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Atherogenic index of plasma and obesity-related risk of stroke in middle-aged and older Chinese adults: a national prospective cohort study

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Abstract

Backgroud The association between the atherogenic index of plasma (AIP) and stroke risk is uncertain. Overweight and obese individuals frequently develop atherosclerosis, suggesting AIP may mediate the relationship between body mass index (BMI) and stroke risk. This study investigates whether AIP mediates the BMI-stroke association and evaluates the interaction effects of AIP and BMI on stroke risk in middle-aged and older Chinese adults.

Method This study analyzes data from the China Health and Retirement Longitudinal Study (CHARLS), an ongoing nationally representative prospective cohort study that began in 2011. It includes 8 598 middle-aged and older Chinese adults without stroke at baseline. A mediation analysis, employing a novel two-stage regression method, was conducted to evaluate the indirect effect of BMI on stroke through AIP.

Results During a median follow-up of 7.1 years, 615 (7.2%) participants developed a stroke. After adjusting for confounders, AIP was significantly associated with stroke risk (hazard ratio [HR] per 1-SD increase, 1.24; 95% CI 1.14–1.35). Mediation analysis indicated that compared to normal weight, obesity similarly raised stroke risk by 78.0% (HR 1.78, 95% CI 1.40–2.27), with 29.67% (95% CI 14.27–45.08%) of the association mediated through AIP (HR 1.15, 95% CI 1.08–1.23). No significant multiplicative or additive interactions were observed between BMI and AIP on stroke.

Conclusions This study found that the AIP appeared to be associated with stroke risk and mediates the association between obesity and stroke among middle-aged and older Chinese adults.

Keywords Stroke, Atherogenic index of plasma, Body mass index, CHARLS

Intrduction

Stroke remains a leading cause of disability and mortality worldwide, particularly among middle-aged and older adults [1, 2]. Identifying modifiable risk factors and understanding their interactions are crucial for developing preventive strategies [3]. Obesity, as measured by body mass index (BMI), is a well-established risk factor for stroke [4–6]. The prevalence of obesity is rising globally and is projected to increase by 40% by 2027 [7], highlighting the urgency of addressing its health implications. In addition to obesity, dyslipidemia, characterized by

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elevated levels of triglycerides and cholesterol, is a significant contributor to stroke [3, 8–11].

Atherogenic index of plasma (AIP), calculated as the logarithm of the ratio of plasma triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C) [12], has emerged as a robust predictor of cardiovascular risk [13, 14]. Higher AIP values reflect an atherogenic lipid profile, which is strongly associated with increased stroke risk [15, 16]. Previous studies [15–17] have primarily focused on individual risk factors rather than their combined effects on stroke. Moreover, the potential mediating role of AIP in the relationship between BMI and stroke risk remains underexplored. Understanding this mediation pathway could provide valuable insights into the mechanisms underlying stroke development and identify potential targets for intervention.

To date, limited studies have explored the joint effects of AIP and BMI on stroke risk, particularly in the Chinese population. Moreover, the potential mediating role of AIP in the association between BMI and stroke remains under-investigated. This nationwide prospective cohort study aims to fill this gap by examining the interacting and joint effects of AIP and BMI on stroke risk among middle-aged and older Chinese adults. We hypothesize that AIP significantly mediates the relationship between BMI and stroke risk, thus highlighting the importance of lipid management in obese individuals for stroke prevention.

Methods

Study design and population

This study used data from the China Health and Retirement Longitudinal Study (CHARLS), a publicly available dataset. CHARLS, a longitudinal survey, follows participants biennially, targeting individuals aged 45 and older living in private households across mainland China [18]. To ensure national representativeness, CHARLS employs a multi-stage probability sampling design, encompassing 28 provinces, 150 counties or districts, and 450 villages or urban communities [18]. Detailed information about the study design of the CHARLS is provided in Supplementary Methods.

In this present study, we utilized data from 2011 to 2018 of CHARLS, covering the wave from 1 to 4, all participants were followed up every 2 years after the baseline survey (wave 1). Trained interviewers conducted the data collection. When respondents were unable or unwilling to participate, proxy respondents, usually a spouse or another family member, were used, accounting for about 8% of all interviews. CHARLS gathered data on demographic information, social connections, health conditions and diagnoses, medical examination results, lifestyle behaviors, and blood samples. The approach, sampling techniques, and quality control measures of CHARLS are thoroughly documented in other sources. Of the 17 808 participants, we excluded 2 493 individuals aged < 45 years, those with stroke at baseline or lost to follow-up. We further excluded 6 617 participants due to missing or extreme AIP and BMI values, resulting in a final sample of 8 598 participants for analysis. The detailed selection process is presented in Fig. 1. A comparison of baseline characteristics between included and excluded analysts is presented in Table S1.

All participants provided informed consent, and the protocol was approved by the Ethical Review Committee of Peking University (IRB00001052-11,015). This study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [19].

Definitions of Exposure, Mediator, and Outcome

BMI, calculated from height and weight records as weight in kilograms divided by height in meters squared, was categorized according to the Chinese BMI Classification [20] definition into underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–23.9 kg/m^2), overweight (BMI 24.0–27.9 kg/m^2), and obesity (BMI ≥ 28 kg/m^2). Underweight and normal weight were combined into one group, collectively referred to as normal weight. The mediator AIP was determined using the formula ln [TG (mg/dl)/HDL-C (mg/dl)] [15] and divided into quartiles: Quartile 1 (< 0.26), Quartile 2 (0.26 ~ 0.72), Quartile 3 (0.73 ~ 1.23), and Quartile 4 (> 1.23). The outcome

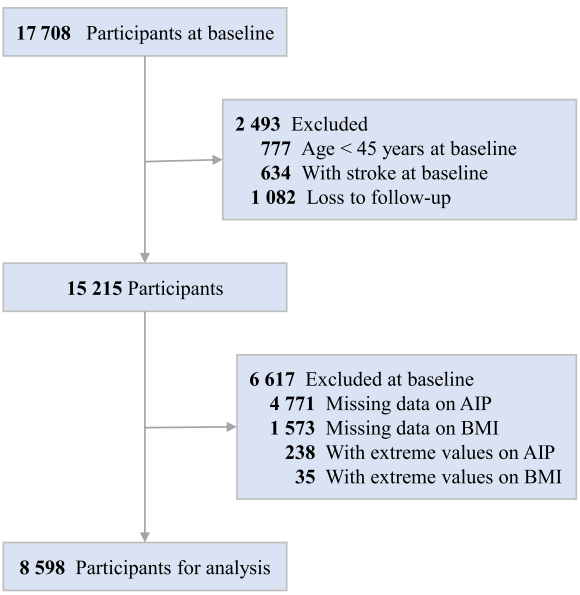

Fig. 1 Selection process of the study population. AIP, Atherogenic index of plasma; BMI, Body mass index

of interest, stroke, was defined, consistent with previous studies [21], as self-reported physician-diagnosed stroke (see Supplementary Methods for details). The date of stroke diagnosis was documented as the interval between the date of the last interview and the date of the interview reporting the incident stroke [21].

Covariates

Covariates of interest included sociodemographic characteristics (age, gender, marital status, education level, and living residence), health behaviors (smoking status, drinking status), and health status indicators (systolic blood pressure [SBP], diastolic blood pressure [DBP], history of diabetes, hypertension, kidney disease, and heart disease; glycated hemoglobin [HbA1c], C-reactive protein [CRP], estimated glomerular filtration rate [eGFR]). Detailed information on covariates is provided in Supplementary Methods.

Statistical analysis

Statistical analysis was conducted from May 13, 2024, to June 15, 2024. Data were presented as percentages for categorical variables and means ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and compared between groups using the chi-squared test, analysis of variance or the Kruskal–Wallis test, as appropriate.

Cox proportional hazards regression model was first used to estimate the associations of BMI and AIP with stroke, the proportional hazards assumption was examined by creating a product term of follow-up time and BMI or AIP, and we found no significant deviation from the assumption, the effect sizes were denoted hazard ratios (HRs) with 95% confidence intervals (CIs). Then, multiple linear regression was used to estimate th association between BMI and AIP, the effect sizes were denoted regression coefficient (β) with 95%CIs.

We further conducted a stratified analysis by BMI to investigate associations of AIP quartiles with stroke. To assess the additive and multiplicative interactions of BMI and AIP on stroke, we included a product term of BMI (categorized as normal weight, overweight, and obesity) and AIP (Quartiles 1 to 4) in the model. The HR with its 95% CI for the product term assessed interaction on the multiplicative scale. For the additive scale, interaction was measured using the synergy index (SI) [22] and its 95% CI, calculated from the coefficients, standard errors, and covariance matrix of the product term, BMI, and AIP. An SI greater than 1 denotes a synergistic interaction, while an SI less than 1 indicates an antagonistic interaction [22].

To assess the joint associations of BMI and AIP with stroke, we classified participants into 12 groups based on BMI (categorized as normal weight, overweight, and obesity) and AIP (Quartiles 1 to 4). We then estimated HRs for incident stroke in each group compared to those with normal weight and AIP in Quartile 1.

To assess the mediation of the association between BMI and stroke via AIP, we employed the two-stage regression method proposed by VanderWeele [23] (see Supplementary Methods for details). The proportion of the association between BMI and stroke mediated through AIP was calculated as a measure of the indirect association's contribution relative to the total association on the log-transformed HR scale, using log(indirect association HR)/log(total association HR) [24, 25].

In all regression analyses, we estimated two models. Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, marital status, residence, education level, smoking status, drinking status, SBP, DBP, and history of diabetes, hypertension, kidney disease, and heart disease, as well as HbA1C, CRP, and eGFR. Missing values of covariates were assumed to be missing at random and were imputed using chained equations based on the covariates in the adjustment model. The missing rates of covariates were summarized in Table S2-3.

We used the area under receiver operating characteristic curves (AUC) and decision curve to assess the predictive value of AIP and BMI alone or in combination for stroke, and we used the net reclassification index (NRI) [26] to compare whether AIP and BMI combined were more predictive of stroke than AIP and BMI alone.

To test potential variations across different subgroups, we stratified all analyses by sex. We also conducted several sensitivity analyses to assess robustness. First, we repeated the main analysis in subpopulations of 8 371 participants with complete data. Second, we excluded adjustments for SBP, DBP, diabetes, hypertension, kidney disease, and heart disease, as these factors may mediate the relationship between BMI and stroke [27–29]. Third, we excluded participants with incident stroke during the second wave of follow-up to reduce potential reverse causation. Finally, to ensure the temporality between exposure and mediator, we repeated the main analysis using AIP at wave 3 as the mediator, excluding participants with a history of stroke before wave 3.

We conducted all statistical analysis using R software (version 4.3.3). Interaction analysis was performed with the epiR package (version 2.0.74), and mediation analysis with the CMAverse package (version 0.1.0). P-values < 0.05 were considered statistically significant.

Results

Baseline characteristics of the study population

A total of 8598 participants from CHARLS were included in the analysis. The mean age of participants

was 59.07 ± 9.20 years, with 3985 (46.3%) being men. Baseline characteristics categorized by BMI are presented in Table 1, and by AIP quartiles in Table 2. Additionally, baseline characteristics of participants using unimputed data are described in Tables S4 and S5, showing similar results to Tables 1 and 2. At baseline, the mean AIP was 0.76 ± 0.69, the mean BMI was 23.39 ± 3.62 kg/m^2, with an overweight prevalence of 29.1% (2 504/8 598) and an obesity prevalence of 10.8% (931/8 598). During a median follow-up of 7.1 years, 615 (7.2%) participants developed stroke.

Associations of BMI and AIP with incident stroke

Table S6 presents the association of BMI with the risks of incident stroke. After adjusting for confounders, overweight and obese participants had significantly elevated risks of incident stroke compared to normal-weight participants (overweight: HR 1.23, 95% CI 1.02–1.48; obesity: HR 1.38, 95% CI 1.08–1.75). Table S7 presents the association of AIP with the risks of incident stroke. After adjusting for confounders, compared to quartile 1, the adjusted HRs were 1.29 (95% CI 0.99–1.67) for quartile 2, 1.62 (95% CI 1.26–2.07) for quartile 3, and 1.69 (95% CI 1.32–2.16) for quartile 4. These findings indicate a linear

Table 1 Baseline characteristics of participants categorized by BMI

Variables	Normal weight (n = 5163)	Overweight (n = 2504)	Obesity (n = 931)	P value
Age (years), mean ± SD	60.11 ± 9.47	57.76 ± 8.66	56.85 ± 8.19	< 0.001[a]
Age ≥ 60 years, n (%)	2477 (48.0%)	980 (39.1%)	324 (34.8%)	< 0.001[b]
Men, n (%)	2676 (51.8%)	1015 (40.5%)	294 (31.6%)	< 0.001[b]
Married, n (%)	4207 (81.5%)	2178 (87.0%)	804 (86.4%)	< 0.001[b]
Rural residence, n (%)	3638 (70.5%)	1489 (59.5%)	518 (55.6%)	< 0.001[b]
Education level, n (%)				< 0.001[b]
No formal education	1605 (31.1%)	673 (26.9%)	257 (27.6%)	
Primary school	2198 (42.6%)	973 (38.9%)	356 (38.2%)	
Middle or high school	1236 (23.9%)	754 (30.1%)	289 (31.0%)	
College or above	124 (2.4%)	104 (4.2%)	29 (3.1%)	
Smoking status, n (%)				< 0.001[b]
Never	2868 (55.5%)	1695 (67.7%)	701 (75.3%)	
Former	414 (8.0%)	234 (9.3%)	79 (8.5%)	
Current	1881 (36.4%)	575 (23.0%)	151 (16.2%)	
Drinking status, n (%)				< 0.001[b]
Never	2885 (55.9%)	1564 (62.5%)	632 (67.9%)	
Former	433 (8.4%)	191 (7.6%)	85 (9.1%)	
Current	1845 (35.7%)	749 (29.9%)	214 (23.0%)	
SBP (mmHg), mean ± SD	126.65 ± 21.03	132.03 ± 21.18	136.17 ± 21.14	< 0.001[a]
DBP (mmHg), mean ± SD	73.09 ± 11.76	77.53 ± 11.97	80.52 ± 12.16	< 0.001[a]
Diabetes, n (%)	624 (12.1%)	437 (17.5%)	224 (24.1%)	< 0.001[b]
Hypertension, n (%)	1702 (33.0%)	1162 (46.4%)	588 (63.2%)	< 0.001[b]
Kidney disease, n (%)	288 (5.6%)	151 (6.0%)	55 (5.9%)	0.709[b]
Heart disease, n (%)	487 (9.4%)	329 (13.1%)	175 (18.8%)	< 0.001[b]
HbA1c (%), mean ± SD	5.20 ± 0.75	5.32 ± 0.85	5.45 ± 0.84	< 0.001[a]
CRP (mg/l), median (IQR)	0.84 (0.48, 1.85)	1.14 (0.64, 2.16)	1.69 (0.90, 3.36)	< 0.001[c]
eGFR, ml/min/1.73 m^2, median (IQR)	72.46 (52.76, 94.96)	72.91 (55.20, 97.19)	72.87 (55.19, 95.75)	0.117[c]
BMI(kg/m^2), mean ± SD	21.03 ± 1.98	25.72 ± 1.13	30.19 ± 2.02	< 0.001[a]
TG (mg/dl), median (IQR)	92.93 (68.14, 131.87)	118.15 (84.96, 170.80)	138.95 (99.56, 190.27)	< 0.001[c]
HDL-C, mean ± SD	54.94 ± 15.24	47.87 ± 12.90	44.60 ± 11.71	< 0.001[a]
AIP, median (IQR)	0.55 (0.13, 1.02)	0.93 (0.48, 1.44)	1.15 (0.74, 1.58)	< 0.001[c]

AIP Atherogenic index of plasma, *BMI* Body mass index, *CRP* C-reactive protein, *DBP* Diastolic blood pressure, *eGFR* Estimated glomerular filtration rate, *HbA1c* Glycated hemoglobin, *HDL-C* High-density lipoprotein cholesterol, *IQR* Interquartile range, *SBP* Systolic blood pressure, *SD* Standard deviation, *TG* Triglyceride

[a] Calculated by one-way analysis of variance

[b] Calculated by Pearson's Chi-squared test

[c] Calculated by Kruskal–Wallis rank sum test

Table 2 Baseline characteristics of participants categorized by AIP quartiles

Variables	Quartile 1 (n = 2150)	Quartile 2 (n = 2149)	Quartile 3 (n = 2149)	Quartile 4 (n = 2150)	P value
Age (years), mean ± SD	59.56 ± 9.59	59.14 ± 9.23	59.09 ± 9.14	58.50 ± 8.78	0.002[a]
Age ≥ 60 years, n (%)	984 (45.8%)	954 (44.4%)	957 (44.5%)	886 (41.2%)	0.019[b]
Men, n (%)	1102 (51.3%)	1010 (47.0%)	936 (43.6%)	937 (43.6%)	< 0.001[b]
Married, n (%)	1788 (83.2%)	1765 (82.1%)	1789 (83.2%)	1847 (85.9%)	0.007[b]
Rural residence, n (%)	1553 (72.2%)	1449 (67.4%)	1374 (63.9%)	1269 (59.0%)	< 0.001[b]
Education level, n (%)					0.065[b]
No formal education	656 (30.5%)	642 (29.9%)	636 (29.6%)	601 (28.0%)	
Primary school	901 (41.9%)	893 (41.6%)	870 (40.5%)	863 (40.1%)	
Middle or high school	544 (25.3%)	547 (25.5%)	582 (27.1%)	606 (28.2%)	
College or above	49 (2.3%)	67 (3.1%)	61 (2.8%)	80 (3.7%)	
Smoking status, n (%)					0.001[b]
Never	1246 (58.0%)	1304 (60.7%)	1363 (63.4%)	1354 (63.0%)	
Former	189 (8.8%)	165 (7.7%)	178 (8.3%)	195 (9.1%)	
Current	715 (33.3%)	680 (31.6%)	608 (28.3%)	601 (28.0%)	
Drinking status, n (%)					< 0.001[b]
Never	1130 (52.6%)	1265 (58.9%)	1322 (61.5%)	1363 (63.4%)	
Former	149 (6.9%)	184 (8.6%)	213 (9.9%)	162 (7.5%)	
Current	871 (40.5%)	700 (32.6%)	614 (28.6%)	625 (29.1%)	
SBP (mmHg), mean ± SD	126.48 ± 21.25	128.08 ± 21.05	130.34 ± 21.53	131.96 ± 20.96	< 0.001[a]
DBP (mmHg), mean ± SD	73.08 ± 12.12	74.28 ± 11.73	76.11 ± 12.31	77.21 ± 12.00	< 0.001[a]
Diabetes, n (%)	185 (8.6%)	261 (12.1%)	340 (15.8%)	499 (23.2%)	< 0.001[b]
Hypertension, n (%)	698 (32.5%)	760 (35.4%)	947 (44.1%)	1047 (48.7%)	< 0.001[b]
Kidney disease, n (%)	123 (5.7%)	132 (6.1%)	123 (5.7%)	115 (5.3%)	0.740[b]
Heart disease, n (%)	188 (8.7%)	207 (9.6%)	274 (12.8%)	323 (15.0%)	< 0.001[b]
HbA1c (%), mean ± SD	5.15 ± 0.62	5.21 ± 0.71	5.27 ± 0.82	5.40 ± 0.96	< 0.001[a]
CRP (mg/l), median (IQR)	0.76 (0.45, 1.74)	0.89 (0.51, 1.87)	1.08 (0.58, 2.20)	1.32 (0.72, 2.68)	< 0.001[c]
eGFR, ml/min/1.73 m^2, median (IQR)	70.77 (52.33, 91.69)	72.38 (51.98, 94.43)	72.87 (53.67, 95.91)	76.17 (56.72, 100.74)	< 0.001[c]
BMI(kg/m^2), mean ± SD	21.86 ± 3.13	22.77 ± 3.40	23.92 ± 3.58	25.00 ± 3.55	< 0.001[a]
TG (mg/dl), median (IQR)	61.06 (52.22, 71.68)	88.50 (77.00, 101.78)	123.01 (106.20, 140.71)	195.59 (161.07, 244.26)	< 0.001[c]
HDL-C, mean ± SD	67.08 ± 13.54	54.65 ± 10.20	47.27 ± 8.54	38.05 ± 7.99	< 0.001[a]
AIP, median (IQR)	− 0.03 (− 0.24, 0.13)	0.50 (0.38, 0.62)	0.96 (0.84, 1.09)	1.59 (1.39, 1.91)	< 0.001[c]

AIP Atherogenic index of plasma, *BMI* Body mass index, *CRP* C-reactive protein, *DBP* Diastolic blood pressure, *eGFR* Estimated glomerular filtration rate, *HbA1c* Glycated hemoglobin, *HDL-C* High-density lipoprotein cholesterol, *IQR* Interquartile range, *SBP* Systolic blood pressure, *SD* Standard deviation, *TG* Triglyceride

[a] Calculated by one-way analysis of variance

[b] Calculated by Pearson's Chi-squared test

[c] Calculated by Kruskal–Wallis rank sum test

and positive association between AIP and the risk of incident stroke (for trend, P < 0.001). For each SD increase in AIP, stroke risk increased by 24.0% (HR 1.24, 95% CI 1.14–1.35).

Associations of BMI with AIP

Table S8 presents the association between BMI and AIP levels. After adjusting for confounders, overweight and obese participants had significantly elevated AIP levels compared to normal-weight participants (overweight: β 0.31, 95% CI 0.28–0.34; obesity: β 0.46, 95% CI 0.41–0.51).

Interaction and joint analysis of BMI and AIP with incident stroke

Figure 2 illustrates the joint association of BMI and AIP on stroke. The HR for stroke among individuals with obesity and quartile 4 of AIP, compared to those with normal weight and quartile 1 of AIP, was 2.01 (95% CI 1.39–2.90) after adjusting for confounders. This pattern was consistent when stratified by sex. Figure 3 presents the interaction of BMI and AIP on stroke. A higher AIP level was associated with increased stroke risk across various BMI subgroups. However, no significant multiplicative or additive interactions were observed between BMI

A: All participants

AIP	BMI	Event / total No.	HR (95% CI), model 1 [a]	HR (95% CI), model 2 [b]
Quartile 1	Normal weight	81 / 1697	Reference	Reference
Quartile 1	Overweight	18 / 374	1.06 (0.63–1.76)	0.93 (0.56–1.56)
Quartile 1	Obesity	4 / 79	1.13 (0.41–3.10)	0.80 (0.29–2.18)
Quartile 2	Normal weight	79 / 1448	1.17 (0.86–1.60)	1.14 (0.84–1.56)
Quartile 2	Overweight	44 / 555	1.77 (1.22–2.55)	1.59 (1.09–2.30)
Quartile 2	Obesity	11 / 146	1.77 (0.94–3.33)	1.18 (0.62–2.24)
Quartile 3	Normal weight	81 / 1137	1.53 (1.12–2.08)	1.40 (1.03–1.91)
Quartile 3	Overweight	69 / 726	2.21 (1.60–3.05)	1.74 (1.25–2.42)
Quartile 3	Obesity	33 / 286	2.74 (1.82–4.11)	1.92 (1.26–2.91)
Quartile 4	Normal weight	69 / 881	1.79 (1.30–2.47)	1.59 (1.15–2.20)
Quartile 4	Overweight	75 / 849	1.98 (1.45–2.72)	1.58 (1.14–2.19)
Quartile 4	Obesity	51 / 420	2.98 (2.09–4.24)	2.01 (1.39–2.90)

B: Men

Quartile 1	Normal weight	49 / 953	Reference	Reference
Quartile 1	Overweight	5 / 129	0.69 (0.27–1.73)	0.58 (0.23–1.47)
Quartile 1	Obesity	1 / 20	0.88 (0.12–6.37)	0.51 (0.07–3.73)
Quartile 2	Normal weight	38 / 733	1.03 (0.67–1.57)	0.99 (0.65–1.52)
Quartile 2	Overweight	22 / 230	1.91 (1.16–3.17)	1.64 (0.98–2.75)
Quartile 2	Obesity	3 / 47	1.24 (0.39–3.97)	0.79 (0.24–2.57)
Quartile 3	Normal weight	39 / 570	1.34 (0.88–2.04)	1.21 (0.79–1.86)
Quartile 3	Overweight	33 / 286	2.45 (1.57–3.81)	1.82 (1.15–2.87)
Quartile 3	Obesity	13 / 80	3.52 (1.91–6.49)	2.54 (1.34–4.79)
Quartile 4	Normal weight	39 / 420	1.96 (1.28–2.98)	1.80 (1.17–2.75)
Quartile 4	Overweight	36 / 370	2.01 (1.30–3.09)	1.65 (1.05–2.59)
Quartile 4	Obesity	22 / 147	3.26 (1.97–5.40)	2.21 (1.30–3.76)

C: Women

Quartile 1	Normal weight	32 / 744	Reference	Reference
Quartile 1	Overweight	13 / 245	1.33 (0.70–2.54)	1.27 (0.66–2.43)
Quartile 1	Obesity	3 / 59	1.28 (0.39–4.19)	1.01 (0.31–3.30)
Quartile 2	Normal weight	41 / 715	1.34 (0.84–2.13)	1.34 (0.84–2.14)
Quartile 2	Overweight	22 / 325	1.64 (0.95–2.82)	1.56 (0.90–2.70)
Quartile 2	Obesity	8 / 99	2.15 (0.99–4.66)	1.50 (0.68–3.30)
Quartile 3	Normal weight	42 / 567	1.75 (1.10–2.76)	1.64 (1.03–2.61)
Quartile 3	Overweight	36 / 440	2.02 (1.25–3.25)	1.67 (1.03–2.71)
Quartile 3	Obesity	20 / 206	2.39 (1.37–4.19)	1.69 (0.95–3.00)
Quartile 4	Normal weight	30 / 461	1.59 (0.97–2.61)	1.39 (0.84–2.31)
Quartile 4	Overweight	39 / 479	1.93 (1.21–3.09)	1.51 (0.93–2.45)
Quartile 4	Obesity	29 / 273	2.78 (1.68–4.60)	1.94 (1.15–3.27)

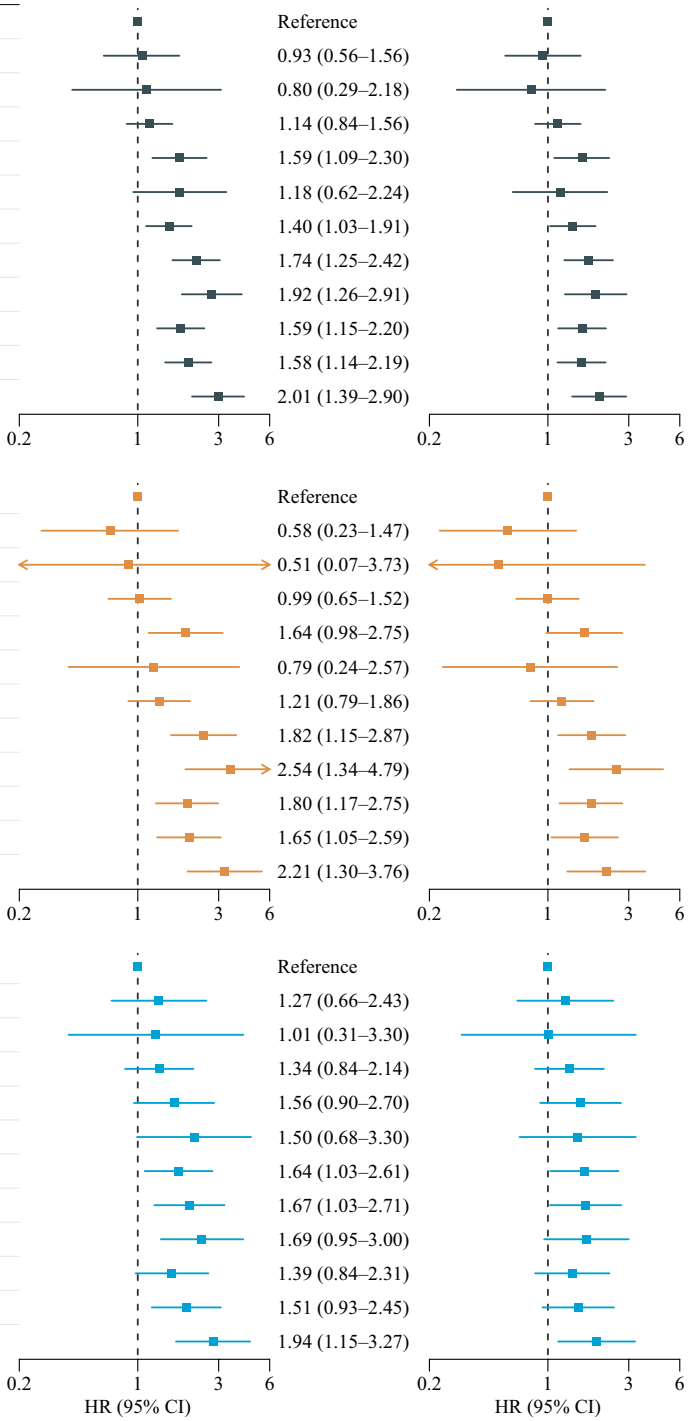

Fig. 2 Joint associations of AIP and BMI with stroke. Graphs show HRs and 95% CIs for stroke in all participants (**A**), men (**B**) or women (**C**) adjusted for age and gender in model 1 (a); and adjusted for age, gender, marital status, residence, education level, smoking status, drinking status, systole blood pressure, diastolic blood pressure, diabetes, hypertension, kidney disease, heart disease, glycated hemoglobin, high-sensitivity C-reactive protein, and estimated glomerular filtration rate in model 2 (b). AIP, Atherogenic index of plasma; BMI, Body mass index; CI, Confidence interval; HR, Hazard ratio

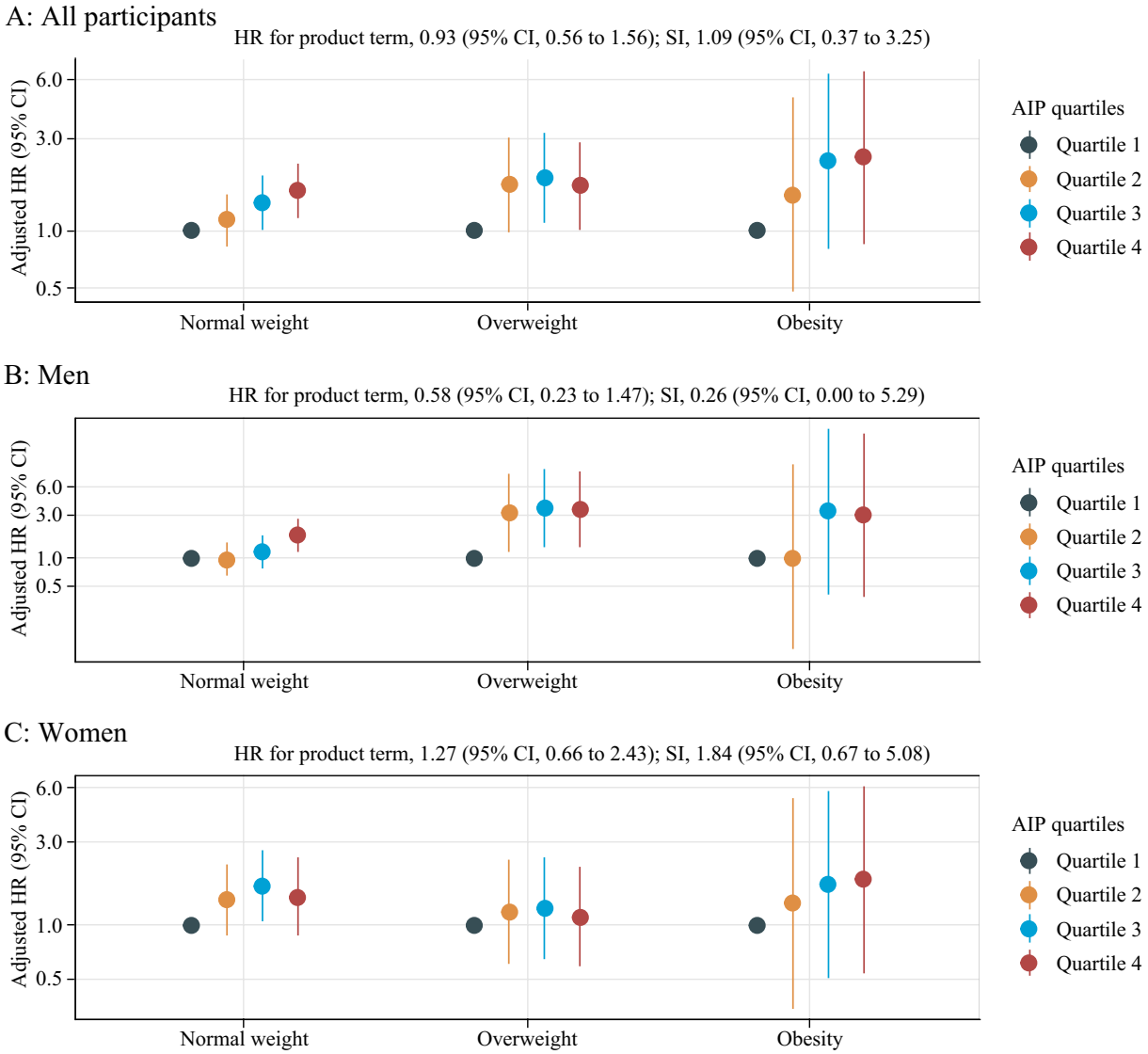

Fig. 3 Associations of AIP with incident stroke by BMI. HRs and 95% CIs for stroke in all participants (**A**), men (**B**) or women (**C**) adjusted for age, gender, marital status, residence, education level, smoking status, drinking status, systole blood pressure, diastolic blood pressure, diabetes, hypertension, kidney disease, heart disease, glycated hemoglobin, high-sensitivity C-reactive protein, and estimated glomerular filtration rate. A Multiplicative interaction was evaluated using HRs for the product term between the AIP and BMI and the multiplicative interaction was statistically significant when its CIs did not include 1. dditive interaction was evaluated using SI between the AIP and BMI, and the additive interaction was statistically significant SI's CIs did not include 1. AIP, Atherogenic index of plasma; BMI, Body mass index; CI, Confidence interval; HR, Hazard ratio; SI, synergy index

and AIP on stroke (Multiplicative interaction: HR 0.93, 95% CI 0.56–1.56; Additive interaction: SI 1.09, 95% CI 0.37–3.25). These patterns were consistent in both men and women.

Mediation analysis of AIP on association of BMI with incident stroke

Mediation analysis (Table 3) revealed an indirect association with a HR of 1.08 (95% CI 1.04–1.13) for overweight versus normal weight, increasing to 1.15 (95% CI 1.08–1.23) for the obesity group after adjusting for confounders. The proportions mediated were 25.73% (95% CI 9.74–41.71) for overweight and 29.67% (95% CI 14.27–45.08) for obesity. These results were consistent across both men and women.

Table 3 Decomposition of the total association between BMI and the risk of stroke into direct and indirect associations mediated by the AIP

Models	Association, HR (95% CI)			Proportion mediated, %
	Total	Direct	Indirect	
All participants				
Model 1[a]				
Normal weight	1 (Reference)			
Overweight	1.43 (1.20 to 1.71)	1.30 (1.09 to 1.57)	1.10 (1.05 to 1.14)	29.68 (12.34 to 47.03)
Obesity	1.96 (1.55 to 2.47)	1.67 (1.31 to 2.12)	1.17 (1.10 to 1.25)	30.14 (16.49 to 43.79)
Model 2[b]				
Normal weight	1 (Reference)			
Overweight	1.43 (1.20 to 1.72)	1.32 (1.10 to 1.59)	1.08 (1.04 to 1.13)	25.73 (9.74 to 41.71)
Obesity	1.78 (1.40 to 2.27)	1.55 (1.21 to 1.99)	1.15 (1.08 to 1.23)	29.67 (14.27 to 45.08)
Men				
Model 1[a]				
Normal weight	1 (Reference)			
Overweight	1.58 (1.23 to 2.04)	1.40 (1.08 to 1.81)	1.13 (1.06 to 1.21)	31.80 (11.01 to 52.60)
Obesity	2.31 (1.62 to 3.28)	1.91 (1.33 to 2.74)	1.21 (1.09 to 1.34)	30.64 (14.00 to 47.27)
Model 2[b]				
Normal weight	1 (Reference)			
Overweight	1.60 (1.23 to 2.08)	1.44 (1.10 to 1.88)	1.11 (1.05 to 1.19)	27.16 (8.13 to 46.19)
Obesity	2.14 (1.47 to 3.12)	1.81 (1.23 to 2.66)	1.18 (1.08 to 1.30)	29.15 (11.42 to 46.88)
Women				
Model 1[a]				
Normal weight	1 (Reference)			
Overweight	1.31 (1.02 to 1.68)	1.22 (0.95 to 1.58)	1.07 (1.02 to 1.13)	27.50 (– 2.78 to 57.78)
Obesity	1.77 (1.30 to 2.39)	1.55 (1.13 to 2.12)	1.14 (1.04 to 1.25)	28.65 (6.84 to 50.47)
Model 2[b]				
Normal weight	1 (Reference)			
Overweight	1.28 (0.99 to 1.65)	1.21 (0.94 to 1.57)	1.06 (1.00 to 1.11)	24.62 (– 6.49 to 55.74)
Obesity	1.61 (1.18 to 2.20)	1.44 (1.04 to 1.98)	1.12 (1.03 to 1.23)	28.91 (3.62 to 54.21)

AIP Atherogenic index of plasma, *BMI* Body mass index, *CI* Confidence interval, *HR* Hazard ratio

[a] Adjusted for age and gender

[b] Adjusted for age, gender, marital status, residence, education level, smoking status, drinking status, systole blood pressure, diastolic blood pressure, diabetes, hypertension, kidney disease, heart disease, glycated hemoglobin, high-sensitivity C-reactive protein, and estimated glomerular filtration rate

Predictive value of BMI combined with AIP on incident stroke

We evaluated the improved predictive value of combining BMI and AIP versus their individual performance. The ROC curve showed an AUC of 0.59 (95% CI 0.57–0.61) for the combined metric (Fig. 4A), and the decision curve validated its clinical significance (Fig. 4B). Notably, the BMI + AIP combination significantly outperformed the individual BMI and AIP metrics (Fig. 4C). For example, the continuous NRIs were significant when comparing BMI + AIP to BMI (NRI 0.135, 95% CI 0.053–0.217) or AIP (NRI 0.130, 95% CI 0.048–0.212).

Sensitivity analysis

When using complete data without imputation, consistent results were observed in the joint analysis (Figure S1), interaction analysis (Table S9), and mediation analysis (Table S10). Furthermore, the results remained consistent with the main analyses after excluding adjustments for SBP, DBP, diabetes, hypertension, kidney disease, and heart disease (Figure S2 and Table S11-12); excluding participants who experienced a stroke within the second wave of follow-up (Figure S3 and Table S13-14); and using AIP at wave 3 as the mediator (Figure S4 and Table S15-16).

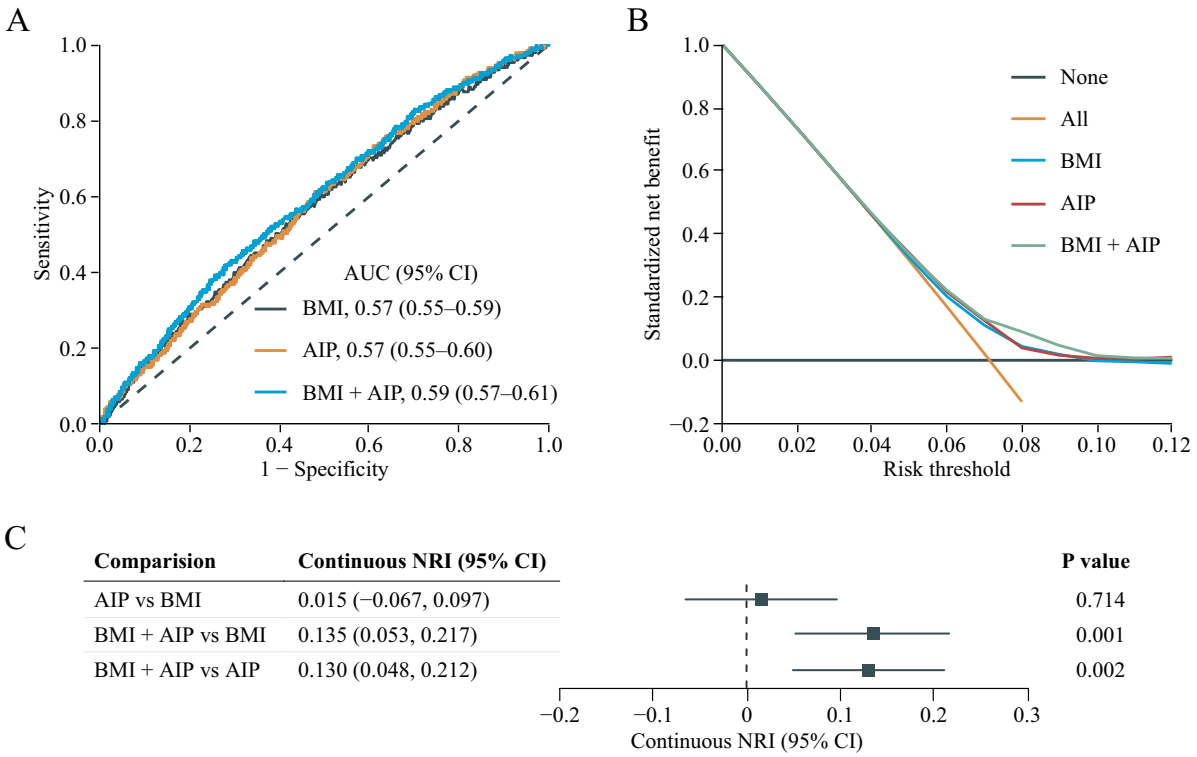

Fig. 4 Predictive performance of the combined AIP and BMI for stroke. **A** The receiver operating characteristic (ROC) curve evaluating the discriminative capabilities by calculating the AUC; **B** Decision curve analysis to compare the clinical utility, the y-axis represents net benefits, calculated by subtracting the relative harm (false positives) from the benefits (true positives). The x-axis calculates the threshold probability; **C** NRI index for AIP combined with BMI. AIP, Atherogenic index of plasma; AUC, Area under curve; BMI, Body mass index; CI, Confidence interval; NRI, Net reclassification index

Discussion

In this large prospective cohort study, we have identified a robust association between the AIP and the risk of stroke in Chinese adults. Additionally, our analysis reveals that AIP mediates a significant proportion of the relationship between obesity, as measured by BMI, and stroke risk. These findings underscore the importance of lipid profiles in understanding and mitigating the cardiovascular risks associated with obesity.

Obesity is a well-established risk factor for various cardiovascular diseases, including stroke [4–6]. Numerous population-based studies have documented that higher BMI is associated with an increased incidence of stroke [30–34]. For instance, Strazzullo's meta-analysis [34] demonstrated a progressively increasing risk of ischemic stroke associated with overweight and obesity. Our study corroborates these findings, showing that individuals with higher BMI, particularly those classified as obese, are at a substantially higher risk of experiencing stroke compared to individuals with normal body weight, which showing the importance of weight control in preventing all ischemic strokes [35]. This association can be attributed to several obesity-related metabolic and physiological changes, such as increased atherosclerosis, insulin resistance, dyslipidemia, and systemic inflammation, all of which contribute to the pathogenesis of stroke [36–38].

The serum lipid level is strongly associated with atherosclerosis [39]. While the AIP, defined as the logarithm of the molar ratio of plasma triglycerides to HDL-C, is an emerging marker of atherogenicity and cardiovascular risk [12, 15]. Elevated AIP levels indicate an imbalance favoring pro-atherogenic lipoproteins, which predisposes individuals to atherosclerosis and subsequent stroke events. A study of 8 727 Chinese participants aged 45 and older, all without a history of stroke, found that higher baseline AIP levels significantly increased the risk of stroke [15]. Another study of 97,959 participants in the Kailuan cohort also found that elevated levels of both baseline and long-term updated mean AIP increased stroke risk [16]. In addition, a higher cumulative AIP was significantly associated with an increased risk of major adverse cardiac events (MACE), stroke and myocardial infarction (MI) independent of traditional cardiovascular risk factors in a community-based population, and the association of cumulative AIP and stroke was particularly

pronounced in the elderly population [40]. As with these studies, our multivariable-adjusted models demonstrate that baseline AIP is independently associated with an increased risk of stroke over the follow-up period. Notably, we found that AIP significantly mediated the association between BMI and stroke, proportions mediated were 25.73% for overweight, and 29.67% for obesity. This substantial mediation effect highlights the critical role of lipid abnormalities in the cardiovascular risk profile of obese individuals. It suggests that the adverse impact of obesity on stroke risk is, to a significant extent, driven by the pro-atherogenic lipid profile represented by AIP.

Our study investigated the interaction between BMI and the AIP on stroke risk. Contrary to our hypothesis, there was no significant synergistic interaction between these factors. Both BMI and AIP independently contribute to stroke risk, but their combined effect does not exceed the sum of their individual impacts. This complexity arises because stroke is a multifactorial condition influenced by various factors such as hypertension, smoking, diet, genetics, and metabolic health [41–43]. These factors may moderate the interaction between BMI and AIP. Additionally, BMI and AIP might affect stroke risk through distinct pathways—BMI is linked to adiposity and its metabolic consequences [44], while AIP reflects lipid metabolism and atherogenic potential [45]. Despite the lack of synergy, the study underscores the importance of considering BMI and AIP together in stroke risk assessment. Individuals with elevated levels of both BMI and AIP have a higher stroke risk than those with elevated levels of only one. This joint consideration could enhance stroke prediction and prevention strategies. Further research should explore the specific mechanisms and potential clinical applications of these findings to improve stroke prevention efforts.

These findings have profound clinical and public health implications. Given the increasing prevalence of obesity in China, there is an urgent need for effective strategies to address this growing public health challenge. Interventions aimed at reducing obesity and improving lipid profiles could play a crucial role in mitigating the heightened stroke risk associated with obesity [3]. Lifestyle modifications, including dietary changes, increased physical activity, and weight management, are foundational strategies for reducing obesity and improving lipid profiles [46]. Diets low in saturated fats and refined sugars but high in fiber, fruits, vegetables, and whole grains can help lower triglyceride levels and improve HDL-C levels, thereby reducing AIP. Regular physical activity is also essential for weight management and cardiovascular health [47].

From a clinical perspective, monitoring AIP could provide valuable insights into an individual's stroke risk profile, particularly in obese patients. Regular assessment of lipid parameters, including triglycerides and HDL-C, should be incorporated into routine clinical practice. Identifying individuals with elevated AIP could enable healthcare providers to implement targeted interventions aimed at reducing cardiovascular risk, such as pharmacological treatments for dyslipidemia and lifestyle counseling. Pharmacological interventions may also be necessary for individuals who cannot achieve optimal lipid levels through lifestyle modifications alone [48].

Our study has several strengths that enhance the reliability and generalizability of our findings. The large sample size and prospective design allow for robust statistical analysis and long-term follow-up, providing a comprehensive view of the associations between BMI, AIP, and stroke risk. Additionally, we utilized an innovative analytical tool based on the counterfactual framework. Unlike traditional mediation analysis methods, this tool allows for a mathematically consistent decomposition of the overall association into direct and indirect components, resulting in clear and interpretable outcomes [24, 25]. However, there are also limitations to consider. First, in line with earlier study, [21] the identification of stroke relied on self-reported physician diagnoses, which could introduce misclassification bias. Nonetheless, Glymour et al. [49] found that such misreporting was nonsystematic, indicating that self-reported stroke data can be effectively used to study stroke incidence and risk factors in the HRS. This suggests that any potential misclassification bias is minimal. Second, we used BMI as the sole measure of obesity, which does not capture the distribution of body fat or differentiate between lean and fat mass [50]. Measures such as waist circumference [51], waist-to-hip ratio [52], or direct assessments of body fat composition [53] could provide more detailed insights into the relationship between adiposity and stroke risk. Third, although we adjusted for several potential confounders, residual confounding cannot be entirely ruled out. Unmeasured variables such as dietary habits, physical activity levels, and genetic predispositions could influence the observed associations. Finally, our study population was limited to Chinese adults, and obesity is also defined according to the Chinese BMI Classification, which may affect the generalizability of our findings to other ethnic groups.

Conclusions

Our study suggests that the AIP is a valuable marker for identifying individuals at increased risk of stroke and that it mediates a substantial portion of the association

between obesity and stroke risk. These findings underscore the importance of lipid profiles in understanding and mitigating the cardiovascular risks associated with obesity. Public health efforts to reduce obesity and improve lipid profiles could play a crucial role in decreasing the burden of stroke in the Chinese population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-024-01481-y.

Supplementary Metarial 1

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Author contributions
Lu Zhai: writing—original draft, writing—review & editing, data curation, methodology. Rong-Rui Huo: formal analysis, visualization, software, writing—review & editing. Yan-Li Zuo: conceptualization, supervision, writing—review & editing.

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Availability of data and materials
Online repositories contain the datasets used in this investigation. The names of the repositories and accession numbers can be found at http://charls.pku.edu.cn/en. No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by the Ethics Review Committee of Peking University. The patients/participants provided their written informed consent to participate in this study.

Competing interests
The authors declare no competing interests.

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