Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Joint associations of the atherogenic index of plasma and waist-to- height ratio with incident cardiometabolic multimorbidity among middle-aged and older Chinese adults: a nationwide prospective cohort study

Yixiao Liang
Beijing Hospital
Wenjie Huo
Beijing Hospital
Hu Ai
aihumd@aliyun.com

Beijing Hospital

Research Article

Keywords: Atherogenic index of plasma, Waist-to-height ratio, Cardiometabolic multimorbidity, Central adiposity, Atherogenic dyslipidemia, CHARLS, Joint exposure.

Posted Date: September 17th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10617608/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Atherogenic dyslipidemia and central adiposity are two interrelated metabolic features implicated in the progression from single cardiometabolic disease to cardiometabolic multimorbidity (CMM). This study investigated the separate and joint associations of the atherogenic index of plasma (AIP) and waist-to-height ratio (WHtR) with incident CMM, while how this phenotype relates to broader metabolic-inflammatory risk layers remains unclear.

Methods

This prospective cohort study used CHARLS data from 2011 to 2020 and included 8,747 participants without baseline CMM. Cox proportional hazards models were used to examine the associations of AIP, WHtR, AIP&WHtR, and AIP-WHtR with incident CMM. Additive and multiplicative interactions, cross-lagged paths, and mediation analyses were used to characterize the interrelationship between AIP and WHtR. WQS component contribution analysis was performed to estimate the relative contribution of AIP- and WHtR-related components. Risk-layer stratified analyses combining the AIP and WHtR joint groups with CRP, RC, and TyG were conducted to evaluate inflammatory, remnant cholesterol, and insulin resistance-related risk layers. Prediction analyses, subgroup analyses, and sensitivity analyses were further performed to assess the risk-stratification value and robustness of the combined assessment of AIP and WHtR.

Results

During follow-up, 994 participants (11.36%) developed incident CMM. After full adjustment, elevated AIP and elevated WHtR were separately associated with higher CMM risk, with HRs of 1.54 (95% CI: 1.34–1.76) and 1.75 (95% CI: 1.51–2.04), respectively. The greatest risk was observed among participants with simultaneous elevation of both markers, who had a 2.32-fold higher risk of incident CMM than those with Low AIP + Low WHtR (95% CI: 1.90–2.83). Formal tests did not show significant additive or multiplicative interaction. WQS analysis showed that waist circumference was the leading contributor to the combined exposure structure, with a weight of 61.3%. When CRP, RC, and TyG were incorporated as additional stratification layers, participants with all-marker elevation showed the highest CMM risk, especially those with High AIP + High WHtR and high CRP (HR 2.84, 95% CI: 2.19–3.67). The corresponding HRs were 2.40 (95% CI: 1.93–2.99) for high RC and 2.65 (95% CI: 2.14–3.29) for high TyG. The model including both AIP and WHtR achieved the highest ROC AUC of 0.738.

Conclusion

In this nationwide prospective cohort of middle-aged and older Chinese adults, concurrent elevation of AIP and WHtR identified participants at the highest risk of incident CMM. These findings suggest that the joint assessment of atherogenic dyslipidemia and central adiposity may provide an interpretable lipid-adiposity phenotype for CMM risk stratification. Additional inflammatory, remnant cholesterol, and insulin resistance-related markers, particularly CRP, further refined risk stratification, although the overall predictive gain remained modest.

Trial registration

Not applicable.

Introduction

Cardiometabolic multimorbidity (CMM) has become an important form of chronic disease accumulation in aging populations[1]. The coexistence of diabetes, heart disease, and stroke represents more than the simple addition of individual diseases, it marks a state in which metabolic and vascular disorders cluster within the same person and substantially worsen long-term prognosis[2]. Large cohort evidence has shown that mortality risk rises sharply as cardiometabolic diseases accumulate, and a study of more than one million Chinese adults reported that CMM prevalence more than doubled over recent decades[3]. Compared with individuals with only one cardiometabolic condition, those with CMM often experience higher mortality, greater disability, reduced life expectancy, and heavier healthcare use[4, 5]. Against the background of rapid population aging and persistent cardiometabolic disease burden in China, identifying simple phenotypes that signal progression toward CMM is increasingly relevant for early risk stratification.

Atherogenic dyslipidemia is a central metabolic disturbance involved in the development of cardiometabolic diseases. The atherogenic index of plasma (AIP), calculated from triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C), reflects the balance between atherogenic and anti-atherogenic lipid fractions and has been proposed as a compact marker of atherogenic lipid metabolism[6, 7]. Previous studies have linked elevated AIP to insulin resistance and diabetes[8], new-onset stroke[9], and incident cardiovascular disease[10], supporting its relevance to multiple components of cardiometabolic risk. Nevertheless, the progression from isolated cardiometabolic abnormalities to CMM is unlikely to be driven by lipid disorders alone. Central adiposity represents another closely related metabolic burden, contributing to cardiometabolic deterioration through free fatty acid overflow, chronic low-grade inflammation, blood pressure elevation, and vascular dysfunction[11, 12]. Waist-to-height ratio (WHtR), which accounts for abdominal fat accumulation relative to body size, has been shown to complement or outperform traditional general adiposity measures in cardiometabolic risk assessment[13–15]. In this context, AIP and WHtR may capture two interrelated but non-overlapping dimensions of lipid-adiposity burden: one reflecting atherogenic dyslipidemia and the other reflecting

central adiposity. Their combined assessment may therefore provide a more comprehensive characterization of cardiometabolic risk than either indicator alone.

Previous studies have increasingly integrated lipid- or insulin-resistance-related indices with adiposity measures to improve cardiometabolic risk characterization[16]. AIP combined with obesity-related indicators has been associated with cardiovascular disease and mortality, and cumulative changes in AIP-related obesity derivatives may add risk information beyond AIP alone[17–19]. TyG-related adiposity indices, including TyG-WHtR and TyG-BRI, have also been associated with stroke and cardiovascular outcomes in middle-aged and older adults[20–23]. These findings support the broader value of combining metabolic and adiposity dimensions, but several issues remain insufficiently addressed. Most available studies have focused on single cardiovascular outcomes, prevalent disease, or the predictive performance of a specific composite index, whereas prospective evidence for the joint role of AIP and WHtR in the development of incident CMM remains limited[24, 25]. More importantly, the clinical meaning of this combination has not been fully characterized, it is unclear whether AIP and WHtR mainly represent independent risk dimensions, whether their coexistence is accompanied by interaction, or whether they show a longitudinal relationship over follow-up. This uncertainty extends beyond the two-marker phenotype itself.

Beyond the lipid-adiposity phenotype defined by AIP and WHtR, systemic inflammation, remnant cholesterol burden, and insulin resistance-related metabolic disturbance may provide additional layers for cardiometabolic risk stratification[26–29]. C-reactive protein (CRP) is an accessible marker of low-grade systemic inflammation[30, 31], remnant cholesterol (RC) reflects cholesterol carried by triglyceride-rich lipoprotein remnants and residual atherogenic lipid burden[32–34], and TyG is widely used as a surrogate marker of insulin resistance-related lipid-glucose disturbance[28, 35, 36]. Previous studies have linked these markers to cardiovascular disease, diabetes, stroke, and CMM, and some evidence suggests that they may add risk information when considered together with lipid or adiposity indicators[29, 30, 32, 36]. However, whether CRP, RC, and TyG further refine the association between the combined assessment of AIP and WHtR and incident CMM remains unclear. Examining these three risk layers may help determine whether individuals with concurrent atherogenic dyslipidemia and central adiposity also carry a broader metabolic-inflammatory burden.

To address these gaps, we used data from the China Health and Retirement Longitudinal Study (CHARLS) to investigate the associations of AIP, WHtR, and their combined assessment with incident CMM among middle-aged and older Chinese adults. We aimed to examine whether AIP and WHtR were separately and jointly associated with CMM risk, and whether their combined evaluation, based on joint exposure categories and the AIP-WHtR index, could provide additional information beyond either indicator alone. We further characterized the interrelationship between AIP and WHtR by assessing interaction and longitudinal patterns, and evaluated whether CRP, RC, and TyG could refine the lipid-adiposity risk profile. Finally, we assessed the risk-stratification value and robustness of the combined AIP and WHtR framework through prediction analyses, component-contribution evaluation, mediation analyses, subgroup analyses, and sensitivity analyses.

Methods

Study Population

This nationwide prospective cohort study was based on data from the China Health and Retirement Longitudinal Study (CHARLS)[37], an ongoing longitudinal survey designed to collect nationally representative information on the health, socioeconomic status, and aging-related characteristics of Chinese middle-aged and older adults. The 2011 survey was used as baseline, and follow-up information was obtained from the 2013, 2015, 2018, and 2020 waves. The CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University, and all participants provided written informed consent before participation (IRB00001052-11015). In the present analysis, we included adults aged 45 years or older who had available baseline information on AIP and WHtR and could be followed for incident CMM through 2020.

Among 11,847 initially extracted participants, 430 were younger than 45 years and were excluded. Of the remaining 11,417 participants, 515 had CMM at baseline and were removed. We further excluded 1,833 participants with missing baseline AIP or WHtR data. To reduce the influence of extreme exposure values, participants with AIP or WHtR values at or below the 1st percentile or at or above the 99th percentile were excluded (n = 151). After excluding 171 participants without valid follow-up CMM outcome information or follow-up time, 8,747 participants were included in the final analysis (Fig. 1; **Table S1**).

Assessment of AIP, WHtR, and Joint Exposure Groups

AIP was calculated as $\log_{10}$(TG/HDL-C)[6, 7], with TG and HDL-C expressed in mmol/L. WHtR was calculated as WC divided by height, with both measures recorded in the same unit[13, 14].

For the joint exposure analysis, AIP and WHtR were dichotomized using their median values, 0.320 for AIP and 0.535 for WHtR. Participants were then classified into four groups: Low AIP + Low WHtR, High AIP + Low WHtR, Low AIP + High WHtR, and High AIP + High WHtR. The Low AIP + Low WHtR group was used as the reference group (**Table S3**).

AIP and WHtR were also examined separately as continuous and categorical variables. In addition, AIP-WHtR was calculated as AIP multiplied by WHtR and was evaluated as a composite lipid-adiposity index. The median value of AIP-WHtR was 0.171, and quartiles of AIP-WHtR were used in additional Cox models.

CRP, remnant cholesterol (RC), and TyG were used for supplementary risk-layer stratified analyses. RC was calculated as total cholesterol (TC) minus HDL-C minus low-density lipoprotein cholesterol (LDL-C) [32], with negative values treated as missing. TyG was calculated as ln[TG × fasting plasma glucose/2] [28]. CRP, RC, and TyG were dichotomized at their median values (**Table S3**).

Ascertainment of Incident Cardiometabolic Multimorbidity

CMM was defined as the coexistence of at least two cardiometabolic diseases, including diabetes, heart disease, and stroke[2]. Participants with CMM at baseline were excluded, whereas those with one cardiometabolic disease at baseline were retained and followed for progression to CMM.

Incident CMM was identified when a participant first met this definition. Heart disease and stroke were based on self-reported physician diagnosis. Diabetes was identified from self-reported physician diagnosis, glucose-lowering treatment, or available glycemic measurements(FBG ≥ 7.0 mmol/L or HbA1c ≥ 6.5%)[38].

Because exact dates of CMM onset were not available in CHARLS, event time was assigned as the midpoint between the last wave in which the participant was free of CMM and the first wave in which CMM was reported. Participants who did not develop CMM were censored at their last available follow-up wave.

Covariates

Covariates were selected according to established cardiometabolic risk factors and the structure of the present exposure variables. Model I adjusted for age and sex. Model II further included education level, marital status, residence, smoking status, and drinking status. Model III additionally included systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, dyslipidemia, antihypertensive treatment, and lipid-lowering treatment.

Variables that were components of the exposures or supplementary stratification layers were not included in the primary Model III. These included triglycerides, HDL-C, waist circumference, height, BMI, AIP, WHtR, AIP-WHtR, CRP, RC, TyG, total cholesterol, and LDL-C. Baseline CMD count was evaluated in subgroup or sensitivity analyses rather than included in the primary model.

Statistical Analysis

Baseline characteristics were described by incident CMM status and by the AIP and WHtR joint groups. Continuous variables were summarized as mean (SD) or median (IQR), and categorical variables were summarized as numbers and percentages. Group comparisons were performed using tests selected according to variable type and distribution, including analysis of variance, Kruskal-Wallis test, chi-square test, or Fisher's exact test.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident CMM. The proportional hazards assumption was evaluated using Schoenfeld residual-based tests and was not violated for the main exposure models. Multicollinearity was assessed using the generalized variance inflation factor (GVIF), and all GVIF values were below 3, indicating no substantial collinearity (**Table S5; Table S6**). The main joint exposure analysis compared the four AIP and

WHtR joint groups, using the Low AIP + Low WHtR group as the reference. AIP, WHtR, and AIP-WHtR were also assessed as standardized continuous variables and categorical variables. Restricted cubic spline models were fitted with four knots placed at the 5th, 35th, 65th, and 95th percentiles to characterize potential dose-response patterns of AIP, WHtR, and AIP-WHtR with incident CMM. The joint relationship between AIP and WHtR was examined on both multiplicative and additive scales. Multiplicative interaction was tested by including a product term between high AIP and high WHtR in the Cox model. Additive interaction was assessed using the relative excess risk due to interaction, attributable proportion, and synergy index.

For risk-layer stratified analyses, the AIP and WHtR joint groups were further combined with CRP, RC, or TyG status. The Low AIP + Low WHtR + low marker group was used as the reference. Additional product terms were used to examine whether high CRP, RC, or TyG status modified the association of the High AIP + High WHtR phenotype with CMM risk.

Prediction analyses used Model III covariates as the base model. Expanded models were constructed by adding AIP, WHtR, AIP and WHtR together, or the AIP-WHtR index. Model discrimination was evaluated using the C-index and time-dependent ROC AUC. Continuous net reclassification improvement and integrated discrimination improvement were calculated to quantify incremental predictive information. Decision curve analyses were performed as supplementary evaluations of model performance.

To further describe the composition and temporal pattern of the lipid-adiposity phenotype, several ancillary analyses were conducted. WQS component contribution analysis was used to estimate the relative contribution of waist circumference, ln triglycerides, inverse HDL-C, and inverse height to the combined exposure structure. Cross-lagged panel analysis was applied to AIP and WHtR measured in 2011 and 2015 to compare temporal paths between the two indicators. Bidirectional mediation analyses were performed to examine the statistical interrelationship between AIP and WHtR in relation to incident CMM. AIP and WHtR were both dichotomized at their median values and were alternately specified as the exposure and mediator. Total, direct, and indirect effects, as well as the proportion mediated, were estimated using the mediation package with a Weibull survival outcome model. These analyses were exploratory and were not intended to establish causality.

Subgroup analyses were conducted by age, sex, BMI, diabetes, and hypertension. The main contrast remained the 2 x 2 AIP and WHtR joint exposure, and interaction P values were calculated for each subgroup factor. Sensitivity analyses included excluding participants who developed CMM within the first 2 years, excluding participants with one baseline cardiometabolic disease, excluding participants with BMI > 28 kg/m2, and repeating the analysis using multiple imputation by chained equations. Complete-case analysis was used as the primary analysis, with baseline missingness summarized in **Table S2**. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using R software (version 4.4.4).

Results

Baseline Characteristics of the Study Population

A total of 8,747 participants were included in the final analytical sample. During a median follow-up of 9 years, 994 participants developed incident cardiometabolic multimorbidity (CMM), corresponding to an event rate of 11.36%, while 7,753 participants remained free of CMM **(**Fig. 1; **Table S1)**. The median cutoffs used to define high exposure groups were 0.320 for AIP, 0.535 for WHtR, and 0.171 for the AIP-WHtR index (**Table S3**).

Participants who developed CMM were generally older and had less favorable cardiometabolic profiles at baseline. Compared with those who remained free of CMM, they tended to have higher adiposity-related measures, less favorable lipid and glycemic profiles, and a higher burden of cardiometabolic risk factors. When participants were classified according to the 2 x 2 joint categories of AIP and WHtR, the High AIP + High WHtR group showed the most adverse baseline metabolic profile, whereas the Low AIP + Low WHtR group had the lowest cardiometabolic risk burden (Table 1).

Table 1
Baseline characteristics according to AIP and WHtR joint groups

Characteristics	Level	Overall	Low AIP + Low WHtR	High AIP + Low WHtR	Low AIP + High WHtR	High AIP + High WHtR	P value
Number of participants		8747	2748	1625	1625	2749	
Age, years (mean (SD))		59.08 (9.26)	59.11 (9.29)	58.18 (8.93)	59.87 (9.77)	59.13 (9.05)	< 0.001
Sex (%)	Male	4083 (46.7)	1667 (60.7)	973 (59.9)	493 (30.3)	950 (34.6)	< 0.001
	Female	4664 (53.3)	1081 (39.3)	652 (40.1)	1132 (69.7)	1799 (65.4)	
Education level (%)	Above junior high school	847 (9.7)	257 (9.4)	195 (12.0)	123 (7.6)	272 (9.9)	< 0.001
	Illiterate	2585 (29.6)	745 (27.1)	399 (24.6)	582 (35.8)	859 (31.2)	
	Junior high school and below	5315 (60.8)	1746 (63.5)	1031 (63.4)	920 (56.6)	1618 (58.9)	
Marital status (%)	Married	7661 (87.6)	2402 (87.4)	1448 (89.1)	1397 (86.0)	2414 (87.8)	0.056
	Other	1086 (12.4)	346 (12.6)	177 (10.9)	228 (14.0)	335 (12.2)	
Residence (%)	Urban	1465 (16.8)	349 (12.7)	273 (16.8)	281 (17.3)	562 (20.5)	< 0.001
	Rural	7278 (83.2)	2399 (87.3)	1351 (83.2)	1343 (82.7)	2185 (79.5)	
Smoking status (%)	No	6068 (69.6)	1618 (59.1)	955 (58.9)	1322 (81.6)	2173 (79.4)	< 0.001
	Yes	2651 (30.4)	1121 (40.9)	666 (41.1)	299 (18.4)	565 (20.6)	

Note. Continuous variables are presented as mean (SD) or median [IQR], and categorical variables as n (%). AIP and WHtR joint groups were defined using the median cutoffs for AIP (0.320) and WHtR (0.535). AIP, atherogenic index of plasma; WHtR, waist-to-height ratio; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; RC, remnant cholesterol; TyG, triglyceride-glucose index.

Characteristics	Level	Overall	Low AIP + Low WHtR	High AIP + Low WHtR	Low AIP + High WHtR	High AIP + High WHtR	P value
Drinking status (%)	No	5856 (70.7)	1601 (62.9)	1011 (65.4)	1176 (75.2)	2068 (78.8)	< 0.001
	Yes	2425 (29.3)	946 (37.1)	536 (34.6)	387 (24.8)	556 (21.2)	
BMI, kg/m² (mean (SD))		23.43 (3.87)	20.79 (2.53)	21.60 (2.61)	25.03 (3.61)	26.20 (3.38)	< 0.001
WC, cm (mean (SD))		85.09 (10.03)	77.00 (6.09)	79.03 (6.30)	90.55 (7.00)	93.54 (7.39)	< 0.001
Height, cm (mean (SD))		157.87 (8.60)	159.37 (8.19)	160.47 (8.36)	154.62 (8.62)	156.76 (8.32)	< 0.001
Weight, kg (mean (SD))		58.56 (11.46)	53.05 (9.04)	55.86 (9.62)	60.13 (11.21)	64.73 (11.53)	< 0.001
WHtR (mean (SD))		0.54 (0.07)	0.48 (0.03)	0.49 (0.03)	0.59 (0.05)	0.60 (0.04)	< 0.001
SBP, mmHg (mean (SD))		129.33 (21.31)	124.52 (20.39)	126.57 (19.65)	131.89 (21.43)	134.27 (21.78)	< 0.001
DBP, mmHg (mean (SD))		75.28 (12.18)	72.32 (11.85)	74.50 (11.93)	76.10 (11.62)	78.24 (12.22)	< 0.001
TG, mg/dL (median [IQR])		105.32 [74.34, 152.22]	72.57 [58.41, 87.61]	144.26 [119.47, 191.16]	79.65 [64.61, 94.69]	157.53 [123.90, 216.82]	< 0.001
HDL-C, mg/dL (mean (SD))		51.41 (15.36)	61.94 (14.57)	43.62 (10.26)	59.06 (12.69)	40.98 (9.56)	< 0.001
LDL-C, mg/dL (mean (SD))		116.79 (35.01)	112.18 (31.53)	113.49 (34.67)	121.60 (31.76)	120.51 (39.34)	< 0.001
TC, mg/dL (mean (SD))		193.84 (38.70)	186.51 (35.68)	191.65 (38.15)	194.73 (36.18)	201.93 (41.68)	< 0.001
FPG, mg/dL (mean (SD))		109.11 (35.52)	102.85 (25.44)	109.27 (37.35)	105.13 (26.46)	117.61 (44.84)	< 0.001
HbA1c, % (mean (SD))		5.25 (0.78)	5.13 (0.63)	5.17 (0.75)	5.24 (0.69)	5.41 (0.94)	< 0.001

Note. Continuous variables are presented as mean (SD) or median [IQR], and categorical variables as n (%). AIP and WHtR joint groups were defined using the median cutoffs for AIP (0.320) and WHtR (0.535). AIP, atherogenic index of plasma; WHtR, waist-to-height ratio; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; RC, remnant cholesterol; TyG, triglyceride-glucose index.

Characteristics	Level	Overall	Low AIP + Low WHtR	High AIP + Low WHtR	Low AIP + High WHtR	High AIP + High WHtR	P value
TyG index (median [IQR])		8.59 [8.22, 9.02]	8.19 [7.95, 8.42]	8.92 [8.69, 9.24]	8.30 [8.08, 8.51]	9.06 [8.76, 9.47]	< 0.001
CRP, mg/L (median [IQR])		1.03 [0.55, 2.15]	0.75 [0.44, 1.61]	0.92 [0.51, 1.93]	1.02 [0.56, 2.11]	1.40 [0.76, 2.73]	< 0.001
RC, mg/dL (median [IQR])		19.72 [11.60, 32.09]	11.60 [7.35, 17.01]	28.22 [20.49, 39.43]	13.14 [8.51, 18.85]	32.09 [22.42, 46.49]	< 0.001
eGFR, mL/min/1.73 m² (mean (SD))		92.00 (14.68)	93.34 (13.72)	92.19 (14.89)	92.09 (14.43)	90.50 (15.48)	< 0.001
Hypertension (%)		3541 (40.7)	744 (27.2)	555 (34.4)	748 (46.1)	1494 (54.5)	< 0.001
Diabetes (%)		1290 (14.9)	240 (8.8)	233 (14.5)	198 (12.3)	619 (22.7)	< 0.001
Heart disease (%)		794 (9.1)	201 (7.4)	139 (8.6)	146 (9.0)	308 (11.3)	< 0.001
Stroke (%)		138 (1.6)	42 (1.5)	22 (1.4)	24 (1.5)	50 (1.8)	0.633
CKD (%)		277 (3.2)	70 (2.5)	51 (3.1)	50 (3.1)	106 (3.9)	0.051
Dyslipidemia (%)		845 (9.9)	126 (4.7)	115 (7.3)	153 (9.6)	451 (16.7)	< 0.001
Antihypertensive treatment (%)		1616 (18.6)	259 (9.5)	225 (14.0)	329 (20.3)	803 (29.4)	< 0.001
Antidiabetic treatment (%)		253 (2.9)	46 (1.7)	26 (1.6)	38 (2.4)	143 (5.2)	< 0.001
Lipid-lowering treatment (%)		395 (4.6)	50 (1.8)	45 (2.8)	70 (4.4)	230 (8.6)	< 0.001
AIP (median [IQR])		0.32 [0.12, 0.55]	0.09 [-0.04, 0.20]	0.51 [0.41, 0.66]	0.16 [0.04, 0.25]	0.57 [0.44, 0.75]	< 0.001

Note. Continuous variables are presented as mean (SD) or median [IQR], and categorical variables as n (%). AIP and WHtR joint groups were defined using the median cutoffs for AIP (0.320) and WHtR (0.535). AIP, atherogenic index of plasma; WHtR, waist-to-height ratio; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; RC, remnant cholesterol; TyG, triglyceride-glucose index.

Characteristics	Level	Overall	Low AIP + Low WHtR	High AIP + Low WHtR	Low AIP + High WHtR	High AIP + High WHtR	P value
AIP-WHtR (median [IQR])		0.17 [0.06, 0.30]	0.04 [-0.02, 0.10]	0.25 [0.20, 0.33]	0.09 [0.02, 0.14]	0.34 [0.26, 0.46]	< 0.001

Note. Continuous variables are presented as mean (SD) or median [IQR], and categorical variables as n (%). AIP and WHtR joint groups were defined using the median cutoffs for AIP (0.320) and WHtR (0.535). AIP, atherogenic index of plasma; WHtR, waist-to-height ratio; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; RC, remnant cholesterol; TyG, triglyceride-glucose index.

Individual and Joint Associations of AIP and WHtR With Incident CMM

Both AIP and WHtR were associated with incident CMM after full multivariable adjustment. In Model III, participants with high AIP had a higher risk of incident CMM than those with low AIP (HR 1.54, 95% CI 1.34–1.76; P < 0.001), and each SD increment in AIP was associated with a 23% higher risk of CMM (HR 1.23, 95% CI 1.16–1.31; P < 0.001). Similarly, high WHtR was associated with a higher risk of incident CMM (HR 1.75, 95% CI 1.51–2.04; P < 0.001), with each SD increment corresponding to a 35% higher risk (HR 1.35, 95% CI 1.26–1.44; P < 0.001) (Table 2).

Table 2
Associations of AIP, WHtR, the AIP-WHtR index, and AIP and WHtR joint groups with incident CMM

Exposure	Level	Incidence rate	Model I HR (95% CI)	Model I P value	Model II HR (95% CI)	Model II P value	Model III HR (95% CI)	Model III P value
AIP								
	Low	9.50	Reference	-	Reference	-	Reference	-
	High	18.16	1.93 (1.69, 2.20)	< 0.001	1.84 (1.61, 2.11)	< 0.001	1.54 (1.34, 1.76)	< 0.001
	Per SD		1.38 (1.30, 1.45)	< 0.001	1.35 (1.28, 1.43)	< 0.001	1.23 (1.16, 1.31)	< 0.001
WHtR								
	Low	8.37	Reference	-	Reference	-	Reference	-
	High	19.37	2.31 (2.01, 2.65)	< 0.001	2.20 (1.91, 2.54)	< 0.001	1.75 (1.51, 2.04)	< 0.001
	Per SD		1.56 (1.47, 1.66)	< 0.001	1.54 (1.45, 1.63)	< 0.001	1.35 (1.26, 1.44)	< 0.001
AIP-WHtR								
	Q1	8.19	Reference	-	Reference	-	Reference	-
	Q2	10.20	1.26 (1.02, 1.56)	0.035	1.22 (0.98, 1.52)	0.077	1.17 (0.93, 1.46)	0.179
	Q3	15.12	1.86 (1.52, 2.26)	< 0.001	1.80 (1.47, 2.21)	< 0.001	1.54 (1.25, 1.90)	< 0.001
	Q4	21.95	2.72 (2.25, 3.29)	< 0.001	2.54 (2.09, 3.09)	< 0.001	1.91 (1.56, 2.34)	< 0.001
	Per SD		1.41 (1.34,	< 0.001	1.38 (1.31,	< 0.001	1.25 (1.17,	< 0.001

Note. Model I adjusted for age and sex. Model II further adjusted for education level, marital status, residence, smoking status, and drinking status. Model III further adjusted for systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, dyslipidemia, antihypertensive treatment, and lipid-lowering treatment. AIP and WHtR joint groups refer to the 2 x 2 joint classification; the AIP-WHtR index refers to AIP multiplied by WHtR. AIP, atherogenic index of plasma; WHtR, waist-to-height ratio; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; RC, remnant cholesterol; TyG, triglyceride-glucose index.

Exposure	Level	Incidence rate	Model I HR (95% CI)	Model I P value	Model II HR (95% CI)	Model II P value	Model III HR (95% CI)	Model III P value
			1.49)		1.46)		1.32)	
AIP and WHtR joint groups								
	Low AIP + Low WHtR	6.81	Reference	-	Reference	-	Reference	-
	High AIP + Low WHtR	11.05	1.66 (1.33, 2.07)	< 0.001	1.61 (1.28, 2.03)	< 0.001	1.46 (1.15, 1.85)	0.002
	Low AIP + High WHtR	14.17	2.05 (1.65, 2.54)	< 0.001	1.99 (1.59, 2.47)	< 0.001	1.69 (1.35, 2.11)	< 0.001
	High AIP + High WHtR	22.54	3.35 (2.79, 4.02)	< 0.001	3.14 (2.60, 3.79)	< 0.001	2.32 (1.90, 2.83)	< 0.001

Note. Model I adjusted for age and sex. Model II further adjusted for education level, marital status, residence, smoking status, and drinking status. Model III further adjusted for systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, dyslipidemia, antihypertensive treatment, and lipid-lowering treatment. AIP and WHtR joint groups refer to the 2 x 2 joint classification; the AIP-WHtR index refers to AIP multiplied by WHtR. AIP, atherogenic index of plasma; WHtR, waist-to-height ratio; CMM, cardiometabolic multimorbidity; HR, hazard ratio; CI, confidence interval; SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; RC, remnant cholesterol; TyG, triglyceride-glucose index.

In the joint exposure analysis, the crude event proportion increased across the lipid-adiposity categories, from 5.75% in the Low AIP + Low WHtR group to 18.04% in the High AIP + High WHtR group. Compared with participants with Low AIP + Low WHtR, those with High AIP + Low WHtR (HR 1.46, 95% CI 1.15–1.85; P = 0.002) and Low AIP + High WHtR (HR 1.69, 95% CI 1.35–2.11; P < 0.001) had elevated risks of incident CMM in the fully adjusted model. The highest risk was observed among participants with concurrent High AIP and High WHtR (HR 2.32, 95% CI 1.90–2.83; P < 0.001) (Table 2).

The AIP-WHtR index showed a similar positive association with incident CMM. Each SD increment in AIP-WHtR was associated with a higher risk of CMM (HR 1.25, 95% CI 1.17–1.32; P < 0.001). Compared with the lowest quartile, the third and fourth quartiles of AIP-WHtR were associated with higher CMM risk, with HRs of 1.54 (95% CI 1.25–1.90; P < 0.001) and 1.91 (95% CI 1.56–2.34; P < 0.001), respectively (Table 2).

RCS analyses supported positive dose-response associations of AIP, WHtR, and AIP-WHtR with incident CMM (all P for overall association < 0.001). The association for AIP-WHtR showed evidence of nonlinearity (P for nonlinearity = 0.013), whereas the nonlinear trends for AIP and WHtR did not reach conventional statistical significance (Fig. 2).

Interaction Between AIP and WHtR

Although participants with concurrently high AIP and high WHtR had the highest risk of incident CMM, formal interaction analyses did not show statistically significant additive or multiplicative interaction after full adjustment. In Model III, the additive interaction measures were not significant, and the multiplicative interaction term was also null (HR 0.94, 95% CI 0.71–1.26; P = 0.694). These findings suggest that the increased risk in the dual-high group was mainly reflected by joint risk stratification rather than a statistically significant interaction effect (Table 3).

Table 3
Additive and multiplicative interaction between high AIP and high WHtR for incident CMM

Exposure	Model I	Model II	Model III
High AIP + High WHtR interaction			
Additive effect			
RERI	0.64 (0.08, 1.12)	0.55 (0.03, 1.04)	0.18 (-0.26, 0.57)
AP	0.19 (0.03, 0.32)	0.17 (0.01, 0.33)	0.08 (-0.11, 0.25)
SI	1.38 (1.04, 1.90)	1.34 (1.02, 1.91)	1.15 (0.84, 1.79)
Multiplicative effect	0.99 (0.75, 1.30)	0.98 (0.74, 1.31)	0.94 (0.71, 1.26)

Note. RERI, relative excess risk due to interaction; AP, attributable proportion; SI, synergy index. Model I adjusted for age and sex. Model II further adjusted for education, marital status, residence, smoking status, and drinking status. Model III further adjusted for systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, dyslipidemia, antihypertensive treatment, and lipid-lowering treatment.

Incremental Predictive Performance

The base model showed moderate discrimination for incident CMM, with a C-index of 0.677 (95% CI 0.659–0.695) and an AUC of 0.711. Adding AIP or WHtR modestly improved model discrimination. When AIP and WHtR were added together, the C-index increased to 0.702 (95% CI 0.685–0.719), with an AUC of 0.738, continuous NRI of 0.098 (95% CI 0.006–0.232; P = 0.040), and IDI of 0.007 (95% CI 0.003–0.017; P < 0.001).

The AIP-WHtR index also provided modest incremental predictive information. The base model plus the AIP-WHtR index had a C-index of 0.693 (95% CI 0.676–0.710), an AUC of 0.731, and improved continuous NRI (0.228, 95% CI 0.129–0.270; P < 0.001), although IDI did not reach conventional statistical significance (0.001, 95% CI -0.000 to 0.005; P = 0.060) (Table 4; Fig. 3).

Table 4
Predictive performance of AIP- and WHtR-based models for incident CMM at 8 years

Model	C-index	AUC	NRI	NRI P value	IDI	IDI P value
Base	0.677 (0.659, 0.695)	0.711	Reference	Reference	Reference	Reference
Base + AIP	0.690 (0.673, 0.707)	0.728	0.187 (0.078, 0.229)	< 0.001	0.000 (-0.002, 0.002)	0.520
Base + WHtR	0.696 (0.679, 0.713)	0.730	0.033 (-0.006, 0.084)	0.200	0.007 (0.002, 0.019)	< 0.001
Base + AIP + WHtR	0.702 (0.685, 0.719)	0.738	0.098 (0.006, 0.232)	0.040	0.007 (0.003, 0.017)	< 0.001
Base + AIP-WHtR	0.693 (0.676, 0.710)	0.731	0.228 (0.129, 0.270)	< 0.001	0.001 (-0.000, 0.005)	0.060

Note. The base model included Model III covariates: age, sex, education level, marital status, residence, smoking status, drinking status, systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, dyslipidemia, antihypertensive treatment, and lipid-lowering treatment. AUC indicates the 8-year time-dependent ROC AUC, not an overall ROC AUC. NRI and IDI are continuous net reclassification improvement and integrated discrimination improvement versus the base model. AIP, atherogenic index of plasma; WHtR, waist-to-height ratio; CMM, cardiometabolic multimorbidity.

Time-dependent ROC analyses at 2, 4, 6, and 8 years showed a similar pattern. The model including both AIP and WHtR consistently achieved the highest AUCs across follow-up time points, supporting a modest but stable improvement in discrimination **(**Fig. 4; **Table S16)**. DCA suggested that the net-benefit improvement of the expanded models was limited and was mainly observed at lower threshold probabilities **(Fig S1)**. Overall, these findings indicate incremental but modest predictive improvement beyond conventional risk factors.

Stratified and Exploratory Supplementary Analyses

Stratified analyses incorporating CRP, remnant cholesterol (RC), and TyG suggested that the High AIP + High WHtR phenotype remained associated with elevated CMM risk across additional metabolic and inflammatory strata. Among participants with High AIP + High WHtR, the association was stronger in those with high CRP (HR 2.84, 95% CI 2.19–3.67; P < 0.001) than in those with low CRP (HR 2.38, 95% CI 1.79–3.16; P < 0.001). Similar patterns were observed across RC strata, with HRs of 2.40 (95% CI 1.93–2.99; P < 0.001) for high RC and 2.36 (95% CI 1.76–3.16; P < 0.001) for low RC. For TyG, the High AIP + High WHtR phenotype was associated with higher CMM risk in both high TyG (HR 2.65, 95% CI 2.14–3.29; P < 0.001) and low TyG strata (HR 1.71, 95% CI 1.16–2.51; P = 0.006) (**Table S7-9**).

However, formal risk-layer interaction terms were not statistically significant. Interactions between the High AIP + High WHtR phenotype and high CRP (HR 0.84, 95% CI 0.64–1.10; P = 0.194), high RC (HR 0.79, 95% CI 0.58–1.06; P = 0.120), or high TyG (HR 1.17, 95% CI 0.79–1.75; P = 0.428) were not statistically significant (Table S10).

In WQS component contribution analysis, waist circumference contributed the largest weight to the combined exposure structure (61.3%), followed by ln triglycerides (27.2%), inverse HDL-C (8.7%), and inverse height (2.9%) **(Fig S2; Table S11)**. Cross-lagged analyses suggested bidirectional longitudinal associations between WHtR and AIP, with a stronger path from WHtR in 2011 to AIP in 2015 (estimate 0.136, 95% CI 0.113–0.159; P < 0.001) than from AIP in 2011 to WHtR in 2015 (estimate 0.054, 95% CI 0.029–0.080; P < 0.001) **(Table S12)**. In exploratory mediation analyses, the estimated proportion mediated was 14.2% for the pathway from High WHtR through AIP and 26.7% for the pathway from High AIP through WHtR; these model-based findings were interpreted cautiously and were not used to infer causal mediation **(Fig S3; Table S15)**.

Subgroup and Sensitivity Analyses

Subgroup analyses showed that the association between the High AIP + High WHtR phenotype and incident CMM was generally consistent across strata defined by age, sex, BMI, diabetes, and hypertension. Participants with concurrently high AIP and high WHtR had the highest risk in most subgroups, although the magnitude of association appeared somewhat stronger among participants younger than 60 years and those without hypertension. No statistically significant interaction was observed across the prespecified subgroup factors (Table S13).

Sensitivity analyses yielded results consistent with the main findings. Across analyses excluding early CMM events, excluding participants with a baseline single cardiometabolic disease, excluding participants with BMI > 28 kg/m², and applying MICE multiple imputation, the High AIP + High WHtR group remained associated with higher incident CMM risk. These analyses support the robustness of the main joint exposure findings (**Table S14**).

Discussion

In this nationwide prospective cohort of 8,747 middle-aged and older Chinese adults, both AIP and WHtR were associated with incident CMM, and their joint classification helped identify a high-risk lipid-adiposity profile characterized by concurrent atherogenic dyslipidemia and central adiposity. During a median follow-up of 9 years, participants with concurrently high AIP and high WHtR had the highest CMM risk, whereas elevation of either marker alone was also associated with increased risk. Formal additive and multiplicative interaction tests were not statistically significant, suggesting that the joint phenotype mainly captured the cumulative burden of atherogenic dyslipidemia and central adiposity rather than a clear synergistic interaction. Stratified analyses further suggested that inflammatory, remnant cholesterol, and insulin resistance-related profiles may help characterize the broader metabolic

background of this adverse lipid-adiposity phenotype, while prediction analyses showed modest improvement after incorporating AIP and WHtR into conventional models.

Our findings are consistent with and extend previous evidence linking lipid-related and adiposity-related indices to cardiometabolic outcomes. AIP has been widely used as a surrogate marker of atherogenic lipid metabolism, reflecting the balance between triglyceride-rich lipoproteins and HDL-C. Previous studies have associated elevated AIP with hypertension[39], diabetes[8], cardiovascular disease[10], stroke[9], and metabolic syndrome[40], which are closely related to the development or composition of CMM. In parallel, WHtR has been increasingly used as a simple indicator of central adiposity and has been reported to complement or outperform traditional general adiposity measures in cardiometabolic risk assessment[13, 14]. The present findings are therefore biologically and epidemiologically consistent with prior work, while extending this evidence from individual cardiometabolic conditions or prevalent risk states to the prospective development of incident CMM.

Recent studies have further suggested that integrating metabolic and adiposity information may improve cardiometabolic risk characterization. For example, AIP combined with obesity-related indicators[17–19] and TyG-related adiposity indices have been examined in relation to CMM, stroke, CVD, and other cardiometabolic outcomes[20–22]. These studies support the broader concept that lipid- or insulin-resistance-related markers and adiposity measures provide complementary information[41]. However, much of the existing evidence has focused on single cardiovascular outcomes, cross-sectional or prevalent disease, or the performance of a specific mathematical composite index. Our study adds to this literature by evaluating AIP and WHtR as a joint lipid-adiposity phenotype in a prospective CHARLS cohort, with incident CMM as the outcome. The use of both 2 × 2 joint exposure categories and the AIP-WHtR index allowed us to assess whether the coexistence of atherogenic dyslipidemia and central adiposity identifies a higher-risk group beyond either marker alone.

The joint association of AIP and WHtR is clinically and epidemiologically meaningful because these two markers represent related but non-identical metabolic domains. AIP reflects atherogenic dyslipidemia, including high triglyceride burden, low HDL-C, and the tendency toward smaller and denser LDL particles. This lipid phenotype often coexists with insulin resistance, hepatic lipid overproduction, endothelial dysfunction, and vascular inflammation[42, 43]. WHtR, in contrast, reflects central adiposity, which is more closely related to visceral fat accumulation than BMI. Visceral adiposity is metabolically active and may contribute to impaired glucose homeostasis, dyslipidemia, chronic inflammation, and vascular dysfunction[44–47]. Therefore, individuals with both high AIP and high WHtR may have simultaneous lipid-metabolic and adiposity-related disturbances, forming a lipid-adiposity profile that is more informative than either marker alone.

Of note, WHtR appeared to carry particularly important information in this study. The association for high WHtR alone was stronger than that for high AIP alone, and participants with Low AIP + High WHtR had a higher risk than those with High AIP + Low WHtR. These findings are in line with the notion that central adiposity may be a prominent feature in the development of CMM[11, 12]. Excess abdominal adiposity

may precede or accompany multiple metabolic abnormalities, including dysglycemia, lipid disorders, blood pressure elevation, and inflammatory activation[48, 49]. The WQS analysis also indicated that waist circumference contributed the largest weight among the core components of the combined exposure structure, further emphasizing the central role of abdominal adiposity within the lipid-adiposity phenotype.

Dose-response analyses were generally consistent with the main Cox results. AIP, WHtR, and the AIP-WHtR index all showed positive associations with incident CMM, while evidence of nonlinearity was mainly observed for the AIP-WHtR index. These findings should be interpreted as descriptive risk patterns rather than as definitive clinical thresholds, particularly because standardized cutoffs for the combined AIP and WHtR phenotype have not yet been established.

Although the High AIP + High WHtR group had the highest risk of incident CMM, formal tests did not support statistically significant additive or multiplicative interaction. This suggests that AIP and WHtR may contribute complementary information through cumulative or partly parallel cardiometabolic risk dimensions, rather than through a clear synergistic effect. From a risk-stratification perspective, the value of the 2 × 2 joint grouping lies in its ability to identify individuals with a heavier combined lipid-adiposity burden in a simple and interpretable manner.

The additional stratified analyses with CRP, RC, and TyG placed the dual-high phenotype into a broader cardiometabolic risk context[50–52]. Participants with High AIP + High WHtR and simultaneously elevated CRP, RC, or TyG generally showed higher CMM risk, supporting the view that dyslipidemia, central adiposity, inflammation, remnant cholesterol burden, and insulin resistance-related lipid-glucose disturbance may cluster in individuals at higher risk of CMM[53]. Notably, the highest estimate was observed among participants with High AIP + High WHtR and high CRP, suggesting that inflammatory burden may be particularly informative for further distinguishing risk within the adverse lipid-adiposity phenotype. This observation is consistent with the concept that low-grade inflammation often accompanies both central adiposity and atherogenic dyslipidemia and may mark a broader metabolic-inflammatory risk state. However, formal interaction terms with CRP, RC, and TyG were not significant; therefore, these markers should be viewed as supplementary stratification layers that describe risk accumulation, rather than as evidence of definite effect modification.

Prediction analyses suggested that adding AIP and WHtR to conventional risk factors produced modest improvements in discrimination and reclassification, with similar patterns in time-dependent ROC analyses. Decision curve analysis also indicated that the net-benefit gain of the expanded models was limited and mainly observed over selected threshold ranges. Thus, the combined assessment of AIP and WHtR should not be viewed as a stand-alone prediction model, but rather as a simple supplementary approach for population-level cardiometabolic risk stratification.

Several exploratory analyses provided additional insight into the structure and temporal pattern of the joint phenotype. WQS analysis suggested that waist circumference was the dominant contributor among the selected components, followed by TG, HDL-C, and height. Cross-lagged analysis suggested a

stronger temporal association from WHtR to later AIP than from AIP to later WHtR, indicating that central adiposity may precede or contribute to subsequent atherogenic lipid disturbance within the lipid-adiposity phenotype [54]. Bidirectional mediation analyses also indicated statistical interrelationships between AIP and WHtR in relation to CMM, suggesting a possible linkage between atherogenic dyslipidemia and central adiposity within the lipid-adiposity phenotype. Further mechanistic studies are needed to clarify and validate the biological basis of this relationship.

This study has several strengths. First, it used a nationwide prospective CHARLS cohort with long-term follow-up, allowing assessment of incident CMM rather than prevalent CMM alone. Second, the primary exposure framework was based on a simple 2 × 2 joint classification of AIP and WHtR, which is easier to interpret than a purely mathematical composite index and directly reflects the coexistence of atherogenic dyslipidemia and central adiposity. Third, the analysis evaluated not only independent and joint associations, but also nonlinearity, interaction, prediction, risk-layer stratification, component contribution, and multiple sensitivity analyses. Fourth, the main findings were consistent across subgroups and remained stable after excluding early CMM events, excluding participants with baseline single cardiometabolic disease, excluding obesity, and applying multiple imputation.

Several limitations should be acknowledged. First, diabetes, heart disease, and stroke were identified using questionnaire-based CHARLS information and available biomarker or treatment data for diabetes, which may introduce misclassification, particularly for self-reported heart disease and stroke. Second, exact dates of CMM onset were unavailable; therefore, event time was assigned using the midpoint between the last disease-free wave and the first wave reporting CMM. Third, AIP and WHtR were assessed at baseline, and changes in lipid metabolism, abdominal adiposity, medication use, or lifestyle during follow-up were not fully incorporated into the primary analysis. Fourth, although the models adjusted for major demographic, behavioral, and clinical factors, residual confounding from diet, sleep, socioeconomic conditions, physical activity intensity, and other unmeasured factors remains possible. Fifth, median cutoffs were used to define high and low AIP and WHtR, because standardized clinical thresholds for their joint phenotype are not yet established. Finally, the findings were derived from Chinese adults aged 45 years or older and may require validation in younger populations and other ethnic groups.

Conclusion

In conclusion, elevated AIP and WHtR were separately associated with a higher risk of incident CMM, and participants with concurrent high AIP and high WHtR had the greatest risk. The joint assessment of AIP and WHtR showed a stronger association with incident CMM than either indicator alone, supporting the value of considering atherogenic dyslipidemia and central adiposity together in cardiometabolic risk stratification. Additional stratification by CRP, RC, and TyG further characterized the broader metabolic-inflammatory risk context of this lipid-adiposity phenotype, while prediction analyses indicated modest incremental value beyond conventional risk factors. These findings suggest that the combined assessment of AIP and WHtR may serve as a practical supplementary approach for identifying

individuals at elevated risk of CMM. Further studies are warranted to validate these findings and to clarify the temporal relationship between central adiposity, atherogenic dyslipidemia, and progression to CMM.

Abbreviations

AIP
atherogenic index of plasma
WHtR
waist-to-height ratio
CMM
cardiometabolic multimorbidity
CHARLS
China Health and Retirement Longitudinal Study
CVD
cardiovascular disease
CKM
cardiovascular-kidney-metabolic
CRP
C-reactive protein
RC
remnant cholesterol
TyG
triglyceride-glucose index
TG
triglycerides
TC
total cholesterol
HDL-C
high-density lipoprotein cholesterol
LDL-C
low-density lipoprotein cholesterol
WC
waist circumference
BMI
body mass index
FBG
fasting blood glucose
HbA1c
glycated hemoglobin A1c
eGFR

estimated glomerular filtration rate
CMD
cardiometabolic disease
WQS
weighted quantile sum
RCS
restricted cubic spline
ROC
receiver operating characteristic
AUC
area under the curve
C-index
concordance index
NRI
net reclassification improvement
IDI
integrated discrimination improvement
DCA
decision curve analysis
GVIF
generalized variance inflation factor
MICE
multiple imputation by chained equations
HR
hazard ratio
CI
confidence interval
SD
standard deviation
IQR
interquartile range.

Declarations

Ethics approval and consent to participate

The CHARLS study was approved by the Biomedical Ethics Review Committee of Peking University. All participants in the original CHARLS cohort study provided written informed consent. The present study was a secondary analysis of de-identified publicly available data and was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Availability of data and materials

The data used in this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS). CHARLS data are publicly available to registered users through the CHARLS official website: http://charls.pku.edu.cn/.

Competing interests

The authors declare no competing interests.

Funding

This work was supported by the National High Level Hospital Clinical Research Funding (BJ-2025-159).

Authors' contributions

YL ,WH and HA contributed to the study conception and design. YL performed the statistical analysis and drafted the manuscript. WH performed conceptualization, data curation, formal analysis and writing-original draft. HA supervised the study, interpreted the results, and critically revised the manuscript for important intellectual content. Both authors read and approved the final manuscript.

Acknowledgements

The authors gratefully acknowledge the China Health and Retirement Longitudinal Study research team and all participants for their contributions to this cohort study.

Trial registration

Not applicable.

References

1. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380:37–43.
2. Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, Burgess S, et al. Association of Cardiometabolic Multimorbidity With Mortality. JAMA.

2015;314:52–60.

3. Han Y, Hu Y, Yu C, Guo Y, Pei P, Yang L, Chen Y, Du H, Sun D, Pang Y, et al. Lifestyle, cardiometabolic disease, and multimorbidity in a prospective Chinese study. Eur Heart J. 2021;42:3374–84.
4. Jin Y, Liang J, Hong C, Liang R, Luo Y. Cardiometabolic multimorbidity, lifestyle behaviours, and cognitive function: a multicohort study. Lancet Healthy Longev. 2023;4:e265–73.
5. Dove A, Guo J, Marseglia A, Fastbom J, Vetrano DL, Fratiglioni L, Pedersen NL, Xu W. Cardiometabolic multimorbidity and incident dementia: the Swedish twin registry. Eur Heart J. 2023;44:573–82.
6. Dobiásová M. [AIP–atherogenic index of plasma as a significant predictor of cardiovascular risk: from research to practice]. Vnitr Lek. 2006;52:64–71.
7. Dobiásová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). Clin Biochem. 2001;34:583–8.
8. Yin B, Wu Z, Xia Y, Xiao S, Chen L, Li Y. Non-linear association of atherogenic index of plasma with insulin resistance and type 2 diabetes: a cross-sectional study. Cardiovasc Diabetol. 2023;22:157.
9. Qu L, Fang S, Lan Z, Xu S, Jiang J, Pan Y, Xu Y, Zhu X, Jin J. Association between atherogenic index of plasma and new-onset stroke in individuals with different glucose metabolism status: insights from CHARLS. Cardiovasc Diabetol. 2024;23:215.
10. Min Q, Wu Z, Yao J, Wang S, Duan L, Liu S, Zhang M, Luo Y, Ye D, Huang Y, et al. Association between atherogenic index of plasma control level and incident cardiovascular disease in middle-aged and elderly Chinese individuals with abnormal glucose metabolism. Cardiovasc Diabetol. 2024;23:54.
11. Ross R, Neeland IJ, Yamashita S, Shai I, Seidell J, Magni P, Santos RD, Arsenault B, Cuevas A, Hu FB, et al. Waist circumference as a vital sign in clinical practice: a Consensus Statement from the IAS and ICCR Working Group on Visceral Obesity. Nat Rev Endocrinol. 2020;16:177–89.
12. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P, St-Onge MP. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021;143:e984–1010.
13. Ashwell M, Gibson S. A proposal for a primary screening tool: 'Keep your waist circumference to less than half your height'. BMC Med. 2014;12:207.
14. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. Obes Rev. 2012;13:275–86.
15. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0·5 could be a suitable global boundary value. Nutr Res Rev. 2010;23:247–69.
16. Wang H, Zhang H, Zhang L, Zheng X, Yang M. Combined effects of insulin resistance and dyslipidaemia on cardiometabolic multimorbidity in Chinese middle-age and older adults: a longitudinal cohort study. Sci Rep. 2025;15:38060.

17. Wang X, Qin S, Xiang H, Tao Y, Chen S, Lu H. Association of the atherogenic index of plasma combined with obesity indices with cardiovascular disease and mortality. Lipids Health Dis 2026, 25.
18. Zhang N, Xie G, Jian G, Jiang K, Lu Z, Wang Z, Wang J, Lan H, Wang W, He S, et al. Association of cumulative changes in atherogenic index of plasma and its obesity-related derivatives with cardiovascular disease: emphasis on incremental risk of diabetes status. Cardiovasc Diabetol. 2025;24:435.
19. Xu Y, Liu M, Yang W, Zhang W, Fan H, Xu Y, Zhou J, Yuan Z. Association between the atherogenic index of plasma, body mass index, and cardiovascular diseases in Chinese middle and old-aged adults: a mediation analysis. Front Cardiovasc Med. 2025;12:1597749.
20. Liang W, Ouyang H. The association between triglyceride-glucose index combined with obesity indicators and stroke risk: A longitudinal study based on CHARLS data. BMC Endocr Disord. 2024;24:234.
21. Huo RR, Liao Q, Zhai L, You XM, Zuo YL. Interacting and joint effects of triglyceride-glucose index (TyG) and body mass index on stroke risk and the mediating role of TyG in middle-aged and older Chinese adults: a nationwide prospective cohort study. Cardiovasc Diabetol. 2024;23:30.
22. Hong J, Zhang R, Tang H, Wu S, Chen Y, Tan X. Comparison of triglyceride glucose index and modified triglyceride glucose indices in predicting cardiovascular diseases incidence among populations with cardiovascular-kidney-metabolic syndrome stages 0–3: a nationwide prospective cohort study. Cardiovasc Diabetol. 2025;24:98.
23. Ruan X, Ling Y, Chen J, Xiang Y, Ruan H, Zhang W, Jing L, Gao X, He Y, Lu X, et al. Joint effects of triglyceride glucose index and its obesity-related derivatives with estimated glucose disposal rate on cardiometabolic multimorbidity in middle-aged and older Chinese adults: a nationwide cohort study. Cardiovasc Diabetol. 2025;24:382.
24. Lai H, Tu Y, Liao C, Zhang S, He L, Li J. 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. Cardiovasc Diabetol. 2025;24:109.
25. Li J, Fan M, Yang M, Huang W, Shi W, Zhang D, Zhu W, Liu C, Xu N, Zhang H, Fan K. Remnant cholesterol and body mass index jointly associate with cardiometabolic Multimorbidity with mediation analysis in CHARLS a prospective cohort study. Sci Rep. 2025;15:42139.
26. Libby P. Inflammation in atherosclerosis. Nature. 2002;420:868–74.
27. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352:1685–95.
28. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord. 2008;6:299–304.
29. Wan B, Wang S, Hu S, Han W, Qiu S, Zhu L, Ruan L, Wei Y, Xu J. The comprehensive effects of high-sensitivity C-reactive protein and triglyceride glucose index on cardiometabolic multimorbidity. Front Endocrinol (Lausanne). 2025;16:1511319.

30. Bafei SEC, Zhao X, Chen C, Sun J, Zhuang Q, Lu X, Chen Y, Gu X, Liu F, Mu J, et al. Interactive effect of increased high sensitive C-reactive protein and dyslipidemia on cardiovascular diseases: a 12-year prospective cohort study. Lipids Health Dis. 2023;22:95.
31. Gao Y, Wang M, Wang R, Jiang J, Hu Y, Wang W, Wang Y, Li H. The predictive value of the hs-CRP/HDL-C ratio, an inflammation-lipid composite marker, for cardiovascular disease in middle-aged and elderly people: evidence from a large national cohort study. Lipids Health Dis. 2024;23:66.
32. Zhao Y, Zhuang Z, Li Y, Xiao W, Song Z, Huang N, Wang W, Dong X, Jia J, Clarke R, Huang T. Elevated blood remnant cholesterol and triglycerides are causally related to the risks of cardiometabolic multimorbidity. Nat Commun. 2024;15:2451.
33. Varbo A, Benn M, Tybjærg-Hansen A, Nordestgaard BG. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation. Circulation. 2013;128:1298–309.
34. Varbo A, Benn M, Tybjærg-Hansen A, Jørgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. J Am Coll Cardiol. 2013;61:427–36.
35. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, Jacques-Camarena O, Rodríguez-Morán M. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010;95:3347–51.
36. Alizargar J, Bai CH, Hsieh NC, Wu SV. Use of the triglyceride-glucose index (TyG) in cardiovascular disease patients. Cardiovasc Diabetol. 2020;19:8.
37. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). Int J Epidemiol. 2014;43:61–8.
38. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes-2026. Diabetes Care. 2026;49:S27–49.
39. Tan M, Zhang Y, Jin L, Wang Y, Cui W, Nasifu L, He B. Association between atherogenic index of plasma and prehypertension or hypertension among normoglycemia subjects in a Japan population: a cross-sectional study. Lipids Health Dis. 2023;22:87.
40. Zheng X, Zhang X, Han Y, Hu H, Cao C. Nonlinear relationship between atherogenic index of plasma and the risk of prediabetes: a retrospective study based on Chinese adults. Cardiovasc Diabetol. 2023;22:205.
41. Chen X, Zhao X, Fei H, Zhang Y, Pang J, Liu Z, Wang W, Qiao J, Xu C. Combined association of triglyceride-glucose index and the atherogenic index of plasma with the incidence of cardiovascular diseases among middle-aged and older population. Cardiovasc Diabetol. 2025;25:19.
42. Wang C, Wang J, Li X, Zhou P, Zhao X, Xin A, Liao G, Huang Y, Zhang Y. Associations between triglyceride-glucose index combined with waist circumference and heart failure in individuals with different body mass indices: a cross-sectional study using NHANES 2011–2020 data. Lipids Health Dis. 2025;24:87.

43. James DE, Stöckli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nat Rev Mol Cell Biol. 2021;22:751–71.
44. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444:840–6.
45. Smith U. Abdominal obesity: a marker of ectopic fat accumulation. J Clin Invest. 2015;125:1790–2.
46. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, Keaney JF Jr., Meigs JB, Lipinska I, Kathiresan S, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. Circulation. 2007;116:1234–41.
47. Tilg H, Ianiro G, Gasbarrini A, Adolph TE. Adipokines: masterminds of metabolic inflammation. Nat Rev Immunol. 2025;25:250–65.
48. Tian Z, Yang L, Li Y, Huang Y, Yang J, Xue F. Associations of different insulin resistance-related indices with the incidence and progression trajectory of cardiometabolic multimorbidity: a prospective cohort study from UK biobank. Cardiovasc Diabetol. 2025;24:257.
49. Cai J, Zheng D, Xu S, Jiang S, Jiang Y, Zhang R, Li C, Zhang L, Wang B. Association of body roundness index with cardiovascular disease in early Cardiovascular-Kidney-Metabolic syndrome stage 0–3: mediation by the triglyceride-glucose index in a national cohort study. Diabetol Metab Syndr. 2025;17:443.
50. Huo G, Tang Y, Liu Z, Cao J, Yao Z, Zhou D. Association between C-reactive protein-triglyceride glucose index and stroke risk in different glycemic status: insights from the China Health and Retirement Longitudinal Study (CHARLS). Cardiovasc Diabetol. 2025;24:142.
51. Ma X, Ma X, Wang Y, Qiu G, Zhang C. Associations of cumulative exposure and dynamic trajectories of the C-reactive protein-triglyceride-glucose index with incident cardiovascular disease in middle-aged and older Chinese adults: a nationwide cohort study. Cardiovasc Diabetol. 2025;24:303.
52. Sun Y, Guo Y, Ma S, Mao Z, Meng D, Xuan K, Lu R, Pan X, Zhu X. Association of C-reactive protein-triglyceride glucose index with the incidence and mortality of cardiovascular disease: a retrospective cohort study. Cardiovasc Diabetol. 2025;24:313.
53. Jiang L, Zhu T, Song W, Zhai Y, Tang Y, Ruan F, Xu Z, Li L, Fu X, Liu D, et al. Assessment of six insulin resistance surrogate indexes for predicting stroke incidence in Chinese middle-aged and elderly populations with abnormal glucose metabolism: a nationwide prospective cohort study. Cardiovasc Diabetol. 2025;24:56.
54. Yang Y, Cao J, Lyu J. Association between changes in the triglyceride glucose-body roundness Index and cardiovascular disease risk in middle-aged and elderly Chinese adults: a nationwide longitudinal study from 2011 to 2015. Front Nutr. 2025;12:1560617.

Figures

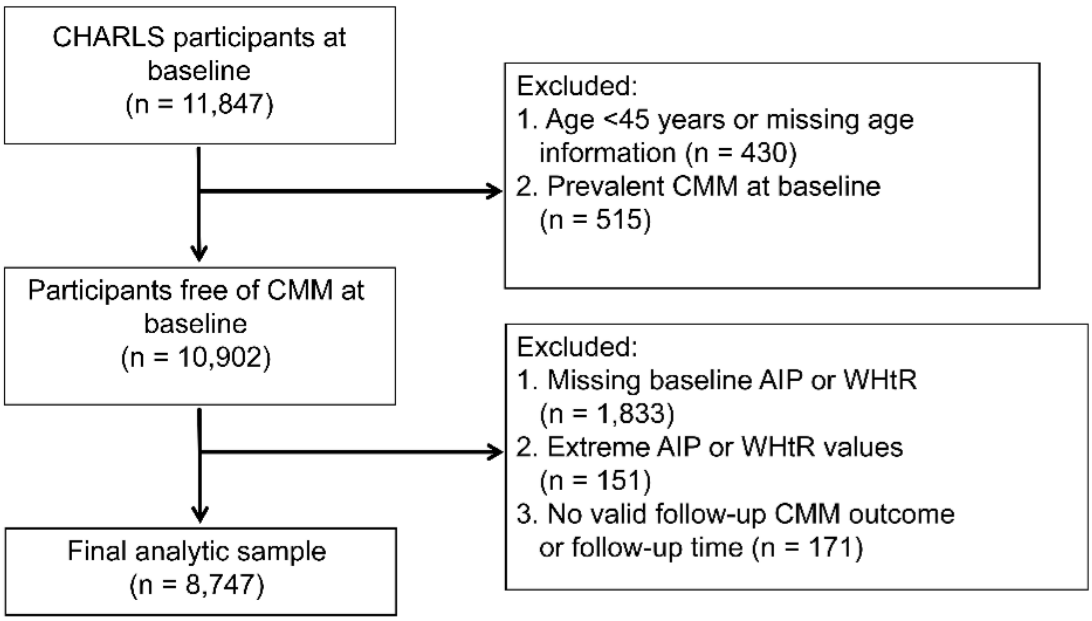


Figure 1

Flowchart for participant selection. CMM, cardiometabolic multimorbidity; AIP, atherogenic index of plasma; WHtR, waist-to-height ratio. Participant counts and exclusion steps correspond to the final analytic sample used in the main Cox analyses.

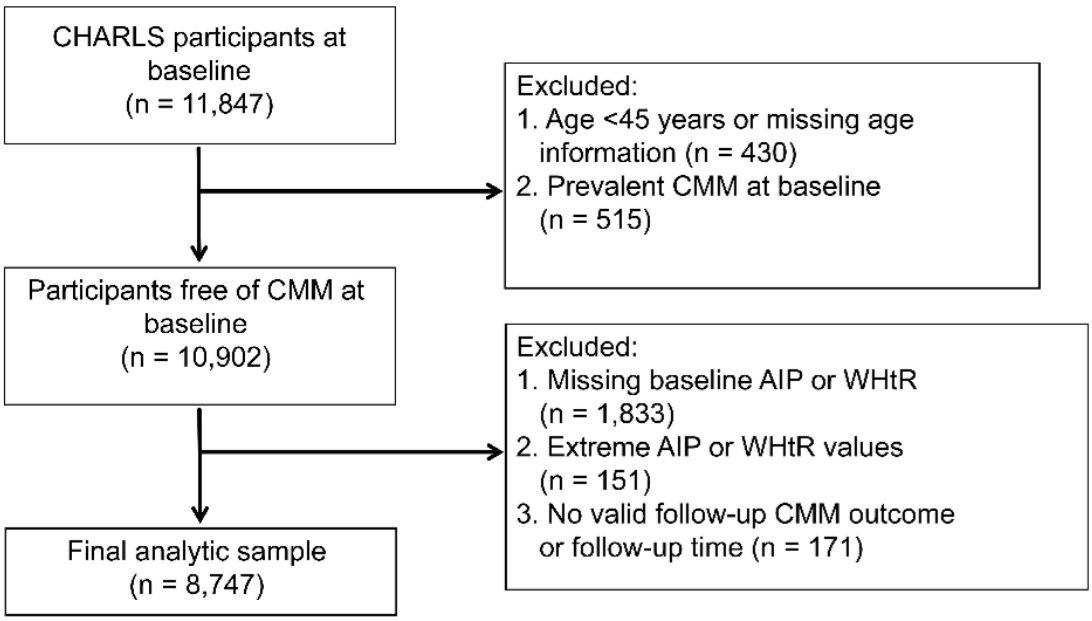


Figure 1

Flowchart for participant selection. CMM, cardiometabolic multimorbidity; AIP, atherogenic index of plasma; WHtR, waist-to-height ratio. Participant counts and exclusion steps correspond to the final analytic sample used in the main Cox analyses.

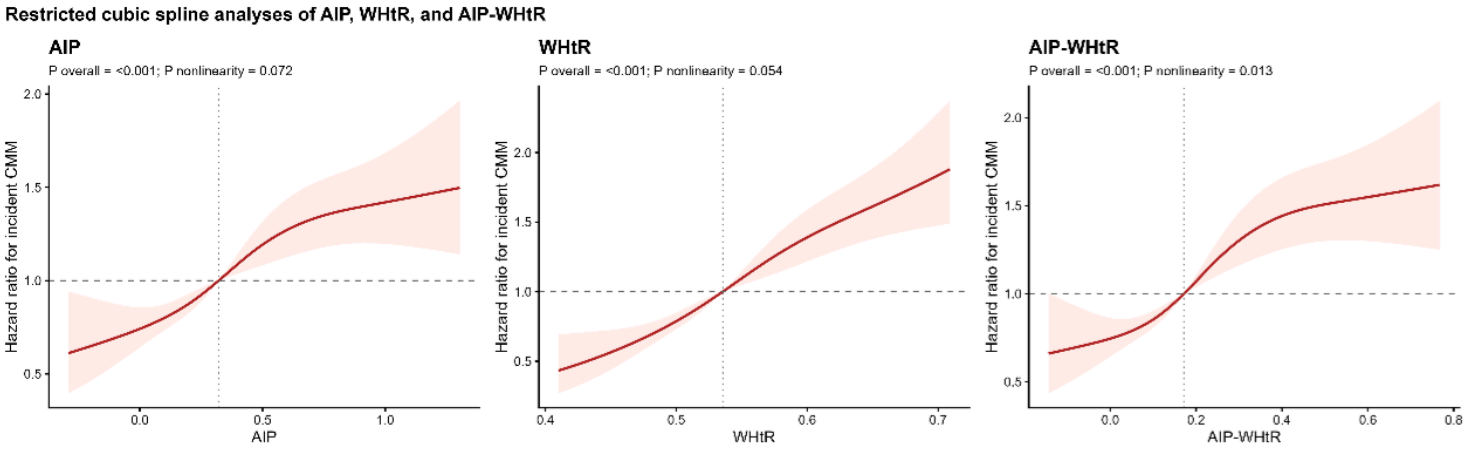


Figure 2

Restricted cubic spline analyses of AIP, WHtR, and the AIP-WHtR index with incident CMM. Curves show HRs for incident CMM with shaded 95% CIs. Models were adjusted using the Model III covariate set.

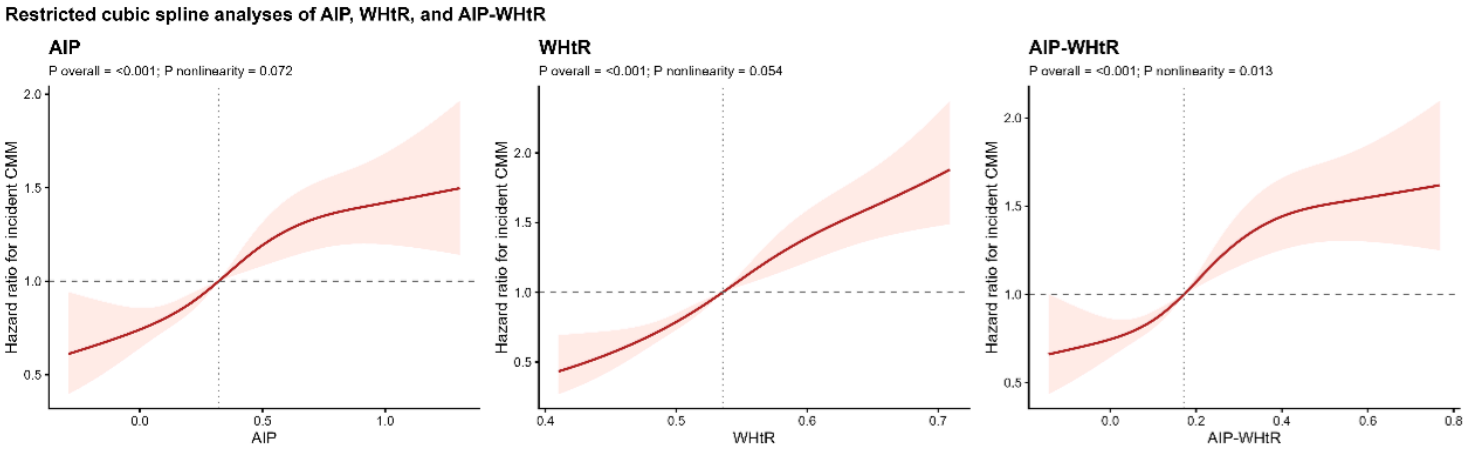


Figure 2

Restricted cubic spline analyses of AIP, WHtR, and the AIP-WHtR index with incident CMM. Curves show HRs for incident CMM with shaded 95% CIs. Models were adjusted using the Model III covariate set.

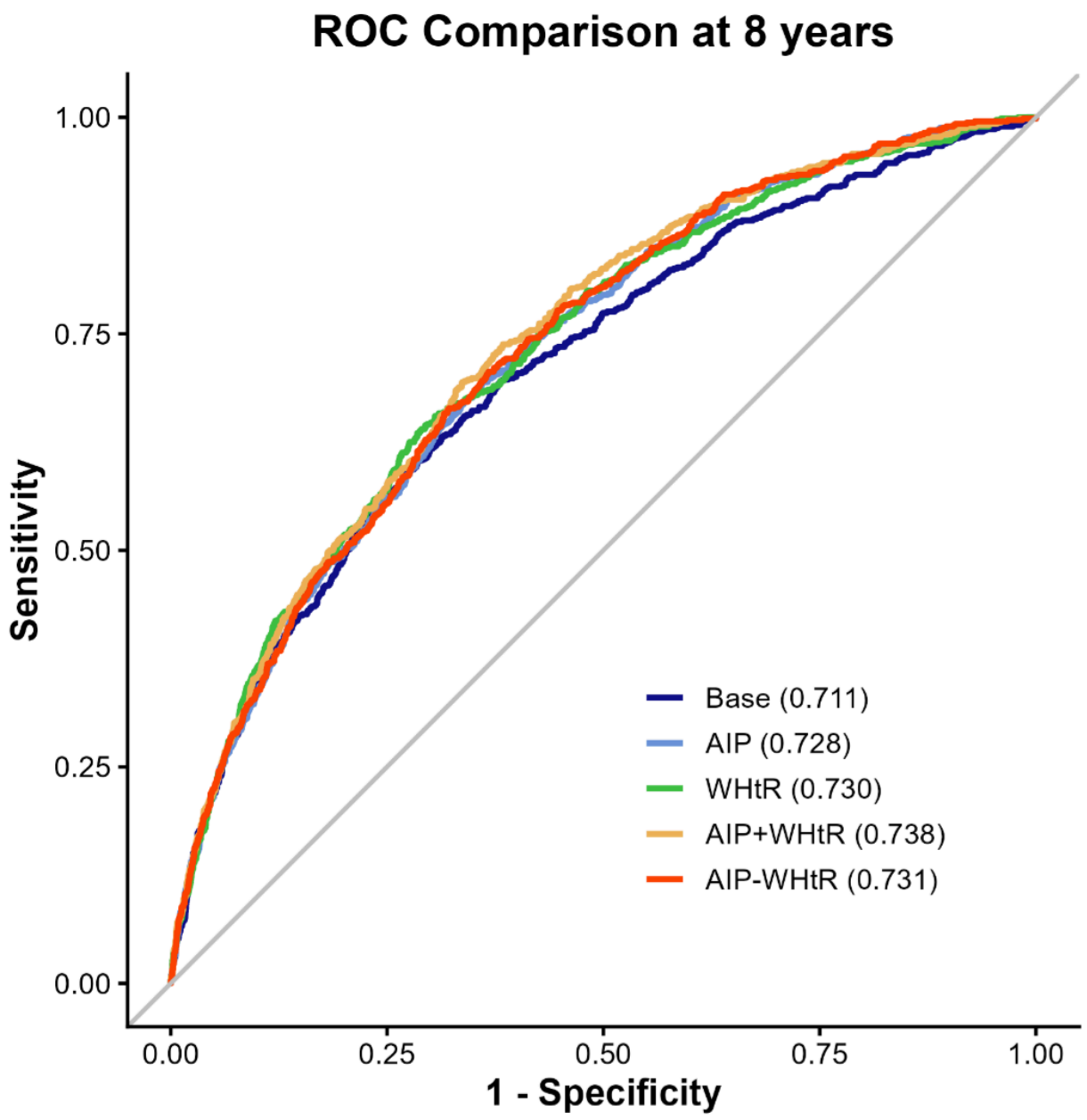


Figure 3

Eight-year time-dependent ROC comparison for incident CMM. AUC values are 8-year time-dependent ROC AUCs. The base model used Model III covariates; expanded models added AIP, WHtR, both AIP and WHtR, or the supplementary AIP-WHtR index.

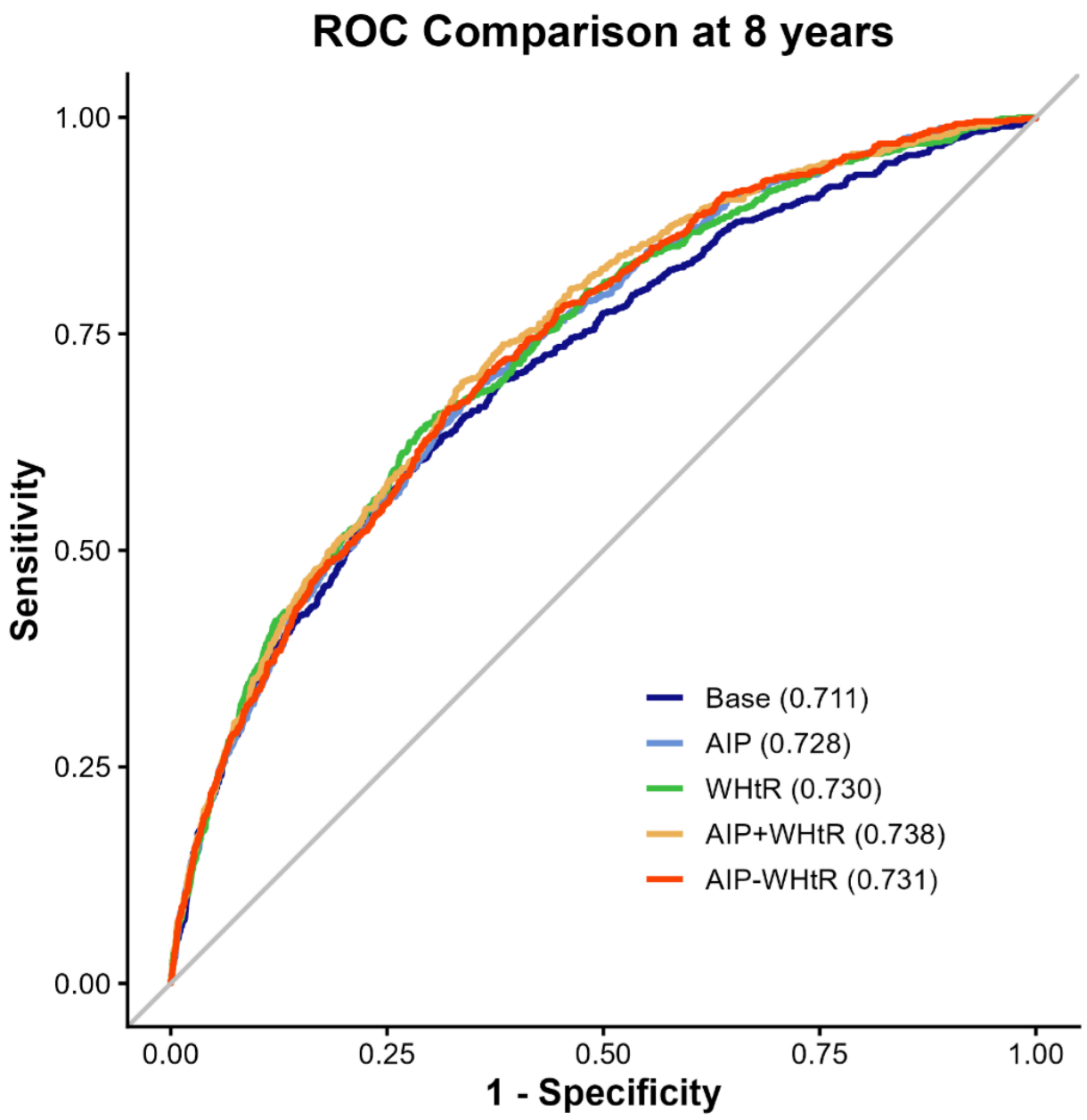


Figure 3

Eight-year time-dependent ROC comparison for incident CMM. AUC values are 8-year time-dependent ROC AUCs. The base model used Model III covariates; expanded models added AIP, WHtR, both AIP and WHtR, or the supplementary AIP-WHtR index.

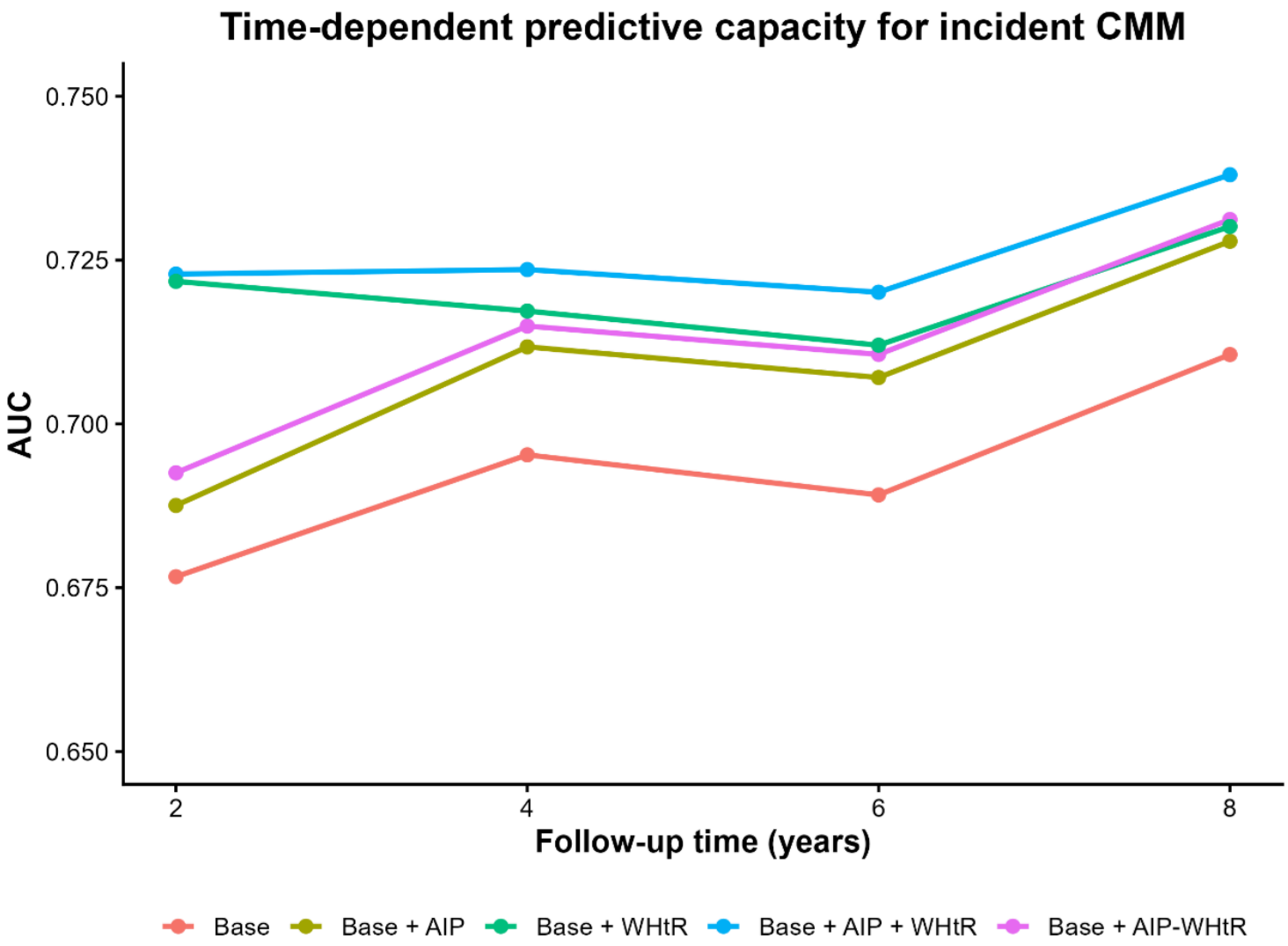


Figure 4

Time-dependent AUCs at 2, 4, 6, and 8 years for incident CMM prediction. Time-dependent ROC AUCs were estimated at 2, 4, 6, and 8 years. The base model used Model III covariates; expanded models added AIP, WHtR, both AIP and WHtR, or AIP-WHtR index.

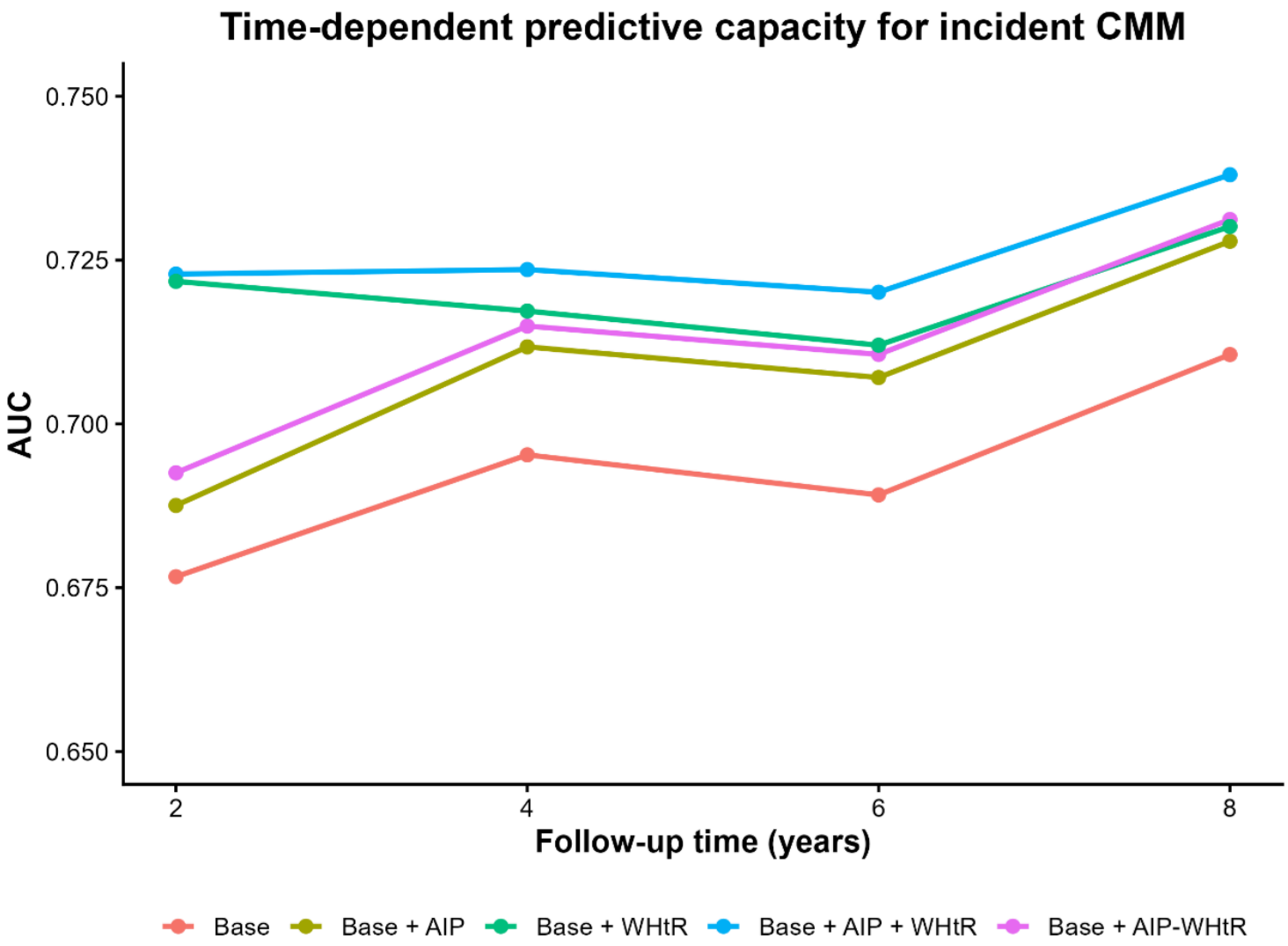


Figure 4

Time-dependent AUCs at 2, 4, 6, and 8 years for incident CMM prediction. Time-dependent ROC AUCs were estimated at 2, 4, 6, and 8 years. The base model used Model III covariates; expanded models added AIP, WHtR, both AIP and WHtR, or AIP-WHtR index.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- C3Table.docx
- C3Table.docx