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Association of the atherogenic index of plasma with frailty in U.S. adults: a cross-sectional study based on NHANES

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Abstract

Background Frailty is a multifactorial syndrome associated with adverse health outcomes. The metabolic underpinnings of frailty, particularly lipid metabolism, are not fully understood. Unlike isolated lipid fractions or inflammatory markers, atherogenic index of plasma (AIP) integrates atherogenic lipid profiles and systemic inflammation. However, its association with frailty has not been extensively studied.

Methods Six thousand four hundred participants from the National Health and Nutrition Examination Survey (NHANES) were enrolled. Frailty was calculated with the frailty index (FI), with scores ≥ 0.21 indicating frailty. Logistic regression adjusted for demographic, socioeconomic, and lifestyle factors evaluated the association between AIP and frailty. Restricted cubic splines (RCS) explored nonlinear associations, and subgroup analyses assessed interactions across age, sex, race, poverty income ratio, smoking status, drinking status, and marital status.

Results This study demonstrated a strong dose–response relationship between AIP and frailty. After full adjustment, Individuals in quartile 3 and 4 showed higher odds of frailty than those in lowest quartile, with ORs (95% CI) of 1.26(1.01,1.57) and 1.73(1.34,2.23), respectively. Continuous AIP measures also exhibited significant associations (OR: 1.82, 95% CI: 1.34–2.47). RCS analysis showed that AIP exhibited a nonlinear association with the risk of frailty. Subgroup analyses showed the associations were more pronounced in the females. The sensitivity analyses substantiated the stability and strength of the results.

Conclusions Our findings suggest that elevated AIP levels are independently associated with frailty risk, particularly in females, highlighting its potential as a cost-effective biomarker for risk stratification. Future longitudinal studies are needed to validate AIP's predictive utility and uncover the underlying mechanisms.

Keywords Frailty, Atherogenic index of plasma, NHANES, Lipid biomarkers, Aging, Metabolic health

Introduction

Frailty, characterized by diminished physiological capacity and heightened susceptibility to stressors, has turned into a critical health issue, particularly among aging populations [1]. Frailty is strongly linked to negative outcomes including falls, hospitalization, and death, creating significant challenges for healthcare systems worldwide [2]. Various tools are available to define frailty, including the frailty phenotype, which is based on just five criteria, and the frailty index (FI), which encompasses multiple items for identification

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purposes [3]. The FI shows better effectiveness in determining frailty status compared to the frailty phenotype [4]. Despite substantial progress in understanding its etiology, the search for robust, easily measurable biomarkers to predict frailty remains critical [5]. Among potential candidates, indices reflecting lipid metabolism and systemic inflammation have garnered increasing attention [6].

The atherogenic index of plasma (AIP), calculated based on the logarithmic ratio of triglycerides(TG) to high-density lipoprotein cholesterol (HDL-C), has increasingly been recognized as a valuable biomarker to evaluate lipid metabolism disruptions and cardiovascular risk [7, 8]. AIP not only reflects traditional dyslipidemia but also captures the equilibrium of atherogenic lipoproteins, providing deeper insights into lipid particle size and atherogenicity [9]. Elevated AIP levels have been linked to a broad spectrum of metabolic disorders, including insulin resistance, metabolic syndrome, and atherosclerotic cardiovascular diseases, which are key contributors to the development of frailty [8, 10–12].

Previous studies mainly focused on traditional markers and frailty risk. Although existing studies highlight the clinical utility of AIP in predicting cardiovascular and metabolic disorders, its relationship with frailty remains underexplored. Both AIP and frailty share common mechanisms, including chronic inflammation, oxidative stress, and dysregulated lipid metabolism, suggesting a potential link [13]. However, to date, no large-scale studies have systematically evaluated the association, limiting our understanding of AIP's role in identifying frailty.

By using data from the National Health and Nutrition Examination Survey (NHANES), the research endeavors to elucidate the capabilities of AIP as a non-invasive, cost-effective biomarker for early identification of frailty, thereby contributing to the development of targeted prevention and intervention strategies.

Methods

Study population

The NHANES database, overseen by the National Center for Health Statistics (NCHS), serves to assess the condition of the American population [14]. We included 34,770 adults from 2007 to 2018. Exclusions were made for pregnant individuals ($N=374$) and those with incomplete or low-quality frailty index (FI) data (less than 80% of the total 49 questions, $N=19,483$). Participants with missing AIP data (missing data on triglyceride:8074; missing data on HDL-C:0) were excluded as well. Finally, 6,400 people were enrolled (Fig. 1). Protocols were approved by the NCHS Institutional Review Board, and written consent was obtained from the participants.

Assessment of AIP

Serum TG levels were assessed with enzymatic methods. HDL-C levels are measured by direct immunoassay or precipitation methods. The AIP index = Log10 [triglycerides (mmol/L)/ HDL-C (mmol/L)] [15].

Definition of frailty

Frailty was determined using a deficit accumulation framework, requiring participants to complete a minimum of 80% of the total 49 questions [16, 17]. The FI scores were derived from dividing deficits reported by the overall deficits evaluated, yielding a scale that spans from 0, signifying an absence of deficits, to 1, indicating the utmost deficit burden. The assessment encompassed 49 distinct criteria across seven areas: physical measurements, laboratory findings, comorbidities, healthcare utilization, cognitive performance, dependency, and depressive signs (Table S1). Due to analytical considerations, the FI scores were classified based on a cutoff of 0.21, aligning with existing research [16].

Covariates

Information was collected via questionnaire-based interviews, encompassing demographics including age, sex, poverty income ratio (PIR), marital status, and races. Additionally, laboratory exams were used to assess serum creatinine (Scr) and uric acid (UA). Categorizations of alcohol intake were as follows: never consumed (less than 12 drinks ever), previously a drinker (at least 12 drinks in a year with none in the last year, or no drinks last year but at least 12 in total), and current drinker (at least 12 drinks and actively drinking) [18]. Categorizations of smoking habits were as follows: never (fewer than 100 cigarettes ever), former (100 or more cigarettes but not smoking currently), and current (100 or more cigarettes and actively smoking). Lipid-lowering medications encompassed statins, fibrates, and ezetimibe.

Statistical analysis

The analysis followed the NHANES protocols, taking into account the intricacies of the survey's design [14]. We utilized the "wtsaf2yr" for the analysis. To derive the new weights, the original two-year weights were divided by six. The weighted analyses were then executed utilizing the "survey" package. People were classified according to their frailty status. Continuous data are depicted by the or median along with interquartile ranges or mean with standard error (SE) whereas categorical data are presented as percentages. Weighted one-way ANOVA and chi-square tests were conducted to uncover differences. Furthermore, multivariable logistic regressions were utilized to determine the odds ratios (ORs) with

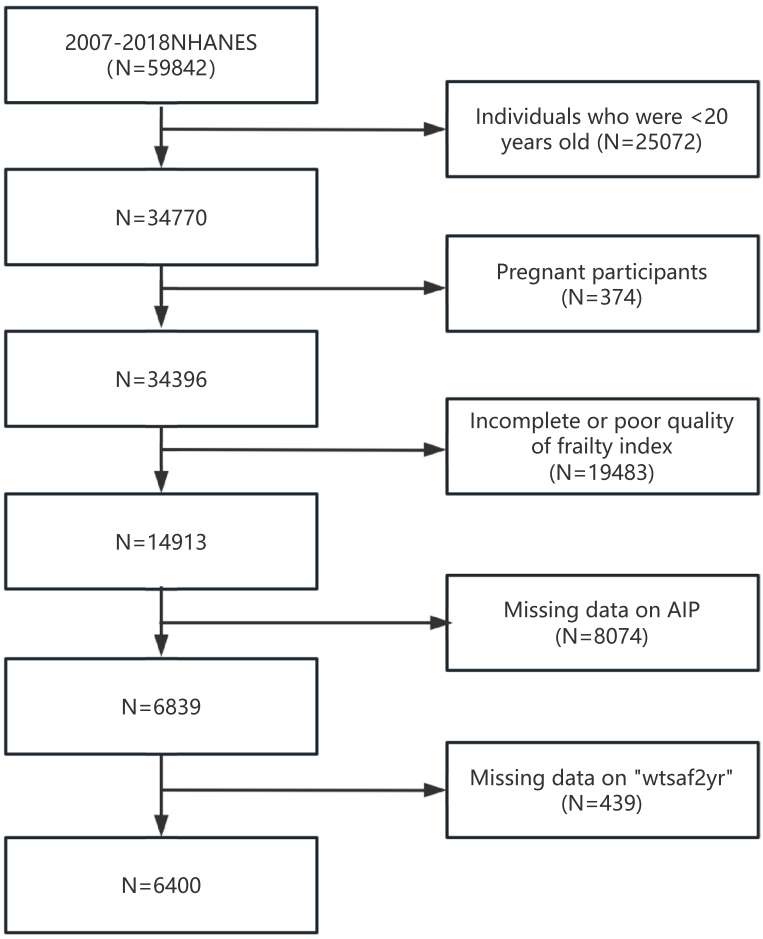

Fig. 1 Flowchart of participant selection

95% confidence intervals (CIs). Model 1 included no variables. Model 2 encompassed age and sex, and Model 3 also integrated extra variables like PIR, UA, Scr, races, marital status, smoking status, education, and alcohol intake. Model 4 further included total energy intake, leisure-time physical activity, and lipid-lowering medications. Trend testing involves incorporating AIP quartiles as ordered variables into a multivariate logistic regression model, and calculating the Wald test *P*-value of the regression coefficients.

The variable with the highest rate of missing data is the Poverty Income Ratio (PIR), at 10.00%. To minimize the potential for inferential bias, we utilized multiple imputations to handle all missing data, employing the R package MICE with five imputations. Subsequently, the "pool" function was utilized to consolidate the five estimates into a single [19]. Restricted cubic spine (RCS) was used to explore nonlinear relationships. Knot placement for the RCS analysis was determined using Harrell's recommended percentiles (5th, 35th, 65th, 95th) to minimize the influence of outliers. The number of knots (4) was selected based on AIC minimization to ensure optimal model fit. The analysis using piecewise regression and likelihood ratio tests revealed differences in the slopes near the inflection point. Furthermore, stratified analysis and interaction testing were conducted across various factors. The interactions between different subgroups were evaluated by likelihood ratio tests. We conducted the following analyses to confirm the validity: 1) modifying the cutoff to 0.25 to reduce false positives; 2) excluding the covariates; 3) examining the relationships between the AIP and pre-frailty. Analyses were deemed statistically significant with a two-tailed p-value threshold of less than 0.05. These analysis was conducted using R Studio(version 4.2.2).

Results

Basic characteristics

This study included 6,400 participants, with a mean age of 60.57 ± 0.26 years; 3,302 individuals (accounting for 53.42%) were female. Table 1 presents participant demographics according to frailty status. As

Table 1 Baseline characteristics of participants according to frailty status

Variable	Total	Non-frailty	Frailty	*P* value
Number(N)	6400	4069	2331	
Demographic factors				
Age (year)	60.57 ± 0.26	60.08 ± 0.32	61.61 ± 0.45	0.007
Sex, n (%)				< 0.001
Female	3302(53.42)	1940(49.30)	1362(62.07)	
Male	3098(46.58)	2129(50.70)	969(37.93)	
Race, n (%)				< 0.001
Non-Hispanic Black	1269(10.11)	742(8.48)	527(13.53)	
Non-Hispanic White	3087(74.02)	1978(76.52)	1109(68.77)	
Mexican American	763(5.08)	499(4.95)	264(5.34)	
Others	1281(10.80)	850(10.05)	431(12.37)	
Education level, n (%)				< 0.001
Less than high school	2891(37.50)	1642(32.63)	1249(47.71)	
College or above	2957(54.83)	2071(60.09)	886(43.80)	
High school	552(7.67)	356(7.28)	196(8.49)	
Marital, n (%)				< 0.001
Married	3384(56.73)	2332(61.01)	1052(47.74)	
Separated	2370(33.01)	1327(28.40)	1043(42.69)	
Unmarried	646(10.26)	410(10.58)	236(9.57)	
Family of poverty ratio, n (%)				< 0.001
< 1.3	2030(23.04)	1047(17.13)	983(35.44)	
1.3–3.5	2781(41.29)	1761(40.04)	1020(43.91)	
> 3.5	1589(35.67)	1261(42.83)	328(20.65)	
Clinical indicators				
Scr, mg/dL	0.93 ± 0.01	0.90 ± 0.01	1.01 ± 0.02	< 0.001
UA, mg/dL	5.50(4.60,6.50)	5.50(4.60,6.40)	5.70(4.60,6.80)	0.005
Behavioral factors				
Smoking status, n (%)				< 0.001
Never	3046(46.63)	2058(50.08)	988(39.40)	
Former	2132(34.04)	1362(34.68)	770(32.71)	
Current	1222(19.32)	649(15.24)	573(27.89)	
Alcohol status, n (%)				< 0.001
Never	973(12.05)	592(11.32)	381(13.57)	
Former	1382(18.49)	737(14.97)	645(25.89)	
Current	4045(69.46)	2740(73.71)	1305(60.54)	
Leisure-time physical activity, n (%)				< 0.001
No	3964(56.46)	2189(48.14)	1775(73.91)	
Yes	2436(43.54)	1880(51.86)	556(26.09)	
Total energy intake (kcal/day)	1998.12 ± 17.13	2053.29 ± 22.89	1882.40 ± 23.88	< 0.001
Lipid-lowering medications, n (%)				< 0.001
No	3972(63.00)	2768(68.12)	1204(52.27)	
Yes	2428(37.00)	1301(31.88)	1127(47.73)	

Mean ± standard error (SE) for continuous variables, Percentage (%) for categorical variables

Scr Serum creatinine, *UA* uric acid

indicated in Table 1, Individuals characterized as frail tended to be of advanced age, with lower levels of education, mostly women, and exhibited increased poverty, higher smoking prevalence, and higher uric acid concentrations. Frail people tended to be previous alcohol consumers, more frequently separated, and identified as Non-Hispanic Black. Additionally, they consumed less energy per day, more likely to intake

higher lipid-lowering medications, and were less likely to participate in leisure-time physical activity. Table 2 presents participants categorized into tertiles based on AIP: Q1(< −0.25), Q2 (−0.25– −0.04), Q3 (−0.04–0.17), and Q4 (≥0.17). Participants with elevated AIP scores were generally younger, Non-Hispanic White,

Table 2 Baseline characteristics of study participants stratified by AIP quartiles

Variable	AIP					*P* value
	Total	Q1(< −0.25)	Q2(−0.25– −0.04)	Q3(−0.04–0.17)	Q4(≥0.17)	
Number	6400	1602	1593	1605	1600	
Demographic factors						
Age (year)	60.57 ± 0.26	60.98 ± 0.59	61.18 ± 0.49	61.34 ± 0.54	58.86 ± 0.49	0.002
Sex, n (%)						< 0.001
Female	3302(53.42)	939(61.77)	847(56.02)	821(52.07)	695(43.66)	
Male	3098(46.58)	663(38.23)	746(43.98)	784(47.93)	905(56.34)	
Race, n (%)						< 0.001
Non-Hispanic White	3087(74.02)	718(72.83)	729(73.04)	768(72.95)	872(77.18)	
Non-Hispanic Black	1269(10.11)	510(15.68)	349(11.18)	259(8.40)	151(4.97)	
Mexican American	763(5.08)	113(3.21)	188(5.02)	234(6.06)	228(6.11)	
Others	1281(10.80)	261(8.28)	327(10.75)	344(12.58)	349(11.74)	
Education level, n (%)						< 0.001
Less than high school	2891(37.50)	665(33.73)	708(37.44)	745(38.70)	773(40.28)	
High school	552(7.67)	90(4.38)	151(9.13)	155(8.35)	156(9.03)	
College or above	2957(54.83)	847(61.89)	734(53.42)	705(52.95)	671(50.70)	
Marital, n (%)						0.176
Married	3384(56.73)	766(54.86)	855(55.29)	874(57.37)	889(59.42)	
Separated	2370(33.01)	616(32.83)	588(34.48)	599(33.78)	567(31.09)	
Unmarried	646(10.26)	220(12.31)	150(10.23)	132(8.85)	144(9.50)	
Family of poverty ratio, n (%)						< 0.001
< 1.3	2030(23.04)	416(18.25)	482(23.20)	526(24.35)	606(26.56)	
1.3–3.5	2781(41.29)	708(38.37)	697(40.45)	713(44.48)	663(42.08)	
> 3.5	1589(35.67)	478(43.38)	414(36.34)	366(31.17)	331(31.36)	
Clinical indicators						
Scr, mg/dL	0.93 ± 0.01	0.91 ± 0.02	0.92 ± 0.01	0.93 ± 0.01	0.97 ± 0.02	0.012
UA, mg/dL	5.50(4.60,6.50)	5.00(4.10,5.90)	5.40(4.60,6.40)	5.70(4.80,6.60)	6.10(5.10,6.90)	< 0.001
Behavioral factors						
Smoking status, n (%)						< 0.001
Never	3046(46.63)	818(51.23)	810(48.91)	783(48.14)	635(38.33)	
Former	2132(34.04)	509(33.03)	526(33.66)	526(33.46)	571(36.00)	
Current	1222(19.32)	275(15.74)	257(17.43)	296(18.40)	394(25.68)	
Alcohol user, n (%)						< 0.001
Never	973(12.05)	237(11.89)	252(12.69)	259(12.16)	225(11.49)	
Former	1382(18.49)	282(14.19)	318(18.39)	366(18.27)	416(23.22)	
Current	4045(69.46)	1083(73.92)	1023(68.92)	980(69.57)	959(65.29)	
Leisure-time physical activity, n (%)						< 0.001
No	3964(56.46)	895(48.31)	972(55.13)	1004(57.05)	1093(65.54)	
Yes	2436(43.54)	707(51.69)	621(44.87)	601(42.95)	507(34.46)	
Total energy intake (kcal/day)	1998.12 ± 17.13	2030.20 ± 31.52	1992.95 ± 37.76	1969.88 ± 39.28	1996.79 ± 32.81	0.757
Lipid-lowering medications, n (%)						< 0.001
No	3972(63.00)	1082(68.86)	992(63.87)	930(58.22)	968(60.68)	
Yes	2428(37.00)	520(31.14)	601(36.13)	675(41.78)	632(39.32)	

Mean ± standard error (SE) for continuous variables, Percentage (%) for categorical variables

Scr Serum creatinine, *UA* uric acid

and male, and these people were more likely current smokers and previous alcohol consumers, less engaged in leisure-time physical activity, and took less lipid-lowering medications in comparison to those in the first quartile. They possessed lower educational attainment, elevated UA levels, increased Scr levels, and were probable to possess lower household incomes (Table 2). We compared the baseline characteristics of participants with missing and non-missing covariates (Table S2).

Associations between AIP and frailty

As shown in Table 3, Individuals in quartile 4 exhibited increased ORs for frailty, spanning from 2.12 (95% CI: 1.76–2.54) to 1.73 (95% CI: 1.34–2.23), which highlights AIP's independent effect on frailty beyond these confounders. Individuals in quartile 3 showed higher risk of frailty (1.26(95% CI:1.01–1.57)). Across all the models, the dose–response trends for both indices were highly significant (p for trend < 0.001), indicating a progressive rise in frailty risk with higher AIP levels. The continuous AIP measurements consistently demonstrated significant associations with frailty(OR: 1.82 (95% CI: 1.34–2.47)) in Model 3. Additionally, females in quartile 4 showed a stronger association between the AIP and frailty (OR = 2.44, 95% CI: 1.64–3.62) compared to males (OR = 1.98, 95% CI: 1.35–2.91) (Table S3). RCS analysis based on Model 3 was performed, as depicted in Fig. 2. The result showed that AIP exhibited a nonlinear association with the risk of frailty, with an inflection point at − 0.123. Log likelihood ratio tests confirmed the nonlinear relationships (P < 0.05) (Table 4).

The robustness of the outcomes was underscored by sensitivity analyses, which revealed stability in defining frailty with an FI cutoff of 0.25 (Table S4). A persistent result was observed after excluding the covariates (Table S5). Analogous result was found in the analysis of AIP's relation to pre-frailty, which was defined as 0.10 < FI < 0.21 (Table S6).

Subgroup analysis

The associations of AIP with frailty remained uniform across various subgroups, except sex. We found the significant interaction effect of sex (P for interaction = 0.025), which indicates a stronger association between the AIP and frailty in females compared to males (Table 5).

Discussion

We identified a strong association between AIP values and frailty among American adults, indicating that AIP could be a standalone risk factor for frailty. These results offered fresh insights into the metabolic basis of frailty and established a foundation for interventions designed to mitigate the risk of frailty.

Our research corroborates scholarly literature emphasizing the role of lipid metabolism in frailty. An analysis from the England demonstrated that elevated TG levels (HR: 1.30) and decreased HDL-C levels (HR: 0.58) at the outset were correlated with a heightened probability of frailty onset within a decade [20]. Mendelian randomization (MR) studies demonstrated that genetically predicted lifelong decreases in low-density lipoprotein cholesterol (LDL-C) levels correlate with decreased frailty in midlife and old age [21]. A cohort study involving 383 individuals revealed that statin users experienced a reduced risk of mortality and fall incidents over a 12-month period compared with non-users [22]. A study encompassing 364 community-dwelling individuals aged 80 years and above demonstrated that elevated HDL-Cl levels correlate with improved functional capabilities [23]. L-carnitine, crucial for energy metabolism from long-chain fatty acids within mitochondria, has been linked to a reduction in degenerative diseases among the older people, particularly in prefrail individuals, with observed improvements in cognitive function

Table 3 The associations of AIP as a continuous variable and quartiles with frailty

AIP	Range	Model1	Model2	Model3	Model4
		OR(95%CI)	OR(95%CI)	OR(95%CI)	OR(95%CI)
Continuous		2.30(1.83,2.87)	2.77(2.18,3.52)	2.17(1.59,2.96)	1.82(1.34,2.47)
Q1	< −0.25	Ref	Ref	Ref	Ref
Q2	−0.25–−0.04	1.19(0.98,1.44)	1.23(1.01,1.50)	1.09(0.92,1.30)	1.03(0.85,1.24)
Q3	−0.04–0.17	1.54(1.24,1.89)	1.64(1.32,2.04)	1.39(1.13,1.73)	1.26(1.01,1.57)
Q4	≥0.17	2.12(1.76,2.54)	2.45(2.00,3.00)	1.97(1.53,2.54)	1.73(1.34,2.23)
P for trend		< 0.001	< 0.001	< 0.001	< 0.001

Model 1: no cofounder; Model 2: adjusted for age and sex; Model 3: further adjusted for races, education level, marital status, Scr,UA, alcohol intake, smoking status, and the family of poverty ratio; Model 4: further adjusted for total energy intake, leisure-time physical activity, and lipid-lowering medications

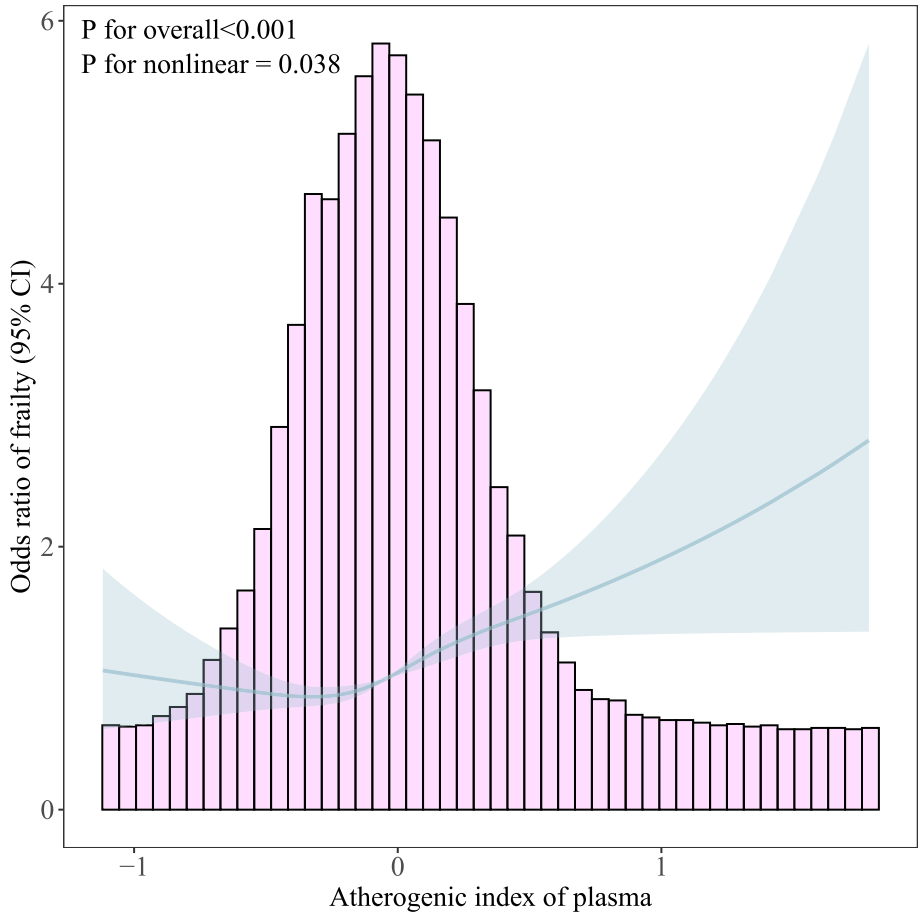

Fig. 2 Restricted cubic spline analysis between AIP and frailty. X-axis: Atherogenic Index of Plasma. Y-axis: Odds ratio (OR) of frailty. Solid line: Estimated ORs. Gray band: 95% confidence interval. ORs were adjusted for age, sex, races, education level, marital status, Scr,UA, alcohol intake, smoking status, and the family of poverty ratio, total energy intake, leisure-time physical activity, and lipid-lowering medications

Table 4 Association of AIP and frailty using piece-wise logistic regression

Threshold effect analysis	OR (95% CI)	*P* value
AIP		
Model 1 Fitting model by standard logistic regression	1.757(1.455–2.122)	< 0.001
Model 2 Fitting model by two-piecewise logistic regression		
Inflection point (K)	−0.123	
< K slope	1.102(0.705–1.731)	0.671
> K slope	2.202(1.674–2.9)	< 0.001
Log likelihood ratio test	0.026	

Adjusted for age, sex, races, education level, marital status, Scr,UA, alcohol intake, smoking status, and the family of poverty ratio, total energy intake, leisure-time physical activity, and lipid-lowering medications

[24]. Proteomic studies on frailty indicated that proteins with varying regulation were predominantly found in pathways and regulatory factors linked to lipid metabolism [25].

Conversely, a study observing the link between statin use and frailty onset in women 65 and older found no significant relationships between ongoing statin use, its duration, or intensity, and the occurrence of frailty [26]. A retrospective analysis of older U.S. Veterans revealed that initiation of statin therapy was not significantly linked to a decreased likelihood of mortality, regardless of frailty condition [27]. This inconsistency may stem

Table 5 The associations of AIP with frailty in various subgroups

Frailty	N	OR (95% CI)	*P* for interaction
Age			0.610
< 60	1749	1.43(0.94,2.18)	
≥ 60	4651	1.60(1.17,2.20)	
Sex			0.025
Male	3302	1.49(1.04,2.16)	
Female	3098	2.72(1.81,4.07)	
Race			0.533
White	3087	1.90(1.33,2.70)	
Non-white	3313	1.65(1.20,2.27)	
Current drinker			0.177
Yes	4045	1.94(1.35,2.79)	
No	2355	1.43(1.03,1.99)	
Current smoker			0.646
Yes	1222	1.53(0.99,2.35)	
No	5178	1.70(1.29,2.25)	
PIR			0.883
< 1.3	2030	1.60(1.14,2.25)	
1.3–3.5	2781	1.74(1.16,2.61)	
≥ 3.5	1589	1.42(0.70,2.91)	
Marital status			0.093
Married	3384	2.25(1.48,3.43)	
Separated	2370	1.75(1.18,2.61)	
Unmarried	646	0.88(0.40,1.94)	

Adjusted for age, sex, races, education level, marital status, Scr,UA, alcohol intake, smoking status, and the family of poverty ratio, total energy intake, leisure-time physical activity, and lipid-lowering medications, if not stratified

from unmeasured confounders (e.g., statin adherence, comorbidity burden) or AIP's ability to capture residual lipid risk beyond LDL-C lowering. Further research should dissect AIP's role in statin-treated populations.

In contrast to previous studies that concentrated on conventional lipid markers, our research highlights the distinctive value of AIP for evaluating frailty risk. Multiple prior studies have indirectly linked AIP to frailty-related outcomes, including sarcopenia and cardiovascular diseases, however, neither examined frailty as a multidimensional syndrome nor evaluated AIP's predictive utility in a general population. The AIP evaluates the size and density characteristics of lipoprotein particles, with elevated AIP values signifying the presence of smaller, denser, and more atherogenic particles [15]. This relationship positions AIP as a surrogate for small dense low-density lipoprotein cholesterol (sd-LDL-C), a subclass of LDL-C that has been consistently linked to increased atherogenic potential [15, 28, 29]. Unlike larger LDL-C particles, sd-LDL-C is more susceptible to atherogenic modifications, such as oxidation and glycation, increasing its contribution to arterial plaque formation and systemic inflammation [30, 31]. However, current methods for measuring sd-LDL-C remain time-intensive and difficult to standardize in clinical settings. In contrast, AIP offers a simpler and more accessible alternative for clinical applications. New research indicates that the AIP surpasses conventional lipid markers in forecasting cardiovascular disease risk and mirrors the intensity of metabolic disorders, including insulin resistance (IR) [32–34]. By integrating key lipid parameters into a single index, AIP provides a more comprehensive picture of metabolic and vascular health, aligning with the multifactorial nature of frailty. Clinically, our results advocate for integrating AIP into routine geriatric assessments. For public health, AIP can be easily derived from standard lipid panels, offering a cost-effective strategy for early risk stratification.

The association between AIP and frailty may be due to various interrelated mechanisms. AIP reflects a predominance of small, dense LDL-C particles, which are pro-inflammatory and pro-oxidative [35, 36]. High AIP levels are significantly correlated with systemic inflammation, as evidenced by elevated C-reactive protein and interleukin-6 levels in individuals with atherogenic dyslipidemia [37, 38]. These inflammatory mediators drive frailty by accelerating muscle degradation via NF-kappaB-mediated proteolysis [39], and impairing immune function through T-cell senescence [40]. Oxidative stress, driven by lipid peroxidation, impairs mitochondrial function via electron transport chain disruption and reduces energy synthesis, accelerating sarcopenia [41–43]. Insulin resistance, another factor linked to high AIP, disrupts glucose metabolism, increases cytokine production, and contributes to muscle loss and metabolic dysfunction [44]. Additionally, atherogenic dyslipidemia accelerates vascular aging, impairing blood flow and nutrient delivery to tissues, which worsens muscle and cognitive function [45–47]. These mechanisms highlight AIP as an effective biomarker for metabolic and inflammatory dysregulation, making it a valuable tool for identifying and managing frailty.

The sex disparity may be attributed to several factors. First, hormonal differences, particularly the decline in estrogen during menopause, could exacerbate lipid metabolism dysregulation and systemic inflammation in females, amplifying the impact of atherogenic lipid profiles on frailty risk [48, 49]. Second, females generally exhibit higher visceral fat sensitivity to lipid perturbations, which may synergize with chronic inflammation to accelerate physiological decline [50]. Future studies should explore sex-specific pathways linking lipid metabolism to frailty, potentially informing targeted interventions for high-risk populations.

Study strengths and limitations

The strength lies in its use of a nationally representative dataset and robust analytical methods, which enhance the generalizability of the findings. Nevertheless, there are a few limitations that deserve attention. Our cross-sectional findings suggest that AIP is significantly associated with frailty. However, the temporal relationship and causality cannot be established due to the study design. The wide confidence intervals in some subgroup analyses may reflect instability in estimates due to insufficient sample size. Future studies should increase the sample size to improve statistical power, particularly in high-AIP subgroups. While NHANES offers a substantial and nationally representative dataset, the dependence on self-reported data for some measures might introduce bias. Additionally, residual confounding by unmeasured variables could influence the observed associations. The applicability of our results to non-U.S. populations remains uncertain, given potential differences in genetic, environmental, and healthcare factors. Subsequent studies should focus on longitudinal research to confirm causal relationships and investigate the mechanisms that connect AIP with frailty.

Conclusion

This cross-sectional study indicates a significant association between AIP and frailty status in American adults. However, its clinical utility as a predictive biomarker for frailty needs to be further validated in longitudinal cohorts.

Abbreviations

AIP	Atherogenic index of plasma
NHANES	National health and nutrition examination survey
WC	Waist circumference
BMI	body mass index
FI	Frailty index
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
TC	Total cholesterol
PIR	The family of poverty ratio
UA	Uric acid
Scr	Serum creatinine
SE	Standard error
OR	Odds ratio
CI	Confidence intervals

Supplementary Information

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Supplementary Material 1: Table S1. Variables in the 49-item frailty index and their respective scorings. Table S2. The comparison of characteristics of participants with missing and non-missing covariates. Table S3. The associations of AIP as a continuous variable and quartiles with frailty in males and females. Table S4. The associations of AIP as a continuous variable and quartiles with frailty (FI ≥ 0.25). Table S5. The associations of AIP as a continuous variable and quartiles with frailty after excluding the covariates ($N = 5064$). Table S6. The associations of AIP as a continuous variable and quartiles with pre-frailty($0.10 < FI < 0.21$, $N = 4069$).

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Authors' contributions

Conceptualization, S.Y.; data curation, S.Y. and K.C.; formal analysis, S.Y.; methodology, K.C.; software, S.Y.; supervision, K.C.; writing-original draft, K.C.; writing—review and editing, J.Y. and H.W.; visualization, S.Y.; All authors have read and agreed to the published version of the manuscript.

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Data availability

The survey data are publicly available on the internet for data users and researchers throughout the world (www.cdc.gov/nchs/nhanes/).

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by NCHS Ethics Review Board. The participants provided their written informed consent to participate in this study.

Consent for publication

All participants in the NHANES study provided consent for publication.

Competing interests

The authors declare no competing interests.

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