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RECEIVED 10 February 2025

ACCEPTED 28 May 2025

PUBLISHED 18 June 2025

## CITATION

Zhang Z, Wang J, Kong L, Li C, Bao W, Tu H  
and Li J (2025) Sex-specific differences in the  
relationship between the atherogenic index  
and hypertension in middle-aged and  
elderly Chinese.  
*Front. Endocrinol.* 16:1574125.  
doi: 10.3389/fendo.2025.1574125

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# Sex-specific differences in the relationship between the atherogenic index and hypertension in middle-aged and elderly Chinese

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**Background:** Despite the already comprehensive epidemiological evidence concerning pre-hypertension, high-normal blood pressure, and hypertension, the influence of gender differences within this context remains inadequately explored. The present study endeavors to meticulously examine the specific impact of the plasma atherogenic index (AIP) on pre-hypertension and hypertension, and ascertain whether there exist significant sex-specific differences in this regard.

**Methods:** This population-based study employed a multi-wave cohort design encompassing 8255 middle-aged and elderly participants (cross-sectional phase) and longitudinal follow-ups in 2015 (n=8092) and 2018 (n=7022). Participants were stratified into normotensive (n=3175 in cross-sectional, n=2415 in 2015 longitudinal cohort study, 1868 in 2018 longitudinal cohort study) and prehypertensive/hypertensive groups (n=5080 (61.5%) in cross-sectional study, n=5677(70.2%) in longitudinal study of 2015, n=5336(76.0%) in 2018). The plasma atherogenic index=log10(triglycerides/high-density lipoprotein)[triglycerides (mg/dL)/HDL-C (mg/dL)] was quantified enzymatically. Multivariable-adjusted logistic regression models with restricted cubic splines were implemented to evaluate nonlinear associations between AIP and blood pressure status, adjusting for age, sex, BMI, smoking, and lipid-lowering therapy. Sensitivity analyses included multiple imputation for missing covariates and sex-stratified effect modification testing.

**Results:** This epidemiological investigation revealed population prevalences of 34.3% for pre-hypertension and 27.2% for hypertension. Both cross-sectional and longitudinal analyses demonstrated a significant positive association between AIP index and blood pressure dysregulation. Adjusted logistic regression models showed that elevated AIP corresponded to increased risks of pre-hypertension/hypertension, with cross-sectional analyses yielding an odds ratio (OR) of 1.69 (95% CI:1.38 to 2.07, P<0.001). Longitudinal cohorts of 2015 and 2018 exhibited persistent temporal trends: OR=1.38 (95% CI:1.13 to 1.67, P=0.012) in 2015 and OR=1.41 (95% CI:1.20 to 1.65, P<0.001) in 2018. Sex-stratified analyses revealed markedly stronger associations in females, where

each AIP unit increase conferred a 1.79-fold cross-sectional risk elevation (OR: 1.79, 95% CI: 1.35 to 2.38,  $P < 0.001$ ), rising to 1.49-fold (2015 cohort: OR: 1.49, 95% CI: 1.14 to 1.95,  $P = 0.003$ ) and 1.64-fold (2018 cohort: OR: 1.64, 95% CI: 1.31 to 2.06,  $P < 0.001$ ) in longitudinal assessments. Conversely, males exhibited attenuated associations (cross-sectional OR: 1.30; 95% CI: 1.12 to 1.79,  $P = 0.006$ ; 2015 longitudinal OR: 1.26, 95% CI: 1.12 to 1.66), with nonsignificant effects in the 2018 follow-up (OR: 0.87, 95% CI: 0.57 to 1.31). A significant gender-AIP interaction ( $P < 0.001$ ) underscored sex-specific metabolic susceptibility to atherogenic lipid profiles.

**Conclusion:** This study identified a significant positive association between elevated atherogenic index of plasma levels and blood pressure dysregulation. Both cross-sectional and longitudinal analyses consistently demonstrated a dose-response relationship, with higher AIP levels associated with increased risk. Stratified analyses by sex revealed that the association between elevated AIP and the incidence of pre-hypertension and hypertension was significantly stronger in women.

#### KEYWORDS

atherogenic index of plasma, sex-specific differences, female, hypertension, pre-hypertension

## 1 Introduction

Hypertension, or elevated blood pressure (HBP), stands as a prevalent and significant cardiovascular concern. Alongside diabetes and abnormal blood lipid levels, it ranks among the top three chronic diseases in our country, with hypertension topping the list, affecting over 270 million individuals (1). According to data from the Noncommunicable Disease Risk Factor Collaboration (NCDRiskC), the global population of individuals with hypertension surpassed one billion in 2019, marking a doubling since 1990 (2, 3). This chronic non-communicable disease profoundly and persistently impacts the daily lives of the populace (4).

The initial stage of hypertension, known as high-normal blood pressure, refers to blood pressure levels that exceed the normal range but fall below the diagnostic threshold for hypertension. This phase is intricately tied to the development of hypertension and the risk of associated complications, underscoring the importance of recognizing and addressing this preliminary stage (5). Notably, numerous epidemiological studies have highlighted that an increase in blood pressure to a pre-hypertensive state can adversely affect multiple vital organs and tissues, including the heart, cerebrovascular system, kidneys, and retina. This elevation is associated with the exacerbation of conditions such as coronary atherosclerotic heart disease, myocardial infarction, kidney damage, stroke, and advanced cognitive decline (6). Compared to individuals with blood pressure within the normal range, those in the pre-hypertension stage exhibit a notably elevated risk of developing

hypertension and cardiovascular disease (CVD) in subsequent years (7). Therefore, accurately identifying individuals in the early stages of hypertension and initiating timely drug treatment and lifestyle interventions are crucial for mitigating the risk of hypertension-related clinical complications and CVD, as well as reducing the likelihood of cardiovascular-related mortality.

The atherogenic index of plasma (AIP) is a well-established biomarker for assessing plasma atherosclerosis (8). Numerous existing studies have consistently demonstrated a close association between AIP and a range of diseases, including cardiovascular disease (CVD), insulin resistance, and diabetes (9, 10). Notably, research conducted by Qin Minghui et al. (11) revealed a significant positive correlation between AIP and both cardiovascular disease mortality (CVM) and all-cause mortality (ACM), with this relationship being particularly evident in middle-aged and older adults. Zheng Yitian (12) and his colleagues observed that individuals with a higher atherogenic index of plasma (AIP) had a significantly elevated likelihood of experiencing major adverse cardiac events (MACE) compared to those with a lower AIP index. Furthermore, there exists a distinct 'J'-shaped relationship between AIP and the risk of MACE occurrence. Hypertension, being one of the more prevalent cardiovascular diseases, has seen relatively limited research examining its correlation with AIP, and even fewer studies have focused on the relationship between pre-hypertension and AIP. Early identification and detection within the pre-hypertensive population hold substantial clinical and societal value in preventing the progression of hypertension and more severe cardiovascular diseases.



Recent studies have demonstrated that abnormal AIP is closely linked to hormonal metabolism, with postmenopausal women exhibiting a higher susceptibility to elevated AIP levels (13, 14). The direct decline in estrogen and inactivation of estrogen receptor signaling pathways directly or indirectly suppress high-density lipoprotein cholesterol (HDL-C) synthesis and impair triglyceride (TG) hydrolysis. Furthermore, female monocyte-macrophages display heightened sensitivity to pro-inflammatory responses in high-AIP environments compared to males. Additionally, genome-wide analyses reveal that DNA methylation modifications at AIP-associated loci (e.g., APOA5, LPL) in females are significantly correlated with systolic blood pressure, whereas no such association is observed in males. Some studies have even suggested that the AIP may serve as a robust independent predictor of coronary artery disease (CAD) risk in Han Chinese postmenopausal women, potentially outperforming conventional lipid parameters (15, 16). These findings suggest that the impact of elevated AIP on blood pressure regulation may be more pronounced in the female population.

Therefore, our study implemented a dual-phase analytical framework integrating cross-sectional and longitudinal methodologies, leveraging nationally representative data from the China Health and Retirement Longitudinal Study (CHARLS), to systematically evaluate the dose-response relationship between atherogenic index of plasma (AIP) trajectories and the progression from normotension to pre-hypertension/hypertension in Chinese adults aged  $\geq 45$  years. Crucially, we incorporated sex-stratified mediation analyses to elucidate the mechanistic divergence in AIP-associated cardiovascular pathophysiology between genders.

## 2 Methods

### 2.1 Research design and included subjects

All the subjects we study are sourced from the CHARLS database. CHARLS is a prospective longitudinal study project led by the National School of Development at Peking University, primarily focusing on the Chinese population aged 45 and above and their spouses. The research covers not only their health status but also delves into the social and economic backgrounds of the residents (17). This study used a multi-stage probability sampling technique to screen the research subjects to ensure that the selected samples are representative. The study began with baseline data collection in 2011, covering 28 provinces in mainland China, with 17,708 participants. The main contents of the survey include biannual questionnaire follow-ups, physical measurements, and the collection and analysis of hematological samples conducted once every two follow-up periods (17, 18).

In this cross-sectional study, we enrolled 17,708 participants in 2011. And then, we excluded 2,002 participants due to missing hypertension-related information, 4,535 with incomplete demographic data, 3,352 lacking hematological test results, and an additional 1,004 with incomplete datasets. After further excluding

9,453 individuals aged below 45 years, the final included population had an age range of 45 to 102 years. Subsequent comprehensive analysis focused on the remaining 8,255 participants: 3,175 normotensive individuals and 5,080 with pre-hypertension or hypertension. Building on these findings, we conducted a longitudinal study after excluding 902 participants lacking 2015 hypertension follow-up data. The final cohort comprised 7,353 subjects, including 2,875 normotensive individuals and 4,478 with pre-hypertension or hypertension, compared with baseline, the overall response rate was 87.15%. In the course of the longitudinal cohort study in 2018, a total of 7,022 subjects were enrolled, including 1,686 subjects with normal blood pressure and 7,022 subjects with pre-hypertension or hypertension, and the overall response rate was 86.46% (Figure 1).

### 2.2 Definition of exposure factors and outcome variables

The exposure factor in the study is AIP, defined as  $AIP = \log_{10} [TG (mg/dL)/HDL-C (mg/dL)]$  (10, 19), the recommended normal reference range for the AIP index is -0.3 to 0.1, a value between 0.1 and 0.24 is considered moderate risk, and a value greater than 0.24 is classified as high risk. The determination of pre-hypertension, which refers to elevated normal blood pressure, is based on the diagnostic criteria outlined in the “Chinese Guidelines for the Prevention and Treatment of Hypertension (2018 Revised Edition)” (20). The pre-hypertension blood pressure range is defined as a systolic pressure greater than 120 mmHg and less than or equal to 139 mmHg and/or a diastolic pressure greater than 80 mmHg and less than or equal to 89 mmHg; the definition of hypertension is a systolic blood pressure  $>140$  mmHg and/or diastolic blood pressure  $>90$  mmHg or currently taking anti-hypertensive medication (20, 21).

The blood pressure data was measured by the interviewer using a specialized automatic blood pressure monitor (Omron<sup>TM</sup> HEM-7200, manufactured by Omron (Dalian) Co., Ltd.) or a calibrated mercury sphygmomanometer from CHNS, with a total of three measurements taken at 45-second intervals. The final blood pressure value included in the study is the average of the three measurements (22).

### 2.3 Covariates

This study considered multiple covariates, including categorical variables (such as sex, smoking status, alcohol consumption, diabetes status, dyslipidemia status, and education level) and continuous variables, such as age, blood pressure, body mass index (BMI), triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), blood glucose (BG), and hemoglobin A1c (HbA1c), and the use of antihypertensive drugs and antilipemic drugs. All information provided by the respondents was measured and recorded by professionally trained interviewers using a standardized

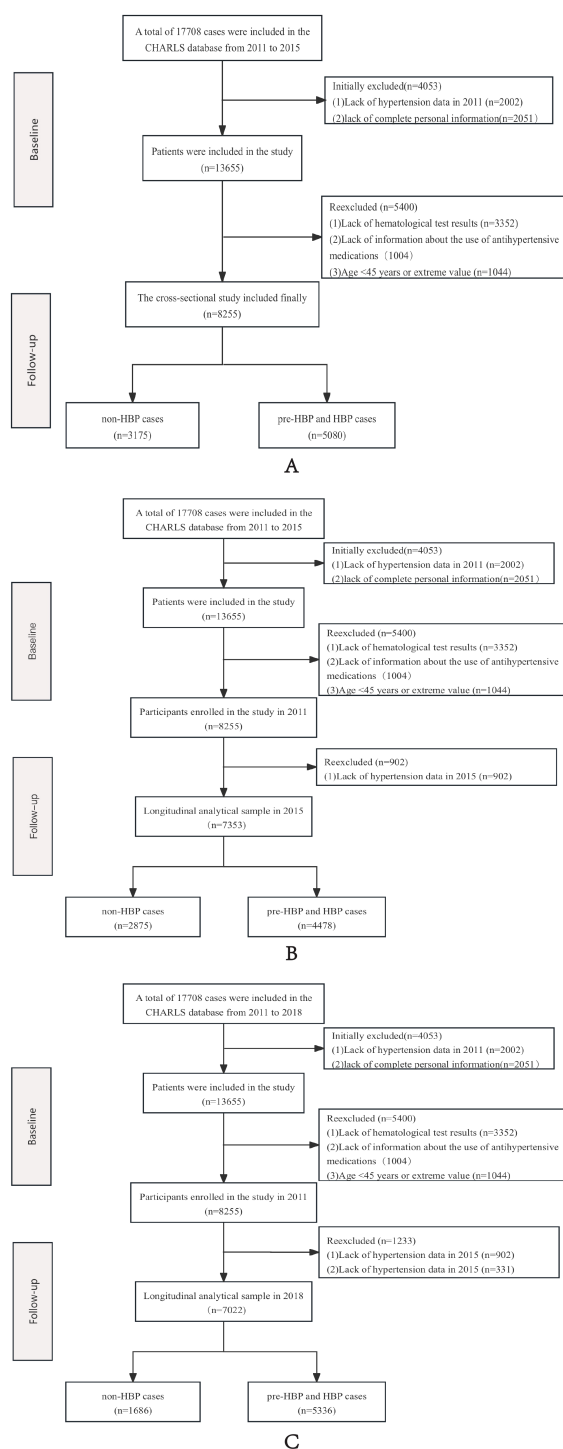


FIGURE 1

The flowchart of study participants. (A) Flow chart of the cross-sectional study, (B) Flow chart of the longitudinal study in 2015, (C) Flow chart of the longitudinal study in 2018.

questionnaire. The hematological indicators were collected by staff from the Chinese Center for Disease Control and Prevention (China CDC) after the subjects had fasted for more than 8 hours, and measurements were taken according to the prescribed

procedures (18, 22, 23). They use enzymatic colorimetry to measure blood glucose and lipids, while HbA1c is measured through boronate affinity high-performance liquid chromatography (24).

## 2.4 Statistical analysis

Statistical analysis of the data was conducted using version 27.0 of SPSS software (IBM SPSS, Armonk, NY, USA), and GraphPad Prism version 9.5.1 was used for plotting (GraphPad Prism 9.5.1 Macintosh Version by Software MacKiev © 1994-2023 GraphPad Software, LLC). All statistical tests are two-tailed, with a *P*-value less than 0.05 considered statistically significant. Continuous variables are expressed as median and mean ± standard deviation, while categorical variables are presented as frequency and percentage. Differences between groups are compared using the Kruskal-Wallis H test, one-way analysis of variance, and the chi-square test.

This study employed multivariate logistic regression models to analyze the association between AIP exposure and the development of pre-hypertension and hypertension, with risk quantified using adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Model 1 utilized unadjusted data, while Model 2 was adjusted for

covariates including sex, age, educational level, diabetes status, smoking and alcohol consumption habits, and BMI. Building on Model 2, Model 3 further incorporated adjustments for additional factors such as LDL-C, TC, BG, HbA1c, and the use of antihypertensive and lipid-lowering medications. A generalized additive model with restricted cubic splines (RCS) was constructed to evaluate the dose-response relationship between atherogenic index of plasma (AIP) exposure and the development of pre-hypertension and hypertension. Additionally, stratified analyses were performed to assess the modifying effects of sex and menopausal status on this association.

## 3 Results

The baseline study included 8255 participants, comprising 3740 males (45.31%) and 4515 females (54.69%), with a mean age of

TABLE 1 Demographic and clinical characteristics of the study population.

Variable	AIP Quartiles					P value
	Total	Q1 ( $< 0.11$ )	Q2 (0.11 to 0.22)	Q3 (0.22 to 0.31)	Q4 ( $\geq 0.31$ )	
Participants(n)	8255	2063	2065	2063	2064	
Sex						
Female(n, %)	4633(53.1%)	1028(49.8%)	1142(55.3%)	1161(56.3%)	1184(57.4%)	<0.001
Male(n, %)	3850(46.9%)	1035(50.2%)	923(44.7%)	902(43.7%)	880(42.6%)	
Age(year)	60.17±8.75	63.02±9.56	62.41±9.67	61.39±9.17	59.78±8.79	<0.001
BMI(kg/m <sup>2</sup> )	24.35±6.94	22.81±8.74	23.77±8.6	25.37±6.88	25.48±6.91	<0.001
<18.5	538(6.5%)	238(11.5%)	164(7.9%)	88(4.3%)	48(2.3%)	<0.001
18.5-23.9	3121(37.8%)	1032(50%)	852(41.3%)	723(35%)	514(24.9%)	
24-24.9	1715(20.8%)	380(18.4%)	438(21.1%)	429(20.8%)	468(22.7%)	
≥25	2766(33.5%)	388(18.8%)	584(28.3%)	791(38.3%)	1003(48.6%)	
SBP(mmHg)	128.2±20.43	121.57±19.40	127.43±17.89	130.80±18.78	133.04±18.02	<0.001
DBP(mmHg)	88.19±9.07	86.32±7.93	87.98±7.43	89.04±8.71	89.95±9.11	<0.001
HBP state						
none-hypertension	3175(38.5%)	901(43.7%)	859(41.6%)	764(37%)	651(31.5%)	<0.001
pre-hypertension	2829(34.3%)	670(32.5%)	697(33.8%)	705(34.2%)	757(36.7%)	
hypertension	2251(27.2%)	492(23.8%)	509(24.6%)	594(28.8%)	656(31.8%)	
HBP Classification						
Grade 1	1641(72.9%)	374(76%)	382(75%)	426(71.7%)	459(70%)	<0.001
Grade 2	394(17.5%)	83(16.9%)	82(16.1%)	106(17.8%)	123(18.8%)	
Grade 3	216(9.6%)	35(7.1%)	45(8.9%)	62(10.5%)	74(11.2%)	
TC(mg/dL)	184.39±35.66	181.15±34.07	185.37±34.43	189.47±35.30	196.88±41.57	<0.001
TG(mg/dL)	138.49±19.97	74.15±17042	108.83±20.59	156.98±31.14	296.61±22.71	<0.001

(Continued)

TABLE 1 Continued

Variable	AIP Quartiles					P value
	Total	Q1 ( $< 0.11$ )	Q2 (0.11 to 0.22)	Q3 (0.22 to 0.31)	Q4 ( $\geq 0.31$ )	
HBP Classification						
HDL-C(mg/dL)	51.73±11.76	61.41±12.14	52.05±8.05	47.56±8.14	42.55±7.58	<0.001
LDL-C(mg/dL)	103.14±28.54	101.20±28.21	109.72±28.43	109.57±28.43	112.37±29.17	<0.001
Blood glucose(mg/dL)	103.29±34.79	96.03±25.97	99.87±24.44	104.19±27.97	117.35±28.13	<0.001
HbA1c(%)	5.99±0.98	5.79±0.67	5.94±0.83	6.01±0.97	6.27±1.32	<0.001
Current smoking(n, %)	1895(22.96%)	516(25.0%)	454(22.0%)	486(23.7%)	439(%)	0.002
Cigarettes intake per day						
<5	151(7.97%)	41(7.95%)	37(8.15%)	34(7.0%)	39(8.9%)	0.812
5 to 20	968(51.08%)	272(52.71%)	223(49.12%)	277(57.0%)	196(44.6%)	
≥20	776(40.95%)	203(39.34%)	194(42.73%)	175(36.0%)	204(46.5%)	
Current drinking(n, %)	2356(28.54%)	657(35.25%)	654(34.86%)	524(27.87%)	521(25.24%)	<0.001
Alcohol intake per day						
<2	1867(82.4%)	500(76.1%)	485(74.16%)	437(83.4%)	445(85.4%)	<0.001
≥2	399(17.6%)	157(23.9%)	79(25.84%)	87(16.6%)	76(14.59%)	
Diabetes						
Yes	1034(12.5%)	134(6.5%)	208(10.1%)	294(14.3%)	398(19.3%)	<0.001
No	6471(78.4%)	1732(84.0%)	1671(80.9%)	1589(77.0%)	1479(71.7%)	
Dyslipidemia						
Yes	1768(21.4%)	262(12.7%)	340(16.5%)	511(24.8%)	655(31.7%)	<0.001
No	5736(69.5%)	1604(77.8%)	1539(74.5%)	1371(66.5%)	1222(59.2%)	
Take medicine for HBP						
Yes	2360 (28.6%)	434 (21.0%)	486 (23.5%)	675 (32.7%)	765 (37.1%)	<0.001
No	4992 (60.5%)	1394 (67.6%)	1350 (65.4%)	1171 (56.8%)	1077 (52.2%)	
Take medicine for hyperlipidemia						
Yes	947 (11.5%)	122 (5.9%)	199 (9.6%)	263 (12.8%)	363 (17.6%)	<0.001
No	6557 (79.4%)	1744 (84.5%)	1680 (81.4%)	1619 (78.5%)	1514 (73.4%)	

60.17 ± 8.75 years. Among them, 2829 cases (34.3%) were classified as prehypertensive and 2251 cases (27.2%) as hypertensive. Demographic and clinical characteristics of the study population were compared through stratified analysis based on baseline AIP quartiles (Table 1). Notably, all variables, except for daily cigarette consumption, exhibited statistical significance across the four AIP categories. Participants with higher AIP levels generally demonstrated higher BMI values, elevated blood pressure (both systolic and diastolic), and increased BG levels compared to those with lower AIP levels.

Regardless of covariate adjustments, AIP is significantly positively associated with the incidence of pre-hypertension and hypertension among study participants. We divided AIP into 4 groups according to

quartiles, using Q1 as the baseline group to evaluate the association between AIP and pre-hypertension and hypertensive disorders. Covariates such as sex, age, education level, history of smoking and drinking, diabetes, BMI, TC, LDL-C, HbA1c, and use of anti-hypertensive and lipid-lowering drugs were adjusted.

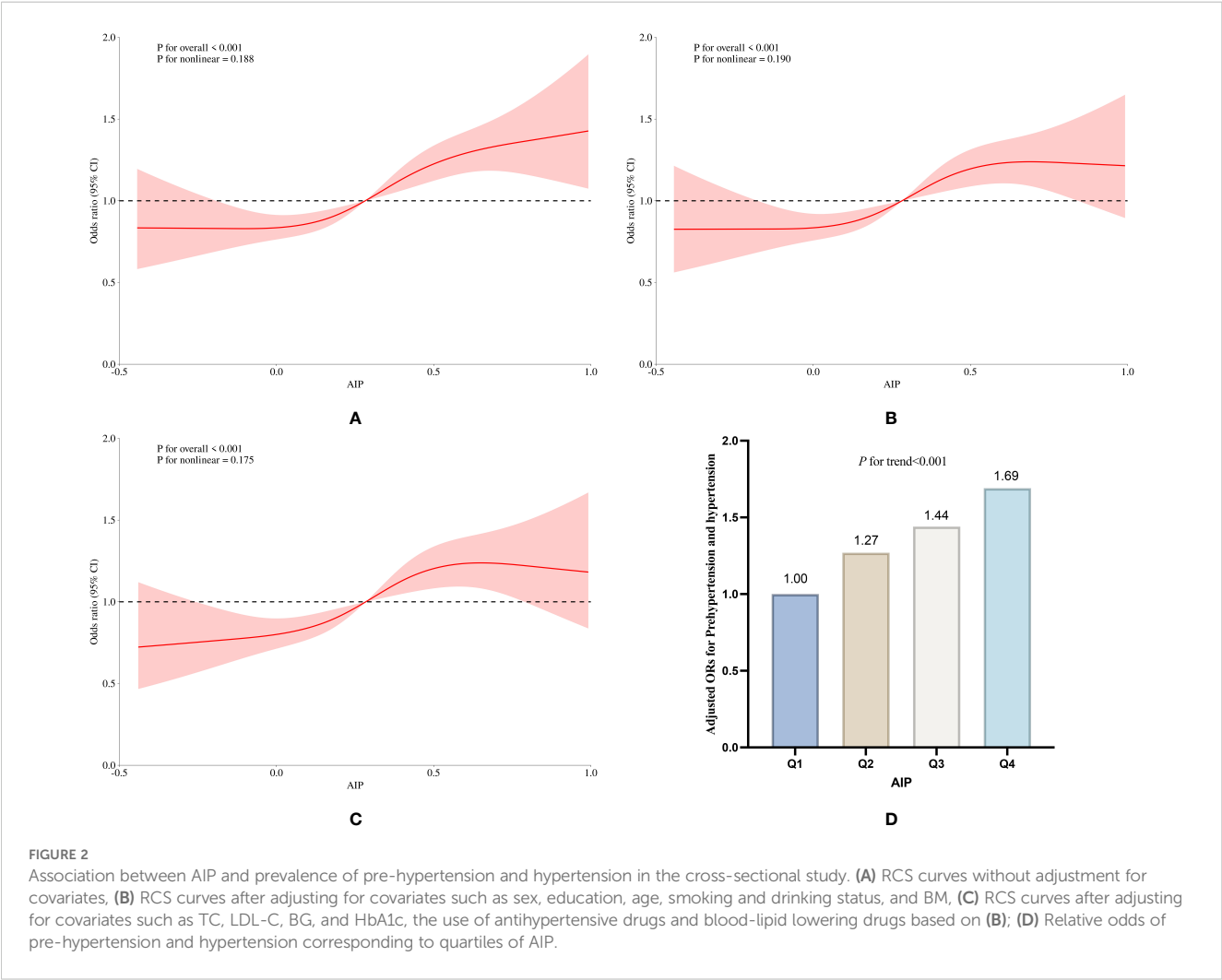
In the cross-sectional study, compared with the reference group of Q1, the ORs for the development of pre-hypertension and hypertension in the other groups were Q2 (OR: 1.27, 95%CI: 1.06 to 1.51,  $P=0.008$ ), Q3 (OR: 1.44, 95%CI: 1.20 to 1.74,  $P<0.001$ ), and Q4 (OR: 1.69, 95%CI: 1.38 to 2.07,  $P<0.001$ ),  $P$  for trend was less than 0.001 (Table 2, Figure 2).

In the longitudinal study of 2015, we found that compared with Q1, the odds ratios for pre-hypertension and hypertension in the

**TABLE 2** The relative risks of pre-hypertension and hypertension in all subjects were calculated according to different AIP models in the cross-sectional study of 2011.

AIP	Pre-hypertension and hypertension OR (95%CI)					
	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Per-SD increase	1.81(1.62,2.07)	<0.001	1.74(1.55,1.91)	<0.001	1.51(1.34,1.77)	<0.001
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.18 (1.02,1.37)	0.026	1.23 (1.05,1.43)	0.01	1.27 (1.06,1.51)	0.008
Q3(0.22 to 0.31)	1.38 (1.19,1.60)	<0.001	1.42 (1.21,1.66)	<0.001	1.44 (1.20,1.74)	<0.001
Q4(≥ 0.31)	1.59 (1.36,1.85)	<0.001	1.64 (1.39,1.94)	<0.001	1.69 (1.38,2.07)	<0.001
P for trend		<0.001		<0.001		<0.001

OR, Odds Ratio; CI, Confidence Interval.  
Model 1: was adjusted for none.  
Model 2: was adjusted for age, sex, education, diabetes, current smoking, alcohol intake and BMI.  
Model 3: was adjusted for age, sex, education, diabetes, current smoking, alcohol intake, BMI, LDL\_C, TC, blood glucose, HbA1c, the use of antihypertensive drugs and blood-lipid lowering drugs.





other groups were Q2 (OR:1.10, 95%CI: 0.93 to 1.30,  $P=0.257$ ), Q3 (OR:1.20, 95%CI: 1.01 to 1.43,  $P=0.045$ ) and Q4 (OR:1.38, 95%CI: 1.13 to 1.67,  $P=0.001$ ). This trend is also completely consistent with the results of the RCS curve (Supplementary Figure S1, Supplementary Table S1). In the 2018 longitudinal cohort, a dose-dependent elevation in pre-hypertension and hypertension risk was observed with increasing index of AIP levels. Compared to baseline, Q2 exhibited a 1.08-fold risk increase (95% CI: 0.93 to 1.26,  $P=0.296$ ), Q3 a 1.25-fold increase (95% CI: 1.07 to 1.46,  $P=0.005$ ), and Q4 demonstrated the most pronounced risk escalation (OR:1.41, 95% CI: 1.20 to 1.65,  $P<0.001$ ). In summary, our findings demonstrate a dose-dependent increase in the incidence of pre-hypertension and hypertension with rising AIP levels, revealing a statistically significant correlation between these parameters ( $P$  for trend  $<0.001$ ) (Figure 3, Table 3).

Both cross-sectional and longitudinal studies have demonstrated that exposure to high levels of AIP increases the incidence of pre-hypertension and hypertension. In the cross-sectional study, individuals in the highest AIP exposure group exhibited a 72% increase in the incidence of pre-hypertension

(OR: 1.72, 95% CI: 1.37 to 2.17,  $P<0.001$ ) compared to those in the lowest exposure group. Additionally, the risk of developing hypertension increased by 95% (OR: 1.95, 95% CI: 1.44 to 2.64,  $P<0.001$ ) in the highest exposure group. In the cross-sectional study, after adjusting for the covariates including sex, age, education level, smoking history, drinking history, diabetes, BMI, TC, LDL-C, HbA1c, as well as antihypertensive and lipid-lowering medications, we observed that the risk of developing hypertension in the Q2, Q3, and Q4 groups was significantly increased compared to the Q1 group. Specifically, the ORs and 95% CIs for the Q2, Q3, and Q4 groups were 1.04 (95% CI: 0.85 to 1.29), 1.28 (95% CI: 1.03 to 1.58), and 1.62 (95% CI: 1.30 to 2.03), respectively. Notably, except for the Q2 group, statistically significant differences were found between AIP exposure and the incidence of hypertension in both the Q3 and Q4 groups (Table 4, Figure 4).

In longitudinal cohort studies, individuals with the highest exposure to the AIP index exhibited a 51% increased risk of developing pre-hypertension in 2015 (OR:1.51, 95% CI: 1.24 to 1.83,  $P<0.001$ ) and a 62% elevated risk of hypertension (OR:1.62, 95% CI: 1.30 to 2.03,  $P<0.001$ ) (Supplementary Table S2,

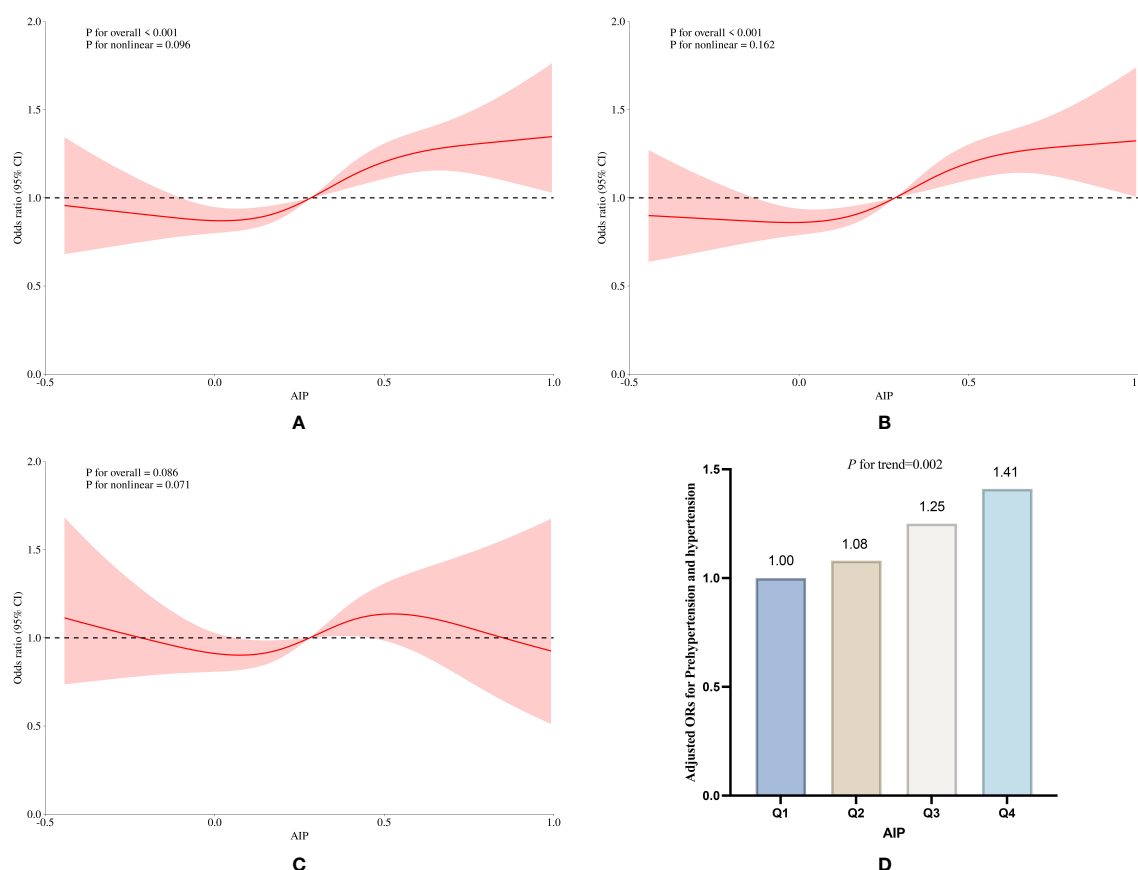


FIGURE 3

Association between AIP and prevalence of pre-hypertension and hypertension in the longitudinal studies of 2018. (A) RCS curves without adjustment for covariates, (B) RCS curves after adjusting for covariates such as age, sex, education, age, smoking and drinking status, and BMI and income, (C) RCS curves after adjusting for covariates such as LDL-C, TC, BG, and HbA1c, the use of antihypertensive drugs and blood-lipid lowering drugs based on (B); (D) Relative odds of pre-hypertension and hypertension corresponding to quartiles of AIP.

TABLE 3 The relative risks of pre-hypertension and hypertension in all subjects were calculated according to different AIP models in 2018.

AIP	Pre-hypertension and hypertension OR (95%CI)					
	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Per-SD increase	1.61(1.30,1.77)	<0.001	1.50(1.38,1.71)	0.019	1.31(1.18,1.47)	0.034
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.05 (0.92,1.20)	0.41	1.10 (0.96,1.27)	0.182	1.08 (0.93,1.26)	0.296
Q3(0.22 to 0.31)	1.21 (1.05,1.39)	0.018	1.27 (1.10,.47)	0.001	1.25 (1.07,1.46)	0.005
Q4(≥0.31)	1.47 (1.28,1.70)	<0.001	1.61 (1.38,1.87)	<0.001	1.41 (1.20,1.65)	<0.001
P for trend		0.013		0.004		0.002

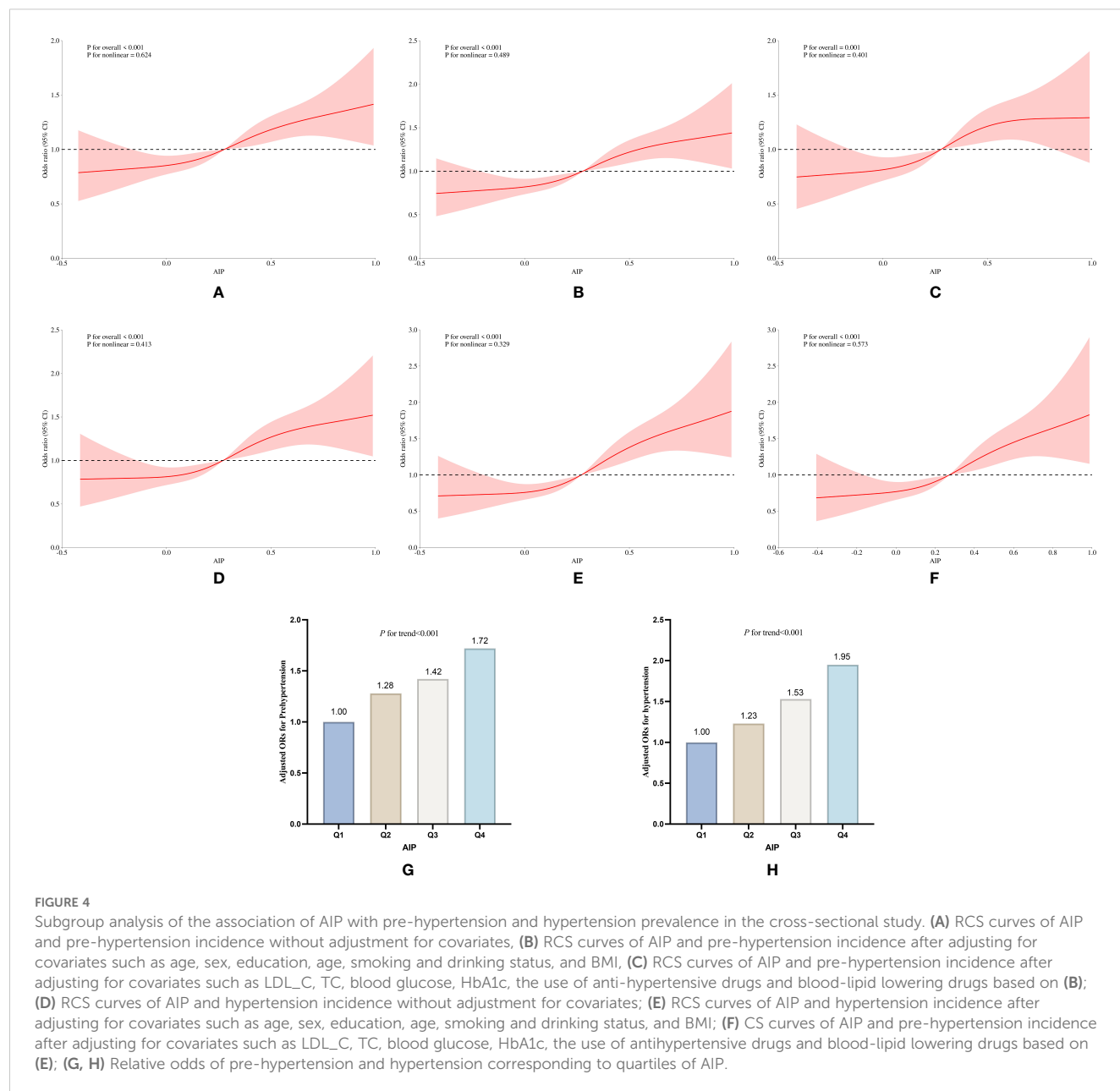
OR, Odds Ratio; CI, Confidence Interval.  
Model 1: was adjusted for none.  
Model 2: was adjusted for education, diabetes, current smoking, alcohol intake and BMI.  
Model 3: was adjusted for education, diabetes, current smoking, alcohol intake, BMI, LDL\_C, TC, blood glucose, HbA1c, the use of antihypertensive drugs and blood-lipid lowering drugs.

TABLE 4 Multivariate logistic regression analysis of the relationship between AIP and pre-hypertension as well as hypertension in cross-sectional study.

AIP	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Pre-hypertension						
Per-SD increase	1.54(1.37,1.77)	<0.001	1.68(1.45,1.92)	<0.001	1.71 (1.55,2.07)	<0.001
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.18 (1.01,1.39)	0.048	1.23 (1.04,1.47)	0.018	1.28 (1.05,1.56)	0.014
Q3(0.22 to 0.31)	1.31 (1.10,1.54)	0.002	1.38 (1.15, 1.65)	<0.001	1.42 (1.15,1.76)	0.001
Q4(≥ 0.31)	1.53 (1.29,1.81)	<0.001	1.66 (1.38,2.00)	<0.001	1.72 (1.37,2.17)	<0.001
P for trend		<0.001		<0.001		<0.001
Hypertension						
Per-SD increase	1.65(1.33,2.18)	<0.001	1.68(1.54,2.22)	0.001	1.81 (1.66,2.21)	0.037
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.18 (0.96,1.46)	0.125	1.25 (0.99,1.59)	0.066	1.23 (0.94,1.61)	0.127
Q3(0.22 to 0.31)	1.47 (1.19,1.81)	<0.001	1.65 (1.30,2.09)	<0.001	1.53 (1.15,2.03)	0.004
Q4(≥ 0.31)	1.67 (1.34,2.07)	<0.001	2.08 (1.63,2.66)	<0.001	1.95 (1.44, 2.64)	<0.001
P for trend		<0.001		<0.001		<0.001
P value for interaction		<0.001		<0.001		<0.001

OR, Odds Ratio; CI, Confidence Interval.  
Model 1: was adjusted for none.  
Model 2: was adjusted for age, education, diabetes, current smoking, alcohol intake and BMI.  
Model 3: was adjusted for age, education, diabetes, current smoking, alcohol intake, BMI, LDL\_C, TC, blood glucose, HbA1c, the use of antihypertensive drugs and blood-lipid lowering drugs.

Supplementary Figure S2). In the 2018 longitudinal cohort, these risks were 48% (OR: 1.48, 95% CI: 1.23 to 1.77,  $P<0.001$ ) for pre-hypertension and 59% (OR:1.59, 95% CI: 1.30 to 1.99,  $P<0.001$ ) for hypertension (Table 5, Figure 5). As demonstrated across both the 2011 cross-sectional study and longitudinal cohort studies in 2015 and 2018, elevated atherogenic index of plasma levels were consistently associated with a progressive rise in the risks of hypertension and pre-hypertension ( $P$  for trend  $<0.05$ ).



Our study revealed significant sex-specific differences in the relationship between AIP exposure and the development of pre-hypertension and hypertension. To investigate this, we validated the two independent components used to calculate AIP, HDL-C and TG, and found that only AIP itself exhibited sex-specific variations. Detailed subgroup analyses demonstrated that as AIP levels increased across different models, the risk of these conditions became markedly more pronounced in women, with an OR of 1.79 (95% CI:1.35 to 2.38,  $P=0.001$ ). In the fully adjusted Model 3, elevated AIP levels in men showed no statistically significant association with pre-hypertension or hypertension risk ( $P=0.051$ ) (Table 6). The findings from the logistic multivariate regression analysis align well with those derived from the RCS curve, suggesting that AIP has a more notable impact on the risk of developing pre-hypertension and hypertension among females (Figure 6).

Stratified analyses conducted in 2015 and 2018 revealed a notable sex-specific pattern: females with elevated AIP exhibited a significantly higher risk of developing pre-hypertension and hypertension compared to their male counterparts. In the 2015 longitudinal cohort study, Model 3 revealed that females with the highest AIP exhibited a 49% increased risk of developing the aforementioned conditions compared to baseline levels (OR:1.49, 95% CI:1.14 to 1.95,  $P=0.003$ ), while males showed only a 26% increase (OR:1.26, 95% CI:1.12 to 1.66,  $P=0.047$ ) (Supplementary Table S3, Supplementary Figure S3). By 2018, this risk escalated to 64% in females (OR:1.64, 95% CI:1.31 to 2.06,  $P<0.001$ ), whereas males even demonstrated a 13% reduction in risk (OR:0.87, 95% CI:0.57 to 1.31,  $P>0.05$ ) (Table 7, Figure 7). Notably, the RCS curves and multivariable logistic regression analyses demonstrated findings essentially consistent with the aforementioned trends,

TABLE 5 Multivariate logistic regression analysis of the relationship between AIP and pre-hypertension as well as hypertension in 2018.

AIP	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Pre-hypertension						
Per-SD increase	1.41(1.22,1.87)	0.016	1.50(1.33,1.82)	0.007	1.61(1.37,1.90)	0.002
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.18 (1.03,1.45)	0.047	1.10 (1.01,1.30)	0.252	1.11 (0.94,1.32)	0.233
Q3 (0.22 to 0.30)	1.28 (1.121,1.59)	0.013	1.21 (1.12,1.40)	0.03	1.27 (1.16,1.52)	0.016
Q4 (≥0.31)	1.55 (1.29, 1.81)	<0.001	1.45 (1.22,1.71)	<0.001	1.48 (1.23,1.77)	<0.001
P for trend		0.035		0.019		<0.001
Hypertension						
Per-SD increase	1.43(1.24,1.66)	0.023	1.51(1.24,1.79)	0.018	1.61(1.41,2.01)	0.002
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.09 (1.03,1.29)	0.27	1.03 (0.85,1.25)	0.756	1.09 (0.88,1.36)	0.441
Q3(0.22 to 0.31)	1.44 (1.27,1.76)	0.015	1.25 (1.03,1.53)	0.025	1.39 (1.12,1.74)	0.003
Q4(≥0.31)	1.51 (1.35,1.88)	<0.001	1.55 (1.27,1.89)	<0.001	1.59 (1.27,1.99)	<0.001
P for trend		0.002		0.001		<0.001
P value for interaction		<0.001		<0.001		<0.001

OR, Odds Ratio; CI, Confidence Interval.  
Model1: was adjusted for none.  
Model2: was adjusted for age, education, diabetes, current smoking, alcohol intake and BMI.  
Model3: was adjusted for age, education, diabetes, current smoking, alcohol intake, BMI, LDL-C, TC, blood glucose, HbA1c, the use of antihypertensive drugs and blood-lipid lowering drugs.

further indicating that elevated AIP exerts a more pronounced impact on the risks of progressing to pre-hypertension and hypertension in female populations.

Considering the potential influence of menopausal status and hormone levels on AIP, we performed a stratified analysis by menopause status in the female population of the 2018 longitudinal cohort study. The results demonstrated that elevated AIP levels were associated with a higher risk of pre-hypertension and hypertension in postmenopausal women compared to premenopausal women. Among postmenopausal women, the highest AIP quartile (Q4) showed a 58% increased risk of developing pre-hypertension and hypertension relative to baseline (OR:1.58, 95% CI:1.20 to 2.07,  $P=0.001$ ), whereas the corresponding risk increase in premenopausal women was 38% (OR:1.38, 95% CI:1.07 to 1.72,  $P=0.008$ ) (Table 8, Figure 8).

Given the influence of lipid-related indicators, particularly triglycerides and HDL, on the atherogenic index of plasma, we analyzed lipid and glucose variables from 2011 as independent predictors and blood pressure values from 2015 as the outcome to construct receiver operating characteristic (ROC) curves. The area under the curve (AUC) was used to assess predictive accuracy (25). The ROC curve analysis revealed that AIP (AUC=0.6051, 95% CI:0.5912 to 0.6190,  $P<0.001$ ), BMI (AUC=0.5801, 95% CI: 0.5658

to 0.5944,  $P<0.001$ ), TG (AUC=0.5750, 95% CI:0.5596 to 0.5903,  $P<0.001$ ), HDL-C (AUC=0.5652, 95% CI: 0.5463 to 0.5841,  $P<0.001$ ), and blood glucose (AUC=0.5643, 95% CI:0.5487 to 0.5799,  $P<0.001$ ) all had significant impacts on the incidence of pre-hypertension and hypertension in the middle-aged and elderly population.

It is noteworthy that combined models including AIP\_BMI, AIP\_LDL-C, and AIP\_TC also demonstrated modest predictive value, with results as follows: AIP\_BMI (AUC=0.5498, 95% CI:0.5354 to 0.5643,  $P<0.001$ ), AIP\_LDL-C (AUC=0.5499, 95% CI:0.5342 to 0.5655,  $P<0.001$ ), and AIP\_TC (AUC=0.5487, 95% CI:0.5330 to 0.5644,  $P<0.001$ ). Importantly, the AIP, calculated using HDL-C and TG, exhibited significantly greater predictive value compared to other lipid-related indicators and combined models (Figure 9).

### 4 Discussion

This study aimed to investigate the association between AIP exposure and the risk of developing pre-hypertension and hypertension. Individuals with higher AIP exposure exhibited a significantly elevated risk of developing both pre-hypertension and

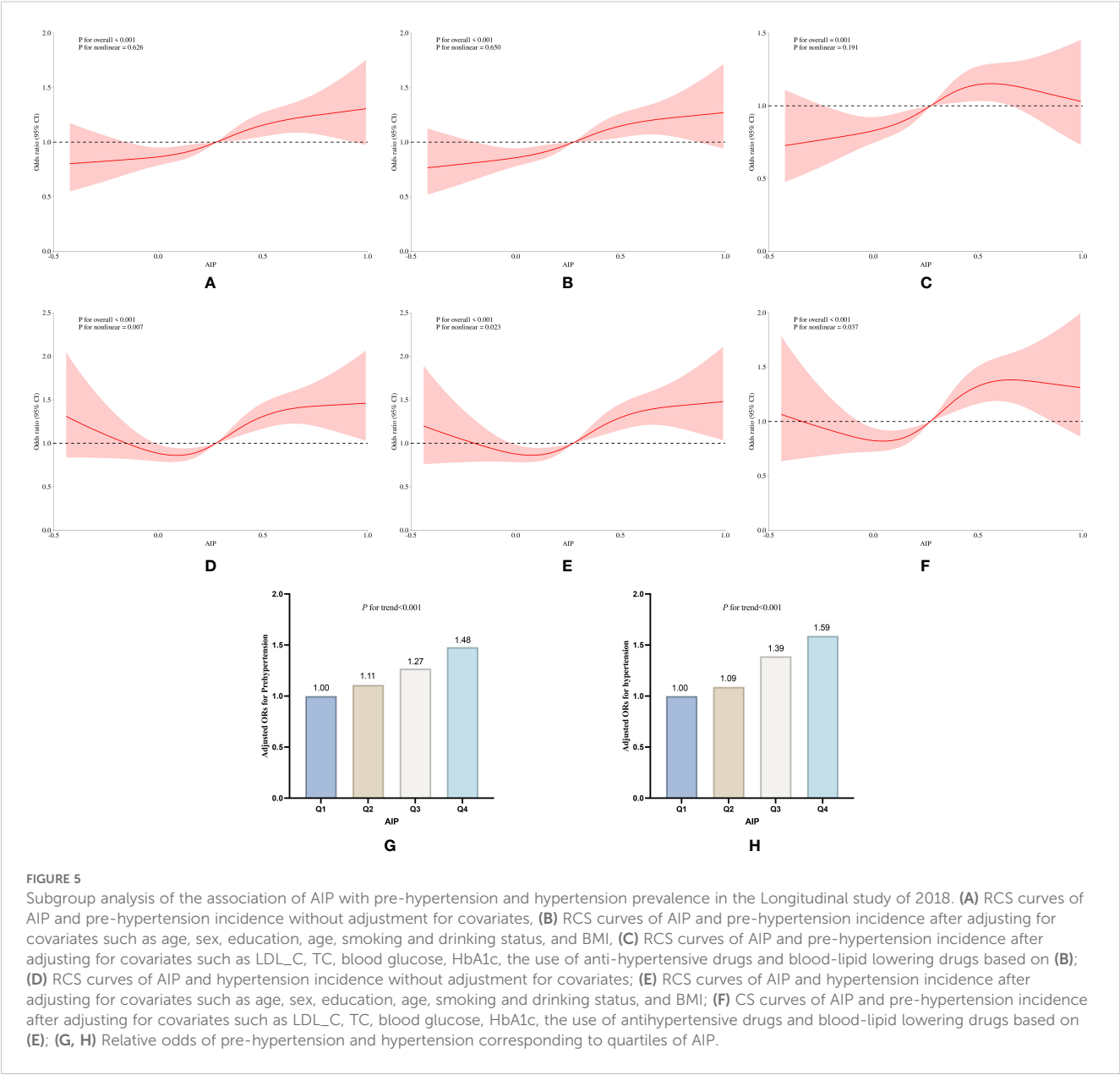


TABLE 6 Relative risk of pre-hypertension and hypertension in males and females under different AIP models in the cross-sectional study.

AIP	Pre-hypertension and hypertension OR (95%CI)					
	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Female						
Per-SD increase	2.09(1.63,2.51)	<0.001	1.89(1.71,2.14)	<0.001	1.69(1.33,2.07)	<0.001
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.18 (1.02,1.37)	0.026	1.24 (1.06,1.46)	0.006	1.23 (1.03,1.47)	0.024
Q3(0.22 to 0.31)	1.55 (1.26,1.90)	<0.001	1.51 (1.21,1.90)	<0.001	1.51 (1.16,1.96)	<0.001
Q4(≥ 0.31)	1.83 (1.49,2.25)	<0.001	1.85 (1.48,2.33)	<0.001	1.79 (1.35,2.38)	<0.001

(Continued)



TABLE 6 Continued

AIP	Pre-hypertension and hypertension OR (95%CI)					
	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Quartiles						
P for trend		<0.001		<0.001		<0.001
Male						
Per-SD increase	1.55(1.27,1.99)	<0.001	1.27(1.11,1.41)	0.003	1.11(1.01,1.40)	0.051
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.08 (1.02, 1.27)	0.202	1.14 (1.06,1.36)	0.371	1.03 (1.03,1.47)	0.254
Q3(0.22 to 0.31)	1.18 (1.09, 1.40)	<0.001	1.25 (1.13,1.71)	<0.001	1.22 (1.08,1.653)	0.055
Q4(≥ 0.31)	1.39 (1.16, 1.55)	<0.001	1.43 (1.16,1.85)	<0.001	1.30 (1.17,1.79)	0.006
P for trend		<0.001		<0.001		0.051
P value for interaction		<0.001		<0.001		0.001

OR, Odds Ratio; CI, Confidence Interval.  
Model1: was adjusted for none.  
Model2: was adjusted for age, education, diabetes, current smoking, alcohol intake and BMI.  
Model3: was adjusted for age, education, diabetes, current smoking, alcohol intake, BMI, LDL\_C, TC, blood glucose, HbA1c, the use of antihypertensive drugs, and blood-lipid lowering drugs.

hypertension compared to those with lower AIP levels, a trend particularly pronounced in postmenopausal women. Our findings further demonstrated that AIP serves as a more accurate predictor of pre-hypertension and hypertension risk in menopausal women than other lipid-related parameters (11, 26).

Moreover, pertinent evidence also suggests that the AIP index similarly influences the risk of cardiovascular disease occurrence and overall mortality, as reported in studies (27, 28). With the continuous improvement in living standards and the gradual acceleration of global aging, the population suffering from dyslipidemia is steadily growing. Among these individuals, atherosclerosis is becoming increasingly prevalent, and the AIP index, which is associated with atherosclerosis, has garnered significant attention in recent studies (28).

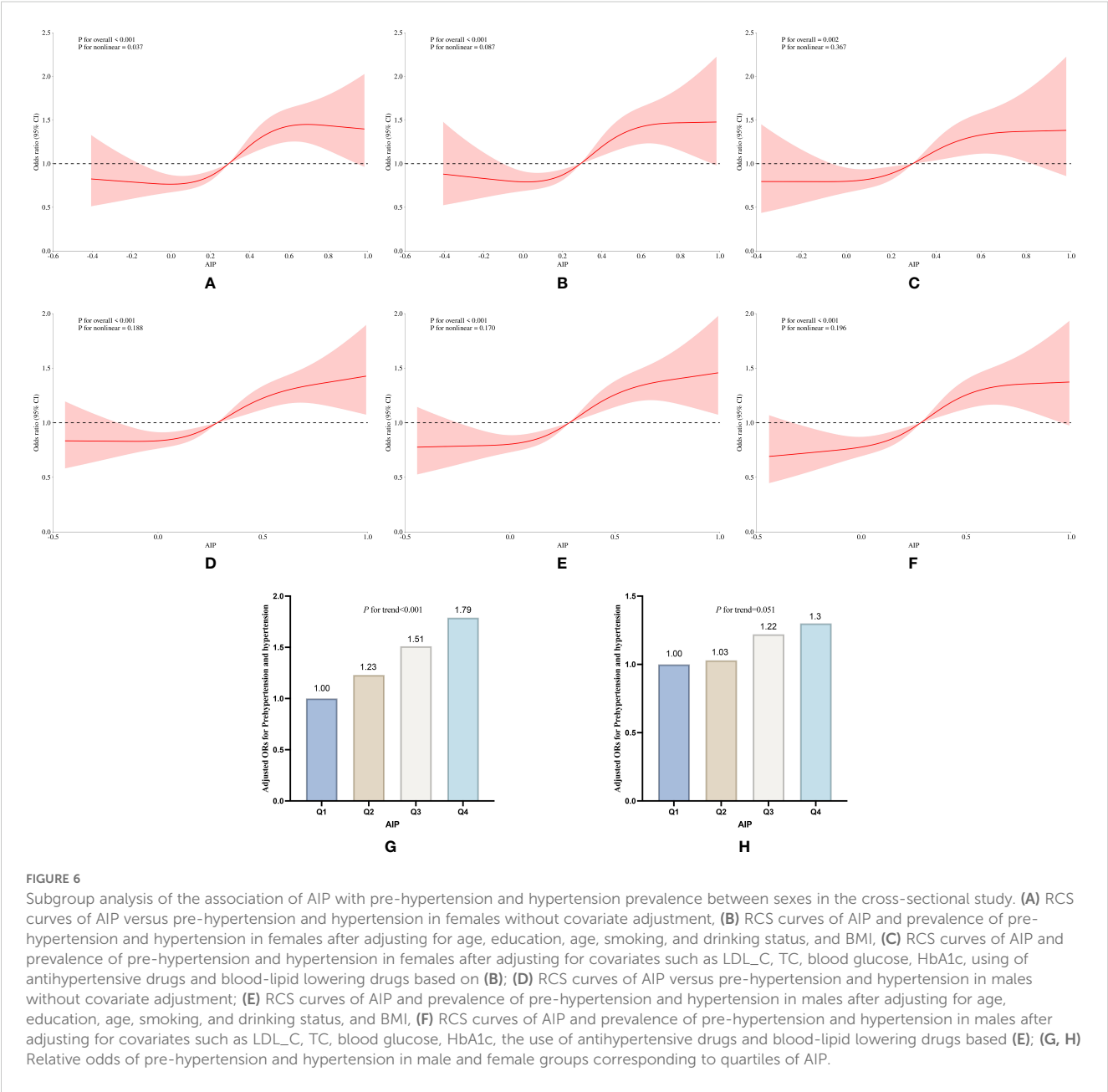
Our results confirmed a significant, nonlinear relationship between the AIP index and both pre-hypertension and hypertension among individuals, with notable sex-specific differences. When compared to the group with the lowest AIP values, the highest AIP group showed a 69% increased risk of developing pre-hypertension and hypertension (OR: 1.69, 95% CI: 1.38 to 2.07,  $P<0.001$ ). Further subgroup analysis unveiled that the women in the high-AIP group exhibited a 79% increased risk (OR: 1.79, 95% CI: 1.35 to 2.38,  $P<0.001$ ), whereas men showed only a 30% increase (OR: 1.30, 95% CI: 1.12 to 1.79,  $P=0.006$ ). The  $P$  value for interaction was less than 0.001.

A study conducted by researchers in Gifu Prefecture, Japan, has revealed a significant positive correlation between higher AIP values and the risk of developing pre-hypertension or hypertension. This trend was particularly evident among female participants in the

highest quartile of AIP (Q4), with an odds ratio (OR) of 2.19 and a  $P$ -value of 0.001. Notably, the middle-aged group, approximately 50 years old, exhibited the most pronounced association, with an OR of 2.20 and a  $P$ -value of 0.007 (29), this study suggests that, due to changes in physiological cycles and hormones, the mechanisms underlying dyslipidemia and hypertension may differ between women and men. In women, menopause-induced estrogen deficiency may lead to metabolic disruptions, commonly manifesting as decreased HDL-C levels and increased LDL-C and TG levels during the perimenopausal period.

The existing literature indicates that, in middle-aged and elderly women, the reduction and depletion of endogenous ovarian hormones following menopause is a primary factor contributing to the heightened risk of visceral obesity (30). Similarly, Gurka, Matthew J. et al. (31) discovered that postmenopausal women exhibit a higher prevalence of metabolic syndrome and an elevated risk of cardiovascular disease. Ben Ali Samir et al. (32) compared the incidence of hypertension between premenopausal and postmenopausal women and found that the latter group had a significantly higher rate of hypertension. The findings of this study emphasize the significance of considering sex as a modifying factor when assessing the impact of the AIP on blood pressure conditions, particularly in the context of postmenopausal women's health. The observed disparities underscore the necessity for tailored interventions and further investigation into the underlying mechanisms linking AIP, sex, and hypertension risk.

Our stratified analysis revealed an intriguing phenomenon: postmenopausal women exhibited significantly higher lipid profiles and elevated risks of pre-hypertension and hypertension



**FIGURE 6** Subgroup analysis of the association of AIP with pre-hypertension and hypertension prevalence between sexes in the cross-sectional study. **(A)** RCS curves of AIP versus pre-hypertension and hypertension in females without covariate adjustment, **(B)** RCS curves of AIP and prevalence of pre-hypertension and hypertension in females after adjusting for age, education, age, smoking, and drinking status, and BMI, **(C)** RCS curves of AIP and prevalence of pre-hypertension and hypertension in females after adjusting for covariates such as LDL\_C, TC, blood glucose, HbA1c, using of antihypertensive drugs and blood-lipid lowering drugs based on **(B)**; **(D)** RCS curves of AIP versus pre-hypertension and hypertension in males without covariate adjustment; **(E)** RCS curves of AIP and prevalence of pre-hypertension and hypertension in males after adjusting for age, education, age, smoking, and drinking status, and BMI, **(F)** RCS curves of AIP and prevalence of pre-hypertension and hypertension in males after adjusting for covariates such as LDL\_C, TC, blood glucose, HbA1c, the use of antihypertensive drugs and blood-lipid lowering drugs based **(E)**; **(G, H)** Relative odds of pre-hypertension and hypertension in male and female groups corresponding to quartiles of AIP.

**TABLE 7** Relative risk of pre-hypertension and hypertension in male and female under different AIP models in 2018.

AIP	Pre-hypertension and hypertension OR (95%CI)					
	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
<b>Female</b>						
Per-SD increase	1.52(1.23,1.79)	<0.001	1.42(1.22,1.98)	<0.001	1.33(1.25,1.71)	0.004
<b>Quartiles</b>						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.15 (1.04,1.42)	0.202	1.14 (0.94,1.38)	0.177	1.05 (0.85,1.30)	0.644

(Continued)

TABLE 7 Continued

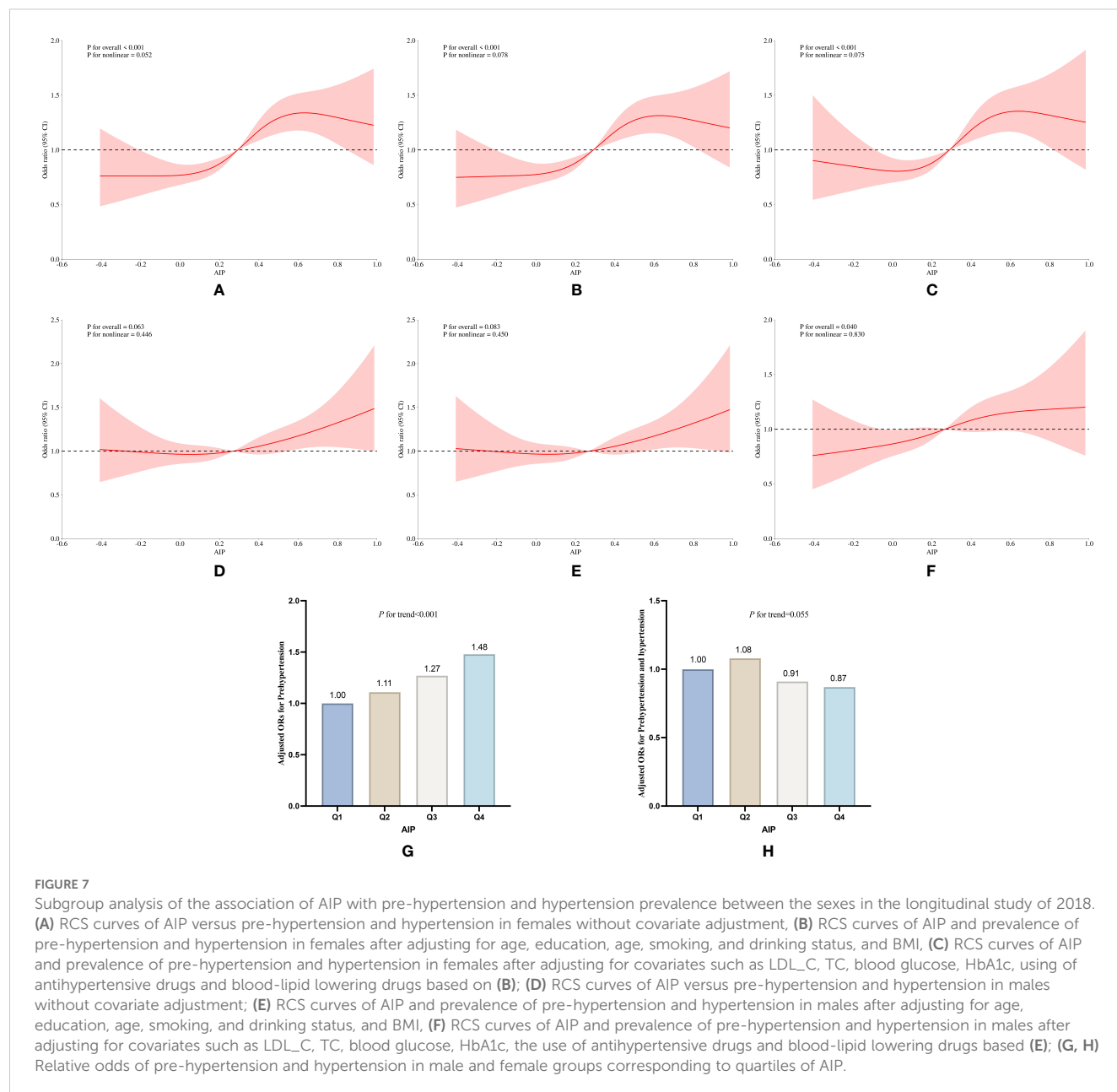
AIP	Pre-hypertension and hypertension OR (95%CI)					
	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Quartiles						
Q3(0.22 to 0.31)	1.41 (1.16,1.72)	<0.001	1.39 (1.14,1.69)	0.001	1.37 (1.10,1.71)	0.006
Q4(≥0.31)	1.73 (1.42,2.12)	<0.001	1.70 (1.39,2.09)	<0.001	1.64 (1.31,2.06)	<0.001
P for trend		<0.001		<0.001		<0.001
Male						
Per-SD increase	1.30(1.11,1.52)	0.003	1.17(1.06,1.51)	0.037	1.01(0.87,1.23)	0.145
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.03 (0.84,1.25)	0.799	1.01 (0.83,1.24)	0.904	1.08 (0.77,1.23)	0.831
Q3(0.22 to 0.31)	1.06 (0.87,1.30)	0.559	1.06 (0.86,1.30)	0.611	0.91 (0.69,1.19)	0.492
Q4(≥ 0.31)	1.29 (1.04,1.60)	0.019	1.27 (1.02,,58)	0.033	0.87 (0.57,1.31)	0.497
P for trend		0.039		0.041		0.055
P value for interaction		0.002		0.023		0.047

OR, Odds Ratio; CI, Confidence Interval.  
Model 1: was adjusted for none.  
Model 2: was adjusted for age, education, diabetes, current smoking, alcohol intake and BMI.  
Model 3: was adjusted for age, education, diabetes, current smoking, alcohol intake, BMI, LDL-C, TC, blood glucose, HbA1c, the use of antihypertensive drugs and blood-lipid lowering drugs.

compared to non-menopausal counterparts. With prolonged follow-up time, the population with a high AIP exhibited a significantly elevated risk of developing prehypertension and hypertension. In the female cohort, the association between high AIP and the risk of prehypertension/hypertension increased from 1.49-fold (OR=1.49, 95% CI:1.14 to 1.95,  $P=0.003$ ) in 2015 to 1.64-fold (OR=1.64, 95% CI:1.31 to 2.06,  $P<0.001$ ) in 2018, with this trend being particularly pronounced among postmenopausal women. We hypothesize that this association may be closely linked to the dramatic decline in endogenous estrogen levels following menopause. Multiple studies have suggested that estrogen regulates lipid metabolism balance through multifaceted mechanisms. In terms of lipid component modulation, estrogen elevates HDL-C levels by promoting its synthesis and inhibiting its breakdown in the liver, while accelerating LDL-C clearance via upregulating hepatic LDL receptor expression. It also maintains triglyceride balance by suppressing hepatic triglyceride synthase activity (33, 34). Postmenopausal estrogen decline leads to weakened HDL-C metabolism, reduced LDL-C clearance efficiency, and increased triglyceride accumulation risks. Regarding fat distribution, estrogen drives region-specific fat deposition in areas like the hips and thighs, whereas estrogen deficiency correlates with visceral fat accumulation and diminished adipocyte lipolysis efficiency. Metabolically, estrogen exerts cardiovascular protection by lowering TC and LDL-C while

enhancing cholesterol reverse transport. However, postmenopausal increases in the LDL-C/HDL-C ratio combined with chronic inflammatory factor release exacerbate lipid dysregulation, significantly raising risks of hypertriglyceridemia and insulin resistance. Molecularly, estrogen activates nuclear receptors to regulate key lipid-metabolizing enzymes (such as LPL and HL) and inhibits the NF- $\kappa$ B pathway to mitigate inflammatory interference in lipid metabolism. These mechanisms collectively highlight the dynamic interplay between estrogen levels and lipid homeostasis, underscoring estrogen’s pivotal role in menopausal metabolic syndrome development (33, 35, 36).

The AIP index, derived from a combination of TG and HDL-C results, demonstrates a certain predictive value for the onset of prehypertension and hypertension, as evidenced by the ROC curve analysis. Both when considered individually (TG or HDL-C) and as the AIP index, they exhibit an AUC value greater than 0.56. Numerous studies have confirmed a close association between elevated levels of TG and altered HDL-C with insulin resistance, suggesting that their ratio may serve as a surrogate marker for this condition (37, 38). These lipids impair insulin’s ability to bind with glucose by inhibiting the activity of insulin receptors on fat cells. Additionally, an increase in HDL-C levels can affect insulin secretion and reduce its sensitivity, ultimately leading to elevated blood glucose levels (11, 39–41). Insulin resistance, an independent high-risk factor for hypertension, exhibits a complex mechanism



that significantly impacts blood pressure regulation (42). Elevated insulin levels promote sodium reabsorption in the proximal renal tubules, resulting in water and sodium retention, which increases blood volume and sustains elevated blood pressure. Furthermore, insulin resistance stimulates the sympathetic nervous system, increasing the concentrations of excitatory neurotransmitters such as catecholamines, thereby exacerbating vascular constriction, increasing peripheral resistance, and contributing to the development of hypertension. Lastly, persistent high insulin levels may disrupt normal endothelial function, inhibiting the production of vasodilators and promoting the production of vasoconstrictors (such as endothelin-1), thus disturbing the balance between vasodilation and vasoconstriction (42, 43).

The prospective longitudinal study conducted by Lin Chia-Hung et al. (44) has further confirmed the close relationship between the progression of hypertension and insulin resistance. Insulin resistance not only plays a pivotal role in the development of cognitive impairment among elderly patients with primary hypertension but also stands as an independent risk factor for its advancement (38). Notably, the primary study index included in this research, the AIP, can largely mirror the blood lipid levels of the study population, thereby indirectly reflecting the intricate association between dyslipidemia, insulin resistance, and hypertension. This discovery aligns with the findings of numerous studies and offers a fresh perspective on understanding the pathogenesis of cardiovascular diseases.

TABLE 8 Relative risk of pre-hypertension and hypertension in postmenopausal and premenopausal female under different AIP models in 2018.

AIP	Pre-hypertension and hypertension OR (95%CI)					
	Model 1		Model 2		Model 3	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Postmenopausal						
Per-SD increase	1.39(1.21,1.69)	<0.001	1.40(1.25,1.76)	<0.001	1.43(1.26,1.80)	0.002
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.14 (0.90,1.43)	0.272	1.14 (0.90,1.44)	0.289	1.08 (0.83,1.39)	0.573
Q3(0.22 to 0.31)	1.46 (1.16,1.86)	0.002	1.48 (1.15,1.89)	0.002	1.48 (1.14,1.94)	0.004
Q4(≥0.31)	1.68 (1.32,2.13)	<0.001	1.75 (1.37,2.25)	<0.001	1.58 (1.20,2.07)	0.001
P for trend		<0.001		<0.001		<0.001
Premenopausal						
Per-SD increase	1.28(1.11,1.49)	0.013	1.15(1.04,1.41)	0.047	1.01(0.89,1.13)	0.112
Quartiles						
Q1(< 0.11)	1.00(Reference)		1.00(Reference)		1.00(Reference)	
Q2(0.11 to 0.22)	1.11 (0.78,1.59)	0.56	1.09 (0.76,1.57)	0.637	0.97 (0.66,1.45)	0.895
Q3(0.22 to 0.31)	1.29 (0.90,1.86)	0.166	1.27 (0.87,1.84)	0.214	1.12 (0.75,1.67)	0.588
Q4(≥0.31)	1.79 (1.23,2.60)	0.002	1.83 (1.24,2.69)	0.002	1.38 (1.07,1.72)	0.008
P for trend		0.017		0.044		0.049
P value for interaction		0.001		0.013		0.051

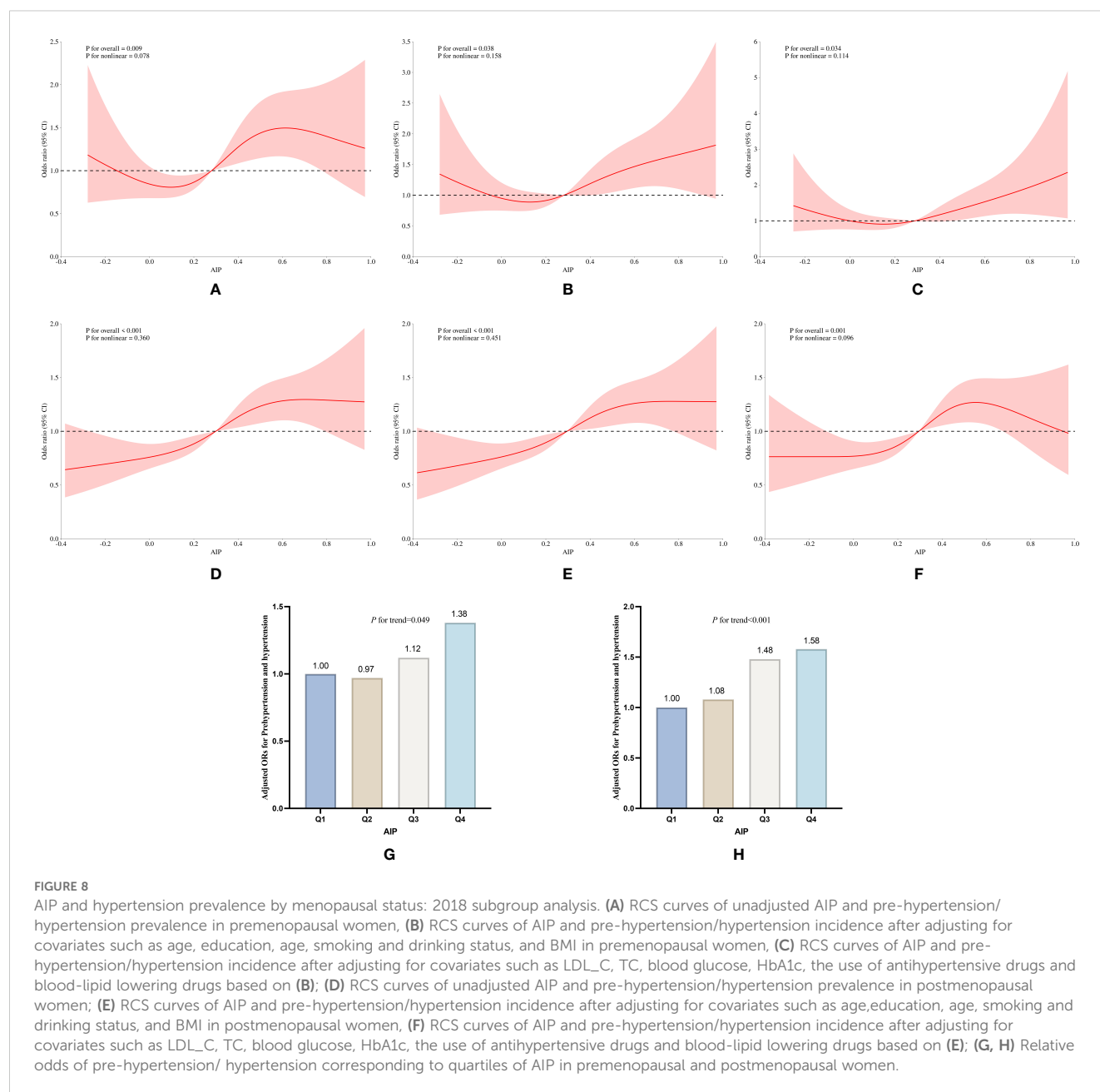
OR, Odds Ratio; CI, Confidence Interval.  
Model 1: was adjusted for none.  
Model 2: was adjusted for age, education, diabetes, current smoking, alcohol intake and BMI.  
Model 3: was adjusted for age, education, diabetes, current smoking, alcohol intake, BMI, LDL\_C, TC, blood glucose, HbA1c, the use of antihypertensive drugs and blood-lipid lowering drugs.

A high AIP index is frequently associated with elevated lipid levels and obesity. Excess weight can induce alterations in adiponectin secretion, resulting in an increase in free fatty acid levels and a decrease in adiponectin levels. These changes, in turn, can impair microvascular function to varying degrees, leading to capillary shedding, arteriolar constriction, and heightened peripheral resistance, ultimately elevating blood pressure (45). Furthermore, in obese individuals, the regulatory mechanism of vascular reactivity often shifts towards vasoconstriction, enhancing the effects of endothelin (a vasoconstrictor) while diminishing the effects of nitric oxide (a vasodilator). Additionally, communication pathways between adipose tissue and the vascular system, including sympathetic nervous activity and the release of adiponectin, are significantly intensified. All these factors contribute to microvascular dysfunction in the body, exacerbating the elevation of blood pressure (46). Our research findings align with these observations, indicating that middle-aged and older women are more significantly affected by the AIP index in terms of blood pressure levels compared to men. Specifically, women with a high AIP index face a notably higher risk of developing pre-hypertension and progressing to hypertension than their male counterparts in the same age group.

The findings of this study suggest that an elevated atherogenic index of plasma (AIP) may serve as a predictive marker for hypertension risk in middle-aged and elderly women, particularly in perimenopausal and postmenopausal populations. This discovery highlights the potential value of early monitoring and intervention strategies for individuals with high AIP levels, which could help reduce the progression rate from prehypertension to overt hypertension and delay the clinical progression of the disease. These insights may contribute to the scientific basis for primary prevention of cardiovascular diseases. Further validation of its predictive efficacy and exploration of AIP-based risk-stratified management models could not only optimize personalized health interventions but also reduce hypertension-related disease burdens, thereby demonstrating potential public health significance and clinical translational relevance.

While this study provides valuable insights, it is crucial to acknowledge its limitations. (1) The study population exclusively comprised Chinese individuals, necessitating caution when generalizing the findings to other ethnic groups or populations from different countries. (2) The cohort predominantly focused on middle-aged and older adults, whereas hypertension prevalence is





demonstrating an increasingly younger-onset trend. Therefore, extending these findings to younger age groups may require further validation. (3) Although the study adjusted for known confounders, potential residual confounding factors, such as dietary habits, exercise patterns, and activity frequency, were not fully accounted for and might influence the outcomes. (4) As the research relied on questionnaire-based data, biases from unmeasurable or unrecognized factors cannot be entirely eliminated. (5) Due to the observational nature of this study, even with the inclusion of a longitudinal cohort design, direct causal inferences between AIP levels and the risks of pre-hypertension and hypertension remain constrained. Further prospective studies or

interventional trials are essential to definitively establish the causal relationship between these variables.

## 5 Conclusion

This study, focusing on middle-aged and older adults in China, revealed that elevated AIP levels exhibited significantly positive associations with both the incidence of pre-hypertension and hypertension. The risk of these conditions progressively increased with rising AIP values, with the most pronounced effects observed in postmenopausal women. Therefore, regular monitoring and

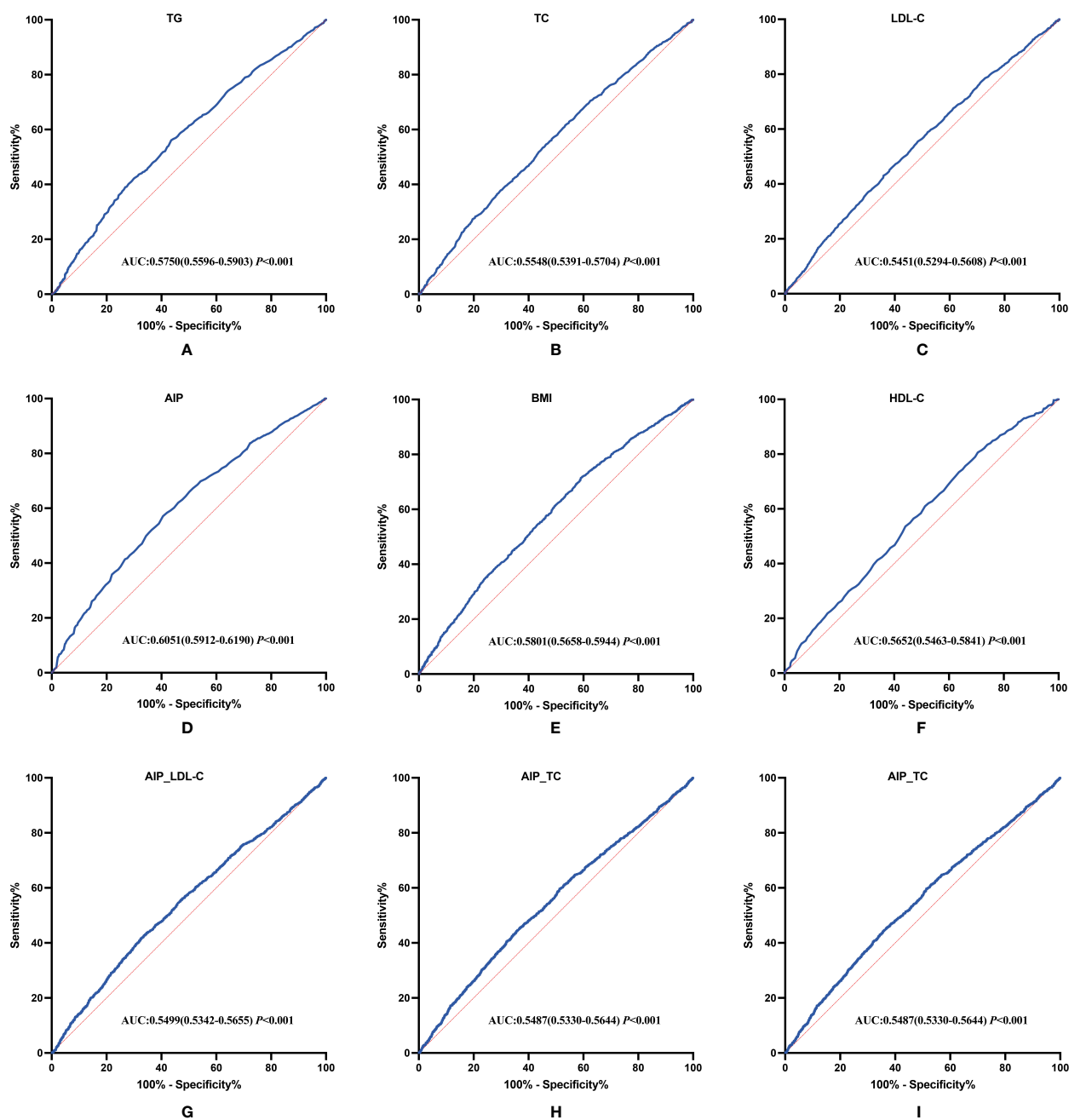


FIGURE 9

ROC curve analysis of hematological parameters for predicting pre-hypertension and hypertension in the middle-aged and elderly Chinese population. (A–I) ROC curve of TG, TC, LDL-C, AIP, BMI, HDL-C, AIP\_LDL-C, AIP\_TC, AIP\_BMI.

maintaining optimal AIP levels play a critical role in preventing hypertension onset and potentially delaying or halting the progression from pre-hypertension to hypertension. In the future, AIP has the potential to serve as a biomarker for hypertension risk surveillance, though further large-scale prospective studies are warranted to validate this hypothesis.

## Data availability statement

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

## Ethics statement

The CHARLS study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Peking University (approval number: IRB00001052-11015). All participants provided written informed consent before participating in the CHARLS study.

## Author contributions

ZZ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JW: Writing – review & editing, Data curation, Investigation, Methodology. LK: Writing – review & editing, Resources, Validation, Visualization. CL: Data curation, Formal Analysis, Project administration, Writing – original draft. WB: Project administration, Resources, Writing – review & editing. HT: Writing – review & editing, Formal Analysis. JL: Writing – review & editing, Conceptualization, Funding acquisition, Software, Supervision.

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## Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This article is funded by the Key Project of Jiangxi Province (20223BBG71006).

## Conflict of interest

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

## Generative AI statement

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2025.1574125/full#supplementary-material>

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