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Association between atherogenic index of plasma and all-cause mortality and cardiovascular disease among individuals with non-alcoholic fatty liver disease or metabolic dysfunction-associated steatotic liver disease

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Abstract

Background Non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD) are common chronic liver diseases worldwide, both of which are closely associated with an increased risk of cardiovascular disease (CVD). Atherogenic index of plasma (AIP), as a biomarker of dyslipidemia, may predict CVD risk and mortality in these patients, but its specific role in patients with NAFLD and MASLD has not been studied in detail. This study adopted a cohort design, using data from the National Health and Nutrition Examination Survey (NHANES, 1988–1994) database, which was conducted by the Centers for Disease Control and Prevention. A total of 12,929 adult participants were analyzed. After participants were grouped according to AIP quartiles, the relationship between AIP levels and CVD risk was explored using multivariate logistic regression models and restricted cubic splines. The relationship between AIP levels and all-cause and CVD mortality was analyzed using multivariate Cox regression models.

Results Participants with the higher AIP quartiles showed high rates of CVD among participants with NAFLD (Quartile 1: 7.57%; Quartile 2: 10.00%; Quartile 3: 11.63%; Quartile 4: 15.08%). Participants with the higher AIP

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quartiles showed high rates of CVD among participants with MASLD (Quartile 1: 9.71%; Quartile 2: 11.30%; Quartile 3: 11.14%; Quartile 4: 15.00%). The findings suggested a linear association between the AIP index and the risk of CVD in participants with NAFLD or MASLD. AIP was significantly associated with CVD in the highest quartile of NAFLD or MASLD patients, and the adjusted hazard ratio indicated that high AIP levels were associated with high risk of CVD among participants with NAFLD (HR: 1.77, 95% CI: 1.24, 2.52) and MASLD (HR 1.76, 95% CI: 1.04, 2.98). In addition, higher AIP levels were also associated with increased all-cause mortality and CVD mortality among participants with NAFLD or MASLD.

Conclusion This study showed that AIP is an effective tool for predicting CVD risk and mortality in patients with NAFLD and MASLD. Regular monitoring of AIP levels can help identify high-risk patients early and provide clinical risk assessment before intervention, thereby improving patient management and prognosis. Future studies need to further explore the role of AIP in different ethnic and economic conditions to optimize cardiovascular disease prevention and treatment strategies.

Clinical trial number
Not applicable.

Keywords Atherogenic index of plasma, Non-alcoholic fatty liver disease, Metabolic syndrome, Cardiovascular disease, Mortality

Introduction

Fatty liver disease results from abnormal lipid accumulation in hepatocytes, primarily due to excessive alcohol consumption, obesity, and metabolic dysfunction. Its prevalence has increased rapidly, making it the most common liver disease worldwide. Fatty liver includes non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD). NAFLD affects nearly one-third of the global population and is linked to an increased risk of advanced liver disease and cardiovascular disease (CVD) [1]. Over the past 30 years, its prevalence has risen from 25.3 to 38.2% [2]. MASLD refines the NAFLD framework by incorporating metabolic risk factors such as obesity, hyperglycemia, and hypertension, highlighting the crucial role of metabolic dysfunction in liver disease progression [3, 4].

Fatty liver disease is strongly linked to increased cardiovascular mortality, with risk rising as disease severity progresses. A meta-analysis confirmed that individuals with fatty liver disease have a significantly higher risk of both fatal and non-fatal CVD, with a greater incidence of cardiovascular events in advanced stage [5, 6]. Similar trends have been observed in MASLD, where worsening disease is associated with a progressive increase in cardiovascular mortality [7–9]. Beyond cardiovascular risks, fatty liver disease is also linked to higher all-cause mortality. Studies indicate that NAFLD, particularly in severe forms, significantly increases all-cause mortality risk [10, 11]. A systematic review reported a 1.05-fold increase in all-cause mortality among NAFLD patients, while MASLD had a mortality rate of 12.6 per 1,000 person-years [2, 12]. The rising global burden of NAFLD and MASLD mortality underscores the need to investigate causes beyond cardiovascular disease.

Insulin resistance (IR) plays a key role in NAFLD and MASLD pathogenesis, contributing to hepatic steatosis and metabolic dysfunction. It is also a major risk factor for coronary artery disease (CAD) and all-cause mortality [13]. While several methods assess IR, they are often invasive, complex, or unstable. The atherogenic index of plasma (AIP), calculated as log[Triglyceride (TG) (mg/dL)/ High-density lipoprotein cholesterol (HDL-C) (mg/dL)], is an emerging biomarker reflecting lipid metabolism dysfunction and indirectly indicating insulin resistance (IR) [14, 15].

AIP has been identified as an independent predictor of CVD risk [16] and has shown a linear dose-response relationship with fatty liver disease risk [17, 18]. Higher AIP levels are significantly associated with increased CVD risk in NAFLD/MASLD patients [19], as well as with CAD in adults [20, 21]. However, some studies have reported no significant association between AIP and all-cause or cardiovascular mortality [16, 22]. Despite its potential prognostic value, few studies have specifically investigated the relationship between AIP and mortality risks in NAFLD/MASLD populations.

This study aims to evaluate the association between AIP and CVD risk, as well as its relationship with all-cause and cardiovascular mortality in NAFLD/MASLD patients. While AIP has been studied in other populations, its prognostic role in fatty liver disease remains underexplored, particularly regarding mortality outcomes. By addressing this research gap, this study seeks to establish the clinical relevance of AIP in identifying high-risk patients and supporting early intervention strategies in both clinical and community settings.

Methods

Study population

The data used in this retrospective cohort study were obtained from the National Health and Nutrition Examination Survey (NHANES) database, a large cross-sectional survey conducted by the Centers for Disease Control and Prevention. The survey was was revised and approved by the Ethics Review Committee of the National Center for Health Statistics, and all participants provided written informed consent [23]. More details of the study can be accessed online: www.cdc.gov/nchs/nhanes/irba98.htm. Data were collected through household interviews, laboratory measurements, and physical examinations. This study is based on an analysis of NHANES III (1988–1994), which used a national, multistage, stratified cluster design to create a representative sample of the U.S. civilian population. Of 20,050 participants (≥ 17 years) from NHANES III, this study excluded those with missing data on pregnant women ($n = 280$), participants who were not eligible for an ultrasound examination (age exclusion) ($n = 3885$) or whose ultrasound was ungradable or missing ($n = 2245$), participants missing data on TG ($n = 640$) or missing data on HDL-C ($n = 71$), leading to the final study's sample of 12,929 participants (Fig. 1).

Definitions of NAFLD and MASLD

The ultrasonic examinations with the Toshiba Sonolayer SSA-90 A (Toshiba America Medical Systems, Tustin, CA) is used to evaluate the presence of hepatic steatosis [24, 25]. SLD is a new comprehensive terminology about hepatic steatosis (including mild, moderate, and severe cases). NAFLD was defined as having SLD without positive hepatitis B and C virus infection or excessive alcohol consumption (≥ 30 g/d for men and ≥ 20 g/d for women). When an adult with SLD meets one of the adult cardiometabolic criteria without other factors contributing to hepatic steatosis or excessive alcohol use, the condition is referred to as MASLD. The criteria for adult cardio metabolism were defined as follows: (1) body mass index (BMI) ≥ 25 kg/m² (23 kg/m² in Asia) or waist circumference (WC) >94 cm for men and >80 cm for women; (2) fasting serum glucose (FBG) ≥ 5.6 mmol/L (100 mg/dL) or 2-hour post-load glucose levels ≥ 7.8 mmol/L (140 mg/dL) or hemoglobin A1c (HbA1c) ≥ 5.7% (39 mmol/mol) or type 2 diabetes or treatment for type 2 diabetes; (3) blood pressure of ≥ 130/85 mmHg or specific antihypertensive medication therapy; (4) TG ≥ 1.70 mmol/L (150 mg/dL) or lipid-lowering therapy; and (5) plasma HDL-C ≤ 1.0 mmol/L (40 mg/dL) for men and ≤ 1.3 mmol/L (50 mg/dL) for women [4].

Assessment of TG, HDL-C, and AIP

At baseline, participants' TG and HDL-C were measured. The AIP index was calculated according to the following formula: log(TG/HDL-C). Based on the AIP value, all individuals were categorized into four quartiles: quartile 1 (-0.72, 0.25), quartile 2 (0.25, 0.48), quartile 3 (0.48, 0.71), and quartile 4 (0.71, 1.68).

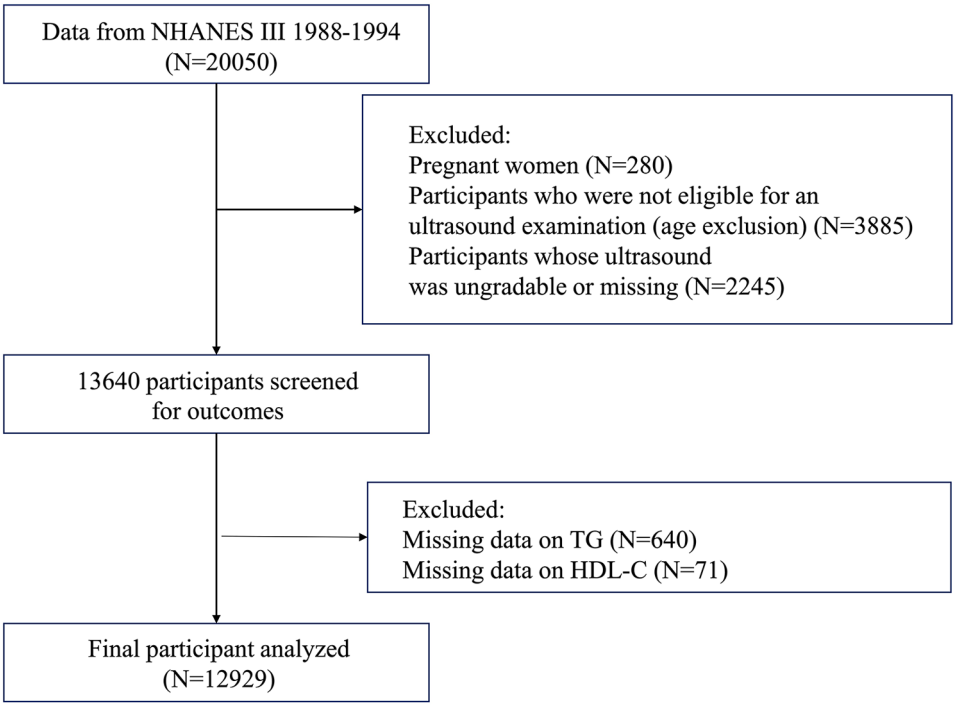

Fig. 1 Flow chart of the sample selection from NHANES III. NHANES: National Health and Nutrition Examination Survey; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol

Assessment of covariates

Race/ethnicity of participants were divided into four categories: non-Hispanic white, non-Hispanic black, Mexican-American, and other races. A low-income level was defined as a poverty-income ratio < 1.3. Smoking status was derived from two questions: "Do you smoke cigarettes now?" and "Have you smoked at least 100 cigarettes in your entire life?". Current smokers were defined if participants answered "yes" to both questions. If a participant indicated that they had not engaged in any of the following physical activities over the previous month: jogging or running, swimming, bicycling, aerobics, calisthenics exercises, other dancing, yard or garden work, weight lifting, or other sports, they were considered to be leading a sedentary lifestyle. BMI was computed by dividing weight (kg) by height (m^2). The homeostasis model assessment of insulin resistance (HOMA-IR), a surrogate for IR, was calculated as follows: HOMA-IR = FBG (mmol/L) × fasting insulin (μU/mL) / 22.5. Non-invasive liver fibrosis assessment included NAFLD fibrosis score (NFS) and Fibrosis-4 index (FIB-4), which were calculated as follows: NFS = − 1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × aspartate aminotransferase (AST)/alanine aminotransferas (ALT) ratio − 0.013 × platelet ($\times 10^9$/L) − 0.66 × albumin (g/dL), and FIB-4 index = [age (years) × AST (U/L)] / [platelet ($\times 10^9$/L) × ALT (U/L)^(1/2)]. Advanced fibrosis was diagnosed if NFS and FIB-4 cut-off values were − 1.455 and 1.3, respectively. Diabetes was defined by FBG level ≥ 126 mg/dL, HbA1c level ≥ 6.5%, and/or self-reported doctor diagnosis and/or anti-diabetic treatment. Hypertension was defined by systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or self-reported doctor diagnosis and/or antihypertensive treatment.

Outcome definitions

Three composite outcomes were defined: time to cardiovascular disease (heart attack, stroke, congestive heart failure, or angina pectoris); time to all-cause mortality (mortality from any cause); and time to CVD mortality. The household interview included self- and proxy-reported personal interview data, with questions about the occurrence of congestive heart failure, stroke, angina pectoris, and heart attack. Participants who answered 'yes' to any of these questions were classified as having cardiovascular disease. The NHANES III data are linked to death certificate records from the National Death Index; this study employed the NHANES public-use linked mortality file as of December 31, 2019, to ascertain all-cause and cause-specific mortality. International Classification of Diseases, Tenth Revision, was used to define cause-specific mortality. Mortality from any cause was defined as all-cause mortality. Cardiovascular mortality refers to deaths caused by major CVD and cerebrovascular diseases (codes: I00–I09, I11, I13, I20–I51, and I60–I69).

Statistical analysis

Due to the complex sampling design of NHANES, sample weights, clustering, and stratification were incorporated into the analyses. Study participants' characteristics were stratified into four groups according to quartiles (Q1–Q4) of the AIP index. Baseline characteristics were expressed as mean ± standard deviation (SD) for continuous variables and as frequency and percentage for categorical variables. Baseline characteristics in AIP quartile groups were compared using a weighted Kruskal-Wallis test for continuous variables and a weighted rank sum test for categorical variables.

Multivariate logistic regression was utilized to investigate odds ratios (OR) and 95% confidence intervals (CI) for the association between the AIP index and the risk of CVD, heart attack, stroke, congestive heart failure, and angina pectoris through three distinct models. In model 1, no covariates were adjusted. Model 2 was adjusted for age, sex, and race or ethnicity. Model 3 included adjustments for age, sex, race or ethnicity, income, education, marital status, sedentary lifestyle, smoking, diabetes, hypertension, and NFS. To further explore potential nonlinear relationships between the AIP index and CVD risk among participants with NAFLD or MASLD, restricted cubic spline (RCS) analysis with four knots was used. The incidence rates of all-cause mortality and CVD mortality for each AIP quartile group were computed during the total follow-up period. To evaluate the independent predictive value of the AIP index, the Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% CI for the association between the AIP index and all-cause mortality and CVD mortality. Additionally, subgroup analyses were conducted to assess the association between the AIP index and CVD among individuals with NAFLD or MASLD. Data were stratified by age (< 60 or ≥ 60), sex (male or female), race or ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other race), income level (low income or non-low income), marital status (not married or married), education years (< 9 or ≥ 9), sedentary lifestyle (no or yes), current smoking status (no or yes), diabetes (no or yes), hypertension (no or yes), BMI (18.5–24.9, 25–30, or > 30), and FIB-4 (> 1.3 or ≤ 1.3).

A two-sided P-value of < 0.05 was considered statistically significant. The statistical analysis was performed using Empower Stats and R software (version 4.4.1) [26, 27].

Result

Baseline characteristics of the participants

In this study, 12,929 participants with completed ultrasound examinations and laboratory data were enrolled. The comparison of clinical characteristics between NAFLD and Non-NAFLD, as well as MASLD and Non-MASLD group is illustrated in Table 1. According to the quartiles of the AIP index, participants were divided into four groups. The baseline demographic and clinical data for the four AIP index groups among participants with NAFLD or MASLD are shown in Table S1 and Table S2.

Compared to those in the first quartile, participants with NAFLD in the highest quartile were more likely to be older, male, married, current smokers, and have a lower education level. They also showed significantly higher levels of metabolic indicators (BMI, WC, TG, HbA1c, glucose, insulin, HOMA-IR, NFS, and FIB-4) and lower levels of HDL-C. Additionally, these participants exhibited higher rates of diabetes, hypertension, and an increased risk of CVD (heart attack, stroke, congestive heart failure, angina pectoris), as well as all-cause and CVD mortality. These results suggest a strong association between a higher AIP index and worsened metabolic status, along with a significantly higher risk of CVD (Table S1).

Table 1 Baseline characteristics of participants, stratified by NAFLD or MASLD status: NHANES III (1988–1994)

Characteristic	NAFLD	Non-NAFLD	*P* value	MASLD	Non-MASLD	*P* value
	(*n* = 3233)	(*n* = 9696)		(*n* = 2799)	(*n* = 10130)	
Age, years, mean (SD)	46.4 (15.55)	43.08 (16.03)	< 0.001	47.75 (15.17)	42.85 (16.03)	< 0.001
Male, n (%)	1620 (50.11)	4531 (46.73)	< 0.001	1450 (51.80)	4701 (46.41)	< 0.001
Race/ethnicity, n (%)			< 0.001			< 0.001
Non-Hispanic white	1215 (37.58)	3588 (37.00)		1064 (38.01)	3739 (36.91)	
Non-Hispanic black	770 (23.82)	2916 (30.07)		628 (22.44)	3058 (30.19)	
Mexican-American	1124 (34.77)	2772 (28.59)		1010 (36.08)	2886 (28.49)	
Other race	124 (3.84)	420 (4.33)		97 (3.47)	447 (4.41)	
Low income, n (%)	929 (31.21)	2913 (32.92)	0.084	801 (31.18)	3041 (32.85)	0.110
Married, n (%)	2185 (67.58)	6036 (62.25)	< 0.001	1936 (69.17)	6285 (62.04)	< 0.001
Education, n (%)			0.002			0.002
More than or equal to high school	2453 (76.16)	7584 (78.74)		2116 (75.92)	7921 (78.69)	
Current smokers, n (%)	839 (25.95)	2824 (29.13)	< 0.001	695 (24.83)	2968 (29.30)	< 0.001
Sedentary lifestyle, n (%)	979 (30.28)	2818 (29.06)	0.188	849 (30.33)	2948 (29.10)	0.206
BMI, kg/m^2, mean (SD)	28.50 (6.05)	26.13 (4.92)	< 0.001	29.28 (5.79)	26.01 (4.96)	< 0.001
WC, cm, mean (SD)	98.50 (15.88)	91.19 (13.72)	< 0.001	101.13 (14.27)	90.77 (13.93)	< 0.001
Diabetes, n (%)	455 (14.07)	702 (7.24)	< 0.001	414 (14.79)	743 (7.33)	< 0.001
Hypertension, n (%)	1314 (40.64)	2970 (30.63)	< 0.001	1240 (44.30)	3044 (30.05)	< 0.001
TG, mg/dL, mean(SD)	171.30 (122.89)	131.51 (100.64)	< 0.001	181.47 (125.09)	130.41 (100.02)	< 0.001
HDL-C, mg/dL, mean (SD)	47.91 (15.06)	51.80 (15.43)	< 0.001	46.76 (14.82)	51.95 (15.41)	< 0.001
HbA1c (%)	5.75 (1.37)	5.46 (1.02)	< 0.001	5.81 (1.37)	5.45 (1.03)	< 0.001
Glucose, mg/dL, mean(SD)	108.64 (47.28)	98.91 (32.42)	< 0.001	110.23 (48.19)	98.89 (32.75)	< 0.001
Insulin, uU/mL, mean (SD)	80.96 (70.00)	59.30 (50.94)	< 0.001	83.10 (71.25)	59.14 (50.74)	< 0.001
HOMA-IR, mean (SD)	378.91 (332.34)	266.26 (230.44)	< 0.001	388.04 (337.28)	266.22 (230.59)	< 0.001
NFS, mean (SD)	-1.89 (1.63)	-2.21 (1.61)	< 0.001	-1.77 (1.59)	-2.22 (1.61)	< 0.001
NFS > -1.455, n (%)	1159 (38.893)	2632 (29.666)	< 0.001	1075 (41.651)	2716 (29.296)	< 0.001
FIB-4, mean (SD)	1.01 (0.83)	0.95 (1.02)	< 0.001	1.02 (0.77)	0.95 (1.03)	< 0.001
FIB-4 > 1.3, n (%)	693 (21.868)	1820 (19.237)	0.001	626 (22.822)	1887 (19.086)	< 0.001
Heart attack (%)	136 (4.21)	297 (3.06)	0.002	125 (4.47)	308 (3.04)	< 0.001
Stroke (%)	71 (2.20)	163 (1.68)	0.057	64 (2.29)	170 (1.68)	0.033
Congresive heart failure (%)	112 (3.46)	243 (2.51)	0.004	99 (3.54)	256 (2.53)	0.004
Angina pectoris (%)	333 (10.30)	808 (8.33)	< 0.001	296 (10.58)	845 (8.34)	< 0.001
CVD (%)	485 (15.00)	1164 (12.00)	< 0.001	434 (15.51)	1215 (11.99)	< 0.001
All-cause mortality, n (%)	1184 (36.62)	2916 (30.07)	< 0.001	1076 (38.44)	3024 (29.85)	< 0.001
CVD mortality, n (%)	358 (11.07)	899 (9.27)	0.003	330 (11.79)	927 (9.15)	< 0.001

**p*-values were derived from a weighted Kruskal-Wallis test for continuous variables and a weighted rank sum test for categorical variables to compare the differences of each variable between groups

NAFLD: Non-alcoholic fatty liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease; SD: Standard deviation; BMI: Body mass index; WC: Waist circumference; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; HbA1c: Hemoglobin A1c; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; NFS: Non-alcoholic fatty liver disease fibrosis score; FIB-4: Fibrosis-4 index; CVD: Cardiovascular disease

Table 2 The association between AIP index and the risk of CVD among participants with NAFLD

CVD	OR (95% CI)		
	Model 1	**Model 2**	**Model 3**
AIP index (continuous)	2.03 (1.53, 2.70)	2.01 (1.49, 2.73)	1.72 (1.22, 2.43)
	P < 0.001	*P* < 0.001	*P* = 0.002
AIP index (quartiles)			
Q1 (≤ 0.25)	Reference	Reference	Reference
Q2 (0.25–0.48)	1.38 (1.01, 1.87)	1.33 (0.97, 1.84)	1.33 (0.93, 1.90)
	P = 0.041	*P* = 0.079	*P* = 0.122
Q3 (0.48–0.71)	1.86 (1.39, 2.49)	1.68 (1.22, 2.31)	1.66 (1.17, 2.35)
	P < 0.001	*P* = 0.001	*P* = 0.005
Q4 (≥ 0.71)	2.16 (1.62, 2.88)	1.97 (1.43, 2.70)	1.77 (1.24, 2.52)
	P < 0.001	*P* < 0.001	*P* = 0.002
P for trend	*P* < 0.001	*P* < 0.001	*P* = 0.001

Model 1: no covariates were adjusted

Model 2: adjusted for age, gender and race/ethnicity

Model 3: adjusted for age, gender, race/ethnicity, income, education, marital status, sedentary lifestyle, smokers, diabetes, hypertension and NFS

*ORs were derived from univariate and multivariate logistic regression

CVD: Cardiovascular disease; OR: Odds ratios; CI: Confidence intervals; AIP: Atherogenic Index of Plasma; Q1–Q4: Quartile 1-Quartile 4; NFS: Non-alcoholic fatty liver disease fibrosis score

Table 3 The association between AIP index and the risk of CVD among participants with MASLD

CVD	OR (95% CI)		
	Model 1	**Model 2**	**Model 3**
AIP index (continuous)	1.81 (1.33, 2.46)	1.94 (1.40, 2.70)	1.70 (1.17, 2.45)
	P < 0.001	*P* < 0.001	*P* = 0.005
AIP index (quartiles)			
Q1 (≤ 0.31)	Reference	Reference	Reference
Q2 (0.31–0.52)	1.45 (1.06, 1.99)	1.23 (0.90, 1.69)	1.16 (0.81, 1.65)
	P = 0.0208	*P* = 0.189	*P* = 0.418
Q3 (0.52–0.74)	1.72 (1.26, 2.34)	1.65 (1.21, 2.23)	1.56 (1.11, 2.19)
	P < 0.001	*P* = 0.001	*P* = 0.011
Q4 (≥ 0.74)	1.91 (1.41, 2.59)	2.05 (1.51, 2.79)	1.75 (1.24, 2.47)
	P < 0.001	*P* < 0.001	*P* = 0.001
P for trend	*P* < 0.001	*P* < 0.001	*P* < 0.001

Model 1: no covariates were adjusted

Model 2: adjusted for age, gender and race/ethnicity

Model 3: adjusted for age, gender, race/ethnicity, income, education, marital status, sedentary lifestyle, smokers, diabetes, hypertension and NFS

*ORs were derived from univariate and multivariate logistic regression

CVD: Cardiovascular disease; OR: Odds ratios; CI: Confidence intervals; AIP: Atherogenic Index of Plasma; Q1–Q4: Quartile 1-Quartile 4; NFS: Non-alcoholic fatty liver disease fibrosis score

A similar pattern was observed among participants with MASLD in the higher AIP quartile; they had higher metabolic indicators (BMI, WC, TG, HbA1c, glucose, insulin, HOMA-IR, and NFS) and lower HDL-C levels. These participants were also more likely to have diabetes, hypertension, and a higher risk of CVD (heart attack, stroke, angina pectoris). These further underscores the importance of the AIP index in assessing CVD risk in the MASLD population (Table S2). Compared with non-CVD participants, those with CVD tended to be older and have higher metabolic indicators (BMI, WC, TG, HbA1c, glucose, NFS, and FIB-4) and lower HDL-C levels, which further certifies the predictive value of AIP for CVD risk (Table S3).

In both the NAFLD and MASLD populations, participants with all-cause or CVD mortality had distinctive features, including being older, having higher metabolic indicators (BMI, WC, TG, HbA1c, glucose, NFS, and FIB-4), and lower HDL-C levels. In particular, men and current smokers were more common in the higher mortality group, emphasizing the importance of maintaining healthy metabolic status in these populations (Tables S4 and S5).

Relationships of AIP index with the risk of CVD

Tables 2 and 3 illustrate the association between the AIP index and the risk of CVD, revealing that a higher AIP index is linked to an elevated risk of CVD among participants with NAFLD or MASLD. In the NAFLD population, this association was significant in model 3 (OR = 1.72, 95% CI: 1.22, 2.43), indicating that each unit increase in the AIP index was associated with a 72% increase in CVD risk. When categorizing the AIP index into quartiles, in model 3, participants in the highest quartile showed a significant 77% increased risk of CVD compared to those in the lowest quartile (OR = 1.77, 95% CI: 1.24, 2.52) (Table 2). Similarly, in the MASLD population, the association was significant in model 3 (OR = 1.70, 95% CI: 1.17, 2.45), with each unit increase in the AIP index associated with a 70% increase in CVD risk. Participants in the highest quartile of the AIP index showed a significant 75% increased risk of CVD compared to those in the lowest quartile (OR = 1.75, 95% CI: 1.24, 2.47) (Table 3).

Tables S6 and S9 revealed a significant increase in risk among NAFLD participants between the AIP index and the risk of heart attack (OR 2.55, 95% CI: 1.37, 4.73) and angina pectoris (OR 1.79, 95% CI: 1.20, 2.66). Sensitivity analyses further verified that the highest quartile of the AIP index was associated with an increased risk of both heart attack and angina pectoris. However, no significant association was found between the AIP index and the risk of stroke or congestive heart failure in NAFLD participants (Tables S7 and S8).

Similarly, Tables S10 and S13 revealed a significant risk increase among MASLD participants between the AIP index and the risk of heart attack (OR 2.69, 95% CI: 1.41, 5.13) and angina pectoris (OR 1.70, 95% CI: 1.11, 2.60). Sensitivity analyses also showed that the highest quartile of the AIP index was significantly associated with an increased risk of stroke (OR 2.42, 95% CI: 1.01, 5.84) (Table S11). However, no significant association was found between the AIP index and the risk of congestive heart failure in the MASLD population (Table S12).

In summary, the results indicate statistically significant associations between the AIP index and an increased risk of CVD among participants with NAFLD or MASLD, particularly for heart attack and angina pectoris. This finding highlights the potential of the AIP index as an important predictor of CVD risk, providing a basis for personalized interventions and risk management.

RCS analysis

After adjusting for all covariates in model 3, restricted cubic spline analyses were conducted to assess the potential non-linear relationship between the AIP index and the risk of CVD, heart attack, stroke, congestive heart failure, and angina pectoris.

There was evidence of a significant linear relationship between the AIP index and the risk of CVD among participants with NAFLD (P for non-linear = 0.082) and MASLD (P for non-linear = 0.150), indicating an approximately linear association between higher AIP levels and increased CVD risk (Fig. 2). Subsequently, the relationship between the AIP index and specific cardiovascular events was further analyzed in Fig. S1. In the NAFLD population, the results showed an approximately linear correlation between the AIP index and heart attack, stroke, and congestive heart failure. Similarly, an approximately linear correlation was observed among MASLD participants (Fig. S1 A-F). Notably, there was a remarkable nonlinear association between the AIP index and angina pectoris among participants with NAFLD or MASLD, suggesting that this relationship is more complex (Fig. S1 G-H).

Overall, the AIP index showed a linear relationship with the risk of most cardiovascular events but demonstrated a nonlinear association with angina, especially in the NAFLD and MASLD populations.

The relationship was evaluated by RCS after adjustment for age, sex, race, income, marital status, education, smoking, sedentary lifestyle, diabetes, hypertension and NFS (model3). The solid lines in the figure represents ORs, and the shaded regions represents the 95% CIs. (A) AIP index in NAFLD; (B) AIP index in MASLD; CI, confidence intervals; OR, odds ratio; CVD, cardiovascular disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; RCS, restricted cubic spline.

Association between AIP indices and all-cause and CVD Mortality and the Risk of CVD

In long-term follow-up study of the NAFLD and MASLD populations, it found that 1,184 people died in the NAFLD population, including 358 deaths due to cardiovascular disease (CVD) (Table S4). In contrast, in the MASLD population, a total of 1,076 people died from

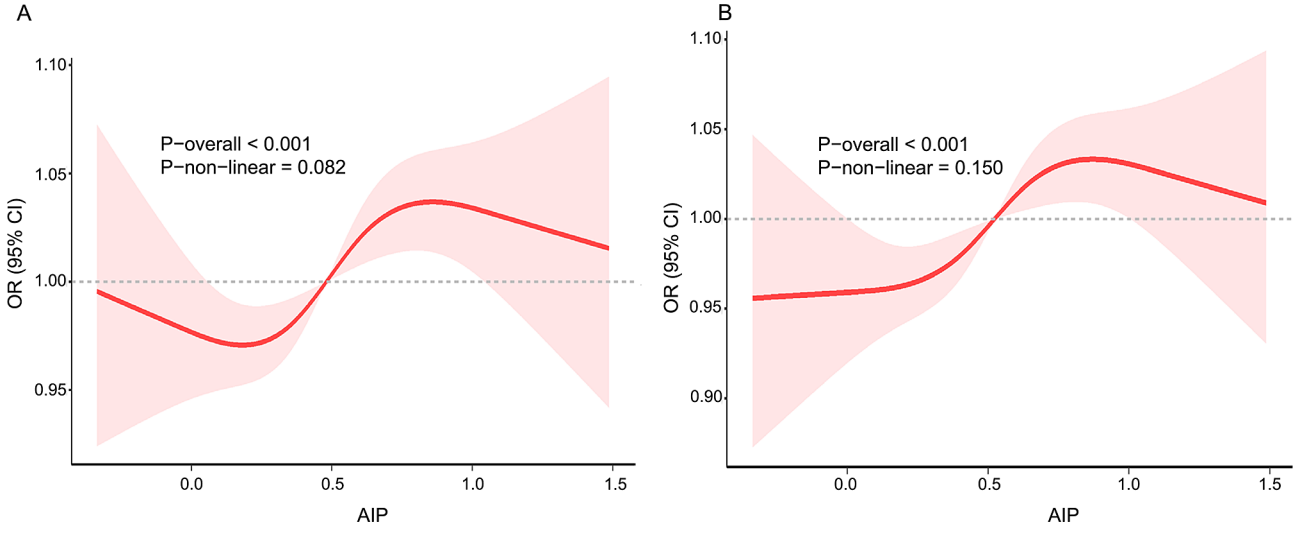

Fig. 2 Nonlinear relationship between AIP index and CVD among participants with NAFLD/MASLD. The relationship was evaluated by RCS after adjustment for age, sex, race, income, marital status, education, smoking, sedentary lifestyle, diabetes, hypertension and NFS (model3). The solid lines in the figure represents ORs, and the shaded regions represents the 95% CIs. (**A**) AIP index in NAFLD; (**B**) AIP index in MASLD. OR: Odds ratios; CI: Confidence intervals; AIP: Atherogenic Index of Plasm; CVD: Cardiovascular disease; NAFLD: Non-alcoholic fatty liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease; RCS: Restricted cubic spline; NFS: Non-alcoholic fatty liver disease fibrosis score

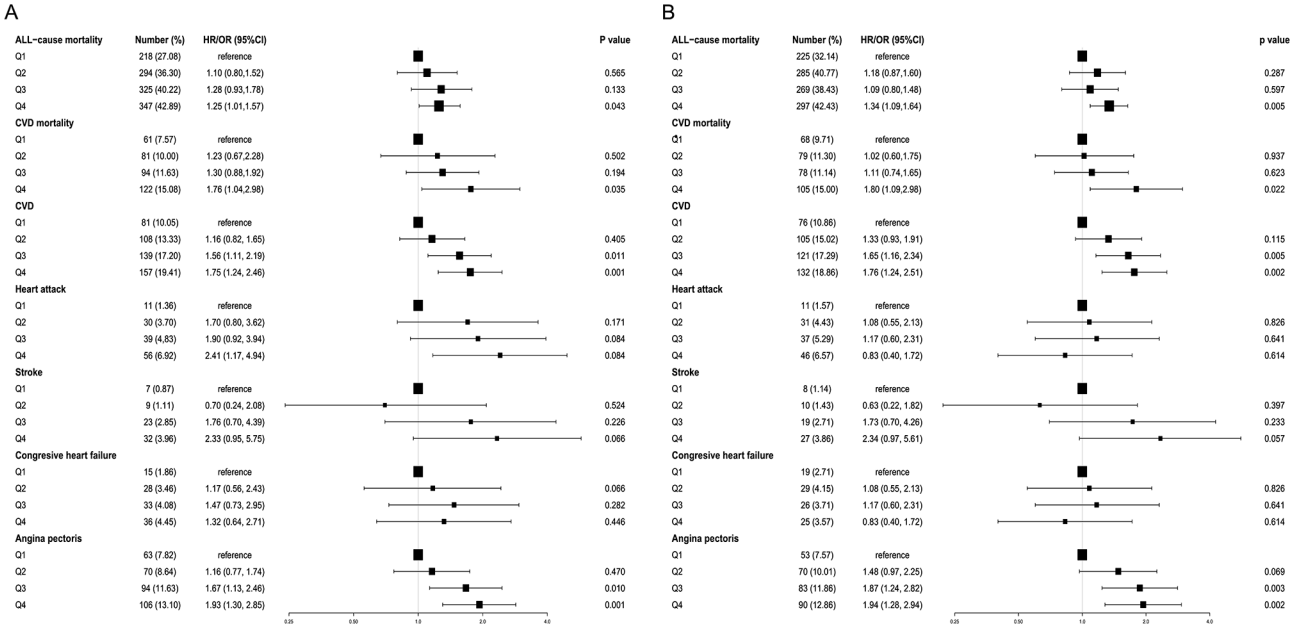

Fig. 3 Association between the AIP index and all-cause and CVD mortality and the risk of CVD in NAFLD(**A**) or MASLD(**B**). ORs were derived from the multivariate logistic regression and HRs were derived from the cox proportional hazards model. OR: Odds ratios; HR: Hazard ratios; CI: Confidence intervals; Q1–Q4: Quartile 1-Quartile 4; CVD: Cardiovascular disease; AIP: Atherogenic Index of Plasma; NAFLD: Non-alcoholic fatty liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease

various causes, including 330 deaths due to CVD (Table S5). After further analysis of the relationship between the AIP index and the risk of death, it was found that NAFLD participants in the highest quartile of AIP were more likely to experience all-cause and CVD mortality (Table S1). Similarly, in the MASLD population, participants with the highest quartile of AIP also showed higher all-cause mortality and CVD mortality (Table S2).

Figure 3 illustrate the relationship of the AIP index with all-cause mortality and CVD mortality. In the NAFLD population, using a multivariable Cox regression model adjusted for relevant covariates in model 3, the results showed that AIP exhibited significant positive correlations or trends of positive correlation with all-cause mortality (HR: 1.25, 95% CI: 1.01, 1.57) and CVD mortality (HR 1.76, 95% CI: 1.04, 2.98). Additionally, the AIP index was highly correlated with the risk of CVD (OR 1.75, 95% CI: 1.24, 2.46) and angina pectoris (OR 1.93, 95% CI: 1.30, 2.85) in NAFLD. There was no significant association between AIP and heart attack, stroke, or congestive heart failure.

Similarly, for participants with MASLD, the relationship of AIP was also significantly and positively associated with all-cause mortality (HR 1.34, 95% CI: 1.09, 1.64) and CVD mortality (HR 1.80, 95% CI: 1.09, 2.98) through a multivariable Cox regression model adjusted for relevant covariates in model 3. Additionally, the AIP index was highly correlated with the risk of CVD (OR 1.76, 95% CI: 1.24, 2.51) and the incidence of angina pectoris (OR 1.94, 95% CI: 1.28, 2.94) in MASLD. There was no significant association between AIP and heart attack, stroke, or congestive heart failure in the MASLD population (Fig. 3).

Subgroup analysis

To further explore the association between AIP index and CVD risk in different populations, this study conducted stratified analyses of NAFLD or MASLD populations based on multiple factors such as age, sex, race or ethnicity, income level, marital status, years of education, sedentary lifestyle, smoking status, diabetes, hypertension, BMI, and advanced fibrosis (FIB-4 > 1.3). The results showed that the association between AIP and CVD risk was closer in individuals aged ≥ 60 years, male, married, with higher education, sedentary lifestyle, diabetic patients, and individuals with BMI of 18.5–24.9 kg/m² and FIB-4 > 1.3. In particular, in the NAFLD population, race/ethnicity and AIP showed a significant interaction (Table S14), while in the MASLD population, the interaction between AIP and race/ethnicity and age was also significant (Table S15).

In addition, this study found that AIP was significantly positively associated with CVD mortality in NAFLD and MASLD populations in non-Hispanic whites and non-low-income populations with advanced fibrosis. This association was highly significant in both populations, with interactions with income and age for CVD mortality (Tables S16 and S18). Meanwhile, AIP showed strong interactions with income, marital status, and hypertension in all-cause mortality, while age and income status

had strong interactions in cardiovascular mortality in both groups, further highlighting the potential of AIP in predicting all-cause and cardiovascular mortality in different populations (Tables S17 and S19).

These findings highlight the importance of personalized interventions and treatments for populations with specific risk factors in public health and clinical practice. This application of the AIP index can not only optimize CVD risk management, but also play a key role in predicting all-cause and cause-specific mortality in specific populations.

Discussion

This was a large-sample cohort study detailing the association between AIP and CVD events, all-cause mortality, and CVD mortality. By analyzing the data of patients with NAFLD and MASL, it was found that a higher AIP index was closely associated with a worse metabolic state and a higher risk of CVD, all-cause mortality, and CVD mortality. RCS analysis and Cox regression model revealed linear and nonlinear associations of the AIP index and further confirmed its significant association with CVD risk and mortality. In addition, subgroup analysis revealed the predictive value of the AIP index in specific populations, such as older age, males, patients with diabetes, habitual sedentary, and patients with a higher degree of fibrosis.

AIP, calculated by calculating the logarithmic transformation of the ratio of TG to HDL-C, is a sensitive indicator for assessing visceral fat accumulation. Studies have shown that AIP is closely associated with the risk of CVD, especially in people with fatty liver, where high AIP values may indicate a higher risk of CVD [24]. AIP shows its potential value as a predictor in different types of fatty liver, such as NAFLD and MASLD. For example, Xie et al. found that higher AIP levels were significantly associated with the occurrence of fatty liver in the Han Chinese population, and the presence of such fatty liver was associated with a higher risk of CVD [25]. In addition, the relationship between AIP and dyslipidemia and insulin resistance further reinforces its importance in CVD risk assessment. Insulin resistance is the common pathophysiological basis of fatty liver and cardiovascular disease, and AIP, as an indicator of lipid metabolism, its changes may reflect the aggravation of this pathological state. Therefore, evaluating AIP levels in different fatty liver populations can help better understand and prevent the development of CVD.

To data, no study has explored in detail the relationship between AIP and CVD events, all-cause mortality, and CVD mortality in different fatty liver populations. Although previous studies have shown the potential of AIP in predicting CVD events [28], the results on the effects of all-cause mortality and CVD mortality are inconsistent. For example, Dong et al. found in a 10-year prospective study that AIP showed a U-shaped relationship with CVD mortality [29], while a 10-year prospective analysis by You et al. [21] found that there is no significant association between AIP and all-cause or CVD-specific mortality. The discrepancies may arise from multiple contributing factors. At the methodological level, heterogeneity in risk assessment metrics, small sample sizes and abbreviated follow-up periods limit the reliability of findings. At the population level, significant heterogeneity in cohort characteristics emerges as a critical consideration: younger cohorts demonstrate distinct cardiovascular risk profiles influenced by lower event rates, while older cohorts exhibit different patterns shaped by elevated baseline risks. Additionally, inadequate adjustment for confounders (metabolic syndrome, inflammation markers) introduces bias. Thus, a large-scale, population-based cohort studies with extended follow-up durations and confounding controls are urgently needed to validate correlative findings.

By analyzing data from patients with NAFLD and MASLD, this study found that AIP levels were positively correlated with all-cause and CVD mortality, that is, the higher the AIP index, the higher the mortality rate. This relationship may be due to the effect of AIP on lipoprotein particle size: AIP is positively correlated with the number of small, dense low-density lipoprotein particles, which are easily oxidized due to their strong permeability and retention in the vascular wall, and may aggravate atherosclerosis, thereby increasing the risk of cardiovascular disease [19]. In addition, lipid metabolism disorders caused by chronic inflammation may be another key factor in the relationship between AIP and cardiovascular-specific mortality [30].

In this study, a detailed subgroup analysis was conducted to explore the effects of age, sex, race, economic conditions, marital status, lifestyle, diabetes, hypertension, BMI, and FIB-4 on the relationship between AIP and CVD events, all-cause mortality, and CVD mortality in patients with NAFLD and MASLD. In particular, the data showed that the positive correlation between AIP levels and all-cause mortality was more significant in men. Previous studies have demonstrated gender differences in AIP. For example, Sadeghi et al. conducted a 15-year cohort study on healthy adults over 35 years old to evaluate the value of AIP in predicting mortality and found that high AIP levels were significantly associated with a significantly increased risk of CVD mortality in men [31]. In addition, several studies on Chinese patients have also shown that AIP is independently associated with the presence and severity of CVD events in patients of different ages in a gender-dependent manner [32, 33]. In contrast, in women, the fourth quartile with higher AIP also had an increased all-cause mortality rate

compared with the first quartile. Previous studies have shown that studies on postmenopausal women have shown that AIP is associated with an increased risk of CVD; people at increased risk of developing atherosclerosis [34, 35].

The results further found that in non-Hispanic whites, AIP was positively correlated with CVD and all-cause mortality. This finding highlights possible differences between different races, although the specific relationship between AIP and the risk of CVD mortality between different races has not been widely studied [31]. In addition, the study by Płaczkowska et al. pointed out that the association between small dense LDL and lipid parameters and AIP was more obvious in the elderly, which is consistent with the result, especially in people over 60 years old, the Q3 or Q4 quantile of AIP showed a significant increase in CVD risk, which may be related to the prolonged duration of metabolic disorders [36]. Therefore, these findings suggest that the impact of AIP may vary depending on the individual's physiological and metabolic characteristics, emphasizing that future studies need to further explore the specific relationship between these variables in order to more effectively optimize CVD prevention and treatment strategies.

This study was conducted using the NHANES database, which covers a wide range of people in the United States and contains rich and standardized individual health data, which greatly reduces data collection bias and enhances the scientific and credibility of the study. By adjusting for covariates, confounding factors were effectively controlled, and the independent association between AIP and CVD incidence and mortality was determined. Linear and nonlinear relationships between AIP and various CVD outcomes (including heart attack, stroke, congestive heart failure, and angina pectoris) were identified, demonstrating that AIP is an effective indicator for assessing CVD risk and holds significant clinical value for the management of patients with NAFLD and MASLD.

Nevertheless, this study still has some limitations. Firstly, as an observational study, this study uses more than 30 years of data and although confounding factors have been adjusted, some unmeasured potential factors (such as dietary patterns, the use of statins and/or antidiabetic drugs, and environmental factors) may introduce biases. And NHANES data adheres to a high degree of standardization, but the variability in data collection has the potential to introduce bias. Secondly, there are certain limitations in the diagnosis of NAFLD and MASLD. Insufficient evaluation of the ultrasound resolution and the lack of liver biopsy may lead to a certain risk of misdiagnosis. Therefore, this study combined relevant laboratory indicators and adopted HOMA-IR, FIB-4, and NFS as supplementary data to improve the accuracy of the assessment of the fatty liver status and reduce the risk of misdiagnosis. In addition, since the AIP data are only derived from baseline blood samples, the metabolic factors or changes of AIP during the follow-up period have not been considered, which limits the ability to evaluate the impact of AIP on CVD over time. Finally, the data on cardiovascular outcomes mainly come from patients' self-reports. This approach is vulnerable to factors such as patients' subjective cognition and memory biases, and there is a certain risk of information bias, which may limit the accuracy and reliability of the data. Despite these limitations, the results are still clinically relevant because the association between AIP and cardiovascular events and mortality was demonstrated.

Conclusion

In this study, the relationship between AIP and CVD risk was explored systematically, all-cause mortality, and CVD mortality in patients with NAFLD and MASLD. The analysis results showed that higher AIP levels were significantly associated with increased all-cause mortality and CVD mortality, and were also closely associated with higher CVD risk. This finding highlights the potential of AIP as an effective predictor in cardiovascular health management, especially for the two high-risk groups of NAFLD and MASLD. As a non-invasive and easily measurable biomarker, regular monitoring and management of AIP can assist clinicians in early identification and intervention of high-risk patients, thereby optimizing treatment strategies and significantly reducing the incidence of serious CVD events.

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
MASLD	Metabolic dysfunction-associated steatotic liver disease
CVD	Cardiovascular disease
IR	Insulin resistance
CAD	Coronary artery disease
AIP	Atherogenic Index of Plasma
TG	Triglyceride
HDL-C	High-density lipoprotein cholesterol
WC	Waist circumference
FBG	Fasting serum glucose
HbA1c	Hemoglobin A1c
BMI	Body mass index
SD	Standard deviation
OR	Odds ratios
CI	Confidence intervals
RCS	Restricted cubic spline
HR	Hazard ratios

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions
Jianghua Zhou and Xupei Jiang and Pan Huang conceived the study; Leyi Zheng conceptualized the article; Jiaxin Shao and Qianrong Zheng participated in data acquisition and performed data visualization; Jijie Jin and Jiayi Teng analyzed the data; Jialu Lv and Jiangnan Yao and Xuepei Jiang drafted and revised the manuscript; Fuman Cai is the guarantor of this work. The final version of the manuscript has been read and approved by all authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The data used in this retrospective cohort study were obtained from the NHANES database. The survey was approved by the Institutional Review Board of the National Center for Health Statistics, and informed consent was obtained from all participants.

Consent for publication
All authors have reviewed the final version of the manuscript and approved it for publication. This manuscript has not been published in whole or in part, nor is it being considered for publication elsewhere.

Competing interests
The authors declare no competing interests.

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