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Joint assessment of abdominal obesity and non-traditional lipid parameters for primary prevention of cardiometabolic multimorbidity: insights from the China health and retirement longitudinal study 2011–2018

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Abstract

Background Obesity and abnormal lipid metabolism increase the risk of various cardiometabolic diseases, including diabetes, heart disease, and stroke. However, the impact of abdominal obesity (AO) and non-traditional lipid parameters on the risk of cardiometabolic multimorbidity (CMM) remains unclear. This study aims to investigate the separate and combined effects of AO and non-traditional lipid parameters on the incidence risk of CMM.

Methods This study enrolled 7,597 eligible participants from the China health and retirement longitudinal study (CHARLS). Cox proportional hazards models were used to perform adjusted regression analyses and mediation analyses, with Kaplan-Meier analysis used for cumulative hazards. Restricted cubic splines were utilized to evaluate the nonlinear relationship between non-traditional lipid parameters and the risk of CMM among participants with AO. Subgroup analyses were conducted with stratification by age, gender, BMI, smoking status, drinking status, and hypertension to investigate interaction effects across different populations. Additionally, sensitivity analyses were further performed to evaluate the impact of various subgroups on diabetes, heart disease, and stroke.

Results During the 7-year follow-up period, a total of 699 participants (9.20%) were newly diagnosed with CMM. Kaplan-Meier curves revealed that the subgroup with both AO and high levels of non-traditional lipid parameters had the highest cumulative hazard for developing CMM. In the fully adjusted model, Cox regression analysis revealed that participants with both high levels of non-traditional lipid parameters and AO exhibited the highest risk of developing CMM. Subgroup and sensitivity analyses further confirmed the robustness of these findings, showing consistent results across different demographic groups and under various analytical conditions. Furthermore, AO was found to significantly mediated the associations between non-traditional lipid parameters and the risk of developing CMM.

Conclusion The separate and combined effects of AO and non-traditional lipid parameters were significantly associated with the risk of developing CMM. Notably, AO may induce CMM by partially mediating the effects of serum

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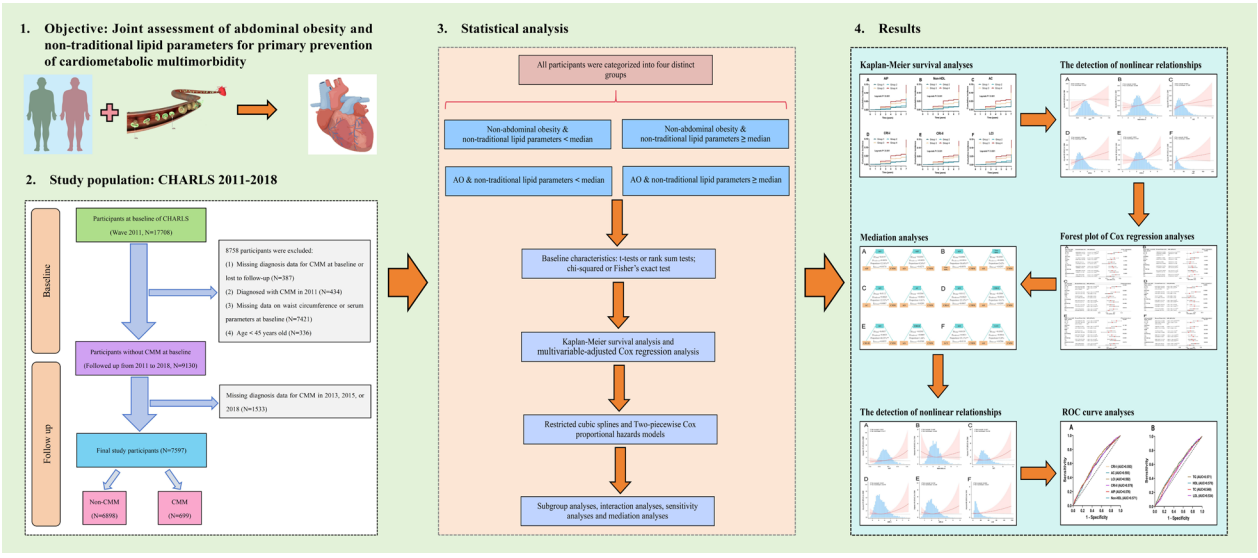
lipids in human metabolism. The findings highlighted the importance of joint evaluation of AO and non-traditional lipid parameters for primary prevention of CMM.

Graphical abstract



Keywords Abdominal obesity, Non-traditional lipid parameters, Cardiometabolic Multimorbidity, CHARLS

Background

The increasing global population aging trend has led to the rapid emergence of multimorbidity as a significant healthcare challenge that poses a threat to global health [1]. Cardiometabolic multimorbidity (CMM) is one of the most severe and prevalent types of multimorbidity worldwide, characterized by the coexistence of two or more cardiometabolic diseases (CMDs) such as diabetes, heart disease, and stroke [2]. Increasing evidence suggests that the CMM is associated with the development and prognosis of various chronic diseases, including disability, dementia, cognitive impairment, and depression [3–6]. Furthermore, compared with single CMDs, CMM has been reported to be associated with a multiplicative increase in mortality and a notable decrease in life expectancy [2, 7]. Results from a nationally representative survey show that the prevalence of CMM among elderly participants in China has increased from 11.6 to 16.9%, and continues to grow rapidly [8]. Therefore, early detection and intervention of CMM is of crucial importance for promoting healthy aging and reducing the healthcare burden on society.

Previous studies have shown that obesity, as defined by body mass index (BMI), is an important risk factor for cardiovascular diseases (CVD) [9]. However, the IAS and ICCR Working Group on Visceral Obesity argue that BMI alone is not sufficient to properly assess or manage the cardiometabolic risk associated with increased adiposity in adults [10]. In the latest framework for the diagnosis, staging, and management of obesity in adults, the European Association for the Study of Obesity highlights that the accumulation of abdominal fat is associated with an increased risk of developing cardiometabolic complications and is a stronger determinant of disease development than BMI [11]. Evidence suggests that abdominal obesity (AO) significantly increases the risk of CMDs in adults [12]. Even among participants considered to have normal weight based on BMI definitions, AO was also significantly associated with an increased risk of cardiovascular mortality [13]. The American Heart Association also supports AO, as determined by waist circumference, as a CVD risk marker that is independent of BMI [14].

The non-traditional lipid parameters, which are derived from multiple traditional lipid parameters, primarily include the atherogenic index of plasma (AIP), non-HDL-C, and the lipoprotein combine index (LCI). Accumulating evidence has confirmed the significant role of lipid metabolism in the development of CMDs, and demonstrated that non-traditional lipid parameters have superior predictive value for CMDs compared to traditional lipid parameters [15–17]. CMDs are typically associated with intertwined metabolic abnormalities, including obesity, abnormal lipid metabolism, and insulin resistance (IR). Genetic and biochemical studies suggest that adipose tissue plays a key role in the development of IR, possibly by releasing lipids and circulating factors that

promote IR [18]. Adipocytes produce hormones such as adiponectin and leptin, as well as cytokines including tumour necrosis factor and IL-1β, which induce IR and promote the progression of CMDs [19]. Recent studies have demonstrated that the lipoprotein profiles linked to obesity are significantly correlated with an elevated CVD risk score, and that lipids partially mediate the association between obesity and cardiometabolic risk [20, 21]. A study also found that abdominal obesity-related lipid metabolites [PC3 (O-21:2), SM (d21:1), and PG (43:6)] may mediate the relationship between AO and abnormal glucose regulation, highlighting the intertwined nature of obesity and lipid metabolism [22]. Another study demonstrated that obesity could partly mediate the association between environmental factors (e.g., occupational noise) and lipid abnormalities, thereby further suggesting a potential mediating role of obesity in lipid-related metabolic abnormalities [23]. However, as of now, there are no detailed studies elucidating the relationship between obesity-mediated abnormal lipid metabolism and the risk of CMDs. Therefore, We speculate that AO and non-traditional lipid parameters may jointly or interactively contribute to the increased risk of CMM. However, the exact relationship between them remains unclear.

In view of the above, we used data from the China health and retirement longitudinal study (CHARLS), aiming to investigate the combined or reciprocal mediating effects of AO and non-traditional lipid parameters on the incidence of CMM in the population aged 45 years or older.

Methods

Study design and participants

This study obtained its data from the 2011 and 2018 waves of the CHARLS survey, which is freely available to the public (http://charls.pku.edu.cn/). CHARLS was a prospective, nationwide cohort study that provided reliable information on the health statuses and related determinants of middle-aged and elderly Chinese adults. The baseline survey was conducted from June 2011 to March 2012, encompassing a total of 17,708 residents from 450 villages and residential areas in 28 provinces [24]. The baseline survey achieved a high response rate of 80.5%, which significantly reduced the potential for selection bias and enhanced the representativeness of the cohort. Trained personnel collected anthropometric measurements and venous blood samples for the study. All participants provided informed written consent prior to participation, and the CHARLS survey project was approved by the Peking University Biomedical Ethics Review Committee (IRB00001052-11015).

In the current study, a total of 17,708 participants were initially included in the baseline survey. According to the study protocol, our primary objective was to examine the combined or reciprocal mediating effects of AO and non-traditional lipid parameters on the incidence of CMM. To ensure the validity and reliability of our findings, only participants aged 45 years or older were included. Participants were excluded based on the following criteria: (1) missing diagnosis data for CMM at baseline or lost to follow-up (N = 387); (2) diagnosed with CMM in 2011 (N = 434); (3) missing data on waist circumference (WC) or serum parameters at baseline (N = 7421); (4) age < 45 years old (N = 336); (5) missing diagnosis data for CMM in 2013, 2015, or 2018 (N = 1533). Finally, a total of 7,597 participants were eligible for subsequent analysis. The detailed inclusion and exclusion process is shown in Fig. 1.

Data collection and measurement

Trained personnel collected anthropometric measurements and venous blood samples. Information on various demographic and health-related factors was gathered, including age, gender, height, weight, waist circumference (WC), marital status, residence, education level, smoking status, drinking status, as well as self-reported or physician-diagnosed diseases such as hypertension, diabetes, heart disease, and stroke. Weight was measured with the subject not wearing footwear and recorded to the nearest 0.1 kg. Height was recorded to the nearest 0.1 cm using a vertical stadiometer. WC was measured horizontally around the subject's umbilical level, to the nearest 0.1 cm. The participants' blood pressure (BP) was calculated as the average of three BP measurements taken with an Omron HEM-7200 sphygmomanometer.

Fasting venous blood samples were collected by medical professionals, stored at − 20 °C, and then transported by a cold chain transport company to the Chinese Center for Disease Control and Prevention in Beijing for further analysis. Serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG) were measured based on an enzymatic colorimetric test. Serum creatinine (μmol/L) was measured using the rate-blanked and compensated Jaffe creatinine method. High-sensitivity C-reactive protein (hs-CRP) was measured using an immunoturbidimetric assay on a Hitachi 7180 chemistry analyzer (Hitachi, Tokyo, Japan). The coefficient of variation (CV) for all blood biomarker measurements is less than 5%, ensuring high reliability of the results.

Assessment of abdominal obesity and general obesity

According to the latest standards for defining AO in China, the waist circumference thresholds for diagnosing AO in men and women were set at ≥ 85 cm and ≥ 80 cm, respectively [25]. According to the criteria set by the Working Group on Obesity in China (WGOC),

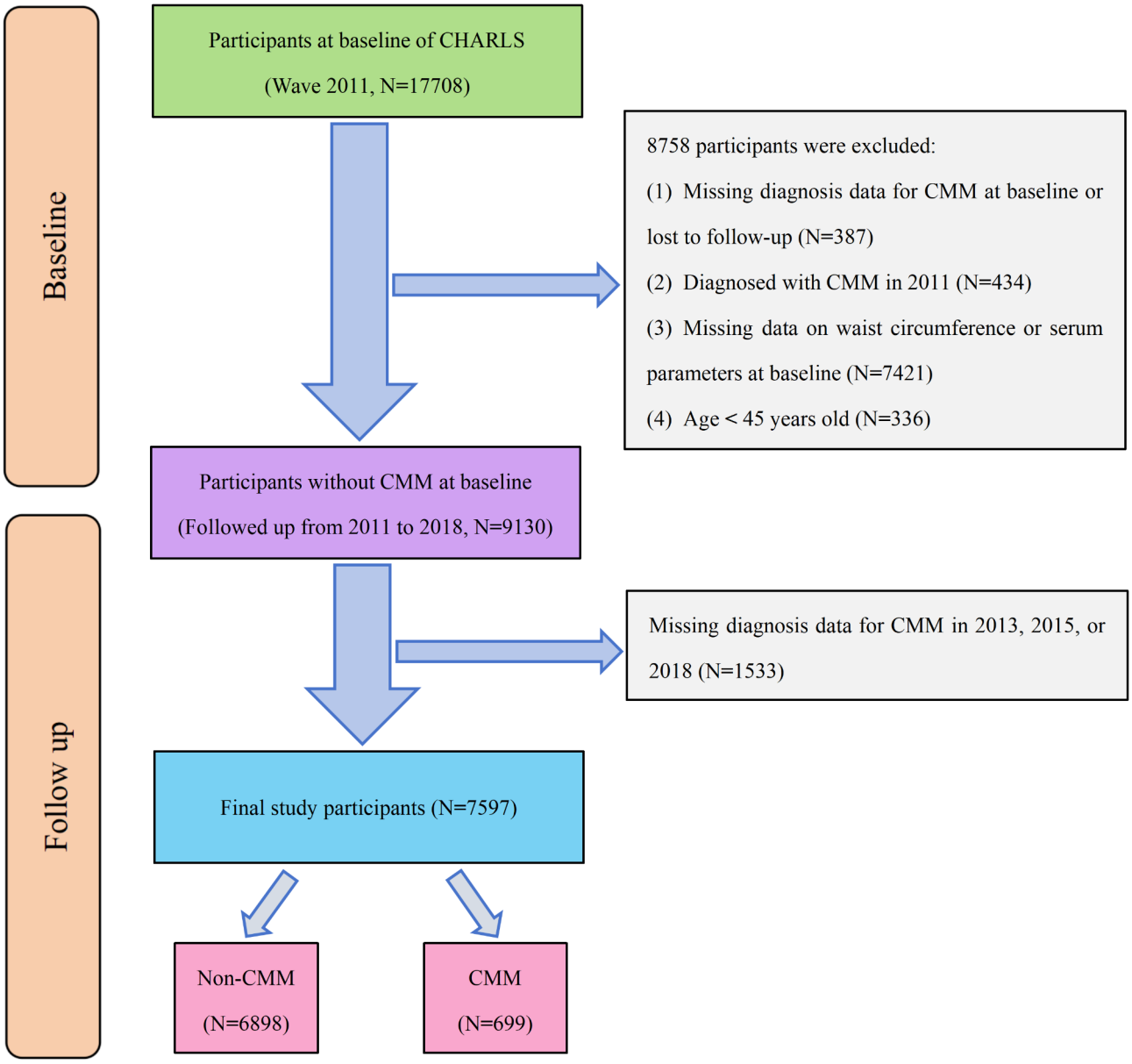


Fig. 1 Flow chart of inclusion and exclusion criteria of participants

general obesity is clearly defined using BMI. Participants were categorized based on their BMI as follows: obesity (≥ 28.0 kg/m²), overweight (24.0–28.0 kg/m²), and normal weight (18.5–24.0 kg/m²) [26].

Calculation of non-traditional lipid parameters

The following formulas were used for calculating non-traditional lipid parameters

(1) Atherogenic index of plasma (AIP) = lg (TG / HDL-C) [27];
(2) Non-HDL-C = TC – HDL-C [28];
(3) Atherogenic coefficient (AC) = Non-HDL-C / HDL-C [29];
(4) Castelli's index-I (CRI-I) = TC / HDL-C [30];
(5) Castelli's index-II (CRI-II) = LDL-C / HDL-C [30];
(6) Lipoprotein combine index (LCI) = TC × TG × LDL-C / HDL-C [31];

Assessment of CMM events

The primary endpoint event of this study was the occurrence of CMM events, characterized by the coexistence of two or more CMDs, including diabetes, heart disease, and stroke [32]. Diabetes diagnosis were assessed using the following criteria: FPG ≥ 7.0 mmol/L, glycated haemoglobin (HbA1c) levels ≥ 6.5%, current use of anti-diabetic medications, or self-report diagnosis ('Have you been diagnosed with diabetes or hyperglycemia by

a doctor?') [33]. Identification of participants with heart disease or stroke was primarily based on self-reported data collected at baseline and follow-up surveys, or the use of any cardiovascular medications. Information on heart disease and stroke was collected using the standardized question: 'Have you ever been diagnosed by a doctor as having coronary heart disease, angina, congestive heart failure, or any other heart problem?' and 'Have you ever been diagnosed by a doctor as having had a stroke?'. Event time was defined as the interval between the previous interview and the interview at which the new CMM diagnosis was reported. For those without reported CMM during follow-up, we determined follow-up duration by the interval between the baseline assessment and their final survey date [24]. For secondary outcomes, diabetes, heart disease, and stroke were further analyzed separately.

Covariates

The covariates in this study included age, gender, BMI, type of residence, education level, marital status, smoking status, drinking status, hypertension, cancer, systolic blood pressure (SBP), diastolic blood pressure (DBP), night sleep duration, daytime nap duration, FPG, HbA1c, hs-CRP, and estimated glomerular filtration rate (eGFR). BMI was calculated as weight in kilograms divided by height in meters squared. Education was classified as below primary, primary school, middle school, and high school or above. Marital status was classified as married or other types. Smoking status and drinking status was recorded as yes or no. Residence was classified as urban or rural. Hypertension was defined by a self-reported history of hypertension, SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or current use of any antihypertensive medications [34]. Cancer was defined as having a self-reported history of cancer, having undergone chemotherapy, or having undergone surgery related to cancer treatment. According to previous studies, the triglyceride-glucose (TyG) index was calculated as Ln [triglycerides (mg/dL) × glucose (mg/dL)/2] [35]. The eGFR level (mL/min/1.73 m^2) was calculated according to the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [36].

Missing data processing

In our study, there were missing data for the following variables: antidiabetic medication (1, 0.01%), drinking status (5, 0.07%), FPG (5, 0.07%), eGFR (6, 0.08%), history of hypertension (23, 0.30%), antihypertensive medication (24, 0.32%), HbA1c (48, 0.63%), SBP (59, 0.78%), DBP (60, 0.79%), BMI (60, 0.79%), and antidyslipidemic medication (107, 1.41%). 5% (390 of 7,597) of the total data items were missing and were assumed to be missing at random (MAR). To reduce bias resulting from the missing variables, we employed multiple imputation techniques to handle the missing data. we generated five imputed data sets and pooled the results using multiple imputation of the chained equation Markov chain Monte Carlo method.

Statistical analysis

Normally distributed continuous variables are expressed as the mean (standard deviation, SD), while skewed continuous variables are expressed as the median (25th to 75th interquartile range). Between-group differences were compared using t-tests or rank sum tests. Categorical variables were presented as frequencies and percentages, with differences determined by chi-squared or Fisher's exact test. Using waist circumference thresholds for the diagnosis of AO, participants were classified into two groups: those with AO and those with non-abdominal obesity. Due to the lack of clinical cutoff points for non-traditional lipid parameters in relation to cardiometabolic disease risk, we utilized the median values of these parameters as cutoff points and further subdivided participants into low-value and high-value groups. Based on these classifications, participants were categorized into four distinct groups (non-abdominal obesity & non-traditional lipid parameters ≤ median, non-abdominal obesity & non-traditional lipid parameters ≥ median, AO & non-traditional lipid parameters ≤ median, AO & non-traditional lipid parameters ≥ median).

Kaplan-Meier survival analysis was employed to estimate the cumulative incidence of CMM in the four groups. Cumulative hazard curves were constructed using the Kaplan-Meier method, and differences were compared using the log-rank test. Incidence rates of CMM events were reported as per 1000 person-years. To determine the association between AO, non-traditional lipid parameters, and the development of CMM, multivariable-adjusted Cox regression models were used to calculate the hazard ratio (HR) with 95% confidence interval (CI). The proportional hazards assumption was tested using Schoenfeld residuals, and no potential violation was observed. Model I was unadjusted; Model II adjusted for age, gender, BMI, smoking status, drinking status, and chronic diseases (hypertension and cancer); Model III further adjusted for education level, marital status, residence, SBP, DBP, night sleep duration, daytime nap duration, FPG, eGFR, hs-CRP, HbA1c, and medication use (antihypertensive, antidiabetic, antidyslipidemic, cardiovascular medications).

Cox proportional hazards regression models with adjusted restricted cubic splines (RCS) were conducted to identify any nonlinear association between nontraditional lipid parameters and the incidence of CMM among participants with AO. If a nonlinear relationship was identified, the threshold value was estimated by attempting all possible values and selecting the threshold

point with the highest likelihood. Two-piecewise Cox proportional hazards models were constructed on either side of the inflection point to investigate the association between non-traditional lipid parameters and the incidence of CMM among participants with AO.

Additional subgroup and interaction analyses were performed to further validate the robustness of the interaction effect between AO, non-traditional lipid parameters, and the development of CMM. These analyses included subgroups categorized by age (45–59 years, 60–79 years, and ≥ 80 years), gender (male, female), BMI (< 24 kg/m^2, ≥ 24 kg/m^2), smoking (yes, no), drinking (yes, no), and hypertension (yes, no). Several sensitivity analyses were also conducted to ensure the robustness of the results. In sensitivity analysis 1, we used multiple imputation to handle missing data and ensure that the results were not biased by incomplete information. In sensitivity analysis 2, participants who had received treatment for diabetes, heart disease, stroke, hypertension, or dyslipidemia at baseline were excluded from the analysis. In sensitivity analysis 3, participants who had diabetes, heart disease or stroke at baseline were excluded from the analysis. In sensitivity analysis 4, participants with hypertension and cancer at baseline were further excluded to maximize control over residual confounding. In sensitivity analysis 5, we assessed the joint effects of AO and non-traditional lipid parameters on the risk of developing diabetes, heart disease, and stroke, respectively.

Mediation analysis was employed to assess the direct and indirect associations between AO, non-traditional lipid parameters, and the development of CMM. Specifically, the non-traditional lipid parameters were used as predictor variables (X), AO as a mediator (M) and CMM onset as the outcome variable (Y). This method has been commonly used in previous studies to quantify the mediation effect [37]. Subsequently, receiver operating characteristic (ROC) curves were constructed to estimate the predictive ability and accuracy of each lipid parameter for assessing CMM risk among individuals with AO, and to determine the optimal cutoff values.

All statistical analyses were conducted using R statistical software (version 4.3.0) and GraphPad Prism (version 9.0). Mediation analysis was performed using the 'mediation' package, multiple imputation was performed using the 'mice' package, and Cox regression analysis was performed using the 'survival' package. Kaplan-Meier survival analysis and ROC curves were performed using GraphPad Prism. A two-tailed P value < 0.05 was considered statistically significant.

Results

Baseline characteristics of study participants

The present study is based on a total of 7,597 participants in CHARLS from 2011 to 2018, with an average age of 58.00 years and a male composition of 45.20% within the cohort. Over a maximum follow-up period of 7.0 years, 699 participants (9.20% of the total) who initially did not have CMM at baseline subsequently developed CMM. Table 1 delineates the baseline characteristics of the study population, categorized by CMM diagnosis. Participants in the CMM group were more likely to be older, female, with AO, non-smokers, and to reside in urban areas. In addition, the CMM group exhibited a higher proportion of chronic diseases (hypertension, diabetes, heart disease, stroke) and medication use (antihypertensive, antidiabetic, antidyslipidemic, cardiovascular medications) at baseline.Furthermore, compared to those without CMM, participants with CMM had significantly higher levels of SBP, DBP, daytime nap duration, TC, TG, LDL-C, FPG, HbA1c, hs-CRP, AIP, Non-HDL-C, AC, CRI-I, CRI-II, and LCI. Additionally, they had significantly lower levels of night sleep duration, HDL-C, and eGFR (all P < 0.05).

Joint association of non-traditional lipid parameters and abdominal obesity with the risk of developing CMM

Figure 2 shows the cumulative incidence rates of CMM when jointly assessing non-traditional lipid parameters and AO. Individuals exhibiting both AO and high levels of non-traditional lipid parameters demonstrated the highest incidence rate of CMM. Subsequently, we conducted a multivariable-adjusted Cox regression analysis to ascertain the association between non-traditional lipid parameters and AO with the risk of developing CMM. In the fully adjusted model, participants with AO and higher non-traditional lipid parameters had the highest risk of CMM, compared to those with non-abdominal obesity and lower non-traditional lipid parameters (below the median level). This was followed by participants with AO and lower non-traditional lipid parameters, and subsequently by those with non-abdominal obesity and higher non-traditional lipid parameters, as shown in Table 2. Among these subgroups, individuals with AO and high AIP index demonstrated the highest risk of developing CMM (HR = 2.23, 95% CI = 1.73–2.87).

The detection of nonlinear relationships

As shown in Fig. 3, multivariable-adjusted RCS analyses were conducted to visualise the relationships between non-traditional lipid parameters and the risk of CMM among participants with AO. Specifically, AIP, Non-HDL-C, AC, CRI-I, and CRI-II demonstrated a linear positive relationship with the risk of CMM (P for non-linearity > 0.05). Notably, LCI demonstrated a nonlinear relationship with the risk of CMM (P for non-linearity < 0.05). To further evaluate this nonlinear relationship, the two-piecewise Cox proportional hazards regression model was employed. After fully adjusting for the relevant covariates, we identified the inflection points for

Table 1 Baseline characteristics of participants with and without CMM

Characteristics	Overall	Non-CMM	CMM	*P* value
	***N*=7,597**	***N*=6,898**	***N*=699**	
Age, years	58.00 (51.00, 64.00)	57.00 (51.00, 64.00)	60.00 (54.00, 66.00)	< 0.001
Gender, n(%)				0.004
Male	3434 (45.20)	3154 (45.72)	280 (40.06)	
Female	4163 (54.80)	3744 (54.28)	419 (59.94)	
BMI, kg/m^2, n(%)				< 0.001
< 24	4434 (58.83)	4159 (60.78)	275 (39.63)	
≥ 24	3103 (41.17)	2684 (39.22)	419 (60.37)	
Education level, n(%)				0.872
Below primary	3641 (47.93)	3312 (48.01)	329 (47.07)	
Primary school	1683 (22.15)	1521 (22.05)	162 (23.18)	
Middle school	1530 (20.14)	1393 (20.19)	137 (19.60)	
High school or above	743 (9.78)	672 (9.74)	71 (10.16)	
Residence, n (%)				0.002
Urban	2520 (33.17)	2252 (32.65)	268 (38.34)	
Rural	5077 (66.83)	4646 (67.35)	431 (61.66)	
Married, n (%)	6455 (84.97)	5862 (84.98)	593 (84.84)	0.918
Abdominal obesity, n (%)	4457 (58.67)	3908 (56.65)	549 (78.54)	< 0.001
Smoking, n (%)	2878 (37.88)	2638 (38.24)	240 (34.33)	0.042
Drinking, n (%)	2920 (38.46)	2670 (38.73)	250 (35.82)	0.132
SBP, mmHg	125.50 (113.00, 140.00)	124.50 (112.50, 139.00)	133.50 (120.50, 150.00)	< 0.001
DBP, mmHg	74.00 (66.50, 82.50)	74.00 (66.50, 82.00)	78.50 (70.00, 86.50)	< 0.001
Night sleep duration, hours	6.00 (5.00, 8.00)	6.25 (5.00, 8.00)	6.00 (5.00, 8.00)	0.010
Daytime nap duration, minutes	1.00 (0.00, 60.00)	1.00 (0.00, 60.00)	7.00 (0.00, 60.00)	< 0.001
TC (mmol/L)	4.93 (4.34, 5.56)	4.91 (4.33, 5.55)	5.07 (4.46, 5.78)	< 0.001
TG (mmol/L)	1.19 (0.85, 1.73)	1.17 (0.84, 1.69)	1.44 (1.01, 2.20)	< 0.001
HDL-C (mmol/L)	1.28 (1.05, 1.55)	1.29 (1.06, 1.56)	1.17 (0.94, 1.41)	< 0.001
LDL-C (mmol/L)	2.96 (2.42, 3.56)	2.95 (2.42, 3.54)	3.06 (2.43, 3.72)	0.006
FPG (mg/dL)	102.24 (94.32, 112.68)	101.70 (93.96, 111.42)	110.34 (99.00, 129.51)	< 0.001
HbA1c (%)	5.10 (4.90, 5.40)	5.10 (4.90, 5.40)	5.30 (5.00, 5.80)	< 0.001
eGFR (mL/min/1.73 m^2)	99.44 (89.32, 106.03)	99.75 (89.64, 106.38)	97.76 (86.27, 103.58)	< 0.001
hs-CRP (mg/L)	1.00 (0.54, 2.09)	0.96 (0.53, 1.98)	1.47 (0.72, 2.95)	< 0.001
AIP	-0.04 (-0.24, 0.19)	-0.05 (-0.25, 0.18)	0.09 (-0.12, 0.32)	< 0.001
Non-HDL-C	3.59 (3.00, 4.26)	3.57 (2.99, 4.22)	3.86 (3.18, 4.61)	< 0.001
AC	2.82 (2.09, 3.76)	2.77 (2.05, 3.69)	3.34 (2.46, 4.63)	< 0.001
CRI-I	3.82 (3.09, 4.76)	3.77 (3.05, 4.69)	4.34 (3.46, 5.63)	< 0.001
CRI-II	2.32 (1.77, 2.97)	2.30 (1.75, 2.94)	2.63 (2.00, 3.43)	< 0.001
LCI	13.70 (7.48, 25.75)	13.30 (7.33, 24.15)	20.50 (9.94, 38.55)	< 0.001
Basal chronic disease, n (%)				
Hypertension	1885 (24.89)	1502 (21.85)	383 (54.79)	< 0.001
Diabetes	335 (4.41)	217 (3.15)	118 (16.88)	< 0.001
Heart disease	747 (9.83)	532 (7.71)	215 (30.76)	< 0.001
Stroke	120 (1.58)	85 (1.23)	35 (5.01)	< 0.001
Cancer	59 (0.78)	48 (0.70)	11 (1.57)	0.109
Medications, n (%)				
Antihypertensive	1885 (24.89)	1502 (21.85)	383 (54.79)	< 0.001
Antidiabetic	189 (2.49)	115 (1.67)	74 (10.59)	< 0.001
Antidyslipidemic	326 (4.35)	237 (3.49)	89 (12.81)	< 0.001
Cardiovascular medications	492 (6.48)	333 (4.83)	159 (22.75)	< 0.001

Date are presented as median (25th to 75th interquartile range) or n (%)

Abbreviations: *CMM* cardiometabolic multimorbidity, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *FPG* fasting plasma glucose, *eGFR* estimated glomerular filtration rate, *hs-CRP* High-sensitivity C-reactive protein, *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *CRI-I* Castelli's index-I, *CRI-II* Castelli's index-II, *LCI* lipoprotein combine index

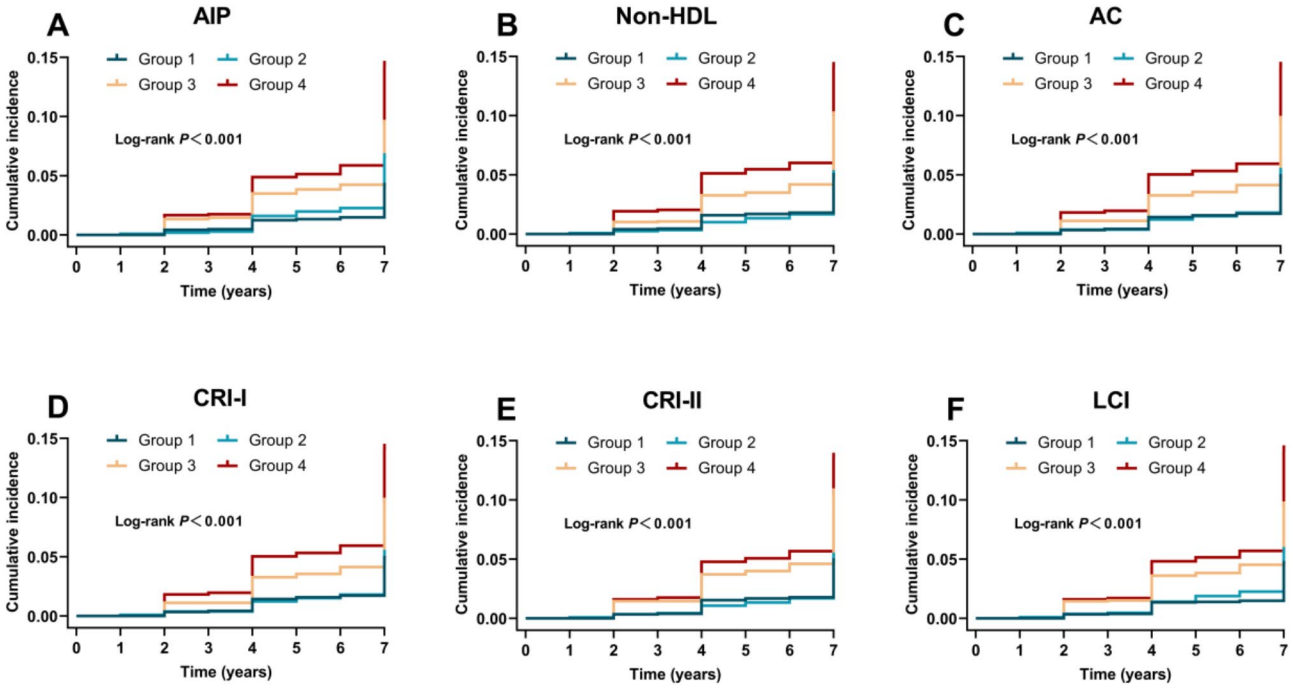


Fig. 2 K-M plot of CMM risk by abdominal obesity and non-traditional lipid parameters (**A-F**). Group 1 refers to non-abdominal obesity & non-traditional lipid parameters ≤ median; Group 2 refers to non-abdominal obesity & non-traditional lipid parameters ≥ median; Group 3 refers to abdominal obesity & non-traditional lipid parameters ≤ median; Group 4 refers to abdominal obesity & non-traditional lipid parameters ≥ median. *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *CRI-I* Castelli's index-I, *CRI-II* Castelli's index-II, *LCI* lipoprotein combine index

LCI in relation to the onset risk of CMM as 42.78 (*P* for log-likelihood ratio test < 0.05) (Table 3). When LCI was < 42.78, increased LCI was significantly associated with increased risk of CMM (HR = 1.02, 95% CI = 1.01–1.03). But there was no significant association between LCI and CMM when LCI > 42.78 (HR = 1.00, 95% CI = 0.99–1.01).

Moreover, the relationships between non-traditional lipid parameters and the risk of CMM among participants without AO were examined. As depicted in Figure S1, AIP, AC, CRI-I, and LCI demonstrated a linear positive relationship with the risk of CMM (*P* for non-linearity > 0.05). Additionally, CRI-II demonstrated a nonlinear relationship with the risk of CMM, with an inflection point of 4.06 identified by threshold effect analysis. It was also found that there was a significant positive correlation between CRI-II and CMM risk after the inflection point (HR = 2.07, 95% CI = 1.78–2.37). However, the association between CRI-II and CMM risk was not significant before the inflection point (HR = 0.96, 95% CI = 0.75–1.23) (Additional file 1: Table S1).

Subgroup and sensitivity analyses

Figure 4 presents the results of serial subgroup analyses stratified by age, gender, BMI, smoking status, drinking status, and hypertension. Notably, there was an interaction between hypertension in relation to the risk of developing CMM (*P* for interaction < 0.05), but both of the subgroups showed close associations with CMM. However, the interactions of age, gender, BMI, smoking status, and drinking status with the risk of CMM were not significant. This indicates that the joint impact of non-traditional lipid parameters and AO on the risk of developing CMM is consistent across various demographic and clinical subgroups.

To validate the robustness of the main findings, several sensitivity analyses were conducted. First, the results remained consistent among the complete data set without missing data (7,207 participants) and the multiple imputed data sets (Additional file 1: Table S2). Second, further excluding participants who had received treatment for diabetes, heart disease, stroke, hypertension, or dyslipidemia at baseline yielded similar results (Additional file 1: Table S3). Third, after excluding participants with diabetes, heart disease or stroke at baseline, the separate and combined effects of AO and non-traditional lipid parameters remained significantly associated with the risk of developing CMM during the follow-up period (Additional file 1: Table S4). Fourth, participants with hypertension and cancer at baseline were further excluded to maximize control over residual confounding. Similarly, the results were still robust in the remaining study population (Additional file 1: Table S5). Finally, we evaluated the separate and combined effects of AO and non-traditional lipid parameters on the risks of developing diabetes, heart disease, and stroke, respectively.

Table 2 Association of the non-traditional lipid parameters and abdominal obesity with the risk of CMM

Subgroups	Incidence rate[a]	Model I		Model II		Model III	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
AIP and AO							
Group 1	5.67	Reference	—	Reference	—	Reference	—
Group 2	9.27	1.65 (1.20, 2.27)	0.002	1.55 (1.13, 2.15)	0.007	1.56 (1.13, 2.16)	0.007
Group 3	13.51	2.43 (1.86, 3.17)	< 0.001	2.07 (1.58, 2.72)	< 0.001	1.88 (1.43, 2.47)	< 0.001
Group 4	20.91	3.82 (3.01, 4.85)	< 0.001	2.85 (2.23, 3.65)	< 0.001	2.23 (1.73, 2.87)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
Non-HDL-C and AO							
Group 1	6.74	Reference	—	Reference	—	Reference	—
Group 2	7.09	1.05 (0.76, 1.46)	0.757	1.00 (0.72, 1.39)	0.992	0.99 (0.71, 1.37)	0.938
Group 3	14.40	2.17 (1.69, 2.79)	< 0.001	1.80 (1.39, 2.32)	< 0.001	1.62 (1.25, 2.10)	< 0.001
Group 4	20.68	3.16 (2.52, 3.98)	< 0.001	2.39 (1.88, 3.03)	< 0.001	1.83 (1.43, 2.34)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
AC and AO							
Group 1	6.63	Reference	—	Reference	—	Reference	—
Group 2	7.37	1.11 (0.80, 1.55)	0.528	1.07 (0.77, 1.50)	0.675	1.07 (0.77,1.50)	0.686
Group 3	13.85	2.12 (1.65, 2.73)	< 0.001	1.79 (1.38, 2.32)	< 0.001	1.62 (1.25, 2.10)	< 0.001
Group 4	20.70	3.22 (2.58, 4.03)	< 0.001	2.43 (1.93, 3.06)	< 0.001	1.90 (1.50, 2.41)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
CRI-I and AO							
Group 1	6.63	Reference	—	Reference	—	Reference	—
Group 2	7.37	1.11 (0.80, 1.55)	0.528	1.07 (0.77, 1.50)	0.675	1.07 (0.77,1.50)	0.686
Group 3	13.85	2.12 (1.65, 2.73)	< 0.001	1.79 (1.38, 2.32)	< 0.001	1.62 (1.25, 2.10)	< 0.001
Group 4	20.70	3.22 (2.58, 4.03)	< 0.001	2.43 (1.93, 3.06)	< 0.001	1.90 (1.50, 2.41)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
CRI-II and AO							
Group 1	6.63	Reference	—	Reference	—	Reference	—
Group 2	7.32	1.11 (0.80, 1.54)	0.549	1.08 (0.78, 1.51)	0.632	1.07 (0.77, 1.49)	0.688
Group 3	15.35	2.36 (1.84, 3.03)	< 0.001	1.98 (1.53, 2.55)	< 0.001	1.73 (1.33, 2.24)	< 0.001
Group 4	19.85	3.08 (2.46, 3.87)	< 0.001	2.35 (1.85, 2.97)	< 0.001	1.84 (1.44, 2.34)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
LCI and AO							
Group 1	6.30	Reference	—	Reference	—	Reference	—
Group 2	8.01	1.28 (0.92, 1.77)	0.143	1.20 (0.87, 1.67)	0.273	1.23 (0.88, 1.71)	0.223
Group 3	13.74	2.22 (1.72, 2.87)	< 0.001	1.88 (1.44, 2.44)	< 0.001	1.70 (1.31, 2.22)	< 0.001
Group 4	20.77	3.41 (2.71, 4.28)	< 0.001	2.55 (2.01, 3.24)	< 0.001	2.01 (1.57, 2.57)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001

Model I: non-adjusted

Model II: adjusted for age, gender, BMI, smoking status, drinking status, and chronic diseases (hypertension and cancer)

Model III: further adjusted for education level, marital status, residence, SBP, DBP, night sleep duration, daytime nap duration, FPG, eGFR, hs-CRP, HbA1c, and medication use (antihypertensive, antidiabetic, antidyslipidemic, cardiovascular medications)

Group 1 refers to non-abdominal obesity & non-traditional lipid parameters ≤ median; Group 2 refers to non-abdominal obesity & non-traditional lipid parameters ≥ median; Group 3 refers to abdominal obesity & non-traditional lipid parameters ≤ median; Group 4 refers to abdominal obesity & non-traditional lipid parameters ≥ median. *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *CRI-I* Castelli's index-I, *CRI-II* Castelli's index-II, *LCI* lipoprotein combine index, *AO* abdominal obesity, *HR* hazard ratio, *CI* confidence interval

[a]Incident rate was presented as per 1000 person-years of follow-up

As shown in Table 4, the results remained statistically significant.

Mediation analysis

Figure 5 summarizes the potential mediating effect of AO on the associations between six non-traditional lipid parameters and the risk of developing CMM. In the fully adjusted analyses, the mediation proportions of AO were 12.18%, 18.60%, 22.32%, 22.32%, 40.35%, and 15.11%, respectively (all $P < 0.01$). Conversely, the mediation proportion for AIP was 9.24% ($P < 0.05$). However, no significant mediation effect was observed for Non-HDL, AC, CRI-I, CRI-II or LCI were observed in the relationship between AO and the risk of developing CMM (all

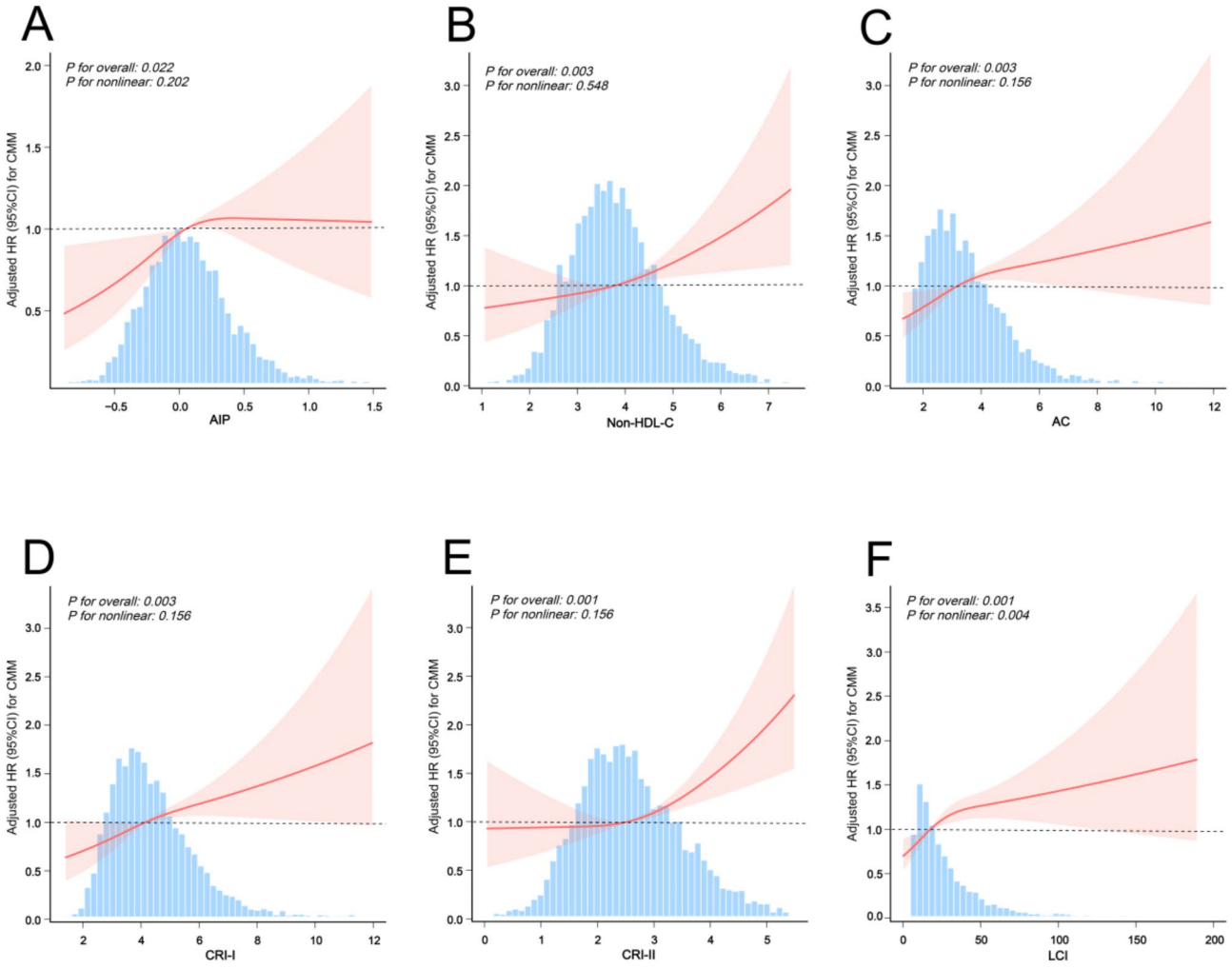


Fig. 3 Dose-response relationship between the non-traditional lipid parameters and the risk of CMM among participants with AO (**A-F**). Spline analyses were adjusted for age, gender, BMI, smoking status, drinking status, education level, marital status, residence, SBP, DBP, night sleep duration, daytime nap duration, FPG, eGFR, hs-CRP, HbA1c, chronic diseases (hypertension and cancer), and and medication use (antihypertensive, antidiabetic, antidyslipidemic, cardiovascular medications). *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *CRI-I* Castelli's index-I, *CRI-II* Castelli's index-II, *LCI* lipoprotein combine index, *HR* hazard ratio, *CI* confidence interval

$P > 0.05$). The results indicate that AO may contribute to the development of CMM by partially mediating the effects of serum lipids in human metabolism.

Discussion

Obesity, especially abdominal fat accumulation, is strongly associated with various cardiometabolic diseases. In the current study, we employed various methodological approaches to confirm that abdominal obesity (AO) can significantly increase the risk of developing CMM in individuals with abnormal lipid metabolism. After adjusting for other established cardiovascular risk factors, particularly medication use (including antihypertensive, antidiabetic, antidyslipidemic, and cardiovascular medications), the highest risk of developing CMM was observed in participants with AO and high levels of non-traditional lipid parameters. Subgroup and sensitivity analyses further confirmed the robustness of these findings. In addition, the results indicated that AO may induce CMM by partially mediating the effects of serum lipids in human metabolism.

Globally, the number of people with multiple comorbidities will increase substantially in the coming decades, with important consequences for healthcare systems and society [38]. CMM is defined as the coexistence of two or three cardiometabolic diseases (CMDs) and has been proven to be closely related to non-traditional lipid parameters and AO [12, 15, 39]. The separate effect of AO and non-traditional lipid parameters on the risk of developing CMDs has been widely evaluated in previous studies. The RCSCD-TCM study found that elevated levels of non-traditional lipid parameters were significantly associated with an increased risk of CMDs [40]. Several large population-based cohort studies have also reported

Table 3 Threshold effect analysis of non-traditional lipid parameters on the risk of CMM in participants with AO

Participants with abdominal obesity	Adjusted HR (95% CI)	*P* value
LCI		
Total	1.00 (1.00, 1.01)	0.004
Fitting by two-piecewise Cox proportional risk model		
Inflection point	42.78	
LCI < 42.78	1.02 (1.01, 1.03)	0.001
LCI > 42.78	1.00 (0.99, 1.01)	0.995
P for log-likelihood ratio		0.002

Cox proportional hazards models were used to estimate HR and 95% CI. Multivariate models were adjusted for age, gender, BMI, smoking status, drinking status, education level, marital status, residence, SBP, DBP, night sleep duration, daytime nap duration, FPG, eGFR, hs-CRP, HbA1c, chronic diseases (hypertension and cancer), and medication use (antihypertensive, antidiabetic, antidyslipidemic, cardiovascular medications). *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *CRI-I* Castelli's index-I, *LCI* lipoprotein combine index, *HR* hazard ratio, *CI* confidence interval.

that AO is associated with an increased risk of cardiovascular diseases [41, 42]. More importantly, even among individuals with normal weight as defined by BMI, AO was still significantly associated with an increased risk of cardiovascular mortality [13]. Similar to the results obtained from the aforementioned study, we have confirmed for the first time that AO and high levels of non-traditional lipid parameters are significantly associated with an increased risk of CMM. Compared to high levels of non-traditional lipid parameters, AO increases the risk of developing CMM more significantly.

The World Heart Federation and the World Obesity Federation announce that increased adiposity (body fat), particularly visceral or abdominal fat, is associated with an increased risk of CMDs through multiple direct and indirect pathophysiological mechanisms [43]. Notably, evidence suggests a complex interaction between adipose tissue and serum lipids metabolism in human metabolism. The study of adipocyte model in *vitro* revealed that LDL-cholesterol and oxidised LDL could induce the expression of lipoprotein-associated phospholipase A2 in adipose tissue and adipocytes, this may further promote inflammation and increase the risk of CMDs [44]. Conversely, adipose tissue releases a large number of bioactive mediators that not only influence body weight homeostasis and insulin resistance (IR) but also cause alterations in lipids and inflammation, leading to endothelial dysfunction and atherosclerosis [45]. Adipose tissue remodeling and dysfunction, characterized by elevated inflammation and insulin resistance, play a critical role in the obesity-related development of cardiometabolic diseases. Previous studies have shown that adipose-specific deletion of Human antigen R (HuR) inhibits the expression of adipose triglyceride lipase (ATGL), subsequently leading to insulin resistance, abnormal lipid metabolism, and systemic inflammation [46]. Furthermore, obesity-induced dysregulation of cellular cholesterol homeostasis, particularly through the down-regulation of sterol regulatory element binding protein 2 (SREBF2), impairs regulatory T cell proliferation, further exacerbating inflammation and insulin resistance in visceral adipose tissue (VAT) [47]. The hallmark of AO is the disproportionate accumulation of visceral and subcutaneous adipose tissue, leading to metabolic complications. Our additional analyses indicated that individuals with AO had significantly higher levels of non-traditional lipid parameters compared to those without AO (Additional file 1: Fig. S2). Moreover, AO was found to significantly mediate the association between non-traditional lipid parameters and CMM risk. This suggests that AO may contribute to CMM development by modulating serum lipid metabolism. However, we did not observe a significant mediation effect of non-traditional lipid parameters on the relationship between AO and CMM, indicating that other pathways, such as systemic inflammation and insulin resistance, may play more dominant roles in linking AO to cardiometabolic diseases.

Previous studies have already confirmed that abdominal adipose tissue is significantly positively correlated with IR and levels of hs-CRP [48, 49]. The triglyceride-glucose (TyG) index has been proposed as a reliable indicator of IR, which also plays an important role in the development of CMDs, including diabetes, heart disease, and stroke [50–52]. hs-CRP can serve as a surrogate marker for assessing human inflammation levels and has been proven to be closely associated with the occurrence of various CMDs [53, 54]. Therefore, we assessed the levels of the TyG index and hs-CRP in different subgroups separately. The results demonstrated that the subgroup exhibiting both AO and higher non-traditional lipid parameters had the highest levels of the TyG index and hs-CRP, when compared to the subgroup with lower non-traditional lipid parameters (below the median level) and without AO (Additional file 1: Fig. S3 and S4). Furthermore, compared to the subgroups with solely AO and solely higher non-traditional lipid parameters, the subgroup exhibiting both AO and high non-traditional lipid parameters demonstrated higher levels of IR and inflammation. This may help explain why participants with both AO and high levels of non-traditional lipid parameters had the highest risk of developing CMM. Collectively, these results highlight the importance of considering both AO and non-traditional lipid parameters in assessing CMM risk.

The risk of developing CMM increases with being female, older age, having abnormal weight, and smoking [55]. In the current study, we observed similar results and found that participants with lower eGFR were more likely to develop CMM. Previous studies also confirmed that lower eGFR levels were associated with an

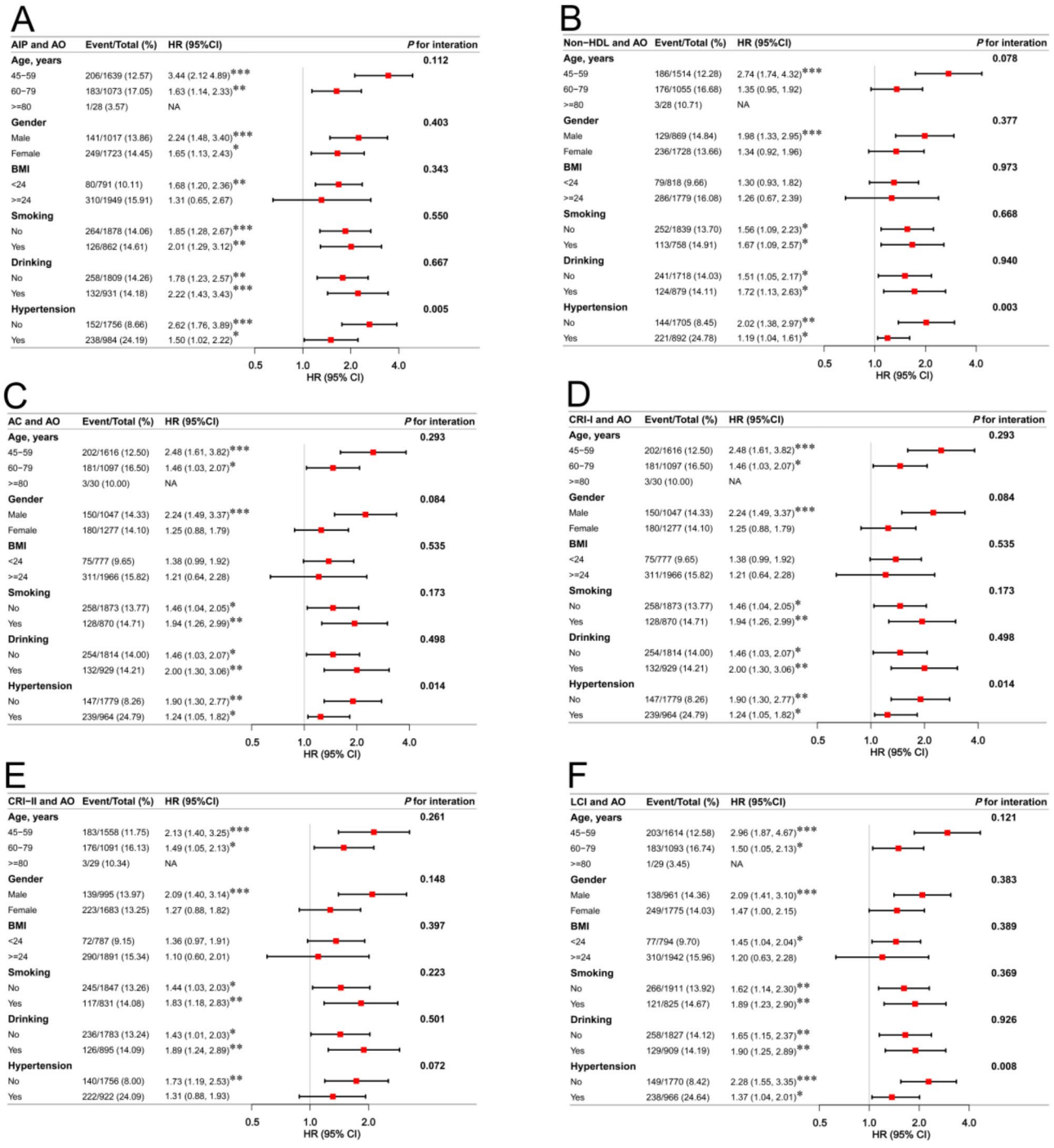


Fig. 4 Forest plot of multivariable-adjusted Cox regression analysis based on the subgroup that comprises abdominal obesity and high levels of non-traditional lipid parameters (**A-F**). Multivariate models were adjusted for age, gender, BMI, smoking status, drinking status, education level, marital status, residence, SBP, DBP, night sleep duration, daytime nap duration, FPG, eGFR, hs-CRP, HbA1c, chronic diseases (hypertension and cancer), and medication use (antihypertensive, antidiabetic, antidyslipidemic, cardiovascular medications), with the exception of the stratification variable. *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *CRI-I* Castelli's index-I, *CRI-II* Castelli's index-II, *LCI* lipoprotein combine index, *HR* hazard ratio, *CI* confidence interval, *NA* not available. **P* < 0.05, ***P* < 0.01, ****P* < 0.001

increased risk of a single cardiometabolic disease [56]. The subgroup and sensitivity analyses further validated the robustness of the joint association of AO and non-traditional lipid parameters with the risk of developing CMM. Furthermore, the latest framework for diagnosing, staging, and managing obesity in adults emphasizes that the accumulation of abdominal fat is associated with an increased risk of cardiometabolic complications, even

Table 4 Sensitivity analyses of the joint effects of AO and non-traditional lipid parameters on the risks of developing diabetes, heart disease, and stroke, respectively (*N* = 6,388)

Subgroups	Diabetes [b]		*P* value	Heart disease [b]		*P* value	Stroke [b]		*P* value
	Incidence rate [a]	HR (95% CI)		Incidence rate [a]	HR (95% CI)		Incidence rate [a]	HR (95% CI)	
AIP and AO									
Group 1	6.47	Reference	—	16.18	Reference	—	6.86	Reference	—
Group 2	11.74	1.50 (1.09, 2.07)	0.012	23.32	1.27 (1.07, 1.50)	0.005	9.27	1.34 (0.96, 1.86)	0.087
Group 3	14.72	1.74 (1.30, 2.34)	< 0.001	26.57	1.23 (1.05, 1.44)	0.010	9.68	1.38 (1.01, 1.91)	0.046
Group 4	23.99	2.45 (1.85, 3.24)	< 0.001	24.67	1.21 (1.04, 1.41)	0.015	12.81	1.58 (1.16, 2.15)	0.003
P for trend			< 0.001			0.034			0.004
Non-HDL-C and AO									
Group 1	7.67	Reference	—	17.94	Reference	—	6.59	Reference	—
Group 2	9.11	0.93 (0.67, 1.28)	0.651	19.56	0.93 (0.78, 1.09)	0.366	9.38	1.49 (1.07, 2.06)	0.017
Group 3	17.34	1.60 (1.21, 2.12)	0.001	23.94	1.18 (1.02, 1.36)	0.023	10.46	1.48 (1.07, 2.04)	0.017
Group 4	22.46	1.83 (1.39, 2.41)	< 0.001	26.61	1.37 (1.20, 1.57)	< 0.001	12.37	1.70 (1.24, 2.33)	0.001
P for trend			< 0.001			< 0.001			0.002
AC and AO									
Group 1	6.84	Reference	—	17.94	Reference	—	6.99	Reference	—
Group 2	10.95	1.27 (0.92, 1.75)	0.147	19.76	0.94 (0.79, 1.12)	0.486	8.97	1.29 (0.92, 1.79)	0.135
Group 3	15.01	1.68 (1.26, 2.24)	< 0.001	26.15	1.24 (1.08, 1.43)	0.003	10.44	1.46 (1.07, 1.99)	0.018
Group 4	23.75	2.22 (1.68, 2.93)	< 0.001	24.96	1.34 (1.18, 1.53)	< 0.001	12.28	1.48 (1.09, 2.01)	0.013
P for trend			< 0.001			< 0.001			0.015
CRI-I and AO									
Group 1	6.84	Reference	—	17.94	Reference	—	6.99	Reference	—
Group 2	10.95	1.27 (0.92, 1.75)	0.147	19.76	0.94 (0.79, 1.12)	0.486	8.97	1.29 (0.92, 1.79)	0.135
Group 3	15.01	1.68 (1.26, 2.24)	< 0.001	26.15	1.24 (1.08, 1.43)	0.003	10.44	1.46 (1.07, 1.99)	0.018
Group 4	23.75	2.22 (1.68, 2.93)	< 0.001	24.96	1.34 (1.18, 1.53)	< 0.001	12.28	1.48 (1.09, 2.01)	0.013
P for trend			< 0.001			< 0.001			0.015
CRI-II and AO									
Group 1	7.56	Reference	—	18.09	Reference	—	6.59	Reference	—
Group 2	9.41	1.00 (0.73, 1.39)	0.978	19.39	0.91 (0.77, 1.08)	0.300	9.55	1.50 (1.08, 2.07)	0.015
Group 3	17.63	1.67 (1.26, 2.20)	< 0.001	25.48	1.20 (1.04, 1.38)	0.011	10.63	1.56 (1.13, 2.14)	0.006
Group 4	22.09	1.89 (1.44, 2.47)	< 0.001	25.41	1.35 (1.19, 1.53)	< 0.001	12.19	1.59 (1.17, 2.18)	0.003
P for trend			< 0.001			< 0.001			0.006
LCI and AO									
Group 1	7.06	Reference	—	16.37	Reference	—	6.91	Reference	—
Group 2	10.51	1.20 (0.87, 1.66)	0.268	22.85	1.20 (1.02, 1.42)	0.029	9.14	1.35 (0.97, 1.88)	0.079
Group 3	14.05	1.58 (1.18, 2.11)	0.002	24.40	1.35 (1.16, 1.55)	< 0.001	10.06	1.44 (1.05, 1.98)	0.023
Group 4	24.39	2.20 (1.67, 2.90)	< 0.001	26.14	1.48 (1.30, 1.69)	< 0.001	12.53	1.55 (1.14, 2.11)	0.005
P for trend			< 0.001			< 0.001			0.007

Group 1 refers to non-abdominal obesity & non-traditional lipid parameters ≤ median; Group 2 refers to non-abdominal obesity & non-traditional lipid parameters ≥ median; Group 3 refers to abdominal obesity & non-traditional lipid parameters ≤ median; Group 4 refers to abdominal obesity & non-traditional lipid parameters ≥ median. *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *CRI-I* Castelli's index-I, *CRI-II* Castelli's index-II, *LCI* lipoprotein combine index, *AO* abdominal obesity, *HR* hazard ratio, *CI* confidence interval

[a] Incident rate was presented as per 1000 person-years of follow-up

[b] Multivariable-adjusted for age, gender, BMI, smoking status, drinking status, education level, marital status, residence, SBP, DBP, night sleep duration, daytime nap duration, FPG, eGFR, hs-CRP, HbA1c, chronic diseases (hypertension and cancer), and medication use (antihypertensive, antidiabetic, antidyslipidemic, cardiovascular medications)

in individuals whose BMI levels fall below the standard cutoff values for diagnosing obesity [11]. Similarly, the Korea National Health Screening Study found that the degree of AO, assessed by waist circumference, exhibited a significant positive correlation with an increased risk of mortality, even among participants considered to have normal weight based on their BMI [57]. Therefore, we conducted additional analyses among participants classified as normal weight based on BMI to validate the aforementioned findings. In the fully adjusted analyses, Table S5 demonstrates that AO remains significantly associated with an increased risk of CMM occurrence (HR = 1.43, 95% CI = 1.09–1.86), even among participants classified as having normal weight based on BMI. The finding

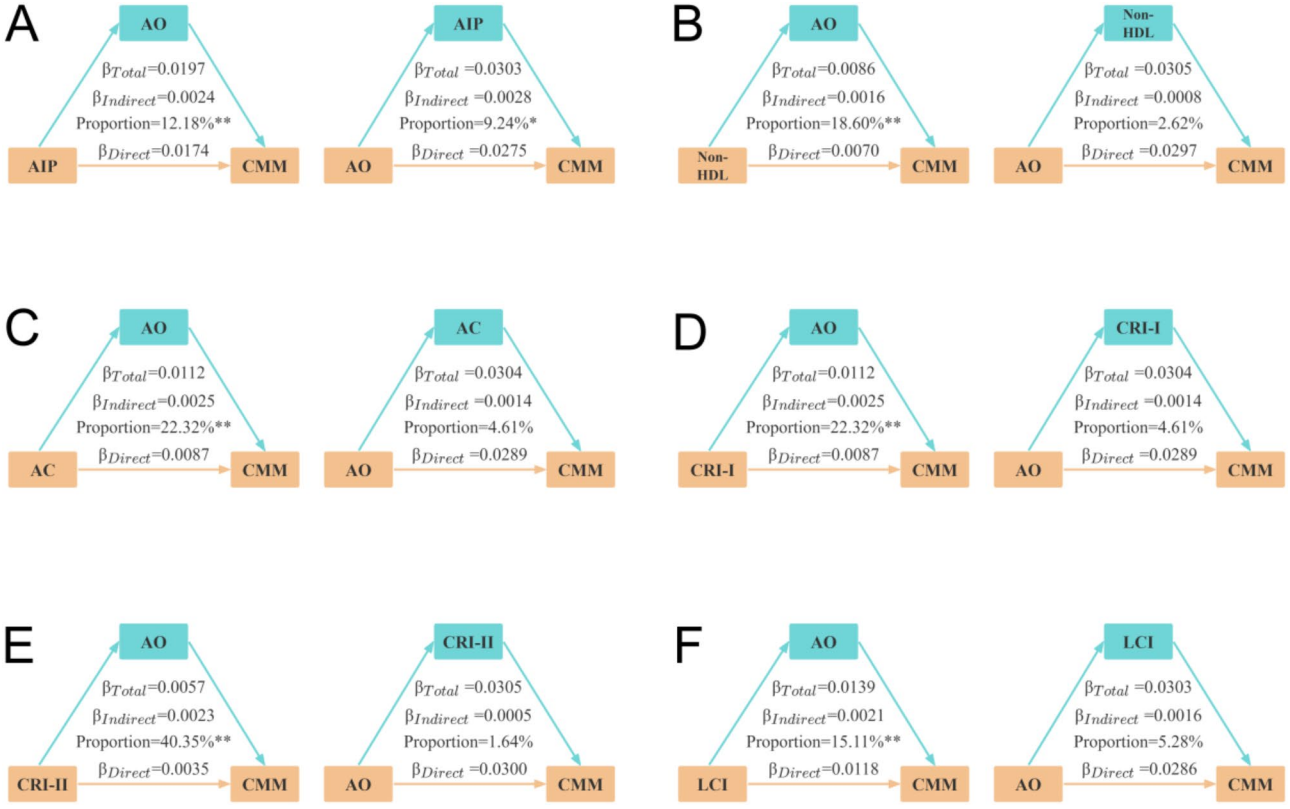


Fig. 5 Mediation analysis of abdominal obesity on the association between non-traditional lipid parameters and the risk of developing CMM. Adjusted for age, gender, BMI, smoking status, drinking status, education level, marital status, residence, SBP, DBP, night sleep duration, daytime nap duration, FPG, eGFR, hs-CRP, HbA1c, chronic diseases (hypertension and cancer), and medication use (antihypertensive, antidiabetic, antidyslipidemic, cardiovascular medications). *AIP* atherogenic index of plasma, *AC* atherogenic coefficient, *CRI-I* Castelli's index-I, *CRI-II* Castelli's index-II, *LCI* lipoprotein combine index, **P* < 0.05, ***P* < 0.01

supports the viewpoint of the IAS and ICCR Working Group on Visceral Obesity, which holds that BMI alone is inadequate for accurately assessing or managing the cardiometabolic risks associated with increased adiposity in adults [10]. Additionally, our results emphasize the significance of including waist circumference in management strategies concurrently to prevent cardiometabolic diseases.

Comparative studies on lipid parameters for predicting the risk of cardiometabolic diseases are still extremely limited. The findings from the NAGALA large longitudinal cohort study and the Korean National Health Examination Survey indicate that elevated non-traditional lipid parameters are significantly associated with an increased risk of new-onset diabetes [29, 58]. Furthermore, non-traditional lipid parameters generally outperform conventional lipid parameters in assessing and predicting future diabetes risk. In the current study, ROC curve analysis was used to compare the ability of non-traditional and traditional lipid parameters for predicting CMM risks in individuals with AO. Figure S5 and Table S7 reveal similar results, indicating that non-traditional lipid parameters typically have better ability to predict CMM compared to traditional lipid parameters. In addition, we observed for the first time that AIP, Non-HDL-C, AC, CRI-I, and CRI-II exhibited a linear positive relationship with the risk of CMM. Conversely, LCI demonstrated a nonlinear relationship with the risk of CMM, with an inflection point of 42.78 identified by threshold effect analysis. When LCI was below 42.78, increased LCI was significantly associated with increased risk of CMM. But there was no significant association between LCI and CMM when LCI was greater than 42.78. However, we observed a linear positive correlation between AIP, AC, CRI-I, LCI, and the risk of CMM among individuals without AO. Additionally, CRI-II demonstrated a nonlinear relationship with the risk of CMM, with an inflection point of 4.06 identified through threshold effect analysis. We also found that there was a significant positive correlation between CRI-II and CMM risk after reaching the inflection point, but no significant correlation was observed before the inflection point. Certainly, some of the results of this study differ from previous studies. Previous studies have found that an increase in baseline AIP levels is significantly associated with the risk of stroke, and a J-shaped association has been observed

between AIP and type 2 diabetes [59, 60]. Based on current research conclusions, individuals with AO can prevent the onset of CMM by reducing non-traditional lipid parameters to an certain level.

Strengths and limitations

Some noteworthy strengths of the present study should be highlighted. First, this is the first study to comprehensively evaluate the joint association between AO and non-traditional lipid parameters with the risk of developing CMM. Our research results emphasize the importance of concurrently incorporating both AO and non-traditional lipid parameters into management strategies to prevent CMM. Second, the research data were derived from a large prospective cohort study involving 28 provinces in mainland China, which may provide robust evidence of the association between non-traditional lipid parameters and AO with the risk of developing CMM. Last, we have discovered for the first time that AO may induce CMM by partially mediating the effects of serum lipids on human metabolism. This establishes the theoretical foundation for further in-depth research into the potential mechanisms that link AO, lipid metabolism, and the risk of cardiometabolic diseases.

Nevertheless, several limitations of the current study should be acknowledged. First, the participants were all individuals aged 45 years or older. The lack of disease status information across all age groups may have led to an underestimation of the incidence rate of CMM. Second, although we attempted to control for confounding variables through multivariate adjustment and subgroup analyses, unmeasured confounders such as diet, physical activity, and socioeconomic status may still affect the results. Third, the identification of participants with diabetes, heart disease, or stroke was primarily based on self-reported data collected during the baseline and subsequent follow-up surveys, which may have introduced information bias. Fourth, owing to the observational nature of the study, we could not confirm the causal association between non-traditional lipid parameters and AO with the risk of developing CMM. Finally, since the study population only consisted of middle-aged and elderly Chinese adults, the practical clinical application of the findings in different ethnic groups, age ranges, or lifestyles needs further validation.

Conclusion

The results of our study indicate that AO may induce CMM by partially mediating the effects of serum lipids in human metabolism, and that the combined effects of AO and non-traditional lipid parameters were significantly associated with an increased risk of developing CMM. Early identification and intervention of AO and abnormal lipid metabolism are of significant importance for both the prevention and treatment of CMM. Considering both AO and non-traditional lipid parameters can improve CMM risk assessment and help early identify high-risk individuals more accurately.

Abbreviations

AO	Abdominal obesity
CMM	Cardiometabolic multimorbidity
CMDs	Cardiometabolic diseases
CHARLS	China health and retirement longitudinal study
CVD	Cardiovascular diseases
IR	Insulin resistance
TC	Total cholesterol
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
HbA1c	Glycosylated hemoglobin A1c
FPG	Fasting plasma glucose
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
hs-CRP	High-sensitivity C-reactive protein
TyG	Triglyceride-glucose index
CKD-EPI	Chronic kidney disease epidemiology collaboration
eGFR	Estimated glomerular filtration rate
HR	Hazard ratio
95% CI	95% Confidence interval
RCS	Restricted cubic splines
ROC	Receiver operating characteristic curve
AUC	Area under the ROC curve

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02667-y.

Supplementary Material 1

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Author contributions

LHR, and TYS designed the study. LHR, TYS, and LCF analyzed the data. LCF and ZS assisted with data collection and interpretation. HL and LJ supervised the study. LHR wrote the manuscript with input from all authors. All authors read and approved the final manuscript.

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Data availability

The data that support the findings of this study are available from the China Health and Retirement Longitudinal Study (CHARLS) repository. Access to these data can be obtained by registering and submitting a request through the official CHARLS website at http://charls.pku.edu.cn.

Declarations

Ethics approval and consent to participate

The CHARLS study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Peking University. All participants provided written informed consent before participating in the CHARLS study.

Competing interests

The authors declare no competing interests.

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