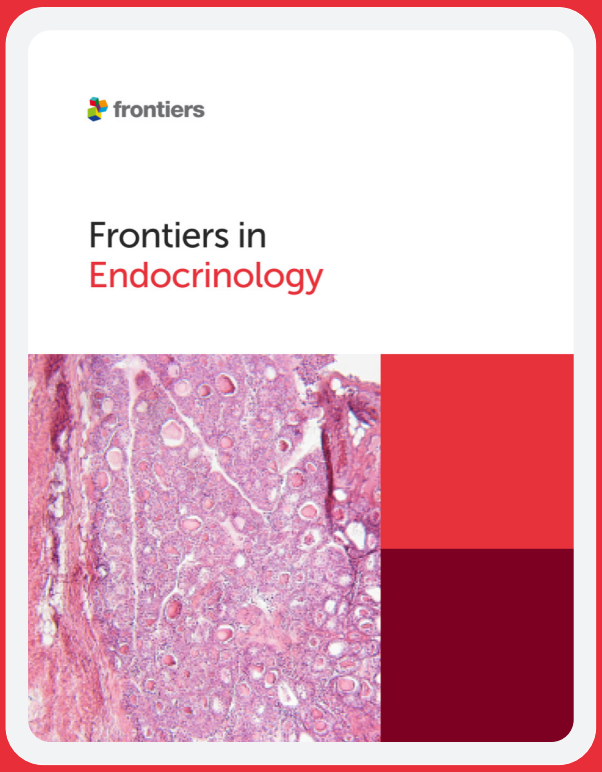

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