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Relationship between plasma atherogenic index and incidence of cardiovascular diseases in Chinese middle-aged and elderly people

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The atherogenic index of plasma (AIP), a novel composite lipid index, is closely linked to cardiovascular disease (CVD). However, lipid levels fluctuate dynamically, and it is unclear whether there are differences in the association of single-timescale, multiple-timescale, or AIP change trajectories with new-onset cardiovascular disease. Hence, the aim of this study was to investigate the correlation between different AIP parameters and the occurrence of CVD. Data were derived from the China Health and Retirement Longitudinal Study (CHARLS) conducted in 2011, 2015, 2018, and 2020, focusing on middle-aged and elderly populations aged over 45 years. Changes in AIP were classified into three groups using K-means cluster analysis: the low-level growth group (Class 1), the medium-level growth group (Class 2), and the high-level decline group (Class 3). Furthermore, participants were grouped based on tertiles (T) of cumulative AIP (Cum-AIP). Our multivariate logistic regression model integrated adjustments for potential confounders in order to investigate the association between Cum-AIP and the occurrence of CVD. Additionally, we employed restricted cubic spline (RCS) modeling to illustrate the dose-response relationship of baseline AIP, mean AIP, and Cum-AIP with CVD risk. During the 5-year follow-up period, 927 participants experienced the onset of CVD. After controlling for various potential confounding factors, it was observed that individuals in Class 2 demonstrated a notably heightened risk of CVD (OR = 1.23, 95% CI: 1.03, 1.46) and stroke (OR = 1.35, 95% CI: 1.02, 1.80) in comparison to those in Class 1. However, there was no significant difference in the risk of heart disease (OR = 1.21, 95% CI: 0.99, 1.48). In contrast, a noteworthy correlation was solely observed in the Class 3 group concerning the risk of stroke occurrence (OR = 1.60, 95% CI: 1.06, 2.42). The adjusted OR (95% CI) for CVD in the T2 and T3 groups were 1.21 (1.00, 1.46) and 1.30 (1.05, 1.62), respectively, compared to the T1 Cum-AIP group (*P* for trend = 0.017). Through the RCS model, we identified a positive and linear relationship between baseline AIP, mean AIP, and Cum-AIP with the incidence of CVD. However, the association between baseline AIP and CVD was weak. Sustained elevation of AIP is linked to a heightened risk of CVD in the general population. The elevated mean, and Cum-AIP levels are associated with a heightened risk of CVD. These findings indicate that AIP can serve as a valuable indicator of dyslipidemia, and continuous monitoring and early intervention targeting AIP may contribute to a further reduction in the incidence of CVD.

Keywords Atherogenic index of plasma, Cardiovascular disease, Cumulative exposure, K-means clustering, CHARLS

Abbreviations

AIP	Atherogenic index of plasma
CVD	Cardiovascular disease

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CHARLS	The China Health and Retirement Longitudinal Study
Cum-AIP	Cumulative-atherogenic index of plasma
RCS	Restricted cubic spline
OR	Odds ratio
CI	Confidence interval
T	Tertiles
CHD	Coronary heart disease
LDL-C	Low-density lipoprotein cholesterol
ASCVD	Atherosclerotic cardiovascular disease
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
AS	Atherosclerosis
MI	Myocardial infarction
BMI	Body mass index
DM	Diabetes mellitus
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
HbA1c	Glycosylated hemoglobin A1c
CRP	C-reactive protein
UA	Uric acid
SD	Standard deviation
IQR	Interquartile range
SSE	Sum of Squared Error
sdLDL	Small dense low density lipoprotein
LDL-P	Low-density lipoprotein particles

Based on the 2016 report released by the World Health Organization (WHO), ischemic heart disease and stroke have been identified as the primary contributors to global mortality. The 2019 China Cardiovascular Health and Disease Report revealed that China currently has 330 million individuals suffering from cardiovascular disease (CVD). Among them, 13 million are affected by stroke, while 11 million are diagnosed with coronary heart disease (CHD), making stroke and CHD the primary and secondary contributors to the disease burden in China[1]. Epidemiological investigations indicate an annual incidence of approximately 2.7 million new cases of stroke in China, equating to a new case occurring every 12 s. This alarming rate has positioned stroke as the foremost cause of death among Chinese residents[2].

The lipid profile has gained growing recognition as a significant predictor and risk factor for CVD[3]. In particular, low-density lipoprotein cholesterol (LDL-C) has been identified as a pivotal therapeutic target. The updated European guidelines for lipid management in 2019 have advanced our comprehension of the association between LDL-C and atherosclerotic cardiovascular disease (ASCVD)[4–6].

The atherogenic index of plasma (AIP) is a composite lipid index represented by a log-transformed value of the ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C)[7]. This index serves as an indicator of impaired plasma lipoprotein metabolism and in vivo inflammation. Notably, AIP exhibits greater sensitivity to the extent of atherosclerosis (AS) compared to individual lipid indices[8]. Its reliability as a marker of AS stems from its significant correlation with the size and density of lipoprotein particles, as well as the peroxidation rate[9]. Mounting evidence establishes a close and robust association between AIP and CVD and its prognosis[10–13]. However, most studies have focused primarily on baseline AIP levels, which limits the ability to observe trends in disease risk, and it is unclear whether there are differences in the correlation between single time scale, multiple time scales, or trajectories of change in AIP and new-onset CVD. Therefore, the primary objective of this study was to explore the impact of different AIP parameters on CVD incidence using a large national cohort dataset.

Methods

Study population

The research utilized an initial cohort of 11,847 participants with blood samples collected during the 2011 baseline survey and identified individuals who met the research objectives based on the following inclusion criteria: (1) age ≥ 45 years at Wave 1 (2011); (2) having TG and HDL-C at Wave 1 and Wave 3 (2015); (3) absence of diagnosed CVD, including heart disease and stroke, at Wave 1 and Wave 3; (4) documented CVD status information during the follow-up period. Ultimately, the study included a total of 5,339 individuals. The participant selection procedure is illustrated in Fig. 1.

Assessment of AIP and Cum-AIP

The exposure assessed in this study was characterized as the variation in AIP values from 2012 to 2015. AIP values were calculated using the formula $AIP = \log_{10}(TG/HDL\text{-}C)$[7]. The mean AIP is calculated using the formula: Mean AIP = $(AIP_{2012} + AIP_{2015}) / 2$. Additionally, we computed the cumulative AIP (Cum-AIP) level between 2012 and 2015 using the formula: Cum-AIP = $(AIP_{2012} + AIP_{2015}) / 2 * \text{time}\ (2015 - 2012)$[14].

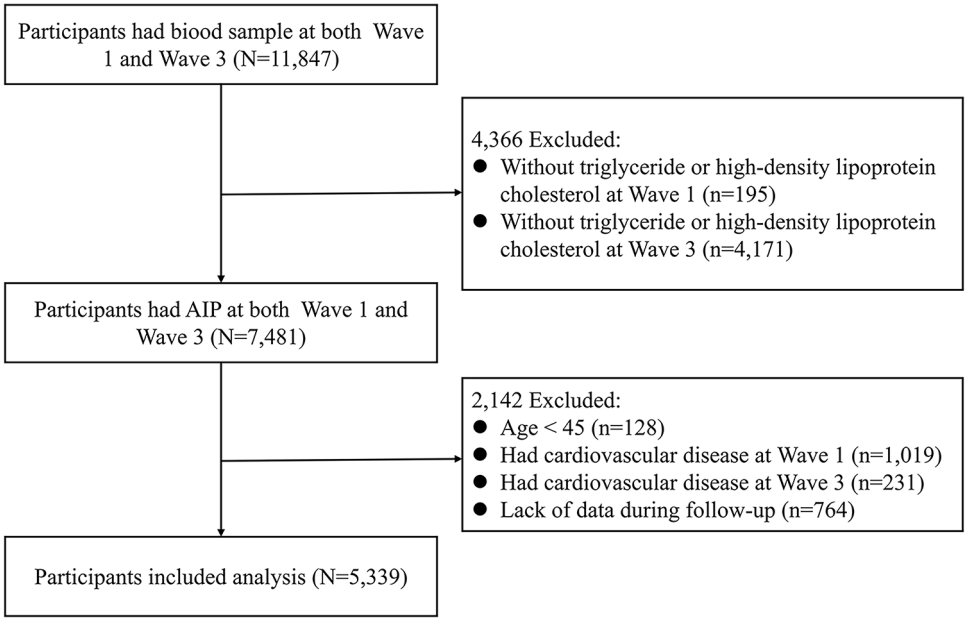

Fig. 1. Flowchart of the screening process.

Definition of cardiovascular disease

The primary endpoint of this study was the occurrence of new-onset CVD, including both CHD and stroke. Consistent with the attributes of the China Health and Retirement Longitudinal Study (CHARLS) database and previous relevant literature, the diagnosis of CVD was determined based on participants' self-reported responses to a specific inquiry in Wave 4 (2020) of the survey: "Has a healthcare provider ever informed you that you have experienced a cardiac condition (such as angina, myocardial infarction (MI), CHD, congestive heart failure, or other heart ailments) or a stroke?" This determination was made through a question-and-answer format. Individuals who responded affirmatively were categorized as having encountered a cardiovascular event[15,16].

Covariates

Baseline information was gathered via in-person interviews, with proficient personnel administering the surveys to the study cohort. The questionnaire covered a spectrum of variables including demographic characteristics (age, gender, marital status), body mass index (BMI), health metrics (hypertension and diabetes mellitus (DM)), lifestyle determinants (smoking, alcohol intake), pharmaceutical intake (lipid-lowering, antihypertensive, and glucose-lowering medications), and socioeconomic status (educational attainment). Marital status was subsequently categorized as married or other (including separated, divorced, widowed, and never married). BMI was computed based on measurements of height and weight[17]. Hypertension was defined as systolic blood pressure (SBP) exceeding 140 mmHg, diastolic blood pressure (DBP) surpassing 90 mmHg, self-reported history of hypertension, or use of antihypertensive medications. DM was delineated as fasting plasma glucose (FPG) ≥ 7.0 mmol/L, self-reported history of DM, or use of hypoglycemic medications. The analysis of peripheral blood samples was conducted by the Chinese Center for Disease Control and Prevention in Beijing. Trained personnel conducted fasting venous blood collection, and measurements of LDL-C, HDL-C, TG, glycosylated hemoglobin A1c (HbA1c), C-reactive protein (CRP), and uric acid (UA) were performed.

Statistical analysis

Data following a normal distribution were reported as mean ± standard deviation (SD), whereas non-normally distributed data were described using median and interquartile range (IQR). Count data were summarized using frequency and percentage (n %). Between-group comparisons were performed utilizing the Wilcoxon rank sum test, t-test, or chi-square test. Multiple imputation was utilized to handle missing data, with the aim of enhancing statistical power and reducing bias resulting from missing data[18,19]. The distribution of missing variables is outlined in Table S1. For AIP grouping, two methodologies were explored: K-means clustering and tertile grouping. The relationship between AIP and new-onset CVD was evaluated using logistic regression models, with adjustments made for potential confounders.

The K-means clustering algorithm is an iterative clustering approach that utilizes distance as a similarity metric to identify K classes within a dataset, with each class having a designated clustering center; the clustering center for each class is determined by the mean of all values within the class[20,21]. We have mentioned the steps of K-means clustering in our previous study[22]. In this paper, the clustering effect is comprehensively evaluated using three methods, namely, the elbow method, silhouette coefficient, and gap statistic method, to determine the range of K values dynamically. The elbow method indicates the degree of aggregation of samples through the Sum of Squared Error (SSE) indicator of the total error of sample clustering, and the smaller its value indicates

the more compact samples between classes[23]. Initially, with a smaller K than the true number of clusters, an increase in K rapidly enhances the compactness of each class, leading to a significant decrease in SSE. As K approaches the true number of clusters, further increases in K result in minimal changes in the degree of sample aggregation, leading to a flattening of the SSE decrease. Thus, an inflection point, or "elbow," emerges in the SSE-K plot, representing the genuine number of clusters[24]. The silhouette coefficient, which scales between −1 and + 1, quantifies the degree of cluster cohesion and separation; a higher score denotes a pronounced alignment of data points within their respective clusters and a diminished affinity with adjacent clusters[25]. The gap statistic computes the sum of squares of Euclidean distances between individual samples in each class and compares them to results obtained from a constructed reference zero-mean homogeneous distribution to determine the optimal number of clusters for the dataset[26]. The number of clusters, K, ranges from 1 to Kmax. The evaluation results are presented in Supplementary Figs. 1–3, revealing that clustering is optimal when K is set to 3.

We stratified the clustered populations based on the information presented in Fig. 2A. In Fig. 2B, for the Class 1 cohort ($n = 1957$), the AIP range increased from 0.05 ± 0.16 in 2012 to 0.14 ± 0.16 in 2015 ($P < 0.001$), yielding a Cum-AIP of 0.29 ± 0.36, and a mild upward trend in AIP. For the Class 2 group ($n = 2414$), the AIP range expanded from 0.40 ± 0.16 in 2012 to 0.43 ± 0.18 in 2015 ($P < 0.001$), resulting in a Cum-AIP of 1.25 ± 0.30 and a moderate increasing trend in AIP. Conversely, the Class 3 group ($n = 968$) witnessed a decrease in the AIP range from 0.85 ± 0.27 in 2012 to 0.75 ± 0.22 in 2015 ($P < 0.001$), producing a Cum-AIP of 2.40 ± 0.52 and a substantial declining trend in AIP. Additionally, Fig. 2 C and 2D visually depict the distribution of AIP in the Classes 1–3 groups, with all three datasets exhibiting normal distribution and highlighting differences between the three groups.

Restricted cubic spline (RCS) modeling was utilized to explore the dose-response relationship between Cum-AIP and CVD risk. Subgroup analyses were performed for conventional risk factors, encompassing age, gender, marital status, smoking, and BMI. In addition, we investigated potential interactions between these risk factors and AIP in the development of CVD, and evaluated trends in exposure levels across various population subgroups.

To validate the findings, sensitivity analyses were carried out. Statistical analyses were conducted employing Stata version 16.0 and R version 4.1.2 (http://www.R-project.org, R Foundation). A two-tailed P-value < 0.05 was considered as statistically significant.

Results

Baseline characteristics of study participants

This study enrolled 5,339 participants aged 45 years and above, with a median age of 57 years (Table 1). Males accounted for 45.65% of the participants; 30.87% had completed secondary education or above, and 91.16% were married or cohabiting. The AIP values in 2012 and 2015 were 0.35 ± 0.34 and 0.38 ± 0.28, respectively. The

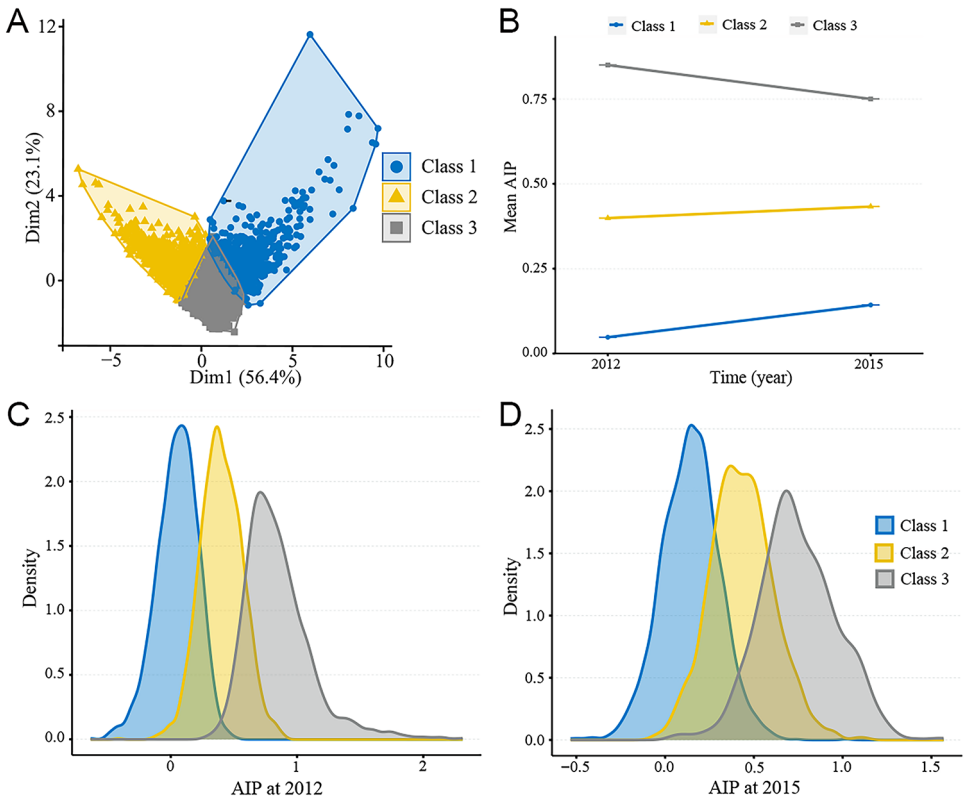

Fig. 2. Changes in AIP analyzed by K-means clustering model.

Characteristics	Total	Tertiles of Cum-AIP index			*P* value
		Class 1	Class 2	Class 3	
N(%)	5339	1957	2414	968	
Age, years, Median (IQR)	57.00 (51.00, 63.00)	58.00 (52.00, 64.00)	57.00 (51.00, 63.00)	56.00 (50.00, 62.00)	< 0.001
Sex, n (%)					< 0.001
Male	2437 (45.65)	962 (49.16)	1066 (44.16)	409 (42.25)	
Education level, n (%)					< 0.001
No formal education	2481 (46.47)	949 (48.49)	1123 (46.52)	409 (42.25)	
Primary school	1210 (22.66)	459 (23.45)	530 (21.96)	221 (22.83)	
Middle or high school	1504 (28.17)	504 (25.75)	702 (29.08)	298 (30.79)	
College or above	144 (2.70)	45 (2.30)	59 (2.44)	40 (4.13)	
Marital status, n (%)					0.225
Married	4867 (91.16)	1775 (90.70)	2196 (90.97)	896 (92.56)	
Other	472 (8.84)	182 (9.30)	218 (9.03)	72 (7.44)	
BMI, kg/m^2, n (%)					< 0.001
≤ 28	4768 (89.31)	1866 (95.35)	2127 (88.11)	775 (80.06)	
> 28	571 (10.69)	91 (4.65)	287 (11.89)	193 (19.94)	
Hypertension, n (%)					< 0.001
Yes	1122 (21.02)	291 (14.87)	535 (22.16)	296 (30.58)	
Diabetes, n (%)					< 0.001
Yes	817 (15.30)	185 (9.45)	343 (14.21)	289 (29.86)	
Lipid-lowering drugs, n (%)					< 0.001
Yes	230 (4.31)	45 (2.30)	108 (4.47)	77 (7.95)	
Antihypertensive drugs, n (%)					< 0.001
Yes	1116 (20.90)	287 (14.67)	534 (22.12)	295 (30.48)	
Hypoglycemic drugs, n (%)					< 0.001
Yes	163 (3.05)	42 (2.15)	69 (2.86)	52 (5.37)	
Smoking status, n (%)					0.006
Yes	2008 (37.61)	786 (40.16)	888 (36.79)	334 (34.50)	
Drinking status, n (%)					0.006
Yes	1204 (22.55)	488 (24.94)	517 (21.42)	199 (20.56)	
TG_{2012}, mg/dL, Median (IQR)	103.54 (74.34, 153.99)	69.92 (56.64, 84.96)	116.82 (94.69, 145.14)	225.68 (181.43, 309.97)	< 0.001
HDL_{2012}, mg/dL, Median (IQR)	49.48 (40.21, 59.92)	61.47 (52.96, 70.75)	47.17 (40.98, 53.74)	35.18 (30.54, 40.21)	< 0.001
AIP_{2012}, Median (IQR)	0.35 ± 0.34	0.05 ± 0.16	0.40 ± 0.16	0.85 ± 0.27	< 0.001
TG_{2015}, mg/dL, Median (IQR)	115.04 (83.19, 169.03)	79.65 (64.60, 97.35)	129.20 (100.88, 165.49)	231.42 (176.11, 332.74)	< 0.001
HDL_{2015}, mg/dL, Median (IQR)	50.19 (43.63, 57.92)	57.92 (50.97, 66.02)	48.26 (42.86, 54.34)	42.86 (38.22, 47.88)	< 0.001
AIP_{2015}, Median (IQR)	0.38 ± 0.28	0.14 ± 0.16	0.43 ± 0.18	0.75 ± 0.22	< 0.001
Cum-AIP, Median (IQR)	1.10 ± 0.83	0.29 ± 0.36	1.25 ± 0.30	2.40 ± 0.52	< 0.001
LDL, mg/dL, Median (IQR)	113.66 (93.17, 136.08)	110.95 (92.01, 130.67)	119.07 (98.20, 143.04)	106.70 (80.80, 131.93)	< 0.001
CRP, mg/L, Median (IQR)	0.95 (0.52, 1.92)	0.75 (0.44, 1.56)	1.01 (0.55, 1.99)	1.28 (0.68, 2.52)	< 0.001
Hba1c, %, Median (IQR)	5.10 (4.90, 5.40)	5.10 (4.80, 5.30)	5.10 (4.90, 5.40)	5.20 (4.90, 5.60)	< 0.001
UA, mg/dL, Median (IQR)	4.22 (3.51, 5.08)	4.06 (3.39, 4.83)	4.21 (3.53, 5.05)	4.64 (3.85, 5.54)	< 0.001

Table 1. Baseline characteristics of study participants.

Cum-AIP was 1.10 ± 0.83. In contrast to the Class 1 group, individuals in the Class 3 group were of a younger age and exhibited lower proportions of males, smokers, and alcohol drinkers, while also demonstrating higher levels of education. The prevalence of hypertension and DM was elevated, consequently, the Class 3 group comprised a greater number of individuals taking lipid-lowering, antihypertensive, and hypoglycemic medications. Additionally, they exhibited higher levels of TG, Cum-AIP, HbA1c, UA, and CRP ($P < 0.001$) and lower LDL-C and HDL-C ($P < 0.001$). Additionally, participants were classified into three groups according to tertiles (T) of Cum-AIP levels (Table S2). As Cum-AIP levels increased, the age distribution of participants tended to be younger. Concurrently, there was a progressive rise in the proportion of participants who were female, married, obese, had hypertension, and had DM. The use of lipid-lowering, antihypertensive, and hypoglycemic medications also increased gradually. Participants generally had higher levels of education ($P < 0.05$). Conversely, there was a gradual decrease in the number of participants who smoked and drank alcohol ($P < 0.05$). Regarding biomarkers, participants demonstrated a progressive elevation in TG, HbA1c, UA, and CRP levels, coupled with a gradual decline in HDL-C levels ($P < 0.001$). In comparison to the T1 group, there was a notable rise in LDL-C levels observed in both the T2 and T3 groups, with the T2 group showing a particularly marked increase ($P < 0.001$).

Relationship between AIP levels with incident cardiovascular disease

Following a 5-year follow-up period, CVD events were observed in 927 (17.36%) subjects, including 687 (12.86%) cases of heart disease and 316 (5.92%) cases of stroke (Fig. 3, Table 2). Upon adjusting for potential confounders, the Class 2 group demonstrated a higher risk of CVD compared to Class 1 (OR = 1.23, 95% CI: 1.03, 1.46), particularly for stroke (OR = 1.35, 95% CI: 1.02, 1.80), while no significant difference was observed for heart disease (OR = 1.21, 95% CI: 0.99, 1.48). In contrast, the Class 3 group displayed a notable correlation solely with the incidence of stroke (OR = 1.60, 95% CI: 1.06, 2.42). Moreover, in the comparison between Cum-AIP levels of T3 and T1, it was noted that the risk of CVD incidence was 1.30 (95% CI: 1.05, 1.62), the risk of heart disease occurrence was 1.25 (95% CI: 0.97, 1.61), and the risk of stroke was 1.63 (95% CI: 1.15, 2.30). Our findings suggest that as Cum-AIP levels increase, there is a corresponding elevation in the risk of both CVD and stroke (P for trend = 0.017 and 0.006, respectively).

Nevertheless, the increased risk of heart disease did not reach statistical significance (P for trend = 0.074). Figure 4 illustrates the association between baseline AIP and the mean AIP Index with CVD risk. In Model 3, subsequent to adjustments for all covariates, a positive correlation between the mean AIP index and the risk of CVD was observed. Particularly, individuals within the uppermost tertile of the mean AIP exhibited a 1.30-fold heightened risk of CVD (95% CI: 1.04, 1.62). On the other hand, although the baseline AIP index showed a tendency towards a positive association with CVD, the wide confidence interval rendered this association statistically non-significant. It is noteworthy that both the baseline AIP and mean AIP index displayed significant associations with stroke ($P < 0.05$).

Notably, utilizing the RCS regression model, we identified a distinct linear correlation between Cum-AIP and the occurrence rates of CVD, heart disease, and stroke (Fig. 5). Furthermore, both the baseline AIP index and mean AIP index demonstrated positive linear relationships with CVD (Figure S4).

Subgroup analysis

Upon stratifying by sex, age, marital status, smoking, and BMI, we identified an interaction between the change in AIP and sex (Fig. 6). Notably, among participants aged ≥ 65 years, male, with BMI ≤ 28 kg/m^2, and smokers, Class 3 was linked with a heightened risk of CVD ($P < 0.05$) (Fig. 6). Furthermore, a subgroup analysis of Cum-AIP tertiles revealed a similar interaction between Cum-AIP and sex (Fig. 7). However, in addition to participants aged ≥ 65 years, male, with BMI ≤ 28 kg/m^2, and smokers, we also observed an increased risk of CVD with rising Cum-AIP in married participants ($P < 0.05$) (Fig. 7).

Sensitivity analysis

In order to mitigate the impact of potential confounding factors on the study findings, we conducted sensitivity analyses by further adjusting for TC levels, SBP and DBP, as well as creatinine individually. The findings indicated minimal alterations in all the results (Tables S3–S5). Moreover, we conducted analyses based on Cum-AIP

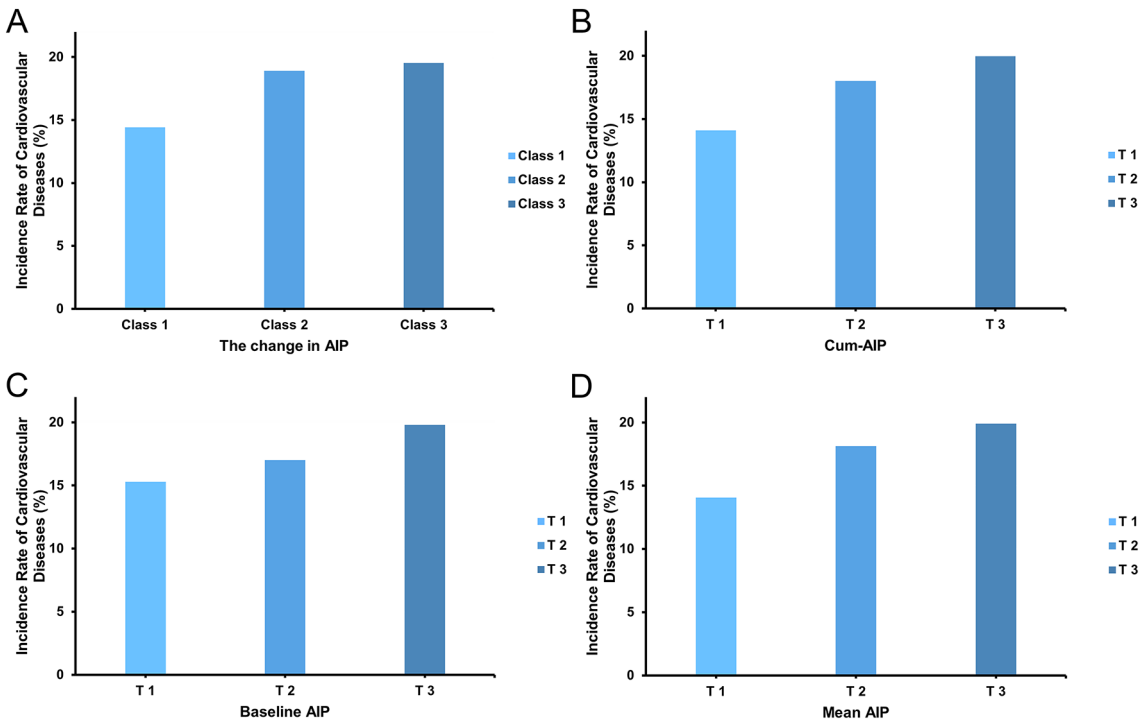

Fig. 3. CVD incidence. **(A)** Categorized by change in AIP; **(B)** Categorized by cumulative AIP tertiles; **(C)** Categorized by baseline AIP tertiles; **(D)** Categorized by mean AIP tertiles.

		Crude		Model 1		Model 2		Model 3	
	No. Events (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Cardiovascular disease									
Change in AIP									
Class 1	282 (14.41)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Class 2	456 (18.89)	1.38 (1.18,1.63)	< 0.001	1.39 (1.18,1.64)	< 0.001	1.26 (1.06,1.49)	0.007	1.23 (1.03,1.46)	0.021
Class 3	189 (19.52)	1.44 (1.18,1.77)	< 0.001	1.48 (1.20,1.81)	< 0.001	1.17 (0.94,1.46)	0.148	1.23 (0.93,1.61)	0.141
Cum-AIP									
< 0.692	251 (14.10)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
0.692–1.403	320 (18.02)	1.34 (1.12,1.60)	0.002	1.34 (1.12,1.61)	0.002	1.24 (1.03,1.49)	0.024	1.21 (1.00,1.46)	0.045
≥ 1.403	356 (19.97)	1.52 (1.27,1.81)	< 0.001	1.55 (1.30,1.86)	< 0.001	1.28 (1.06,1.55)	0.009	1.30 (1.05,1.62)	0.018
P for trend		< 0.001		< 0.001		0.010		0.017	
Heart disease									
Change in AIP									
Class 1	212 (10.83)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Class 2	339 (14.04)	1.34 (1.12,1.61)	0.002	1.34 (1.11,1.61)	0.002	1.21 (1.00,1.46)	0.044	1.21 (0.99,1.48)	0.056
Class 3	136 (14.05)	1.35 (1.07,1.69)	0.012	1.34 (1.06,1.69)	0.013	1.09 (0.85,1.39)	0.514	1.24 (0.90,1.70)	0.183
Cum-AIP									
< 0.692	190 (10.67)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
0.692–1.403	240 (13.51)	1.31 (1.07,1.60)	0.010	1.29 (1.05,1.59)	0.013	1.20 (0.97,1.47)	0.087	1.19 (0.96,1.47)	0.105
≥ 1.403	257 (14.41)	1.41 (1.15,1.72)	0.001	1.40 (1.15,1.72)	0.001	1.17 (0.95,1.45)	0.142	1.25 (0.97,1.61)	0.079
P for trend		0.001		0.001		0.153		0.074	
Stroke									
Change in AIP									
Class 1	85 (4.34)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Class 2	154 (6.38)	1.50 (1.14,1.97)	0.003	1.56 (1.19,2.05)	0.001	1.39 (1.05,1.83)	0.021	1.35 (1.02,1.80)	0.039
Class 3	77 (7.95)	1.90 (1.38,2.62)	< 0.001	2.07 (1.50,2.86)	< 0.001	1.61 (1.14,2.26)	0.006	1.60 (1.06,2.42)	0.025
Cum-AIP									
< 0.692	74 (4.16)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
0.692–1.403	105 (5.91)	1.45 (1.07,1.97)	0.017	1.49 (1.10,2.03)	0.010	1.36 (1.00,1.86)	0.051	1.33 (0.97,1.83)	0.074
≥ 1.403	137 (7.68)	1.92 (1.43,2.57)	< 0.001	2.08 (1.55,2.79)	< 0.001	1.67 (1.23,2.27)	0.001	1.63 (1.15,2.30)	0.006
P for trend		< 0.001		< 0.001		0.001		0.006	

Table 2. Logistic regression analysis to assess the association between the change in AIP and Cum-AIP and CVD. Crude: Unadjusted. Model 1: Adjusted for age, sex, education level, and marital status. Model 2: Model 1 + BMI, hypertension, DM, lipid-lowering drugs, antihypertensive drugs, hypoglycemic drugs. Model 3: Model 2 + smoking status, drinking status, TG, LDL-C, HbA1c, CRP, and UA.

quartiles (Q1–Q4), and observed that the relationships between Cum-AIP and the risk of CVD, heart disease, and stroke remained largely unchanged (Table S6).

Discussion

In the longitudinal study spanning five years and involving 5,339 middle-aged and older adults, it was found that the median ascending group (Class 2), higher Cum-AIP, and mean AIP were significantly linked to an augmented risk of developing CVD. Nevertheless, the association between baseline AIP and risk of CVD was significantly attenuated. This further substantiates the superiority of evaluating CVD by considering the cumulative amount of lipids as opposed to solely measuring individual values. In summary, our results suggest that AIP acts as an independent marker for increased CVD susceptibility among middle-aged and elderly individuals in the Chinese population.

Dyslipidemia emerges as a foremost risk factor for AS, characterized by elevated levels of LDL-C and TG, alongside decreased levels of HDL-C[27]. Numerous studies have demonstrated the close association of TG, LDL-C, HDL-C, and small dense low-density lipoprotein (sdLDL) with CVD[28–31]. Importantly, different lipids may exert slightly varied effects. For example, findings from the Framingham study[32]illustrated a positive association between sdLDL levels and serum TG levels, along with a negative correlation with serum HDL-C levels among individuals with metabolic syndrome[32]. In another prospective cohort investigation, incorporating diverse ethnicities, the comparable predictive efficacy of sdLDL, Apolipoprotein B, and low-density lipoprotein particles (LDL-P) in assessing the risk of CHD in healthy adults with normal blood glucose levels was demonstrated[30]. Furthermore, an extensive cohort analysis exploring the influence of various lipids on CVD risk pinpointed total cholesterol (TC) and LDL-C as notably sensitive indicators for younger individuals, whereas HDL-C and TG emerged as statistically significant predictors for older subjects[28]. In a study encompassing middle-aged and elderly participants (≥ 40 years old) within the Japanese community, heightened levels of sdLDL were observed

	No. Events (%)	Model 1	Model 2	Model 3	P value
CVD					
Baseline AIP	927 (17.36%)	1.45 (1.18,1.78)	1.14 (0.91,1.42)	1.44 (0.96,2.15)	0.075
T1	272 (15.30%)	1(Ref)	1(Ref)	1(Ref)	
T2	303 (17.00%)	1.14 (0.95,1.37)	1.07 (0.90,1.29)	1.05 (0.87,1.27)	0.606
T3	352 (19.79%)	1.39 (1.16,1.65)	1.14 (0.95,1.38)	1.16 (0.93,1.46)	0.182
Mean AIP	927 (17.36%)	1.72 (1.34,2.22)	1.25 (0.96,1.65)	1.51 (1.01,2.26)	0.045
T1	251 (14.07%)	1(Ref)	1(Ref)	1(Ref)	
T2	322 (18.13%)	1.35 (1.13,1.62)	1.25 (1.04,1.50)	1.22 (1.01,1.48)	0.035
T3	354 (19.90%)	1.55 (1.30,1.86)	1.28 (1.06,1.54)	1.30 (1.04,1.62)	0.020
Heart disease					
Baseline AIP	687 (12.87%)	1.28 (1.01,1.61)	1.01 (0.78,1.30)	1.43 (0.89,2.31)	0.141
T1	205 (11.53%)	1(Ref)	1(Ref)	1(Ref)	
T2	222 (12.46%)	1.09 (0.89,1.33)	1.03 (0.84,1.26)	1.03 (0.83,1.27)	0.817
T3	260 (14.61%)	1.31 (1.07,1.60)	1.10 (0.89,1.35)	1.21 (0.93,1.57)	0.151
Mean AIP	687 (12.87%)	1.44 (1.08,1.92)	1.06 (0.78,1.45)	1.38 (0.87,2.21)	0.173
T1	190 (10.65%)	1(Ref)	1(Ref)	1(Ref)	
T2	242 (13.63%)	1.31 (1.07,1.60)	1.21 (0.99,1.49)	1.20 (0.97,1.49)	0.086
T3	255 (14.33%)	1.40 (1.14,1.71)	1.17 (0.94,1.44)	1.24 (0.97,1.60)	0.092
Stroke					
Baseline AIP	316 (5.92%)	2.08 (1.52,2.85)	1.61 (1.14,2.27)	2.39 (1.26,4.51)	0.008
T1	77 (4.33%)	1(Ref)	1(Ref)	1(Ref)	
T2	110 (6.17%)	1.50 (1.11,2.03)	1.40 (1.03,1.89)	1.36 (1.00,1.86)	0.049
T3	129 (7.25%)	1.83 (1.37,2.45)	1.46 (1.08,1.99)	1.39 (0.98,1.97)	0.067
Mean AIP	316 (5.92%)	2.83 (1.92,4.19)	2.02 (1.33,3.09)	2.77 (1.46,5.23)	0.002
T1	74 (4.15%)	1(Ref)	1(Ref)	1(Ref)	
T2	105 (5.91%)	1.50 (1.10,2.03)	1.36 (1.00,1.86)	1.33 (0.97,1.83)	0.072
T3	137 (7.70%)	2.09 (1.56,2.81)	1.68 (1.24,2.29)	1.64 (1.16,2.31)	0.005

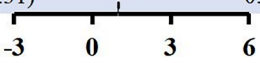

Fig. 4. Association between baseline and mean AIP index and incidence of CVD.

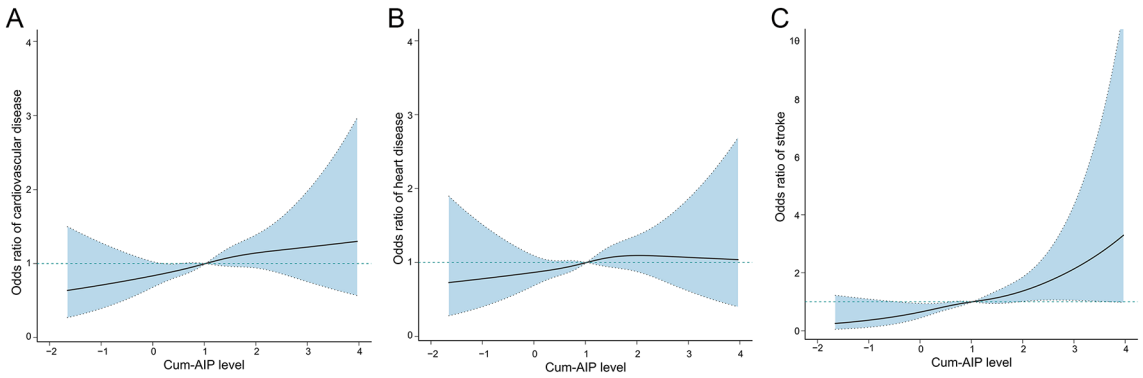

Fig. 5. Linear associations between Cum-AIP and CVD. **(A)** CVD; **(B)** heart disease; **(C)** stroke.

to markedly elevate the risk of CHD, independent of serum LDL-C levels. These findings suggest the superior predictive ability of serum sdLDL compared to LDL-C[33].

The evidence provided above underscores the pivotal role of sdLDL in both the progression and prognosis of CVD. sdLDL is proposed to be more susceptible to oxidative stress compared to other LDL-C fractions, thereby increasing the risk of AS[34]. However, its clinical utility has been constrained by intricate and expensive detection methodologies[35,36]. Alternatively, the TG/HDL-C ratio has been proposed as a simpler and cost-effective surrogate marker for sdLDL levels[37]. Recent studies confirm a positive association between the TG/HDL-C ratio and sdLDL, with this relationship being more prominent in populations with higher LDL-C levels[38]. Notably,

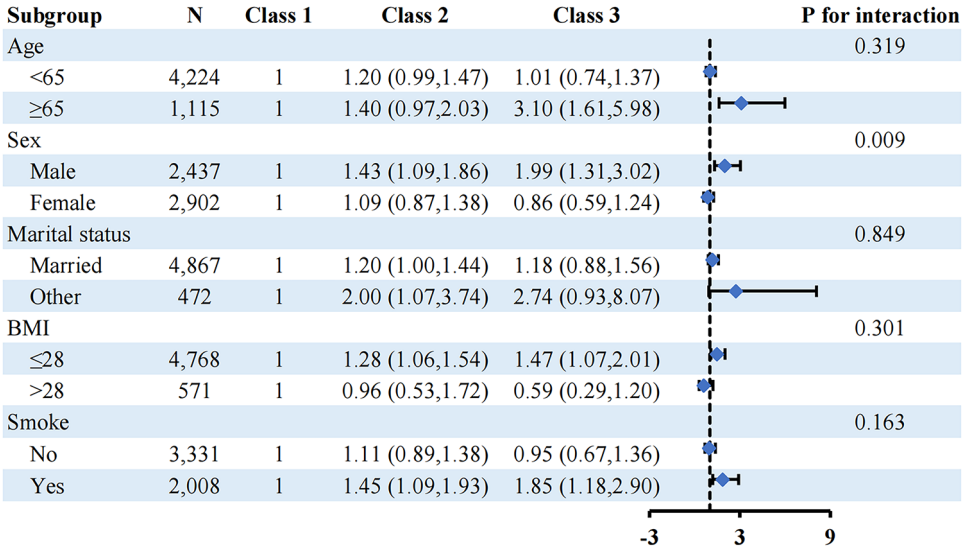

Fig. 6. Subgroup analysis of the association between the change in AIP and CVD risk based on clustering results.

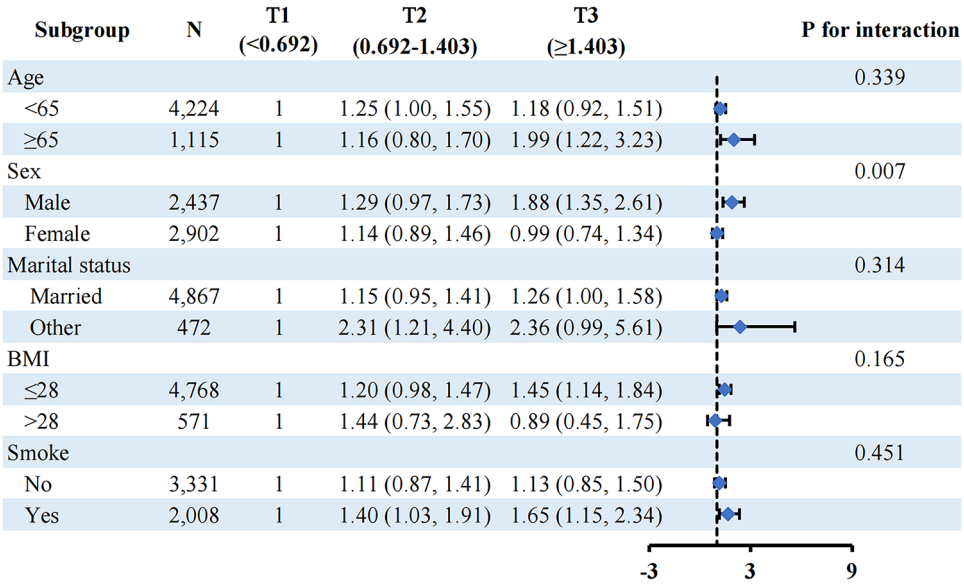

Fig. 7. Subgroup analysis of the association between Cum-AIP and CVD risk based on tertiles.

the TG/HDL-C ratio has demonstrated better predictive performance for sdLDL-related risk factors, making it a more practical tool for assessing CHD risk in clinical settings.

As far back as 2001, a study demonstrated a strong inverse relationship between AIP and the size of LDL-P (r= −0.776). A recent study has shown that in perimenopausal women, small low-density lipoprotein particles and the number of LDL-P are significantly associated with subclinical markers of AS risk[39]. These findings emphasize the necessity of incorporating LDL subfractions into risk stratification models, as these subfractions provide additional insights into atherosclerotic risk that traditional lipid characteristics cannot capture. Furthermore, AIP was proposed as a surrogate marker of plasma atherogenicity[7]. Compared with sdLDL, AIP, as a comprehensive lipid index, can reflect both the TG to HDL-C ratio and LDL-P size, which can more accurately reflect the comprehensive level of lipid metabolism in patients than a single lipid assay. The association between AIP and CVD has been substantiated by a plethora of studies. In middle-aged and elderly Chinese women, AIP has demonstrated enhanced predictive capabilities in forecasting asymptomatic intracranial stenosis, outperforming other traditional or non-traditional lipid indices[40]. In a comprehensive study by Zhang et al. involving 98,861 subjects from the Kailuan cohort, it was revealed that both baseline and multi-temporal mean AIP measurements exhibited robust associations with MI and stroke occurrences. The mean AIP index exhibited a higher risk of MI (36% vs. 30%) compared to the baseline AIP[10], and both associations were comparable with

the risk of stroke occurrence[14]. Additionally, Zhang et al. also investigated Cum-AIP, and the findings suggested that elevated Cum-AIP and prolonged AIP exposure may elevate the risk of MI[41]. Similarly, our investigation delved into baseline AIP, mean AIP, and Cum-AIP, revealing a positive correlation between all three and the incidence of CVD and stroke.

A retrospective study conducted by Kurklu et al. demonstrated that individuals with ≥ 50% coronary artery stenosis exhibited a higher AIP compared to those with < 50% coronary artery stenosis ($P = 0.002$), highlighting the AIP index as a significant predictor of coronary artery disease (CAD)[42]. Furthermore, Ozen and Li et al. emphasized that AIP can function as an independent predictor for the severity of CAD[12,43]. A recent epidemiological study involving 5,843 participants from the Korean community revealed a heightened risk of CVD associated with an increasing trend in AIP levels[44], aligning with our findings. Our study similarly identified an elevated risk of CVD in individuals with a moderate increasing trend in AIP (Class 2 group). Additionally, AIP was linked to CVD prognosis. A retrospective cohort study in China showed that an elevated baseline AIP was linked to a heightened risk of major adverse cardiovascular events (MACE) among patients diagnosed with chronic coronary syndrome (CCS) following a 35-month follow-up of 404 subjects admitted with a CCS diagnosis who underwent coronary angiography[11]. Compared to single-point AIP measurements, Cum-AIP, as a time-integrated measure of long-term lipid metabolism, may better reflect the chronic and dynamic nature of atherosclerotic development. According to the latest research[45], there is a significant correlation between Cum-AIP and the risk of MACE, stroke, and myocardial infarction. In the fully adjusted model, individuals with an increase of one unit in Cum-AIP have a 75% increased incidence of experiencing MACE, and individuals in the highest quartile of Cum-AIP are significantly associated with an increased incidence of MACE (HR = 1.76, 95%CI: 1.27, 2.44, $P < 0.001$). This suggests that Cum-AIP may be a strong independent predictive factor and is of great significance for the early identification of high-risk groups for CVD.

Multiple studies have showcased the correlation between AIP and well-established cardiovascular risk factors such as obesity, BMI, DM, physical inactivity, hypertension, and inflammatory markers. A prospective study from Turkey indicated[46]that high AIP serves as a surrogate for small LDL-P size, reflecting obesity and hyperinsulinemia in males. In females, the high correlation between AIP and CRP suggests a link between AS and pro-inflammatory state. In a cross-sectional study carried out in Iran, researchers observed a positive correlation between AIP and waist circumference as well as BMI. Additionally, they found a negative correlation between AIP and levels of physical activity[3]. Furthermore, a significant positive correlation between AIP and BMI, SBP, DBP, FPG, UA, and TC has been consistently reported[47]. Moreover, AIP also plays a crucial role in both the development and progression of DM and hypertension[48–51]. These factors contribute to an increased risk of CVD by fostering inflammation, oxidative stress, endothelial dysfunction, and other pathological mechanisms that culminate in AS[52].

Elevated levels of TG can result in vascular endothelial dysfunction, vascular injury, procoagulation, and activation of inflammatory responses in vivo, ultimately contributing to AS development[53–55]. On the other hand, HDL-C plays a critical role in reverse cholesterol transport and possesses anti-inflammatory, antioxidant, and cell-protective properties, rendering it a protective factor for the cardiovascular system[56]. The AIP demonstrates a positive association with TG and an inverse relationship with HDL-C, providing a more comprehensive insight into the equilibrium between AS-promoting and anti-AS factors[57]. In comparison to sdLDL, AIP presents advantages such as rapid assessment, noninvasiveness, and cost-effectiveness, which facilitates its widespread utilization in clinical practice.

Strengths and limitations

The current study possesses several strengths. First, this is the first prospective cohort study to show a longitudinal association between the change in AIP, Cum-AIP, baseline AIP, and mean AIP exposure and CVD risk. Secondly, the utilization of cumulative exposures and changing trends in the analysis enhanced the robustness of the results compared to prior studies that focused solely on single measurements when examining the association between AIP and CVD. Additionally, K-means clustering, as an unsupervised learning method, can naturally form clusters based on the characteristics of data points rather than being based on artificially set thresholds. This makes it more flexible and effective in handling complex datasets. When dealing with heterogeneous data, the K-means clustering method can better identify groups with significant differences and prognostic significance compared to traditional tertile-based grouping.

However, this study is subject to certain limitations. First, as it exclusively focused on the Chinese middle-aged and elderly population, it was unable to investigate potential variations in the study results across different racial groups. Second, there is a possibility of bias due to the exclusion of individuals with incomplete TG and HDL data. Third, the limited number of blood tests conducted restricted the acquisition of more comprehensive insights into the progression of AIP levels. Furthermore, since the CVD diagnoses in this study were self-reported by patients, there may be misclassification or reporting bias. Limited by the constraints of the database, we could not obtain more detailed or verified diagnostic data to address this issue. However, such non-differential bias is unlikely to systematically affect the main conclusions. Future studies should utilize validated clinical data to further confirm these findings.

Conclusions

Our findings indicate that elevated baseline, mean, and Cum-AIP are associated with a heightened risk of CVD in the Chinese middle-aged and elderly population. Notably, individuals in the Class 2 group, characterized by high and escalating AIP levels, exhibited a particularly elevated CVD risk. Consequently, we propose that continuous monitoring of AIP levels and early intervention may mitigate the incidence of CVD.

Data availability

The derived data that were generated in the current study are available from the corresponding author upon reasonable request.

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Author contributions
Conceptualization: MZ, MX, and FL; methodology: MZ and FL; software: MZ, HZ, and MX; statistical analysis: MZ, QT, and JJ; visualization: QT, JJ, and HZ; data collection: YC, JJ, and HZ; writing—original draft: MZ; writing—review and editing: MX, QT, HZ, JJ, YC, and FL. All of the authors have read and agreed to the published version of the manuscript. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Ethics approval and consent to participate
Data collection and use of CHARLS were approved by the Biomedical Ethics Review Board of Peking University (IRB00001052-11015) and the Human Research Ethics Committee of Newcastle University (H-2015-0290), respectively.

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