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Association between the atherogenic index of plasma and the systemic immuno-inflammatory index using NHANES data from 2005 to 2018

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The atherogenic index of plasma (AIP) is used to evaluate the risk of atherosclerosis, while the systemic immune-inflammation index (SII) measures inflammation. The AIP and SII are indicators used to predict diseases in various areas. This study aims to explore the relationship between AIP and SII. A cross-sectional study design was used to recruit 70,190 participants from the National Health and Nutrition Examination Survey (NHANES) conducted between 2005 and 2018, excluding AIP missing data, SII missing data, participants under 20 years of age, and participants with missing covariates to eventually include 8163 participants. We used weighted multiple linear regression analysis, trend test, smooth curve fitting and threshold effect analysis to examine the relationship between AIP and SII. Among the 8163 participants included in the study, the mean (± SD) age was 48.412 ± 16.842 years. The mean SII (± SD) for all participants was 519.910 ± 316.974. In a model adjusted for all covariates (Model 3), AIP showed a significant positive correlation with SII [β (95% CI) 32.497 (5.425, 59.569), $P = 0.021$]. The smooth curve fitting results of AIP and SII are an "inverted U-shape" non-linear relationship, and the inflection point is at AIP = 0.82. This positive association between AIP and SII was found only in females and participants under 50. Specifically, for females, the positive correlation between AIP and SII was linear [β (95% CI) 80.791 (44.625, 116.958); $P < 0.001$]. In participants under 50, the positive correlation between AIP and SII was [β (95% CI) 34.198 (3.087, 65.310); $P = 0.034$], and there was also an "inverted U-shape" non-linear relationship with an inflection point of AIP = 0.549. For participants aged 20–50 years and males, the smooth curve showed a "down-flat-down" non-linear relationship. There is a significant positive correlation between AIP and SII. A positive association between AIP and SII was observed exclusively in females and among participants under 50. Furthermore, AIP and SII demonstrated a nonlinear relationship that resembles an "inverted U-shape". These findings offer new insights into the prevention, treatment, and management of cardiovascular disease. However, further comprehensive cohort studies are necessary to validate the relationship between AIP and SII.

Keywords The atherogenic index of plasma, The systemic immuno-inflammatory index, NHANES, Positive correlation, Linear relationship

Abbreviations

AIP	The plasma atherosclerosis index
SII	The systemic immune-inflammation index
CVD	Cerebrovascular disease
NHANES	National Health and Nutrition Examination Survey
CR	Caloric restriction
PIR	Family income-to-poverty ratio
TG	Triglyceride

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HDL-C	High-density lipoprotein cholesterol
LDL	Low-density lipoprotein
NET	Neutrophil extracellular trap
SD	Standard deviation
NAFLD	Nonalcoholic fatty liver disease
NCHS	National Center for Health Statistics
CRP	C-reactive protein
CR	Caloric restriction
MACE	Major adverse cardiovascular event
LPL	Lipoprotein lipase
EPC	Endothelial progenitor cell
ROS	Reactive oxygen specie
ox-LDL	Oxidized low-density lipoprotein
VEGF	Vascular endothelial growth factor

The atherogenic index of plasma (AIP) is a relatively new and effective lipid index used to evaluate the severity of coronary artery disease and predict the risk of cardiovascular disease[1]. AIP is considered a more reliable and convenient indicator of cardiovascular disease risk compared to traditional evaluation methods. One of the key advantages of AIP is its ability to account for both triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) levels[2]. AIP not only reflects the complexity of lipid metabolism in the body, but also is closely related to the existence of various inflammatory diseases, such as insulin resistance, chronic liver disease, liver cancer, hidradenitis suppurativa and other inflammatory diseases[3–6].

The systemic immuno-inflammatory index (SII) is a multifunctional tool that integrates peripheral blood lymphocytes, neutrophils, and platelet counts[7]. This indicator contributes to a more objective and comprehensive understanding of the occurrence and progression of inflammation in the body and is crucial for evaluating and predicting the prognosis of various inflammatory diseases, especially tumors and cardiovascular diseases (CVDs)[8,9]. SII was initially considered a reliable indicator of recurrence and survival in patients with hepatocellular carcinoma, hepatic steatosis, and liver fibrosis[10], then subsequent studies have expanded its use in a variety of other diseases. These diseases include type 2 diabetic nephropathy, abdominal aortic calcification, kidney stones, and among others[11–13].

The AIP and SII are indicators used to predict diseases in various areas[1,2,7–9]. However, the relationship between AIP and SII is unclear, and there is currently limited research on the relationship between AIP and SII. To investigate this connection further, we conducted a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) database from 2005 to 2018.

Methods

Study population

Data from the NHANES database is collected every two years. The National Center for Health Statistics (NCHS) reviewed and approved all study designs, and informed consent was obtained from every participant during recruitment. From 2005 to 2018, a total of 70,190 participants were recruited. We excluded 48,952 participants with missing AIP data, 89 participants with missing SII data, 4064 participants younger than 20 years of age, and 8922 participants with missing covariates. Ultimately, 8163 participants were included in the study (Fig. 1).

Evaluation of the atherogenic index of plasma

The AIP is a crucial metric for evaluating the degree of atherosclerosis in plasma[1]. Within the NHANES database, the AIP index is carefully extracted and calculated using the Cobas 6000 chemical analyzer during designated inspections, whether conducted in vehicles or laboratories[14]. The AIP value is derived from the concentrations of plasma triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) using the formula[1]:

$$\mathrm{AIP} = \log 10\,(\mathrm{TG}/\mathrm{HDL\text{-}C})$$

This index is strongly associated with atherosclerotic burden and cardiovascular events, making it a valuable marker for detecting plasma atherosclerosis[2].

Assessment of the systemic immune-inflammatory index

In the NHANES database, the SII involves collecting whole blood samples (CBC) from the study population using the UniCel DxH 800 analyzer, a quantitative automated blood analyzer designed for in vitro diagnostics[14]. This process is followed by rigorous laboratory testing, adhering to a stringent standardized sampling protocol. Blood samples are typically collected in a survey vehicle or at a designated sampling point, then processed and tested in a specific laboratory to ensure the validity and accuracy of the data. The SII is calculated using the formula[7,11]:

$$\mathrm{SII} = \frac{\text{platelet count} \times \text{neutrophil count}}{\text{lymphocyte count}}$$

This index serves as a new comprehensive inflammatory indicator, reflecting the body's immune-inflammatory state by assessing the counts of platelets, neutrophils, and lymphocytes. Additionally, the SII is non-invasive, easily accessible, and cost-effective, providing reliable reference values for the prognosis of malignant tumors and inflammation-related diseases[7,8,11].

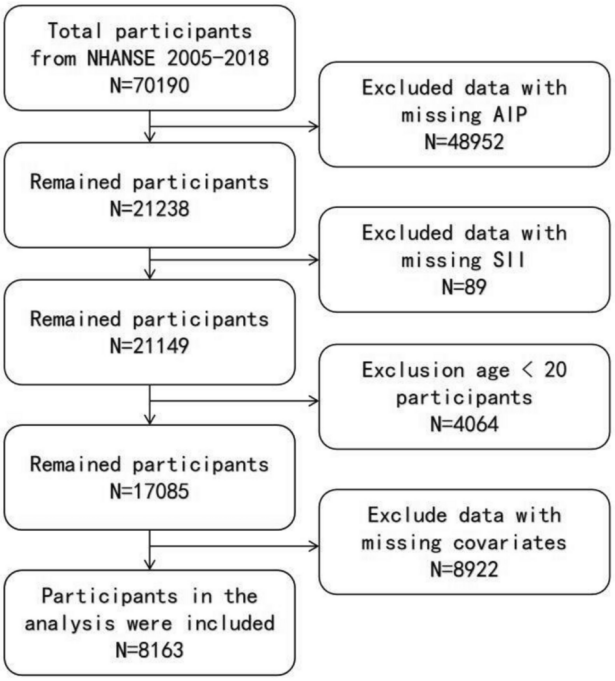

Fig. 1. Flow chart of participants selection. NHANES, National Health and Nutrition Examination Survey; AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

Definition of covariates

Covariates include the following variables: age, family income-to-poverty ratio (PIR), race/ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, other race), gender (male, female), and education level (less than 9th grade, 9–11th grade, high school graduate, some college, and college graduate or above). Additionally, alcohol drinking history (< 5drinks/day, ≥ 5/ < 10drinks/day, ≥ 10drinks/day). Smoking history is classified as smoker or non-smoker. Other health indicators include hypertension (Yes or No), diabetes mellitus (Yes or No), and high cholesterol level (Yes or No).

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are shown as counts (n) with percentages (%). The demographic distribution of study participants was assessed using chi-square tests, analyses of variance (ANOVA), and t-tests, based on the three tertiles of the AIP. The relationship between the AIP and the SII was analyzed using weighted multiple linear regression. The AIP value was transformed from a continuous variable into a categorical variable, and the trend tests were employed to further assess the linear correlation between AIP and SII. In the analysis of the general population, we utilized three models. Model 1 serves as a basic model without any adjustments for covariates. Model 2 incorporates minimal adjustments for age, family income-to-poverty ratio (PIR), gender, race/ethnicity, and education level. Model 3 is a fully adjusted model that accounts for age, PIR, gender, race/ethnicity, education level, smoking history, alcohol drinking history, hypertension, diabetes mellitus, and high cholesterol level. Additionally, smooth curve fitting and threshold effect analysis were conducted to examine the nonlinear relationship between AIP and SII in the general population. To further investigate the relationship between SII and AIP, stratifications by gender (male, female) and age (20–50 years, ≥ 50 years) were performed. In the grouping analysis, we used weighted multiple linear regressions and trend tests to analyze the linear correlation between AIP and SII across gender and age groups. Following this, smooth curve fittings and threshold effect analyses were employed to examine the nonlinear relationship between AIP and SII while considering gender and age. Covariate collinearity analysis found that covariate no collinearity. The statistical software used for the collinearity analysis was Spss (version 27). The statistical analysis in this study utilized R (version 4.2) and Empower (version 4.6). A bilateral P value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Of the 8163 participants included in the study, the mean (± SD) SII value for all participants was 519.910 ± 316.974. The mean (± SD) age was 48.412 ± 16.842 years, of whom 52.946% were males, 48.316% were Non-Hispanic White, and the family income-to-poverty ratio was 2.815 ± 1.653. Participants with Some college education accounted for 2656 (32.537%), non-smokers accounted for 51.256%, alcohol drinking history < 5 (drinks/day) accounted for 86.941%, hypertension accounted for 35.183%, diabetes mellitus accounted for 10.952%, high cholesterol level accounted for 35.526%. AIP values are divided into: Tertile1 (– 0.892 to 0.134), Tertile2 (0.135–

0.422), and Tertile3 (0.423–1.966). Compared to the lowest quantile of AIP, participants with higher AIP were more likely to be those with high levels of SII, older people, males, non-Hispanic whites, smokers, participants with a history of alcohol consumption ≥ 5(drinks/day), hypertension, diabetes, and high cholesterol levels (Table 1). There were statistically significant differences in AIP tertiles at baseline in SII, age, PIR, gender, race, education level, alcohol drinking history, smoking history, hypertension, diabetes mellitus, and high cholesterol level ($P < 0.001$).

Association between AIP and SII

In this study, we used weighted multiple linear regression to examine the relationship between AIP and SII. We build three models to analyze this relationship (Table 2). In the crude model (Model 1), the regression coefficient (β) and 95% confidence interval (CI) of AIP were [35.775 (11.037–60.513), $P = 0.006$]. This shows that for every 1 unit increase in AIP, SII increases by 35.775 units without taking into account any covariates. In the minimum modified model (Model 2), which considers demographic factors such as age, PIR, gender, race, and education level, β and 95% CI of AIP are [43.270 (17.333, 69.207), $P = 0.002$]. Finally, in the fully adjusted model (Model 3), the β and 95% CI of AIP were [32.497 (5.425, 59.569), $P = 0.021$]. The results showed that after adjusting for age, PIR, gender, race, education level, alcohol drinking history, smoking history, hypertension, diabetes mellitus, and high cholesterol level, SII increased by 32.497 units for every 1 unit increase in AIP. The AIP values were divided into three tertiles: Tertile 1 (− 0.892 to 0.134), Tertile 2 (0.135–0.422) and Tertile 3 (0.423–1.966). In a

AIP tertile	Overall	The atherogenic index of plasma (AIP)			*P* value
		Tertile 1 (-0.892–0.134)	Tertile 2 (0.135–0.422)	Tertile 3 (0.423–1.966)	
N	8163	2718	2724	2721	
SII	519.910 ± 316.974	497.884 ± 317.459	527.376 ± 313.155	534.438 ± 319.212	< 0.001
Age (years)	48.412 ± 16.842	46.888 ± 17.448	49.073 ± 17.253	49.272 ± 15.671	< 0.001
Family income-to-poverty ratio (PIR)	2.815 ± 1.653	2.943 ± 1.657	2.815 ± 1.662	2.686 ± 1.630	< 0.001
Gender					< 0.001
Male	4322 (52.946%)	1066 (39.220%)	1463 (53.708%)	1793 (65.895%)	
Female	3841 (47.054%)	1652 (60.780%)	1261 (46.292%)	928 (34.105%)	
Race/ethnicity					< 0.001
Mexican American	1052 (12.887%)	238 (8.756%)	354 (12.996%)	460 (16.906%)	
Other Hispanic	735 (9.004%)	200 (7.358%)	252 (9.251%)	283 (10.401%)	
Non-Hispanic White	3944 (48.316%)	1253 (46.100%)	1316 (48.311%)	1375 (50.533%)	
Non-Hispanic Black	1577 (19.319%)	732 (26.932%)	524 (19.236%)	321 (11.797%)	
Other Race	855 (10.474%)	295 (10.854%)	278 (10.206%)	282 (10.364%)	
Education level					< 0.001
Less than 9th grade	456 (5.586%)	101 (3.716%)	153 (5.617%)	202 (7.424%)	
9–11th grade	911 (11.160%)	249 (9.161%)	317 (11.637%)	345 (12.679%)	
High school grade	1751 (21.450%)	507 (18.653%)	598 (21.953%)	646 (23.741%)	
Some college	2656 (32.537%)	905 (33.297%)	859 (31.535%)	892 (32.782%)	
College graduate or above	2389 (29.266%)	956 (35.173%)	797 (29.258%)	636 (23.374%)	
Smoking history					< 0.001
Smoker	3979 (48.744%)	1148 (42.237%)	1301 (47.761%)	1530 (56.229%)	
Non-smoker	4184 (51.256%)	1570 (57.763%)	1423 (52.239%)	1191 (43.771%)	
Alcohol drinking history (drinks/day)					< 0.001
< 5	7097 (86.941%)	2463 (90.618%)	2370 (87.004%)	2264 (83.205%)	
≥ 5, < 10	844 (10.339%)	210 (7.726%)	289 (10.609%)	345 (12.679%)	
≥ 10	222 (2.720%)	45 (1.656%)	65 (2.386%)	112 (4.116%)	
Hypertension					< 0.001
Yes	2872 (35.183%)	763 (28.072%)	967 (35.499%)	1142 (41.970%)	
No	5291 (64.817%)	1955 (71.928%)	1757 (64.501%)	1579 (58.030%)	
Diabetes mellitus					< 0.001
Yes	894 (10.952%)	170 (6.255%)	262 (9.618%)	462 (16.979%)	
No	7269 (89.048%)	2548 (93.745%)	2462 (90.382%)	2259 (83.021%)	
High cholesterol level					< 0.001
Yes	2900 (35.526%)	690 (25.386%)	980 (35.977%)	1230 (45.204%)	
No	5263 (64.474%)	2028 (74.614%)	1744 (64.023%)	1491 (54.796%)	

Table 1. Basic characteristics of the study population by AIP tertiles in NHANES from 2005 to 2018 (n = 8163). Mean ± SD for continuous variables; N (%) for categorical variables; AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

Outcome: SII	Cases/N	Model 1		Model 2		Model 3	
		β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Overall							
AIP	8163/8163	35.775 (11.037, 60.513)	0.006	43.270 (17.333, 69.207)	0.002	32.497 (5.425, 59.569)	0.021
AIP tertile							
Tertile 1	2718/2718	Reference		Reference		Reference	
Tertile 2	2724/2724	34.863(13.983, 55.744)	0.001	35.654 (14.308, 57.000)	0.002	32.967 (11.735, 54.198)	0.003
Tertile 3	2721/2721	36.954 (17.558, 56.350)	< 0.001	42.014 (21.512, 62.517)	< 0.001	33.308 (11.863, 54.753)	0.003
P for trend		< 0.001		< 0.001		0.003	

Table 2. Association between AIP and SII (n = 8163). Model 1: no adjustment. Model 2: adjusted for age, gender, race, education level, and family income-to-poverty ratio (PIR). Model 3: adjusted for age, gender, race, education level, family income-to-poverty ratio (PIR), smoking history, alcohol drinking history, diabetes mellitus, high cholesterol level and hypertension. *P* value < 0.05, presents significant difference; CI, confidence interval; AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

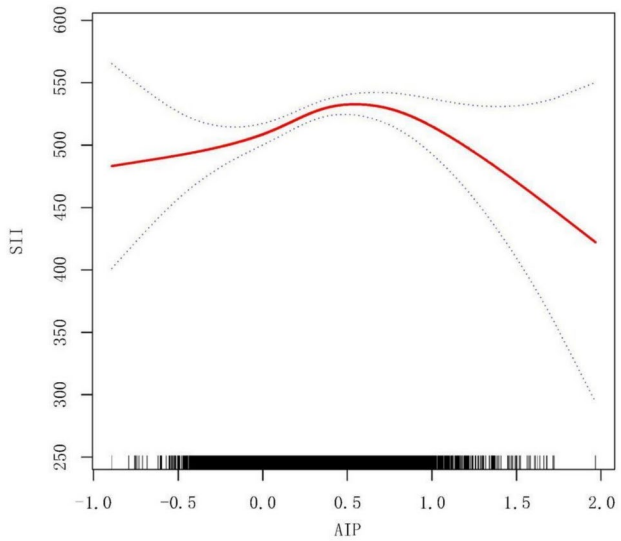

Fig. 2. Smooth curve fitting of SII and AIP. Solid red lines indicate smooth curve fitting. The blue band represents the 95% confidence interval of the fitted curve. AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

fully adjusted model (Model 3), SII increased by an average of 33.308 units ($P = 0.003$) in the third tertile of AIP compared to the first tertile of AIP. Using Tertile 1 as a reference, we find P for trend < 0.01 for the three models, which supports a linear relationship between AIP and SII. Our results confirm a significant positive relationship between AIP and SII.

After adjusting all covariables (Model 3), we found that there was still a nonlinear relationship and a threshold effect between SII and AIP through smooth curve fitting and threshold effect analysis. Figure 2 shows the smooth curve fitting results, showing the nonlinear relationship between AIP and SII, which is characterized by an "inverted U-shape" that rises first and then falls. We performed a threshold effect analysis of the nonlinear relationship between AIP and SII and found an inflection point at AIP = 0.82 (Table 5). In the range of AIP < 0.82, SII increased by 40.086 units for each unit increase of AIP [β (95% CI) 40.086 (15.497, 64.675); $P = 0.0014$]. When AIP = 0.82, SII reaches the maximum value of 551.597 [(95% CI) (536.873, 566.322)]. However, when AIP > 0.82, SII decreased by 161.502 units for every 1 unit increase in AIP [β (95% CI) − 161.502 (− 270.810, − 52.195); $P = 0.0038$]. Therefore, we believe that there is a linear relationship between AIP and SII as well as a non-linear relationship.

Subgroup analysis

To analyze the relationship between AIP and SII, we conducted subgroup analyses by gender (male, female) and age (20–50 years, ≥ 50 years). In females, significant positive associations were found between AIP and SII across all models ($P < 0.001$). Specifically, in the fully adjusted model (Model 3), each 1 unit increase in females AIP led to an 80.791 units increase in SII [β (95% CI) 80.791 (44.625, 116.958); $P < 0.001$]. In a fully adjusted model (Model 3), female participants' SII values, increased by an average of 60.243 units in the third tertile of

Outcome: SII	Cases/N	Model 1		Model 2		Model 3	
		β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Gender							
Male							
AIP	4322/4322	11.720(−25.810, 49.249)	0.542	4.879 (−31.397, 41.155)	0.793	−3.752 (−40.371, 32.866)	0.841
AIP tertile							
Tertile 1	1066/1066	Reference		Reference		Reference	
Tertile 2	1463/1463	39.662 (7.131, 72.193)	0.019	35.644 (3.765, 67.523)	0.031	33.431 (1.341, 65.521)	0.044
Tertile 3	1793/1793	26.841 (−2.999, 56.681)	0.081	20.926 (−8.047, 49.899)	0.160	14.169 (−15.121, 43.460)	0.346
P for trend		0.136		0.252		0.499	
Female							
AIP	3841/3841	120.123 (85.702, 154.545)	< 0.001	93.905 (58.794, 129.016)	< 0.001	80.791 (44.625, 116.958)	< 0.001
AIP tertile							
Tertile 1	1652/1652	Reference		Reference		Reference	
Tertile 2	1261/1261	41.208 (15.261, 67.155)	0.002	32.304 (5.621, 58.987)	0.020	29.422 (3.112, 55.733)	0.031
Tertile 3	928/928	90.608 (61.964, 119.252)	< 0.001	71.362 (42.597, 100.128)	< 0.001	60.243 (30.746, 89.739)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001	

Table 3. Analyzes the relationships between AIP and SII by gender groupings. Model 1: no adjustment. Model 2: adjusted for age, gender, race, education level, and family income-to-poverty ratio (PIR). Model 3: adjusted for age, gender, race, education level, family income-to-poverty ratio (PIR), smoking history, alcohol drinking history, diabetes mellitus, high cholesterol level and hypertension.

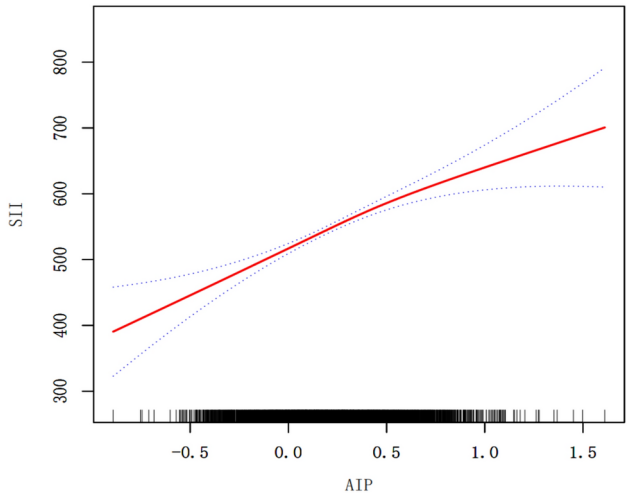

Fig. 3. Smooth curve fitting of AIP and SII in female participants. Solid red lines indicate smooth curve fitting. The blue band represents the 95% confidence interval of the fitted curve. AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

AIP compared to the first tertile of AIP ($P < 0.001$). In contrast, no significant relationships were observed in males ($P > 0.05$). The trend test was significant in females ($P < 0.001$) but not in males ($P > 0.05$). These findings indicate a gender disparity in the association between AIP and SII, with a positive relationship identified only in females (Table 3).

To further analyze gender differences in the relationship between AIP and SII, we used smooth curve fitting after adjusting for all covariables. The results showed a linear positive correlation between AIP and SII among female participants, which was consistent with the results of weighted multiple regression analysis of female participants (Fig. 3). The smooth curve fitting of AIP-SII relationship in male participants was nonlinear in the form of "down-flat-down" (Fig. 4).

In a subgroup analysis by age, we found a significant positive association between AIP and SII in participants under 50, with SII increasing by 34.198 units for every 1 unit increase in AIP [β (95% CI) 34.198 (3.087, 65.310); $P = 0.034$]. No significant association was found in those aged 50 and older ($P > 0.05$). In a fully adjusted model (Model 3), the SII value of participants aged 20–50 years, increased by an average of 36.708 units in the AIP third tertile compared to the AIP first tertile ($P = 0.005$). The trend test was significant in participants under 50

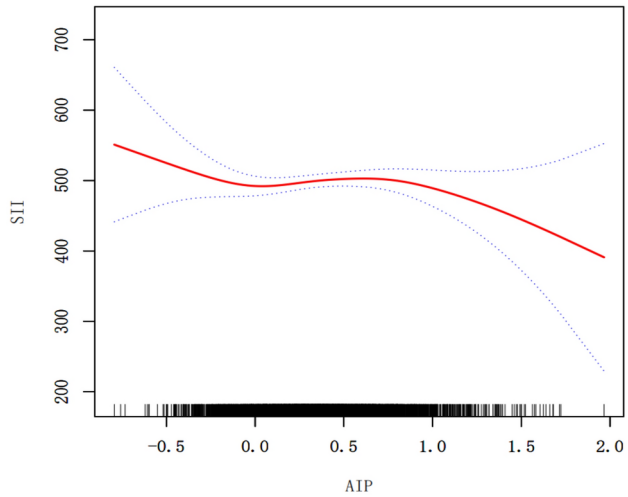

Fig. 4. Smooth curve fitting of AIP and SII for male participants. The solid red line indicates smooth curve fitting. The blue band represents the 95% confidence interval of the fitted curve. AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

		Model 1		Model 2		Model 3	
Outcome: SII	**Cases/N**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**
Age (years)							
Age ≥ 20, < 50							
AIP	4324/4324	35.442 (7.058, 63.827)	0.016	50.422 (20.405, 80.440)	0.001	34.198 (3.087, 65.310)	0.034
AIP tertile							
Tertile 1	1545/1545	Reference		Reference		Reference	
Tertile 2	1393/1393	48.175 (22.313, 74.036)	< 0.001	52.028 (27.117, 76.938)	< 0.001	46.191 (20.761, 71.621)	0.001
Tertile 3	1386/1386	36.611 (13.610, 59.611)	0.002	49.764 (25.514, 74.015)	< 0.001	36.708 (11.502, 61.913)	0.005
P for trend		0.002		< 0.0001		0.004	
Age ≥ 50							
AIP	3839/3839	34.637 (− 10.530, 79.804)	0.136	41.099 (− 4.739, 86.937)	0.082	23.463 (− 21.668, 68.595)	0.311
AIP tertile							
Tertile 1	1173/1173	Reference		Reference		Reference	
Tertile 2	1331/1331	16.388 (− 18.866, 51.643)	0.364	17.797 (− 18.435, 54.029)	0.338	15.150 (− 20.124, 50.425)	0.402
Tertile 3	1335/1335	34.611 (− 0.880, 70.102)	0.059	37.383 (1.483, 73.284)	0.044	24.274 (− 11.143, 59.690)	0.183
P for trend		0.058		0.043		0.177	

Table 4. The relationships between AIP and SII were analyzed by age groups. Model 1: no adjustment. Model 2: adjusted for age, gender, race, education level, and family income-to-poverty ratio (PIR). Model 3: adjusted for age, gender, race, education level, family income-to-poverty ratio (PIR), smoking history, alcohol drinking history, diabetes mellitus, high cholesterol level and hypertension. *P* value < 0.05, presents significant difference; CI, confidence interval; AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

($P < 0.01$), indicating that the positive association between AIP and SII was only present in this younger group. Trend tests were not significant for participants aged 50 years and older (Table 4).

We conducted smooth curve fitting for participants under 50 years of age, revealing an "inverted U-shape" relationship, which first rises and then falls (Fig. 5). A threshold effect analysis indicated that for participants younger than 50, SII increased by an average of 54.112 units for each 1-unit rise in AIP [β (95% CI) 54.112 (24.353, 83.871); $P = 0.0004$], until it reached an inflection point at AIP = 0.549, where SII peaked at 544.925 [(95% CI), (532.684, 557.166)]. Beyond this AIP value, SII decreased by 77.058 units for each 1-unit increase in AIP [β (95% CI) − 77.058 (− 136.547, − 17.569); $P = 0.0111$] (Table 5) . Hence, for participants under 50, AIP = 0.549 is the inflection point. Smooth curve fitting for participants over 50 years of age showed a non-linear relationship of "down-flat-down" (Fig. 6).

Discussion

Our analysis shows that there is a positive correlation between AIP and SII. This positive association was particularly significant in females and individuals under 50 years of age. The positive association between AIP and

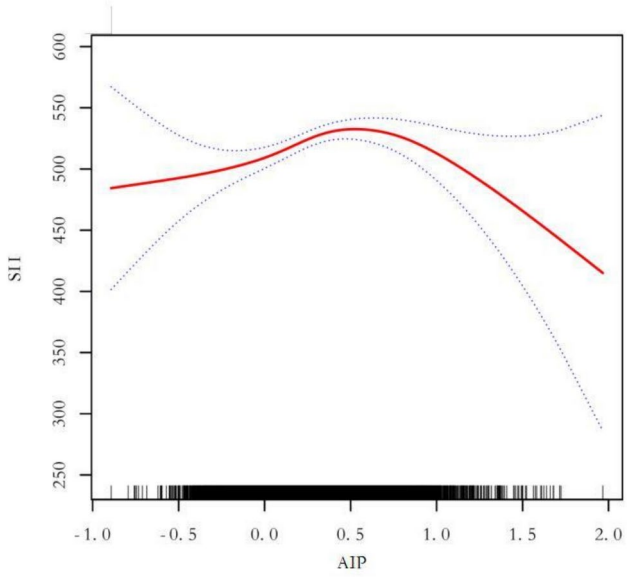

Fig. 5. Smooth curve fitting of SII and AIP in participants under 50. Solid red lines indicate smooth curve fitting. The blue band represents the 95% confidence interval of the fitted curve. AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

Outcome: SII	Adjust all covariates (Model 3)	
Exposure:AIP	**β (95% CI)**	***P* value**
Overall		
AIP < 0.82	40.086 (15.497, 64.675)	0.0014
AIP = 0.82	551.597 (536.873, 566.322)	
AIP > 0.82	− 161.502 (− 270.810, − 52.195)	0.0038
Age ≥ 20, < 50 (years)		
AIP < 0.549	54.112 (24.353, 83.871)	0.0004
AIP = 0.549	544.925 (532.684, 557.166)	
AIP > 0.549	− 77.058 (− 136.547, − 17.569)	0.0111

Table 5. Analysis of threshold effects between AIP and SII (n = 8163). Model 3: adjusted for age, gender, race, education level, family income-to-poverty ratio (PIR), smoking history, alcohol drinking history, diabetes mellitus, high cholesterol level and hypertension.

SII has potential clinical implications for the prevention, diagnosis, treatment, and prognosis of inflammatory and cardiovascular diseases, especially in females and participants under 50.

AIP and SII are important biomarkers for predicting cardiovascular disease (CVD) risk. Including them in risk stratification tools could enhance prediction accuracy and enable early intervention, especially in high-risk populations. Studies have shown that SII is closely related to the prevalence rate of hypertension in the general population, showing an inflection point Ln (SII) = 5.89 in the "u-shaped" relationship[15]. A cohort study of 13,026 obese adults identified SII as an independent risk factor for CVD death, with a 14% increased risk per additional unit[16]. Other studies found that SII dynamic status is significantly associated with CVD risk, with a positive correlation noted over 8.6 years of follow-up[17]. Other studies have found that AIP has a more significant impact on diabetes and prediabetes, suggesting that more attention should be paid to the risk of cardiovascular disease in diabetic patients in clinical practice[18]. In patients with type 2 diabetes, AIP is a predictor of cardiovascular disease independent of traditional risk factors, and AIP is significantly associated with major adverse cardiovascular events (MACE)[1,19]. Onat et al. found that AIP was significantly associated with cardiovascular disease risk in patients with metabolic syndrome, and therefore, AIP could serve as an effective risk stratification tool, especially in patients with metabolic syndrome[20].

The positive association between AIP and SII was more effective in predicting cardiovascular disease risk in females. In patients with type 2 diabetes, AIP more effectively predicts cardiovascular disease risk in females and serves as an independent predictor for female patients[18,19]. A study among Turkish adults also found AIP to be a stronger predictor of cardiovascular disease in females[20]. SII also serves as an independent predictor of cardiovascular disease risk in females, particularly in those with coronary artery disease, where it predicts

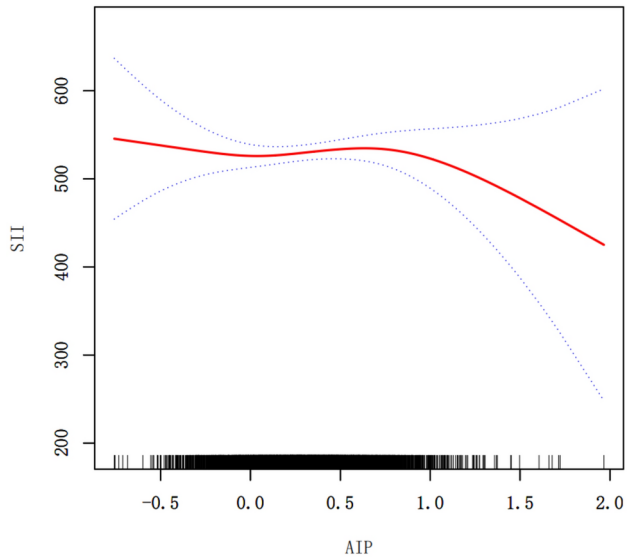

Fig. 6. Smooth curve fitting of SII and AIP in participants aged 50 years and older. Solid red lines indicate smooth curve fitting. The blue band represents the 95% confidence interval of the fitted curve. AIP, the atherogenic index of plasma; SII, the systemic immune-inflammation index.

adverse outcomes more effectively[21]. Additionally, research indicates that SII predicts cardiovascular risk better in female patients with chronic kidney disease[22].

A positive association between AIP and SII was more effective in predicting cardiovascular disease risk in younger adults (20–50 years). Dobiasova M et al. found that in young people with metabolic abnormalities, increased AIP is associated with an increased risk of atherosclerosis[2]. Studies have found that elevated SII is associated with an increased risk of adverse cardiovascular events in young patients[21]. In patients with metabolic syndrome and early atherosclerosis, the combination of AIP and SII has a higher predictive value of cardiovascular disease in young adults[9,23].

The linear positive correlation between AIP and SII, and the "inverted U-shaped" nonlinear relationship may be attributed to the interaction between inflammatory response and dyslipidemia, oxidative stress, vascular endothelial dysfunction, metabolic disorders, and other mechanisms.

First, the interaction between dyslipidemia, atherosclerosis, and inflammation is an important cause. Research shows that inflammatory substances can trigger the clotting system, emphasizing the role of inflammation in pathological thrombosis[24]. A higher AIP indicates increased small dense LDL, which is prone to oxidation and inflammation, raising SII levels[25]. Elevated adipokines such as IL-10 can increase inflammation and worsen acute myocardial infarction (AMI)[26]. Neutrophils also contribute to high SII, with studies linking cholesterol levels to neutrophil counts, as they play a role in plaque formation[27]. They can form extracellular traps (NETs), which may worsen coronary atherosclerosis[28]. When AIP is increased, high-density lipoprotein cholesterol (HDL-C) is reduced, cholesterol reverse transport is reduced, lipid accumulation is increased, and inflammatory effects are increased[29]. In early inflammation, low-density lipoprotein and triglyceride (TG) levels are elevated, leading to elevated AIP[30]. Monocytes migrate to the vessel walls, becoming macrophages that engulf oxidized LDL and form foam cells, which release inflammatory factors, worsening inflammation[31,32]. This process causes SII to increase as AIP increases. In later stages, the lipid core of coronary atherosclerotic plaque increases, and high TG and low HDL inhibit lipoprotein lipase (LPL), and continue to increase AIP[33,34]. With the stabilization of fibrous caps or calcified plaques after treatment, the risk of rupture is reduced, the level of oxidative stress is reduced, and the improvement of lipid levels can reduce SII[35,36]. Thus, the "inverted U-shape" is formed.

Second, we propose that oxidative stress plays a significant role in increasing SII and AIP values. This stress occurs when the body produces excess reactive molecules, especially during the clearance of aging cells or due to harmful stimuli[37]. The resulting imbalance can lead to tissue damage and inflammation, potentially advancing coronary atherosclerosis. As the condition progresses, oxidized low-density lipoprotein (ox-LDL) rises, triggering an inflammatory response that elevates AIP and SII[38,39]. Research shows that a heightened pro-oxidation state raises inflammatory mediators and cardiovascular risk, linking aging, inflammation, and oxidative stress[40]. In early inflammation (low AIP), oxidative stress is increased, promoting foam cell formation and atherosclerotic plaque formation[41,42]. In addition, high oxidative stress can also inhibit the production of nitric oxide, damage vascular function, and form a cycle of inflammation and oxidative stress, and SII increases with the increase of AIP[43,44]. When the SII reaches its peak, along with treatment and the production of antioxidants to protect the mechanism[35,36], endothelial function is enhanced, the level of inflammation in the body is reduced, and SII is decreased[45]. However, the lipid nuclei of coronary atherosclerotic plaques are not reduced, so AIP continues to rise[33,34]. These explain the "inverse U-shape" nonlinear relationship.

Third, elevated AIP levels can lead to endothelial dysfunction, which promotes white blood cell adhesion, worsens inflammation, and increases SII. Vascular endothelial dysfunction plays a crucial role in human growth,

anticoagulation, inflammation, and metabolism[46]. This dysfunction can accelerate vascular thrombosis, linked to inflammation, while vascular endothelial growth factor encourages platelet activation, a key factor in acute coronary syndrome (ACS)[47]. Pathologically, interactions between endothelial and smooth muscle cells can worsen coronary atherosclerosis[48]. Additionally, certain pericytes in blood vessel walls may contribute to chronic inflammatory conditions and the development of fat cells, further exacerbating coronary atherosclerosis[49]. At low AIP levels, endothelial dysfunction leads to dyslipidemia and elevated ox-LDL[36,37], increasing AIP. Inflammation triggers the expression of adhesion molecules (VCAM-1, ICAM-1) that attract monocytes and T cells, thereby increasing inflammation[50]. Concurrently, oxidative stress and thrombosis worsen, increasing reactive oxygen species (ROS) and damaging endothelial cells, contributing to increased SII[51]. After the SII reaches the threshold, endothelial dysfunction leads to lipid metabolism disorders, reduced NO production[44], impaired vasodilation, and increased Endothelin-1 exacerbates, which promotes lipid deposition in blood vessels and continues to raise AIP[47,48]. However, endothelial progenitor cells (EPCs) mobilize to the injury site, and increased vascular endothelial growth factor (VEGF) promotes endothelial repair[41], stabilizes plaques, reduces inflammation, and lowers the SII[52,53]. The two indexes appear "inverted U-shaped" nonlinear relationship.

Finally, we propose that metabolic disorders promote the positive correlation between AIP and SII. Metabolic syndrome encompasses high blood sugar, high blood pressure, dyslipidemia, and abdominal obesity, all linked to inflammation. The American Heart Association highlights the need to manage these risk factors due to their connection to cardiovascular disease[54,55]. Research shows a strong link between immune responses and metabolic regulation, with disruptions potentially leading to chronic disorders such as obesity, type 2 diabetes, and cardiovascular disease, all increasing inflammation risk[56]. In the early stages, abnormal blood sugar can activate advanced glycation end products (AGEs) and oxidative stress[3,37], while high blood pressure can lead to endothelial dysfunction[54,55]. Elevated TG and LDL levels inhibit lipoprotein lipase (LPL) activity, promote foam cell formation, and release pro-inflammatory factors like IL-6 and TNF-α, increasing AIP and SII levels[57,58]. Lipid-lowering therapy, blood glucose control weight management, and blood pressure management during repair increased HDL levels, reduced AGEs, and oxidative stress, and the inflammatory response is weakened[59,60]. At the same time, metabolism is improved, the release of inflammatory factors is reduced, anti-inflammatory factors (such as IL-10) are increased, and decreased SII[35,59,60]. However, with persistent lipid metabolism abnormalities and plaque lipid core accumulation, AIP continues to rise[33,34]. AIP and SII show an "inverted U-shaped" nonlinear relationship.

The positive correlation between AIP and SII was found only in female participants, while a non-linear relationship of "down-flat-down" was observed in male participants. It is influenced by factors such as hormone levels, metabolism, socioeconomic conditions and reproductive events. The American Heart Association stresses that early prevention can reduce females' cardiovascular disease risk, particularly during menopause[61,62]. Research indicates that recognized risk factors, such as high blood pressure and elevated LDL cholesterol, may affect women more significantly[63,64]. Furthermore, lifestyle factors like an unhealthy diet and lack of exercise have a stronger association with cardiovascular disease risk in females[65]. A study on high-risk heart disease during pregnancy found a higher incidence of cardiovascular issues, highlighting the need for early diagnosis and care[66]. Androgen has an inhibitory effect on the immune system, and men have a higher level of androgen, so the immune response is weakened, and there is a trend of "AIP increases and SII decreases"[67].

The positive correlation between AIP and SII was more significant in the 20–50 age group, showing a "down-flat-down" non-linear relationship in participants ≥ 50 years of age. It could be for the following reasons. Younger individuals, especially those under 50, experience higher mental stress and caloric consumption compared to those over 50. The American Heart Association notes that adverse experiences in adolescence can negatively impact cardiometabolic health, increasing the risk of conditions like high blood pressure and heart disease later in life[64]. Research shows that mental stress can lead to serious cardiovascular events due to excessive cardiac excitation[65]. In contrast, studies by Ryu S and Sidorov S have shown that caloric restriction (CR) -induced immunometabolic adaptation can reduce the risk of chronic diseases associated with aging [68]. Older adults are more likely to experience caloric restriction (CR) due to loss of appetite. At the same time, AIP and SII in participants aged 20–50 showed both a linear positive correlation and an "inverted U-shaped" nonlinear relationship, which be related to "the relationship between AIP and SII in the general population".

Early identification of elevated AIP and SII provides important information for lifestyle changes or therapeutic interventions to prevent cardiovascular or other inflammatory diseases. A prospective community cohort study found that early identification of elevated AIP could lead to targeted dietary and pharmacological interventions to reduce cardiovascular disease risk[69]. It has also been proved that SII can be used as an indicator for early identification of inflammatory states and provide evidence for the prevention and treatment of cardiovascular diseases[21]. The Expert Consensus on Clinical Pathways for Coronary Flow Reserve Score Measurement in China highlights the significance of coronary flow reserve score (FFR) in diagnosing and treating coronary heart disease[70]. Elevated AIP suggests a higher risk of coronary atherosclerosis[1], and FFR measurement aids in assessing lesion severity for precise treatment[70]. The Expert Consensus on Antithrombotic Therapy for panvascular Disease in China (2024 edition) provides comprehensive and standardized guidance on antithrombotic therapy for panvascular disease in China, emphasizing individualized therapy and multidisciplinary cooperation [71]. The combined use of AIP and SII improves the ability to predict cardiovascular disease risk in patients with metabolic syndrome[9,23]. This approach has important value in clinical practice to better assess and manage cardiovascular disease risk in this population[9,23].

Classical inflammatory markers CRP and IL-6 have limited predictive power, especially in high-risk populations, and their incremental predictive value is low[72]. Studies have shown that markers such as ESR and TNF-α have limited predictive power and should be combined with other markers[73,74]. In contrast, SII is superior to traditional markers in predicting cardiovascular prognosis[74,75], and AIP is particularly important for patients

with abnormal lipid metabolism[76]. Moreover, the combination of AIP and SII can provide a more comprehensive assessment of inflammation and cardiovascular risk[9,23].

Emerging cardiometabolic markers are increasingly important in assessing the risk of cardiovascular disease and metabolic dysfunction. The TyG index (triglyceride-glucose index) is a reliable marker of insulin resistance, closely linked to metabolic syndrome, type 2 diabetes, gallstone and cardiovascular disease, and helps identify high-risk groups[77–79]. AIP focuses on atherosclerotic lipid composition, correlating with atherosclerosis, coronary heart disease, and stroke, offering high predictive value for cardiovascular risk in those with abnormal lipid metabolism[72]. SII assesses atherosclerotic plaque instability, myocardial damage, overall inflammation, and immune status[74]. Together, the TyG index, AIP, and SII provide valuable insights for evaluating cardiovascular risk based on metabolic dysfunction, lipid metabolism, and inflammatory responses, aiding clinicians in managing at-risk populations[9,70,77].

A key strength of this study is that it uses a complex multi-stage probability sampling design that incorporates weights from the NHANES database. Our analysis includes data from the NHANES database from 2005 to 2018, providing a long time frame and a relatively large sample size, which helps our findings be representative. However the study did have some limitations, and the cross-sectional design prevented us from establishing a causal relationship between AIP and SII. In addition, since AIP and SII are derived from formulas, the data inclusion or calculation methods for these indicators may not be accurate. Then, we were then unable to further analyze drug use that might have influenced the study design and excluded "cancer" and "autoimmune disease patients" from the inclusion in this study because the NHANES database did not have data on participants' specific drug use and a clear diagnosis of "cancer" and "autoimmune disease patients." Finally, the limitations of the NHANES database prevented us from including all potential covariates that could affect subjects' AIP and SII. Despite these limitations, the observed correlation between SII and AIP seems stable enough to suggest that it is unlikely to be significantly influenced by unexplained factors.

Conclusion

The results of this cross-sectional study show that there is a significant positive correlation between AIP and SII. In the fully adjusted model (Model 3), for every 1 unit increase in AIP, the SII increases by 32.497 units ($P = 0.021$). At the same time, there is also an "inverted U-shape" nonlinear relationship between AIP and SII, with an inflection point at AIP = 0.82. The positive association between AIP and SII was significant only among females and participants under 50. Our study fills in the gaps in the relationship between AIP and SII, providing new insights into the immune mechanisms of cardiovascular and inflammatory diseases. At the same time, this suggests that in clinical practice, more aggressive medical and nursing interventions may be needed if patients exhibit high levels of AIP and SII.

Data availability

The study utilized publicly available datasets found in the NHANES database. For further inquiries, please contact the corresponding author. Access the NHANES database at: (https://www.cdc.gov/nchs/NHANES/index.htm).

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Author contributions

Conceptualization and study design: J.Y.-L. and M.S. Data extraction and management: J.Y.-L. and J.R.-L. Data integration, statistics, analysis, and validation: JY-L and R.C.-L. Charts and software: J.Y.-L. and J.R.-L. Writing—Original draft: J.Y.-L. Supervision and review: M.S. and D.H. Manuscript revision: J.Y.-L. All authors contributed to the article and approved the submitted version.

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The authors declare no competing interests.

Ethics approval and consent to participate
Our research involving human materials and data from all participants was conducted in accordance with the Helsinki Declaration. All survey protocols received approval from the National Health Statistics Review Board. Each participant provided written informed consent before taking part in the study.

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