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Joint associations of the atherogenic index of plasma and surrogate indices of insulin resistance with incident cardiovascular disease in middle-aged and older Chinese adults

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Abstract

Background:

The triglyceride-glucose (TyG) index, estimated glucose disposal rate (eGDR), and metabolic score for insulin resistance (METS-IR) are established surrogate markers of insulin resistance (IR), while the atherogenic index of plasma (AIP) reflects atherogenic dyslipidemia. Nevertheless, evidence regarding their combined value in cardiovascular disease (CVD) risk stratification remains limited. We therefore examined the joint associations of AIP and three IR surrogate indices with incident CVD.

Methods:

In this prospective research, 4,117 adults aged 45 years or more from the China Health and Retirement Longitudinal Study (CHARLS) were included, all of whom were free of cardiovascular disease at the beginning. The median was used to split AIP and each IR surrogate index into two categories. Cox models, restricted cubic spline analyses, 7-year time-dependent ROC analyses, integrated discrimination improvement, net reclassification improvement, mediation analyses, subgroup analyses, and sensitivity analyses were conducted.

Results:

During follow-up, 749 participants developed incident CVD. In fully adjusted models, the highest combined categories of TyG-AIP, eGDR-AIP, and METS-IR-AIP were associated with higher CVD risk:1.21, 95% CI: 1.03, 1.43; 1.82, 95% CI: 1.39, 2.37 and 1.43, 95% CI:1.19, 1.73. Among participants with high AIP, only eGDR showed a significant nonlinear association with incident CVD. AIP alone provided limited improvement in discrimination, whereas eGDR showed the greatest predictive gain, increasing the 7-year AUC from 0.578 to 0.628; METS-IR showed a smaller improvement, while TyG added little. Reclassification analyses showed a similar pattern. Mediation analyses indicated that the association between AIP and incident CVD was partly mediated by eGDR and, to a lesser extent, by METS-IR, whereas no significant mediation was observed for TyG. No significant multiplicative or additive interaction was observed between AIP and TyG or eGDR, whereas AIP and METS-IR showed a significant antagonistic interaction on the multiplicative scale.

Conclusion

Higher AIP and adverse IR profiles were jointly associated with incident CVD. Among the three surrogate indices, eGDR showed the most informative overall profile. Combined assessment of AIP and eGDR may improve cardiovascular risk stratification.

Introduction

Despite improvements in medical and public health methods, cardiovascular disease (CVD) has been the primary cause of mortality and disability worldwide for decades[1]. Global Burden of Disease (GBD)

research has continuously pointed out that CVD has a great impact on global health, among which ischemic heart disease and stroke are the main causes of this problem[2, 3]. From 1990 to now, the number of people suffering from CVD has more than doubled, and the death toll has increased from 13.1 million in 1990 to 19.2 million in 2023[2]. To reduce the global CVD burden, we must focus on controlling these risk factors and adopt targeted public health strategies and actions.

Insulin resistance(IR) has been increasingly recognized as an important contributor to CVD[4], which is mainly related to vascular endothelial metabolism [5], inflammatory[6], and dysfunction[7]. In extensive epidemiological research, various surrogate markers such as the triglyceride-glucose index (TyG), metabolic score for insulin resistance (METS-IR), and estimated glucose disposal rate (eGDR) are commonly utilized to assess CVD risk associated with IR[8, 9]. At the same time, the atherogenic index of plasma (AIP), an indicator of atherogenic dyslipidemia, has also been linked to cardiovascular outcomes [10, 11]. It is worth noting that there may be close interaction between AIP and IR. A cross-sectional study found that AIP showed an inverse L-shaped association with IR[12]. However, one study found that in the presence of IR, an elevated TG/HDL-C ratio was as effective as the commonly used total cholesterol/HDL-C ratio in predicting CHD risk[13]. In addition, AIP has been associated with diabetes[14, 15] and metabolic syndrome[16], suggesting its potential value in predicting diabetic complications and informing early intervention strategies. Considering the close biological relationship between IR and atherogenic dyslipidemia, a better understanding of their joint influence on the risk of CVD may help to find the risk earlier. However, prospective evidence on whether AIP provides complementary information beyond established IR surrogate indices for incident CVD remains limited.

Therefore, we used data from the China Health and Retirement Longitudinal Study (CHARLS) to investigate the associations of AIP and three surrogate indices of IR with incident CVD, as well as their joint associations. We further compared their incremental predictive value and potential mediating pathways.

Methods

Study design and participants

CHARLS used a multistage probability sampling design to achieve a sample that represents the nation. A total of 17,708 adults aged 45 and above were enrolled in the baseline survey, spanning 450 communities within 150 counties or districts across 28 provinces in China. The study obtained permission from the Peking University Ethics Review Committee (IRB00001052-11015), and all subjects provided written informed consent.

A detailed description of the CHARLS data collection process is shown in Fig. 1. In order to ensure the integrity of the data, we excluded the participants who met the following conditions: (1) those who lacked the data of TyG, eGDR, METS-IR and AIP; (2) People who have a history of CVD in Wave1 stage or

who have lost their follow-up; (3) Participants under the age of 45; (4) participants with less than 2 years follow-up; (5) People who lack CVD diagnosis data in 2013, 2015 or 2018.

Data collection

In the CHARLS survey, the staff collected demographic characteristics, lifestyle, medical history, anthropometric data and laboratory indicators according to standard procedures after training. Through the structured questionnaire, details about age, gender, marital status, educational background, smoking and drinking habits, along with medical conditions like hypertension, diabetes, heart disease, and stroke diagnosed by physicians were collected. Weight and waist circumference (WC) are measured directly, while blood pressure is taken as the average of three consecutive readings.

Qualified medical staff collected fasting venous blood samples and processed them according to the CHARLS protocol. After storage and cold chain transportation, the samples were sent to the central laboratory for biochemical analysis. They measured serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FPG) by enzymatic method, while high-sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetry.

Calculation of insulin resistance surrogate indices and AIP

We employ three established surrogate indicators to assess insulin resistance, derived from standard biochemical testing and anthropometric measurements[17]. The TyG index calculation is ln [TG (mg/dL) × FPG (mg/dL)/2]. The formula for computation is 21.158 − 0.09 x WC (cm) − 3.407 x hypertension (yes = 1, no = 0) − 0.551 x HbA1c (%). METS-IR is determined by the formula ln[(2 x FPG (mg/dL)) + TG (mg/dL)] x BMI (kg/m²) / ln [HDL-C (mg/dL)]. The AIP calculation method is log10 (TG/HDL-C), with TG and HDL-C represented in molar concentrations.

Outcome definition and ascertainment

The primary outcome was incident cardiovascular disease (CVD), which was ascertained during the second to fourth follow-up surveys. According to previous CHARLS-based research[18], CVD was characterized as self-reported physician-diagnosed heart disease or stroke, or the utilization of prescription medication for these ailments. Participants were categorized as having incident cardiovascular disease if any of these events were initially reported during the follow-up period. The follow-up duration was determined from baseline to the initial report of a CVD incident.

Covariates

Demographic traits, lifestyle habits, clinical data, existing health conditions, and medication usage were used to select baseline covariates. Covariates included Covariates encompassed age, sex, smoking status, alcohol consumption, educational attainment, marital status, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), high-sensitivity C-reactive protein (hs-CRP), uric acid (UA), Blood Urea Nitrogen (BUN), serum creatinine (Scr), hypertension, diabetes, and dyslipidemia. Hypertension was defined as a self-reported physician diagnosis, an SBP of 140 mmHg or above, a DBP of 90 mmHg or higher, or the use of antihypertensive medication[19]. Diabetes was defined as self-reported physician diagnosis, fasting blood glucose > = 126 mg/dL, HbA1c > = 6.5%, or use of antidiabetic medication[20]. Dyslipidemia was defined as self-reported physician diagnosis, use of lipid-lowering medication, or abnormal lipid levels, including TG > = 150 mg/dL, LDL-C > = 160 mg/dL, TC > = 240 mg/dL, or HDL-C < 40 mg/dL [21].

Handling of missing data

Several variables had missing values, as shown in Supplementary **Fig. S1**. To reduce the impact of incomplete data, we used Multiple Imputation by Chained Equations to generate five imputed datasets, and estimates were pooled according to Rubin's rules.

Statistical analysis

Depending on their distribution, continuous variables are expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), and comparisons were made using the Student's t test or Mann-Whitney U test. Continuous variables are expressed as mean ± SD for comparability and categorical variables are given as numbers (percentages) and were compared using either the chi-square test or Fisher's exact test. Because no established clinical cut-off values are available for TyG, eGDR, METS-IR, or AIP, these indices were dichotomized at the median. For joint association analyses, participants were classified into four groups according to each IR surrogate index and AIP: low IR/low AIP, low IR/high AIP, high IR/low AIP, and high IR/high AIP. Because lower eGDR values indicate greater insulin resistance, participants with eGDR below the median were categorized as having high IR. Kaplan-Meier curves and the log-rank test were used to compare cumulative CVD incident among groups, with incidence rates estimated per 1,000 person-years. Cox proportional hazards models were employed to assess the associations between the aggregated AIP categories and each IR surrogate index for incident CVD, with outcomes reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Schoenfeld residuals were employed to assess the proportional hazards assumption. Multicollinearity diagnostics (**Tables S1–S3**) indicated that all generalized variance inflation factors (GVIFs) were below 5, signifying the absence of significant multicollinearity across the covariates[22]. We established three models: Model 1 was unadjusted. Model 2 included adjustments for age, sex, smoking and drinking status, education level, and marital status. Model 3 incorporated additional adjustments for hs-CRP, UA, Scr, and BUN. Further analyses using restricted cubic splines (RCS) were conducted to explore potential nonlinear relationships between each IR surrogate index and the occurrence of CVD based on AIP strata.

To see if the prediction is accurate, we use the 7-year time-dependent ROC curve to further examine the Cox model, and then use an area called time-dependent AUC to measure its distinguishing ability. We also use NRI and IDI methods to see if the new model predicts better than the basic model[23].

Mediation analyses were performed using the mediation package and accelerated failure time models to explore potential bidirectional mediation patterns between AIP and IR surrogate indices in relation to time to incident CVD. Total, direct, and indirect effects were estimated, and the proportion mediated was calculated [24]. Subgroup analyses were performed to examine whether the associations between the combined categories of AIP and IR surrogate indices and incident CVD were consistent across strata of age, sex, BMI, smoking, drinking, hypertension, diabetes, and dyslipidemia. Effect modification was assessed by including interaction terms. Additive interaction was evaluated using the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI) with the interactionR package. Several sensitivity analyses were also made. We further repeated the joint association analyses in participants with complete data only. Index-specific sensitivity analyses were further conducted by additionally adjusting for selected clinical conditions according to the surrogate index evaluated, while avoiding adjustment for variables overlapping with the construction of that index. In addition, heart disease and stroke were analyzed separately as supplementary outcomes to assess whether the associations differed across specific cardiovascular endpoints.

All the analysis was done with R software (version 4.4.3). Mediation package is used for mediation analysis, mice is used to deal with missing data, and survival package is used for Cox regression. P value less than 0.05 (two-sided test) means that the results are statistically significant.

Results

Baseline characteristics of study participants

Table 1 indicates that 749 of the 4,117 participants got new instances of cardiovascular disease during the follow-up period. In comparison to people without CVD, those with newly diagnosed CVD were older, predominantly female, and had a higher prevalence of hypertension, diabetes, and dyslipidemia. They also differed with respect to marital status and smoking status, and had higher BMI, blood pressure, WC, TC, LDL-C, FPG, and HbA1c levels. AIP, TyG, and METS-IR were higher, whereas HDL-C and eGDR were lower. No significant differences were observed for education level, drinking status, TG, Scr, UA, or hs-CRP; BUN was slightly lower in the CVD group.

Table 1
Baseline characteristics of the participants classified by CVD

Variable	Overall	Non-CVD	CVD	p
n	4117	3368	749	
Age, years	58.08 (8.72)	57.72 (8.74)	59.72 (8.47)	**< 0.001**
Sex, n (%)	2247 (54.6)	1791 (53.2)	456 (60.9)	**< 0.001**
Female				
Male	1870 (45.4)	1577 (46.8)	293 (39.1)	
Education level, n (%)	448 (10.9)	362 (10.7)	86 (11.5)	0.604
Senior high school and above				
Junior high school and below	3669 (89.1)	3006 (89.3)	663 (88.5)	
Marriage group, n (%)	3717 (90.3)	3060 (90.9)	657 (87.7)	**0.011**
Married				
Other	400 (9.7)	308 (9.1)	92 (12.3)	
Smoking, n (%)	2541 (61.7)	2061 (61.2)	480 (64.1)	**0.022**
Never				
Former	304 (7.4)	238 (7.1)	66 (8.8)	
Current	1272 (30.9)	1069 (31.7)	203 (27.1)	
Drinking, n (%)	2539 (61.7)	2067 (61.4)	472 (63.0)	0.426
No				
Yes	1578 (38.3)	1301 (38.6)	277 (37.0)	
Hypertension, n (%)	2542 (61.7)	2185 (64.9)	357 (47.7)	**< 0.001**
No				
Data are presented as mean ± SD or n (%).				
Abbreviations: CVD, cardiovascular disease; 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; HbA1c, glycated hemoglobin; AIP, atherogenic index of plasma; TyG, triglyceride-glucose; eGDR, estimate glucose disposal rate; METS-IR, metabolic score for insulin resistance; UA, uric acid; Scr, serum creatinine, hs-CRP, high-sensitivity C-reactive protein; BUN, Blood Urea Nitrogen.				
Baseline characteristics were compared between groups using χ^2 or analysis of variance or Kruskal–Wallis rank sum test where appropriate.				

Variable	Overall	Non-CVD	CVD	p
Yes	1575 (38.3)	1183 (35.1)	392 (52.3)	
Diabetes, n (%)	3500 (85.0)	2890 (85.8)	610 (81.4)	**0.003**
No				
Yes	617 (15.0)	478 (14.2)	139 (18.6)	
Dyslipidemia, n (%)	2330 (56.6)	1935 (57.5)	395 (52.7)	**0.021**
No				
Yes	1787 (43.4)	1433 (42.5)	354 (47.3)	
BMI (kg/m^2)	23.68 (3.91)	23.50 (3.83)	24.47 (4.19)	**< 0.001**
SBP (mmHg)	129.56 (20.64)	128.62 (20.18)	133.80 (22.08)	**< 0.001**
DBP (mmHg)	75.37 (11.68)	74.99 (11.52)	77.08 (12.21)	**< 0.001**
WC (cm)	84.29 (12.92)	83.68 (12.68)	87.02 (13.62)	**< 0.001**
TC (mg/dl)	194.48 (38.81)	193.86 (39.02)	197.25 (37.75)	**0.031**
TG (mg/dl)	131.90 (109.20)	130.47 (110.11)	138.29 (104.85)	**0.076**
HDL (mg/dl)	51.32 (15.27)	51.63 (15.33)	49.91 (14.89)	**0.005**
LDL (mg/dl)	118.05 (35.11)	117.50 (34.80)	120.54 (36.39)	**0.032**
FPG (mg/dl)	109.97 (33.64)	109.09 (31.92)	113.96 (40.24)	**< 0.001**
HbA1C (%)	5.27 (0.80)	5.24 (0.76)	5.38 (0.95)	**< 0.001**
BUN (mg/dL)	15.60 (4.25)	15.68 (4.31)	15.24 (3.97)	**0.010**
Scr (mg/dL)	0.77 (0.18)	0.77 (0.19)	0.76 (0.18)	0.482
UA (mg/dl)	4.35 (1.21)	4.36 (1.21)	4.31 (1.22)	0.335
hs-CRP (mg/L)	2.41 (6.06)	2.34 (5.66)	2.74 (7.59)	0.102
AIP	0.35 (0.34)	0.34 (0.34)	0.39 (0.33)	**< 0.001**

Data are presented as mean ± SD or n (%).

Abbreviations: CVD, cardiovascular disease; 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; HbA1c, glycated hemoglobin; AIP, atherogenic index of plasma; TyG, triglyceride-glucose; eGDR, estimate glucose disposal rate; METS-IR, metabolic score for insulin resistance; UA, uric acid; Scr, serum creatinine, hs-CRP, high-sensitivity C-reactive protein; BUN, Blood Urea Nitrogen.

Baseline characteristics were compared between groups using χ^2 or analysis of variance or Kruskal–Wallis rank sum test where appropriate.

Variable	Overall	Non-CVD	CVD	p
TyG	8.68 (0.66)	8.66 (0.65)	8.77 (0.67)	**< 0.001**
eGDR	9.37 (2.32)	9.54 (2.26)	8.58 (2.41)	**< 0.001**
METS-IR	35.88 (8.63)	35.49 (8.42)	37.64 (9.30)	**< 0.001**

Data are presented as mean ± SD or n (%).

Abbreviations: CVD, cardiovascular disease; 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; HbA1c, glycated hemoglobin; AIP, atherogenic index of plasma; TyG, triglyceride-glucose; eGDR, estimate glucose disposal rate; METS-IR, metabolic score for insulin resistance; UA, uric acid; Scr, serum creatinine, hs-CRP, high-sensitivity C-reactive protein; BUN, Blood Urea Nitrogen.

Baseline characteristics were compared between groups using χ^2 or analysis of variance or Kruskal–Wallis rank sum test where appropriate.

Association of TyG, eGDR, METS-IR, and AIP with the risk of incident CVD

Table S5 indicates that elevated AIP, TyG, and METS-IR levels were strongly correlated with an increased risk of CVD following comprehensive adjustment, while greater eGDR was significantly linked to a reduced risk. According to Table 2, the relationships between the joint categories of IR surrogate indicators and AIP and the incidence of CVD varied. After full adjustment, participants in the highest TyG-AIP category had a 21% higher risk of incident CVD than those in the reference group (HR 1.21, 95% CI 1.03–1.43). For the eGDR-AIP combination, excess risk became evident in the less favorable categories and was most pronounced in Group 4, where the risk of CVD was 82% higher than that in the reference group (HR 1.82, 95% CI 1.39–2.37). For METS-IR-AIP, risk was elevated across Groups 2 to 4, with the highest adjusted HR observed in Group 3 (HR 1.58, 95% CI 1.25-2.00), while Group 4 also remained significantly associated with incident CVD (HR 1.43, 95% CI 1.19–1.73). In addition, all three joint indicators showed significant trends across the combined categories. Figure 2 illustrates clear separation in cumulative CVD incidence across the combined TyG-AIP, eGDR-AIP, and METS-IR-AIP groups, with the greatest divergence observed for eGDR-AIP and METS-IR-AIP (all log-rank $P < 0.001$).

Table 2
Combined effects of IR surrogate indices and AIP on CVD risk

Variable	Model I			Model II			Model III		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
TyG and AIP									
Group 1	Ref	—		Ref	—		Ref	—	
Group 2	1.30	0.97, 1.75	0.081	1.37	1.02, 1.85	**0.038**	1.31	0.97, 1.77	0.079
Group 3	1.15	0.85, 1.57	0.362	1.10	0.81, 1.50	0.549	1.35	1.11, 1.63	**0.003**
Group 4	1.39	1.19, 1.63	**< 0.001**	1.34	1.15, 1.57	**< 0.001**	1.21	1.03, 1.43	**0.024**
P for trend		**< 0.001**			**< 0.001**			**0.019**	
eGDR and AIP									
Group 1	Ref	—		Ref	—		Ref	—	
Group 2	1.24	0.97, 1.59	0.080	1.23	0.96, 1.57	0.098	1.22	0.95, 1.56	0.119
Group 3	2.03	1.63, 2.53	**< 0.001**	1.88	1.51, 2.35	**< 0.001**	1.59	1.20, 2.11	**0.001**
Group 4	2.32	1.91, 2.83	**< 0.001**	2.16	1.77, 2.63	**< 0.001**	1.82	1.39, 2.37	**< 0.001**
P for trend		**< 0.001**			**< 0.001**			**< 0.001**	
METS-IR and AIP									
Group 1	Ref	—		Ref	—		Ref	—	
Group 2	1.42	1.12, 1.81	**0.004**	1.35	1.06, 1.72	**0.016**	1.31	1.03, 1.67	**0.031**
Group 3	1.68	1.34, 2.12	**< 0.001**	1.74	1.39, 2.20	**< 0.001**	1.58	1.25, 2.00	**< 0.001**
Group 4	1.63	1.37, 1.94	**< 0.001**	1.64	1.38, 1.95	**< 0.001**	1.43	1.19, 1.73	**< 0.001**
P for trend		**< 0.001**			**< 0.001**			**< 0.001**	

Model I: non-adjusted

Model II: adjusted for age, sex, smoking status, drinking status, education level, marital status

Variable	Model I			Model II			Model III		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
TyG and AIP									

Model III: further adjusted for hs-CRP, UA, Scr, BUN.

Identifying nonlinear connections

To identify possible nonlinear connections, we used multivariable-adjusted restricted cubic spline analyses to study how IR surrogate indices relate to new cases of CVD, divided by AIP level. In the low AIP stratum, significant overall associations were observed for all three indices, but there was no evidence of nonlinearity. There was a positive correlation between TyG and CVD risk, an inverse linear correlation with eGDR, and a positive linear correlation with METS-IR (all P values for overall < 0.0001 and all P values for nonlinearity > 0.05; Fig. 3A-C). In people with elevated AIP, the relationships between TyG and METS-IR and the occurrence of CVD remained significant overall, although neither showed a statistically significant nonlinear component. In contrast, eGDR demonstrated a significant nonlinear association with incident CVD in the high AIP subgroup (Fig. 3D-F). Further two-piecewise Cox regression analysis identified a significant inflection point for eGDR at 9.26 in the fully adjusted model (P for log-likelihood ratio test < 0.001; **Table S4**).

Predictive performance of IR surrogates and AIP for CVD

As presented in Fig. 4, the basic model demonstrated limited predictive performance for 7-year incident CVD, with a time-dependent AUC of 0.578 (95% CI, 0.547–0.609). The addition of AIP was associated with only a slight improvement in discrimination, increasing the AUC to 0.589 (95% CI, 0.559–0.618). When IR surrogate indices were further incorporated, the magnitude of improvement differed across indices. The gain was most pronounced for eGDR, with the AUC increasing to 0.628 (95% CI, 0.598–0.658), followed by METS-IR, with an AUC of 0.611 (95% CI, 0.581–0.641). In contrast, TyG produced only a marginal increase in AUC to 0.594 (95% CI, 0.564–0.624). These patterns were broadly consistent with the reclassification results shown in Table 3. Specifically, adding eGDR significantly improved reclassification (NRI 0.320, 95% CI 0.123 to 0.404; P = 0.016) and discrimination (IDI 0.019, 95% CI 0.013 to 0.027; P < 0.001), whereas METS-IR showed a smaller but still significant improvement (NRI 0.178, 95% CI 0.088 to 0.311; P = 0.008; IDI 0.010, 95% CI 0.002 to 0.023; P = 0.012). TyG did not significantly improve NRI or IDI.

Table 3
Incremental reclassification performance of AIP and IR indices for incident CVD

Comparison	NRI (95% CI)	P value	IDI (95% CI)	P value
Basic + TyG vs Basic	0.179 (-0.010 to 0.228)	0.144	0.004 (-0.004 to 0.017)	0.359
Basic+eGDR vs Basic	0.320 (0.123 to 0.404)	0.016	0.019 (0.013 to 0.027)	**< 0.001**
Basic+METS-IR vs Basic	0.178 (0.088 to 0.311)	0.008	0.010 (0.002 to 0.023)	**0.012**
Basic + AIP+TyG vs Basic + AIP	0.053 (-0.018 to 0.076)	0.164	0.001 (-0.012 to 0.027)	0.922
Basic + AIP+eGDR vs Basic + AIP	0.310 (0.044 to 0.431)	0.028	0.016 (0.011 to 0.023)	**< 0.001**
Basic + AIP+METS-IR vs Basic + AIP	0.233 (0.022 to 0.294)	0.016	0.007 (0.001 to 0.018)	**0.032**

The basic model was adjusted for age, sex, smoking status, drinking status, education level, marital status, BUN, Scr, UA, hs-CRP

Mediation analyses of IR surrogates and AIP on CVD risk

As shown in Fig. 5, exploratory mediation analyses based on accelerated failure time models suggested that only eGDR and METS-IR showed evidence of mediation in the association between AIP and time to incident CVD. The mediating effect was much stronger for eGDR, which accounted for 49.62% of the association, whereas METS-IR accounted for only 2.69%. No significant mediation was observed for TyG. In the reverse direction, no significant mediation through AIP was detected for any of the three IR surrogate indices.

Subgroup and sensitivity analyses

Subgroup analyses showed that the associations of the combined TyG-AIP, eGDR-AIP, and METS-IR-AIP categories with incident CVD were broadly consistent across strata of age, sex, smoking status, drinking status, BMI, hypertension, dyslipidemia, diabetes (Fig. 6 **and Fig.S2**). In general, participants in the high-risk combined category had a higher risk of CVD than those in the reference category across most subgroups. After completely adjusting for covariates, no notable interactions were found concerning age, sex, smoking habits, drinking habits, BMI, hypertension, dyslipidemia, or diabetes (P for interaction > 0.05). To confirm the reliability of the main results, multiple sensitivity analyses were conducted. First, all analyses were repeated in complete-case participants (n = 4,103). Second, index-specific sensitivity analyses were further conducted by additionally adjusting for selected clinical conditions according to the surrogate index evaluated, while avoiding adjustment for variables overlapping with the construction of that index. Third, heart disease and stroke were analyzed separately as supplementary outcomes (n = 4,117). Significantly, these analyses produced results that aligned with the primary findings (**Table S6-S9**). Exploratory interaction analyses are presented in Supplementary **Table S10**. No clear multiplicative

or additive interaction was observed for AIP with TyG or eGDR, whereas AIP and METS-IR showed an antagonistic interaction on the multiplicative scale.

Discussion

In this national cohort of 4,117 middle-aged and older Chinese adults, higher AIP combined with a more adverse IR profile was associated with a greater risk of incident CVD, although the strength of this pattern differed across surrogate indices. The joint association was strongest for eGDR and AIP. AIP alone provided limited incremental predictive value, whereas eGDR substantially improved discrimination and reclassification; TyG contributed comparatively little. We also found that the association between AIP and incident CVD may be partly mediated by IR, particularly the component reflected by eGDR, whereas evidence for the reverse pathway was limited. Overall, these findings suggest that combined assessment of AIP and selected IR surrogate indices may improve identification of individuals at high risk of CVD, and that this pattern is robust across subgroup and sensitivity analyses.

Our findings are broadly in line with previous studies showing that surrogate markers of IR are associated with cardiovascular risk and that AIP is likewise linked to adverse cardiovascular outcomes. Earlier studies have reported significant associations of TyG, eGDR, and METS-IR with CVD [17, 25–27], while accumulating evidence has also identified AIP as a marker of atherogenic dyslipidemia and cardiovascular risk[28–30]. First, rather than evaluating these markers in isolation, we examined their joint associations and showed that the coexistence of an adverse IR profile and elevated AIP identified individuals at particularly high risk of incident CVD. Second, by comparing three commonly used IR surrogates within the same prospective cohort, we found that the eGDR-AIP combination showed the strongest association, whereas the corresponding patterns for METS-IR-AIP and especially TyG-AIP were less pronounced. These findings add to the limited prospective evidence on the joint assessment of AIP and established IR surrogates for incident CVD and suggest that the value of combining AIP with IR-related markers may vary according to the surrogate index used.

Several mechanisms may help explain the observed joint association of AIP and IR with incident CVD, as well as the stronger performance of eGDR in the present study. One critical pathway involves the promotion of atherosclerosis through reduced vascular smooth muscle cell survival and enhanced inflammatory signaling, such as activation of the CX3CL1/CX3CR1 axis, which may increase plaque vulnerability[31]. IR is associated with an increase in inflammation, atherosclerosis, oxidative stress, and endothelial dysfunction, factors that lead to the development of CVD[32, 33], particularly in younger individuals, indicating that IR not only acts independently but may also amplify other lipid-related risks[34], particularly in younger individuals, indicating that IR not only acts independently but also amplifies other lipid-related risks[35]. In addition, AIP has been reported to correlate with increased levels of glucose, insulin, and inflammatory markers such as C-reactive protein[36, 37]. When these abnormalities coexist, they may identify a more adverse cardiometabolic milieu than either marker alone. In our study, this pattern was most evident for eGDR, which may be because eGDR incorporates WC, hypertension, and HbA1c, and may therefore better capture the chronic metabolic burden relevant to

cardiovascular damage than TyG or METS-IR. In summary, combined assessment of AIP and IR surrogate indices, especially eGDR, may improve early identification of middle-aged and older adults at elevated risk of incident CVD.

Strengths and limitations

This study has several strengths, including its prospective design, the nationally representative CHARLS cohort, and the simultaneous comparison of three IR surrogate indices in combination with AIP. In addition, we used a comprehensive analytic strategy that included joint association analyses, nonlinear modeling, prediction analyses, mediation analyses, and multiple sensitivity analyses, which strengthened the overall interpretation of the findings.

However, several limitations should be considered. First, because of the observational design, causal inferences cannot be made. Second, incident CVD identification relied on self-reported physician diagnoses or medication usage, which could lead to misclassification. Third, TyG, eGDR, and METS-IR are surrogate rather than gold-standard measures of IR, and all exposures were measured at baseline only. Fourth, despite adjustment for a wide range of potential confounders in the multivariable and subgroup analyses, the influence of residual confounding from unmeasured factors, including diet, physical activity, and socioeconomic status, cannot be completely ruled out. Fifth, the joint analyses relied on dichotomization at the median, which facilitated risk stratification but may also have led to some loss of information. Although restricted cubic spline analyses were performed as complementary analyses, the categorization-based results should still be interpreted with this limitation in mind. Finally, because our study was limited to middle-aged and older Chinese adults, additional studies are warranted to evaluate whether these findings can be generalized to other ethnic groups, age ranges, and populations with different lifestyle characteristics.

Conclusion

In summary, higher AIP and poor IR profiles were linked to incident CVD in this national cohort. Among the three indices, eGDR showed the strongest association with AIP, offering the best predictive value and mediation signal. These results suggest that combining AIP with specific IR markers, particularly eGDR, could enhance cardiovascular risk assessment in middle-aged and older adults.

Abbreviations

TyG, triglyceride-glucose

eGDR, estimate glucose disposal rate

METS-IR, metabolic score for insulin resistance

AIP, atherogenic index of plasma

HDL-C, High-density lipoprotein cholesterol

LDL-C, Low-density lipoprotein cholesterol

CVD, Cardiovascular disease

TG, Triglyceride

TC, Total cholesterol

hs-CRP, High-sensitivity C-reactive protein

HbA1c, glycated hemoglobin

IR, Insulin resistance

BUN, Blood Urea Nitrogen

SBP, systolic blood pressure

DBP, diastolic blood pressure

BMI, Body mass index

FPG, fasting plasma glucose

Scr, serum creatinine

UA, uric acid

Declarations

Author contributions

KX conceptualized and designed the study. KX, JS, HD, YW, YR, CW, and LG carried out research. XK, KF and BX performed the data analysis. XK composed the initial draft, while LZ and TD aided in data evaluation and revisions. All authors endorsed the final manuscript.

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Data availability

The CHARLS website (http://charls.pku.edu.cn/) provides access to the data that underpins the findings of this study.

Declarations

Ethics approval and consent to participate

The Biomedical Ethics Review Committee of Peking University conducted and approved this study, adhering to the Declaration of Helsinki principles. The survey received the nod with approval number IRB00001052-11015, and the blood collection process was approved under IRB00001052-11014. Each participant penned their informed consent in writing.

Competing interests

The authors confirm the research involved no commercial or financial interests that might present conflicts.

Clinical trial number

Not applicable.

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Figures

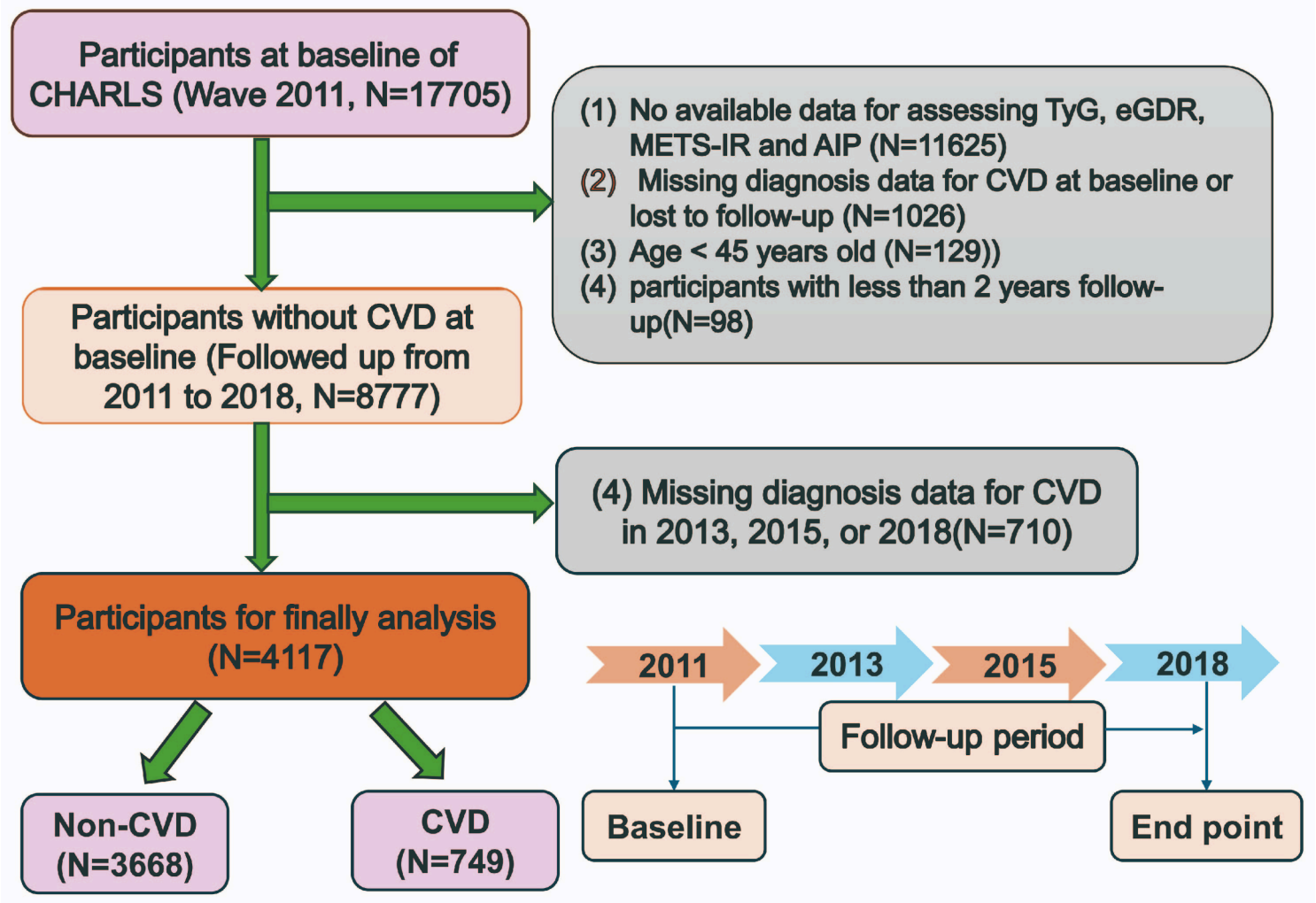


Figure 1

Flowchart of participant selection from the CHARLS.

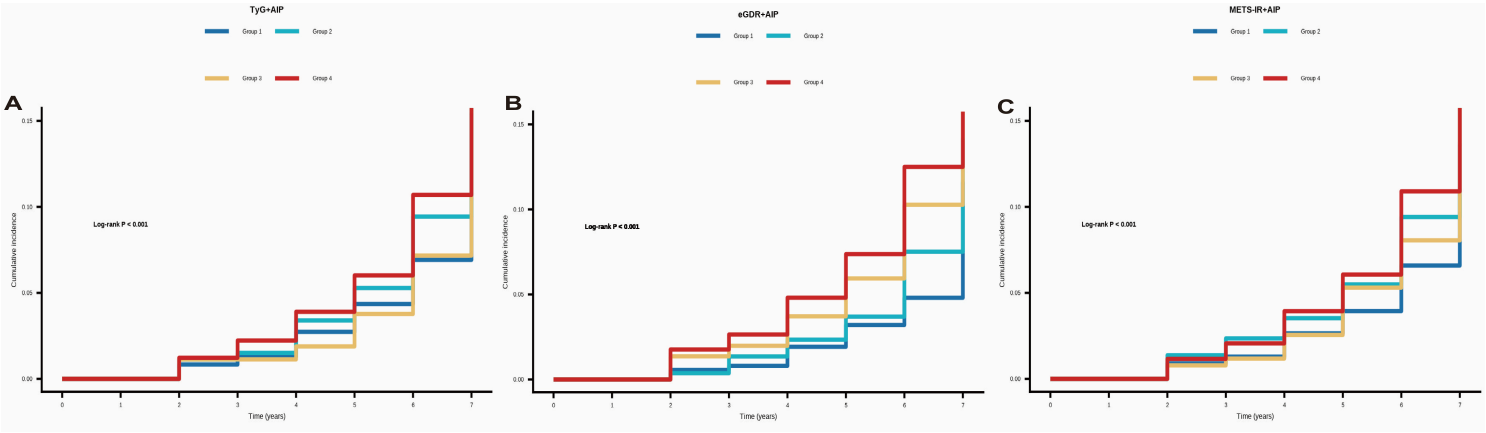


Figure 2

Kaplan–Meier curves for incident cardiovascular disease according to the combined categories of AIP and IR surrogate indices.

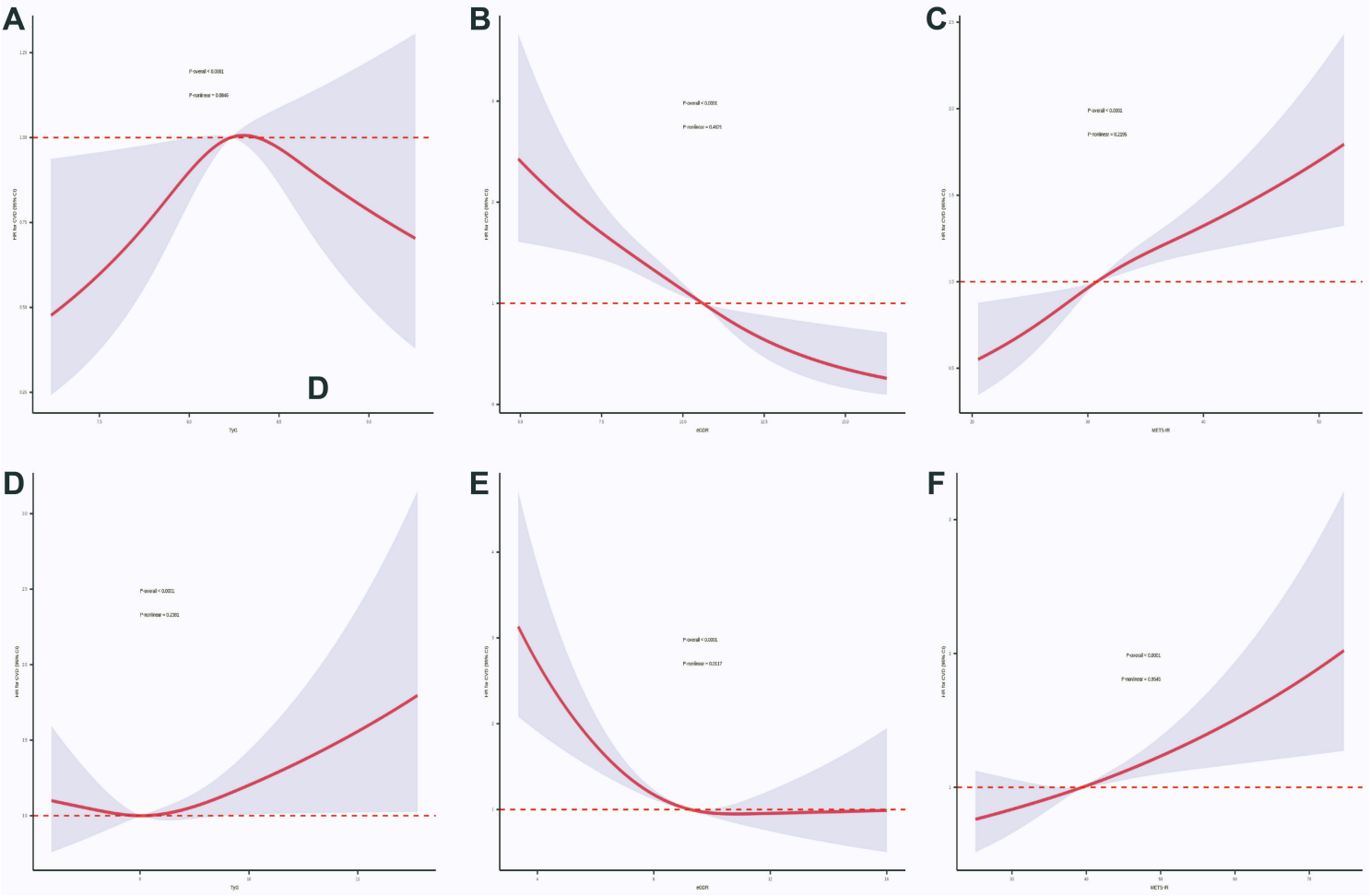


Figure 3

RCS analyses of the associations between IR surrogate indices and incident cardiovascular disease according to AIP strata. Spline analyses were adjusted for age, sex, smoking, drinking, education level, marital status, Scr, hs-CRP, UA, BUN.

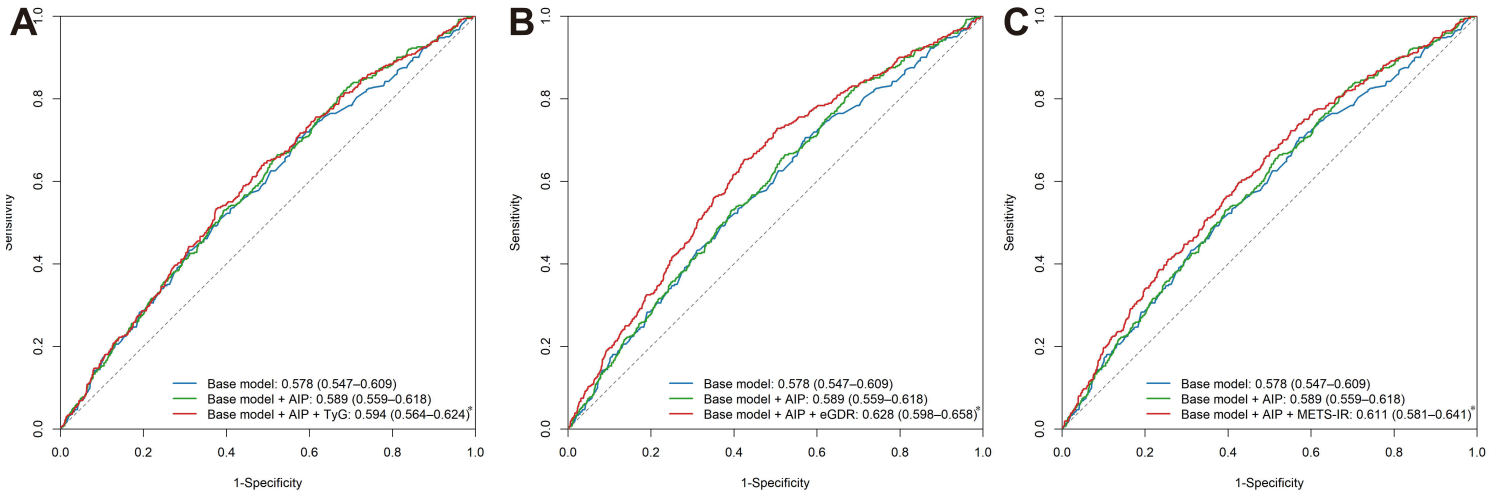


Figure 4

Seven-year time-dependent ROC curves for prediction of incident cardiovascular disease. The basic model was adjusted for age, sex, smoking, drinking, education level, marital status, Scr, hs-CRP, UA, BUN. * indicates significantly improved predictive performance versus the basic model by DeLong's test (P < 0.05)

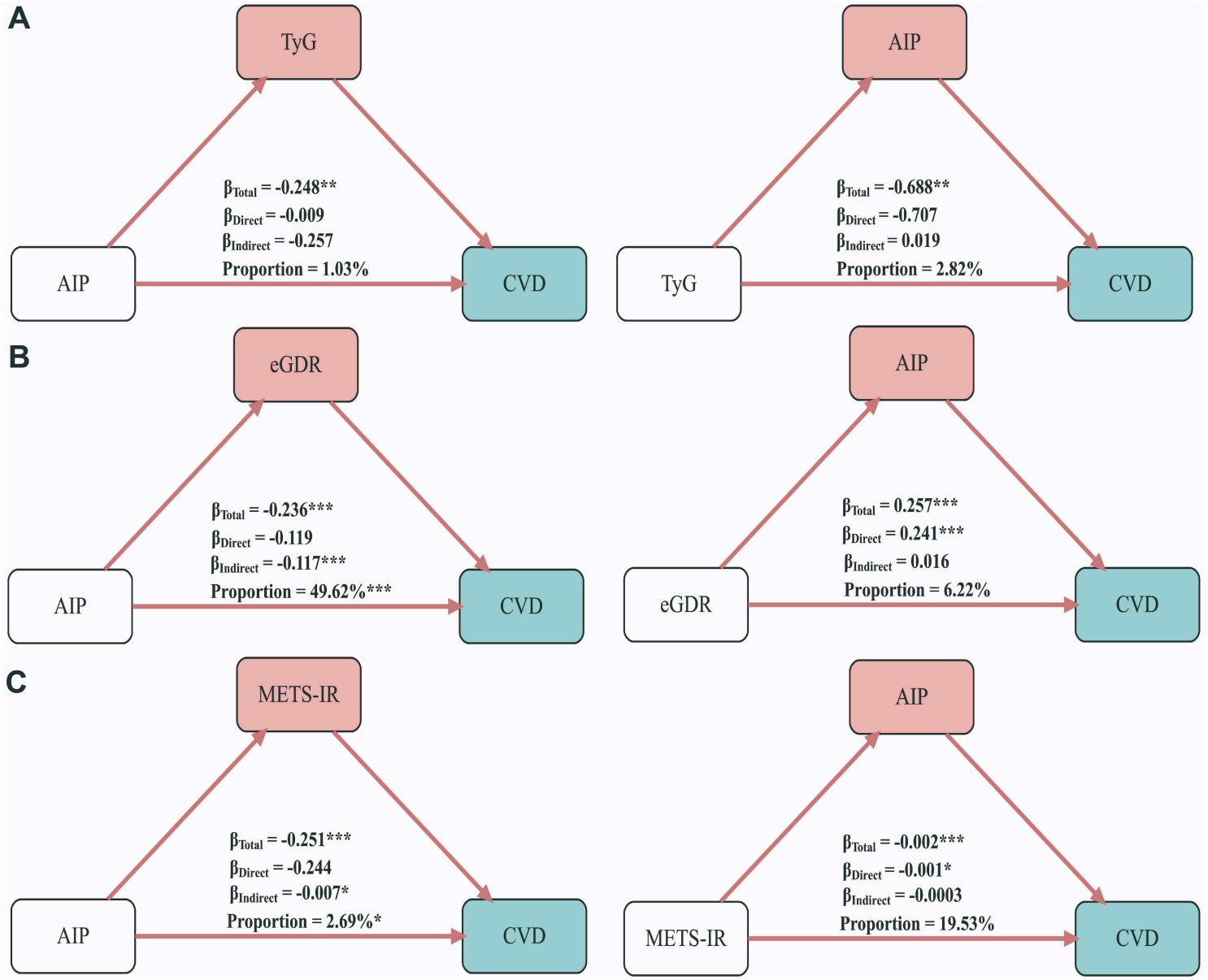


Figure 5

Mediation analyses of the bidirectional relationships between AIP and IR surrogate indices in relation to cardiovascular disease. Adjusted for age, sex, smoking, drinking, education level, marital status, Scr, hs-CRP, UA, BUN. *P < 0.05; **P < 0.01; ***P < 0.001

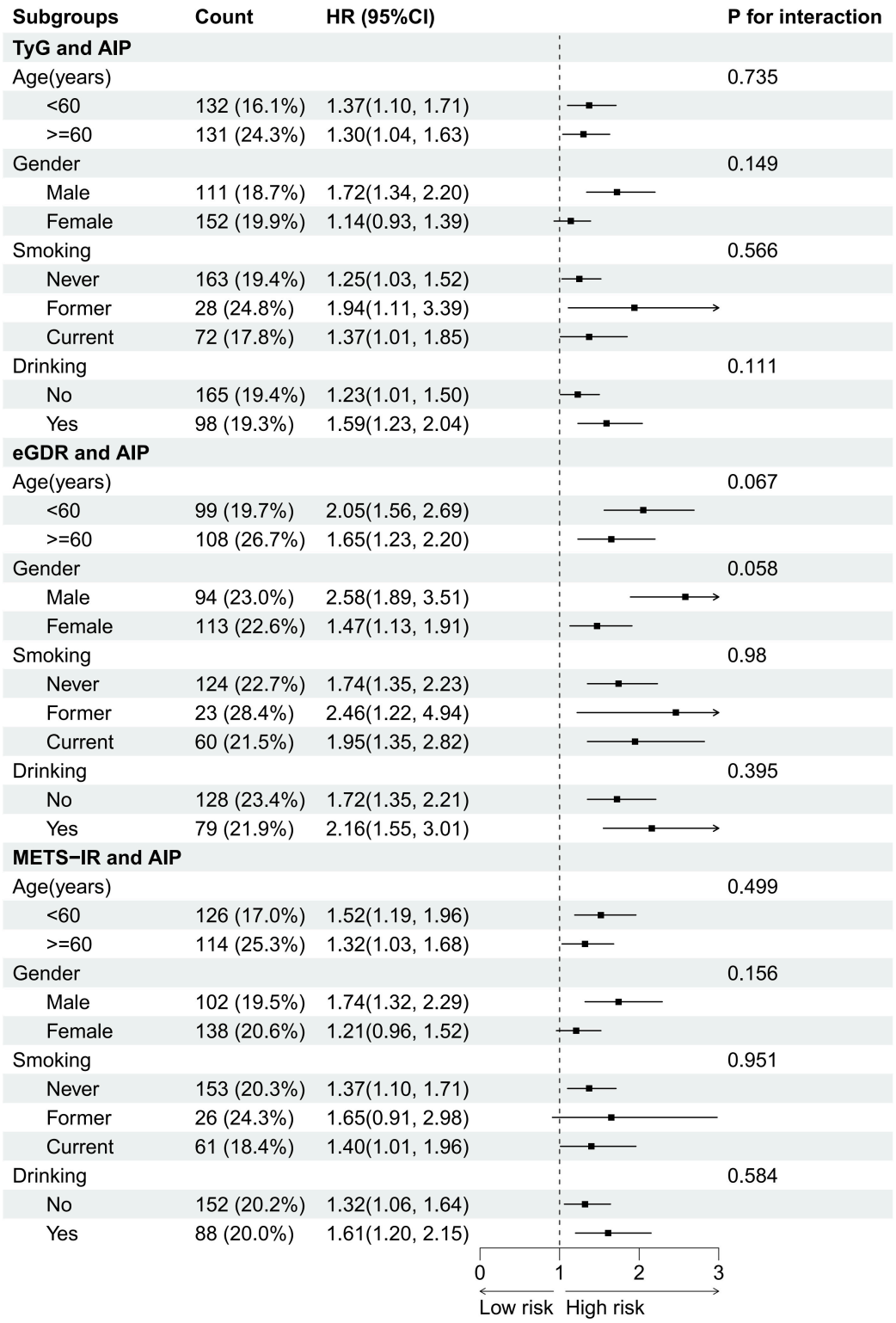


Figure 6

Subgroup analyses of the associations between the combined categories of AIP and IR surrogate indices and cardiovascular disease. Multivariate models were adjusted for age, sex, smoking, drinking, education level, marital status, Scr, hs-CRP, UA, BUN, with the exception of the stratification variable

Supplementary Files

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