BMC Public Health

RESEARCH

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Gender disparities in the association between atherogenic index of plasma and chronic kidney disease

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Abstract

Objective This study investigates the relationship between the atherogenic index of plasma (AIP) and chronic kidney disease (CKD) occurrence in the general population, with a focus on potential gender disparities.

Methods The study included 22,952 adults from the National Health and Nutrition Examination Survey (NHANES). Various statistical models were employed to evaluate the association between AIP and CKD occurrence and explore gender-specific differences.

Results Adjusted for confounding factors, higher AIP levels showed a mild association with increased CKD risk in the general population. Specifically, individuals in the highest AIP quartile had a slightly elevated odds ratio (OR) for CKD compared to the lowest quartile (OR: 1.24, 95% CI: 1.02–1.52, *P* for trend = 0.023). Gender-stratified analysis revealed significant differences. Among males, higher AIP levels were significantly associated with CKD risk (OR: 1.49, 95% CI: 1.15–1.94, *P* for trend < 0.001), whereas in females, the association was weaker and statistically non-significant (*P* for trend = 0.055). U-shaped relationships between AIP and CKD were observed. Mediation analysis provided insights into potential pathways underlying this association. Among males, changes in uric acid accounted for 44.50% of CKD prevalence related to AIP, while glomerular filtration rate (eGFR), BMI, and bicarbonate levels contributed 44.09%, 17.55%, and 15.36%, respectively. Among females, uric acid changes accounted for 45.53%, while eGFR, bicarbonate, C-reactive protein (CRP), sodium, and potassium levels contributed 37.96%, 12.43%, 6.37%, 5.58%, and 3.14%, respectively.

Conclusion Our findings suggest that elevated AIP levels may increase CKD risk, particularly among males in the general U.S. population.

Keywords Atherogenic index of plasma, NHANES, Chronic kidney disease, Gender difference, Mediation Analysis

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Introduction

Chronic kidney disease (CKD) is a major global public health problem with a heavy burden [1–3]. According to the 2017 Global Burden of Disease Study (GBD), the prevalence of adult CKD is approximately 9.1%, resulting in 1.2 million deaths and 35.8 million disability adjusted life years [4]. Between 1990 and 2017, the incidence of CKD increased by 29.3%, with its ranking as a cause of death rising to 12th place. By 2019, CKD ranked 18th in terms of disability-adjusted life years [5]. Therefore, it is crucial to identify CKD risk factors early and take preventive measures.

CKD is defined as a progressive loss of kidney function over time, typically diagnosed when the estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m^2 or when albuminuria (urine albumin-to-creatinine ratio, UACR ≥ 30 mg/g) is present for at least three months, regardless of the underlying cause [6, 7]. The disease is classified into different stages based on eGFR and UACR levels according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [6]. The etiology of CKD is multifactorial, with diabetes mellitus and hypertension being the most common causes, accounting for over 70% of cases in developed countries [7]. Other contributing factors include glomerulonephritis, polycystic kidney disease, and autoimmune disorders [8]. Additionally, metabolic syndrome, obesity, and dyslipidemia have been increasingly recognized as risk factors for CKD progression. Given the complex interplay between lipid metabolism and kidney function, the role of the atherogenic index of plasma in CKD development warrants further investigation.

The atherogenic index of plasma (AIP), calculated as the logarithm of the ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C), is a biomarker reflecting atherosclerosis [9–11]. Multiple research teams worldwide have found through prospective cohorts and cross-sectional observations that AIP is significantly associated with the risk of CKD in populations of different races and regions [9, 12]. However, existing research is limited by insufficient sample size and a lack of long-term follow-up data. At present, the relationship between AIP and CKD has not been accurately evaluated. Gender differences play an important role in the pathogenesis of CKD. Research indicates that gender significantly impacts CKD prevalence and progression, with gender-specific gene expression and hormone receptor activity influencing renal function and structure [13]. However, existing research has shortcomings in gender difference analysis, failing to fully reveal how gender affects the onset and progression of CKD [14, 15]. Therefore, the necessity of conducting CKD research from a gender perspective is increasingly prominent.

This study is a cross-sectional observational study based on the NHANES database. Given that NHANES provides large-scale, nationally representative data at a single time point, this design allows us to assess the association between AIP and CKD prevalence while considering gender differences. This study aims to explore the differences in AIP in the prevalence of CKD among different genders, providing a deeper understanding of CKD pathogenesis and offering new prevention strategies and risk assessment perspectives.

Methods

Study population

This study is a cross-sectional observational study designed to investigate the association between AIP levels and CKD prevalence in different genders using NHANES data. All data were extracted from the NHANES conducted by the Center for Disease Control and Prevention of the United States (CDC). NHANES is an ongoing, national, stratified, and multistage probability sample survey designed to assess the health and nutritional status of the non-institutionalized U.S. population. The current study included secondary data analysis of 101,369 participants enrolled across ten consecutive NHANES cycles from 1999 to 2018. Data collection included structured interviews, physical examinations, and laboratory measurements. The exclusion criteria were as follows: (1) Pregnant or aged under 20 participants ($n = 47,684$); (2) Participants without serum AIP data (TG or HDL-C) ($n = 30,768$); (3) Participants without eGFR or UACR data ($n = 145$). After applying exclusion criteria, 22,952 adult participants (aged ≥ 20 years) were included for final analysis (Fig. 1). The research protocols were approved by the ethics review board of the National Center for Health Statistics. All participants provided informed consent. Information in detail is available on the website http://www.cdc.gov/nchs/nhanes/irba98.htm.

Assessment of CKD and AIP

We utilized the CKD-Epidemiology Collaboration (EPI) equation to calculate eGFR [16]. CKD was diagnosed if eGFR fell below 60 ml/min per 1.73 m^2 or if the UACR was 30 mg/g or higher. AIP was computed using the formula log (TG/HDL-C) [10, 11], with TG representing TG and HDL-C indicating HDL-C. Measurements for TG and HDL-C were conducted during participants' physical examinations.

Covariant evaluation

General demographic variables, including age, sex, race/ethnicity, family income, physical activity, and alcohol consumption, were collected using standardized NHANES questionnaires during interviews [17]. Race/

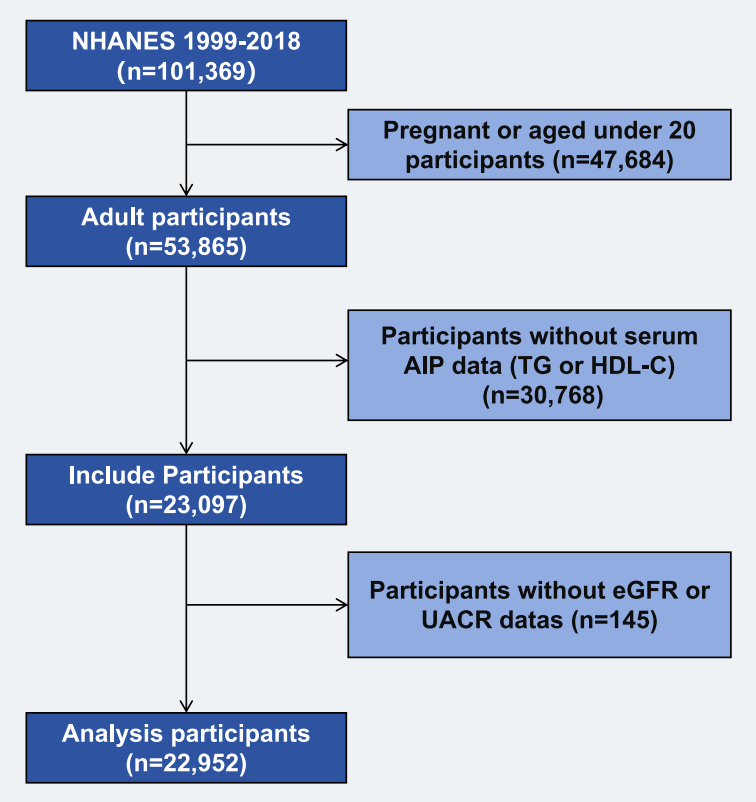

Fig. 1 Flow chart of participants selected from the NHANES database 1999–2018

ethnicity was categorized as non-Hispanic White, non-Hispanic Black, Mexican American, and Other according to NHANES classifications [18]. Leisure physical activity during the past month was classified as vigorous, moderate, or less exercise based on NHANES-defined metabolic equivalent (MET) categories [19]. Anthropometric measurements were conducted during physical examinations in the Mobile Examination Center (MEC) following standardized NHANES protocols. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2), following WHO guidelines [20]. Laboratory parameters, including TG, total cholesterol (TC), low density lipoprotein (LDL), HDL-C, C-reactive protein (CRP), urine albumin/creatinine (U/C), eGFR, blood urea nitrogen (BUN), uric acid, bicarbonate, total calcium, phosphorus, sodium, potassium, chloride, were measured using standard NHANES laboratory methods [21–23]. Hypertension was defined as antihypertensive medication, the average systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg at baseline [24]. Hypercholesterolemia was defined as fasting total cholesterol values ≥ 240 mg/dl [25]. Diabetes mellitus (DM) was defined as glycated hemoglobin (HbA1c) ≥ 6.5%, fasting plasma glucose (FPG) ≥ 126 mg/dL, or the use of anti-diabetic medication [26]. These covariates were included in the multivariate models as potential confounding factors due to their well-established roles in the pathophysiology of CKD, lipid metabolism, and cardiovascular risk [27–29]. By adjusting for these variables, our analysis aims to isolate the independent association between AIP and CKD while minimizing residual confounding effects.

Statistical analyses

Because the NHANES survey utilized complex sampling methods, we incorporated sample weights from different research phases into our analysis to ensure the precision of health statistics. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and expressed as mean ± standard deviation or median [IQR]. Comparisons between groups were conducted using Student's t-test (for normally distributed data) or Mann–Whitney U test (for non-normally distributed data). Categorical variables were presented as frequencies and percentages (%) and compared using the Chi-square test. AIP levels were categorized into quartiles (Q1: ≤ −2.06; Q2: > −2.06 to −0.04; Q3: > −0.04 to 0.18;

Q4: > 0.18), with the first quartile (Q1) serving as the reference.

Restricted cubic spline curves (4 knots, with the 25th percentile as the reference point) were used to evaluate the nonlinear association between AIP and CKD prevalence, with graphics plotted based on Model 3.

Multivariate logistic regression analysis was used to evaluate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between AIP and CKD. Three multivariable models were constructed. Model 1 adjusted for age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American or other), and education level (less than high school, high school or equivalent, or greater than high school); Model 2 adjusted for Model 1 plus BMI (continuous), physical activity (never, moderate or vigorous), PIR (0–1.0, 1.01–4.99 or 5.0), serum cotinine (> 10, LOD-10 or < LOD ng/mL), Model 3 adjusted for Model 2 plus hypertension (yes or no), hypercholesterolemia (yes or no), and diabetes (yes or no). Additionally, we conducted a stratified multivariate logistic regression analysis by gender. Multiplicative interactions were included to determine if the association between AIP and CKD prevalence varied by these potential factors.

The area under the receiver operating characteristic (ROC) curve (AUC) was applied to assess the predictive value of AIP for the occurrence of CKD in male.

We also performed mediation analysis to evaluate whether variables such as BMI, TG, LDL, TC, HDL, CRP, U/C, eGFR, BUN, uric acid, bicarbonate, total calcium, phosphorus, sodium, potassium, and chloride mediated the relationship between AIP and CKD prevalence and to quantify their mediation effects.

Statistical analyses were carried out using Stata software (version 17; StataCorp, College Station, TX, USA) and R (www.r-project.org). Two-tailed p-values < 0.05 were considered statistically significant.

Results

Participant characteristics

Based on AIP categories, Table 1 lists selected demographic characteristics and potential confounding factors. In the NHANES dataset from 1999 to 2018, 22,952 adults aged ≥ 20 years were measured for AIP. The median AIP level was −0.04 (IQR −2.06–0.18) g/L, with the 25th, 50th, and 75th percentiles being −2.06, −0.04, and 0.18, respectively. The average age of the final study sample was 47.11 ± 16.80 years, with 48.8% being male and 51.2% female. The study found that higher AIP levels were more likely among males, older adults, non-Hispanic Whites, obese individuals, those with more than a high school education, moderate household income, lack of leisure physical activity, and cotinine levels > 10 ng/mL. There was a higher prevalence of CKD, hypertension, hypercholesterolemia, and diabetes among those with elevated AIP levels. In patients with frequent laboratory abnormalities, levels of TG, LDL, TC, HDL, CRP, U/C, BUN, uric acid, total calcium, and potassium were higher, whereas levels of eGFR, bicarbonate, phosphorus, sodium, and chloride were lower.

Compared with non CKD patients, CKD patients are more likely to be female, elderly, non Hispanic white individuals, obese individuals, individuals with high school education or above, middle-income families, individuals lacking leisure and sports activities, and individuals with cotinine levels ≤ 10 ng/mL. The prevalence of hypertension, hypercholesterolemia and diabetes is higher in CKD patients. Laboratory indicators are often abnormal, with higher levels of TG, CRP, U/C, BUN, uric acid, bicarbonate, total calcium, phosphorus, and potassium, while lower levels of LDL, TC, HDL, eGFR, sodium, and chloride (Supplementary Table 1).

Males and females have different lipid levels and their trends. Compared to females, males are more prone to disorders of lipid metabolism, as evidenced by higher levels of AIP, TG and LDL and lower levels of TC and HDL (Supplementary Table 2).

Association of AIP with CKD

We performed weighted multivariate COX regression analyses to detect an association between AIP and CKD and found that higher AIP was associated with a higher risk of CKD in the overall population and in the male population. In the overall population, the risk of developing CKD increased with increasing AIP (P for trend = 0.023). After adjusting for potential confounders, the adjusted ORs 95% CI for CKD in quartiles with progressively increasing AIP compared with the lowest quartile were 0.96 (0.81–1.14; P = 0.631), 0.98 (0.83–1.14; P = 0.756), and 1.24 (1.02–1.52; P = 0.032), respectively. The risk of CKD was higher for each increase of 1 standard deviation (SD) increased the risk of developing CKD by 12% (OR 1.12; 95% CI 1.04–1.20; P = 0.004) (Table 2). In the male population, the risk of developing CKD increased with increasing AIP (P for trend < 0.001). The adjusted OR (95% CI) for CKD in quartiles with progressively increasing AIP compared with the lowest quartile after adjusting for potential confounders was 0.91 (0.69–1.19; P = 0.474), 1.09 (0.85–1.41; P = 0.495), and 1.49 (1.15–1.94; P = 0.003), respectively. for every increase of 1 SD was associated with an 18% increased risk of developing CKD (OR 1.18; 95% CI 1.07–1.30; P = 0.001) (Table 3 and Fig. 2). ROC curve analysis showed that AIP was predictive of CKD development in men (AUC = 0.555, 95% CI: 0.541–0.569) (Fig. 3). In the female population, no trend was observed for a significant increase in the risk of

Table 1 The demographic and clinical characteristics of the patients by quartiles of baseline AIP

	Total	Q1 (≤ −2.06)	Q2 (> −2.06 to −0.04)	Q3 (> −0.04 to 0.18)	Q4 (> 0.18)	*P* value
Participants, No	22952	5739	5738	5739	5736	
Female (%)	11622 (51.2)	3657 (65.5)	3086 (54.5)	2767 (48.3)	2112 (35.8)	< 0.001
Age, years	47.11 (16.80)	45.02 (17.08)	46.71 (17.23)	48.36 (17.15)	48.51 (15.39)	< 0.001
Race/ethnicity (%)						< 0.001
Mexican American	4042 (8.2)	633 (5.8)	945 (8.0)	1136 (9.0)	1328 (9.9)	
Other	4057 (12.5)	993 (11.9)	994 (11.8)	1069 (13.6)	1001 (12.6)	
Non-Hispanic white	10273 (68.4)	2325 (65.0)	2530 (68.2)	2595 (68.6)	2823 (72.1)	
Non-Hispanic black	4580 (11.0)	1788 (17.4)	1269 (12.0)	939 (8.8)	584 (5.4)	
Education levels (%)						< 0.001
Less than high school	6287 (17.5)	1157 (12.8)	1505 (16.3)	1694 (19.8)	1931 (21.5)	
High school or equivalent	5262 (24.1)	1207 (20.4)	1340 (24.7)	1350 (24.9)	1365 (26.4)	
Greater than high school	11370 (58.4)	3370 (66.7)	2888 (59.1)	2682 (55.3)	2430 (52.1)	
BMI, kg/m^2	28.77 (6.77)	25.95 (6.00)	28.10 (6.61)	29.99 (6.78)	31.23 (6.48)	< 0.001
BMI (%)						< 0.001
< 25	6792 (31.6)	2792 (52.7)	1940 (35.9)	1253 (23.1)	807 (13.4)	
25–29.9	7680 (33.2)	1650 (28.6)	1916 (33.7)	2014 (34.6)	2100 (36.0)	
≥ 30	8139 (35.2)	1224 (18.7)	1812 (30.4)	2373 (42.3)	2730 (50.6)	
Cotinine (%)						< 0.001
> 10 ng/mL	5750 (26.0)	1242 (20.9)	1368 (24.9)	1469 (27.6)	1671 (31.1)	
LOD −10 ng/mL	11934 (49.9)	3042 (50.0)	3016 (51.0)	2950 (49.7)	2926 (49.0)	
< LOD	5203 (24.0)	1448 (29.1)	1336 (24.1)	1303 (22.7)	1116 (19.9)	
Drinking status (%)	14923 (77.0)	3752 (78.7)	3701 (77.0)	3630 (75.4)	3840 (76.8)	0.023
Physical activity (%)						< 0.001
Never	9685 (34.7)	2128 (29.6)	2373 (34.5)	2551 (36.3)	2633 (38.5)	
Moderate	6591 (32.9)	1892 (37.4)	1691 (33.2)	1535 (31.0)	1473 (29.6)	
Vigorous	6675 (32.5)	1719 (33.0)	1673 (32.2)	1653 (32.7)	1630 (31.9)	
PIR (%)						< 0.001
≤ 1	4268 (14.0)	983 (13.0)	1065 (13.8)	1049 (14.1)	1171 (15.0)	
1.01–4.99	12956 (61.0)	3148 (58.4)	3226 (61.2)	3291 (61.3)	3291 (63.2)	
5	3687 (25.0)	1077 (28.6)	938 (25.0)	903 (24.6)	769 (21.8)	
CKD (%)	4333 (13.9)	824 (11.0)	1009 (12.6)	1157 (14.7)	1343 (17.6)	< 0.001
Hypertension (%)	9859 (37.1)	1937 (27.2)	2356 (34.0)	2664 (40.4)	2902 (47.3)	< 0.001
Hypercholesterolemia (%)	9213 (38.6)	1578 (25.6)	2083 (33.5)	2486 (42.6)	3066 (53.4)	< 0.001
Diabetes mellitus (%)	4483 (14.0)	598 (6.9)	892 (10.3)	1267 (16.0)	1726 (23.5)	< 0.001
TG, mmol/L	1.19 (0.82, 1.75)	0.66 (0.53, 0.79)	1.00 (0.87, 1.16)	1.41 (1.24, 1.64)	2.34 (1.93, 3.04)	< 0.001
LDL, mmol/L	2.92 (2.35, 3.54)	2.61 (2.15, 3.15)	2.95 (2.40, 3.54)	3.08 (2.51, 3.72)	3.13 (2.48, 3.78)	< 0.001
TC, mmol/L	4.97 (4.29, 5.66)	4.71 (4.11, 5.33)	4.86 (4.24, 5.53)	4.99 (4.34, 5.69)	5.30 (4.63, 6.10)	< 0.001
HDL, mmol/L	1.32 (1.09, 1.60)	1.73 (1.50, 2.02)	1.42 (1.24, 1.60)	1.22 (1.09, 1.40)	1.01 (0.88, 1.14)	< 0.001
CRP, mg/L	1.90 (0.80, 4.40)	1.00 (0.45, 2.50)	1.80 (0.73, 3.90)	2.30 (1.00, 5.41)	2.70 (1.20, 5.50)	< 0.001
U/C, mg/g	6.25 (4.16, 11.52)	6.28 (4.21, 11.02)	5.95 (4.07, 10.32)	6.26 (4.12, 11.52)	6.60 (4.26, 13.86)	< 0.001
eGFR, mL/min per 1.73 m^2	96.23 (81.22, 109.95)	99.34 (84.44, 112.90)	96.26 (81.52, 110.41)	94.77 (79.53, 108.89)	94.49 (79.27, 107.21)	< 0.001
BUN, mmol/L	4.64 (3.57, 5.71)	4.64 (3.57, 5.71)	4.64 (3.57, 5.71)	4.64 (3.57, 5.71)	4.64 (3.90, 5.71)	< 0.001
Uric acid, mmol/L	321.20 (263.37, 374.70)	279.60 (237.90, 333.10)	309.30 (261.70, 362.80)	333.10 (279.60, 386.60)	356.90 (303.30, 410.40)	< 0.001

Table 1 (continued)

	Total	Q1 (≤ −2.06)	Q2 (> −2.06 to −0.04)	Q3 (> −0.04 to 0.18)	Q4 (> 0.18)	*P* value
Bicarbonate, mmol/L	24.85 (2.29)	25.12 (2.24)	24.93 (2.26)	24.83 (2.33)	24.51 (2.28)	< 0.001
Total calcium, mmol/L	2.35 (2.28, 2.40)	2.35 (2.28, 2.40)	2.35 (2.28, 2.40)	2.35 (2.28, 2.40)	2.35 (2.30, 2.40)	< 0.001
Phosphorus, mmol/L	1.16 (1.07, 1.29)	1.20 (1.10, 1.29)	1.16 (1.07, 1.26)	1.16 (1.03, 1.26)	1.16 (1.03, 1.26)	< 0.001
Sodium, mmol/L	139.28 (2.30)	139.37 (2.31)	139.37 (2.25)	139.37 (2.35)	139.01 (2.28)	< 0.001
Potassium, mmol/L	4.06 (0.34)	4.03 (0.34)	4.05 (0.34)	4.06 (0.34)	4.09 (0.33)	< 0.001
Chloride, mmol/L	103.44 (2.91)	103.53 (2.92)	103.62 (2.82)	103.47 (2.92)	103.13 (2.95)	< 0.001

All estimates were accounted for complex survey designs

Categorical variables are expressed as number (percentage) [n (%)]. Normally distributed numerical variables are presented as mean ± standard deviation (SD). Non-normally distributed numerical variables are reported as median (interquartile range, IQR)

Abbreviations: AIP atherogenic index of plasma, *BMI* body mass index, *PIR* poverty-income ratio, *CKD* chronic kidney disease, *TG* triglyceride, *LDL* low density lipoprotein, *TC* total cholesterol, *HDL* high density, *CRP* C-reactive protein, *U/C* urine albumin/creatinine, *eGFR* estimated glomerular filtration rate, *BUN* blood urea nitrogen

Table 2 Relative odds of CKD according to AIP in different models among all participants

	Unadjust		Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Per 1 SD	1.23 (1.17–1.30)	< 0.001	1.26 (1.19–1.35)	< 0.001	1.19 (1.11–1.28)	< 0.001	1.12 (1.04–1.20)	0.004
Q1 (≤ −2.06)	ref		ref		ref		ref	
Q2 (> −2.06 to −0.04)	1.16 (1.01–1.34)	0.034	1.09 (0.94–1.27)	0.254	0.99 (0.84–1.17)	0.928	0.96 (0.81–1.14)	0.631
Q3 (> −0.04 to 0.18)	1.39 (1.21–1.60)	< 0.001	1.24 (1.06–1.44)	0.006	1.05 (0.90–1.23)	0.534	0.98 (0.83–1.14)	0.756
Q4 (> 0.18)	1.72 (1.49–1.97)	< 0.001	1.74 (1.47–2.06)	< 0.001	1.47 (1.21–1.78)	< 0.001	1.24 (1.02–1.52)	0.032
P for trend	< 0.001		< 0.001		< 0.001		0.023	

Model 1 adjusted for gender (male, or female), age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American or other), education level (less than high school, high school or equivalent, or greater than high school)

Model 2 adjusted for model 1 + BMI (continuous), physical activity (never, moderate or vigorous), PIR (0–1.0,1.01–4.99 or 5.0), serum cotinine (> 10, LOD-10 or < LOD ng/mL), drinking status (< 12 dozen drinks/yr, ≥ 12 dozen drinks/yr)

Model 3 adjusted for model 2 + hypertension (yes or no), hypercholesterolemia (yes or no), diabetes (yes or no)

CKD onset with increasing AIP (*P* for trend = 0.055). The adjusted OR (95% CI) for CKD in quartiles with progressively increasing AIP compared with the lowest quartile after adjusting for potential confounders was 0.98 (0.79–1.20; *P* = 0.810), 1.06 (0.85–1.32; *P* = 0.607), and 1.23 (0.97–1.57; *P* = 0.092), respectively. For every increased by 1 SD, the risk of developing CKD increased by 7% (OR 1.07; 95% CI 0.97–1.18; *P* = 0.174) (Table 3 and Fig. 2). The association of AIP with the development of CKD was significantly different in males and females (*P* value for interaction = 0.010) (Table 3).

The RCS curves showed a U-shaped association between AIP and CKD in all participants. We also explored the effect of gender on the risk association of AIP with CKD. The results showed a U-shaped association between AIP and CKD in both males and females. Increased AIP scores were associated with a decreased risk of CKD on the left side of the RCS curve, whereas they were associated with an increased risk of CKD on the right side of the RCS curve (Fig. 4).

Mediation analysis

Mediation analysis revealed the biological mechanisms underlying gender differences in the association between AIP and CKD occurrence (Table 4). In males, changes in uric acid accounted for 44.50% of the CKD prevalence related to AIP, while changes in eGFR, BMI, and bicarbonate levels contributed 44.09%, 17.55%, and 15.36%, respectively. In females, changes in uric acid contributed to 45.53% of the CKD prevalence related to AIP, while changes in eGFR, bicarbonate, CRP, sodium ions, and potassium ions levels contributed 37.96%, 12.43%, 6.37%, 5.58%, and 3.14%, respectively.

Table 3 Relative odds of CKD according to AIP in different models among male and female

	Unadjust		Model 1		Model 2		Model 3	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male								
Per 1 SD	1.26 (1.17–1.35)	< 0.001	1.36 (1.25–1.49)	< 0.001	1.25 (1.14–1.38)	< 0.001	1.18 (1.07–1.30)	0.001
Q1 (≤ −0.19)	ref		ref		ref		ref	
Q2 (> −0.19 to 0.03)	1.07 (0.88–1.30)	0.502	1.05 (0.85–1.31)	0.632	0.96 (0.73–1.24)	0.735	0.91 (0.69–1.19)	0.474
Q3 (> 0.03 to 0.25)	1.45 (1.18–1.78)	< 0.001	1.51 (1.21–1.89)	< 0.001	1.21 (0.94–1.57)	0.145	1.09 (0.85–1.41)	0.495
Q4 (> 0.25)	1.85 (1.52–2.25)	< 0.001	2.17 (1.73–2.72)	< 0.001	1.71 (1.31–2.21)	< 0.001	1.49 (1.15–1.94)	0.003
P for trend	< 0.001		< 0.001		< 0.001		< 0.001	
Female								
Per 1 SD	1.31 (1.23–1.39)	< 0.001	1.18 (1.10–1.28)	< 0.001	1.15 (1.05–1.26)	0.004	1.07 (0.97–1.18)	0.174
Q1 (≤ −0.31)	ref		ref		ref		ref	
Q2 (> −0.31 to −0.11)	1.22 (1.02–1.45)	0.029	1.05 (0.88–1.26)	0.574	1.01 (0.82–1.24)	0.908	0.98 (0.79–1.20)	0.810
Q3 (> −0.11 to 0.11)	1.59 (1.32–1.92)	< 0.001	1.21 (0.99–1.48)	0.064	1.13 (0.91–1.40)	0.262	1.06 (0.85–1.32)	0.607
Q4 (> 0.11)	2.12 (1.77–2.53)	< 0.001	1.55 (1.27–1.89)	< 0.001	1.46 (1.16–1.83)	0.001	1.23 (0.97–1.57)	0.092
P for trend	< 0.001		< 0.001		< 0.001		0.055	
P value for interaction	0.071		0.012		0.017		0.010	

Abbreviations: BMI body mass index, *PIR* poverty-income ratio

Model 1 adjusted for age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American or other), education level (less than high school, high school or equivalent, or greater than high school)

Model 2 adjusted for model 1 + BMI (continuous), physical activity (never, moderate or vigorous), PIR (0–1.0,1.01–4.99 or 5.0), serum cotinine (> 10, LOD-10 or < LOD ng/mL), drinking status (< 12 dozen drinks/yr, ≥ 12 dozen drinks/yr)

Model 3 adjusted for model 2 + hypertension (yes or no),hypercholesterolemia (yes or no), diabetes (yes or no)

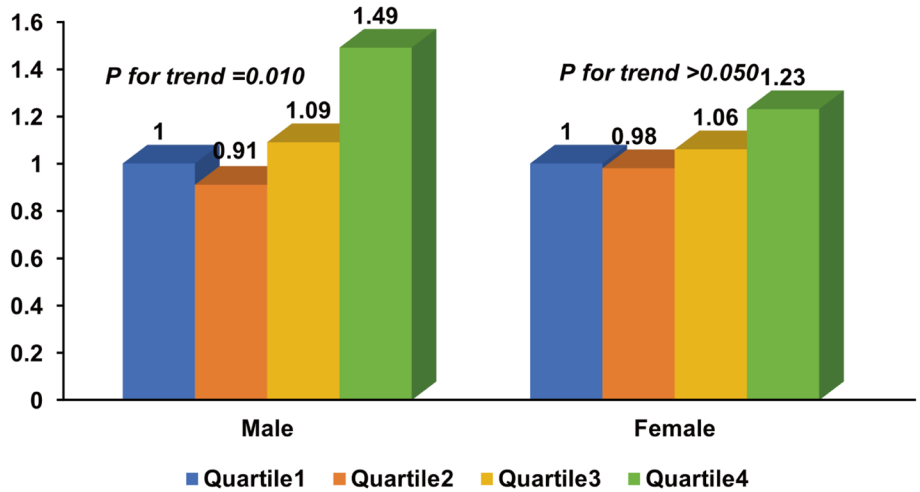

Fig. 2 Association between AIP and the prevalence of CKD. **A** overall population; **B** males; **C** females

Discussion

In a large cross-sectional study of the general population in the United States, it was found that patients with AIP levels > 0.18, especially males, have a significantly increased risk of CKD, and this association is not related to traditional risk factors. Research has shown that uric acid plays the most significant role in mediating the risk of AIP and CKD in both males and females. This study is the first to explore gender differences between AIP levels and the prevalence of CKD in the general population using the NHANES database.

Several studies have evaluated the association of AIP levels with the development of CKD, and the results of these studies are consistent with our findings. A Korean study, the Gangnam Severance Medical Cohort (GSMMC), enrolled 4,176 adults with at least one

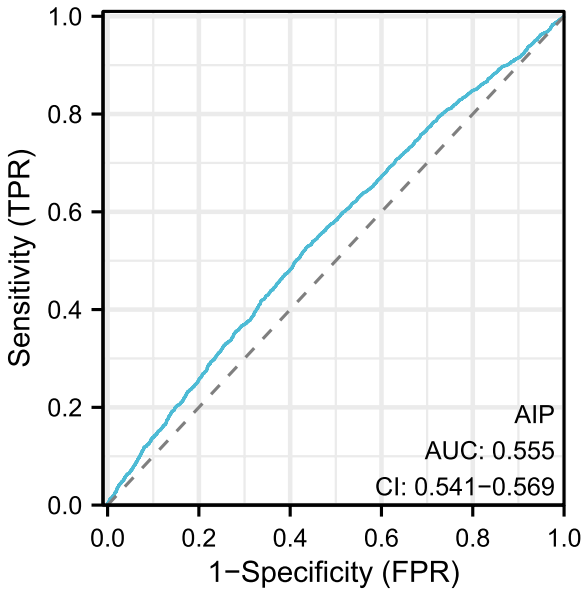

Fig. 3 AIP predictive ROC curves for the risk of developing CKD in male

metabolic disorder-related disease (e.g., diabetes mellitus, fatty liver, and hypertension) between 2006 and 2021. The study indicates a significant association between elevated AIP and CKD risk among adults with metabolic disorders. Stratified analysis reveals that the predictive effect of high AIP on CKD risk is more pronounced in males than in females [9]. An observational case–control study from the Nephrological Counselling Centre of the University Clinical Centre Sarajevo, included 117 patients with non-dialysis nephropathy. The study found that decreased levels of HDL-C and apolipoprotein E (APOE) and increased AIP were associated with eGFR < 60 ml/min/1.73m^2, suggesting that changes in these parameters are associated with CKD [12]. A study evaluated the association of AIP, stress hyperglycemia ratio (SHR), triglyceride-glucose index (TyG), and insulin resistance as assessed by homeostatic modeling (HOMA-IR) with the risk of developing diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2D). The study included 4351 T2D patients and showed that elevated AIP, SHR, TyG, and HOMA-IR were associated with a significantly increased risk of DKD [14].

Previous studies, such as the CRIC study, differ from the present study. The CRIC study, a multicenter, prospective, observational study, found no independent correlation between various lipids (including total cholesterol, TG, Lp(a), VLDLc, LDLc, HDLc, ApoA-I, and ApoB) and kidney disease progression in a CKD patient cohort [30]. This led to the hypothesis that AIP might also not be independently correlated with kidney disease progression. However, our study found that elevated AIP levels may increase CKD risk, particularly in U.S. men. This difference may stem from the study populations: the CRIC study focused on CKD patients with potential confounding pathophysiologic alterations, while our study encompassed a broad U.S. cross-section. Wang et al. found a correlation between AIP and rapid kidney function decline (RKFD) in a Chinese middle-aged and elderly population with normal baseline renal function, but no direct correlation with CKD progression [15]. Population differences, including genetic background, lifestyle, and health care, may influence the AIP-CKD risk relationship.

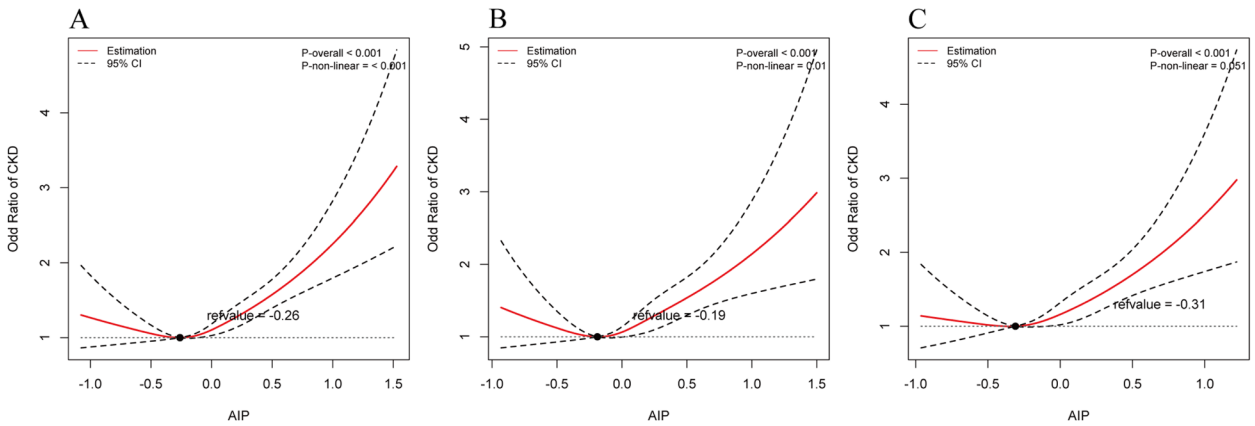

Fig. 4 Relative odds of CKD according to AIP quartile among male and female. The adjustment factors included age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American or other), education level (less than high school, high school or equivalent, or greater than high school), BMI (continuous), physical activity (never, moderate or vigorous), PIR (0–1.0,1.01–4.99 or 5.0), serum cotinine (> 10, LOD-10 or < LOD ng/mL), drinking status (< 12 dozen drinks/yr, ≥ 12 dozen drinks/yr), hypertension (yes or no), hypercholesterolemia (yes or no), diabetes (yes or no)

Table 4 Mediation analysis[a]

	Total effect				Indirect effect				Direct effect				%mediated[b]
	OR	Lower 95% CI	Upper 95% CI	*P*-value	OR	Lower 95% CI	Upper 95% CI	*P*-value	OR	Lower 95% CI	Upper 95% CI	*P*-value	
Male													
BMI, kg/m^2	1.06641	1.04042	1.09429	< 0.001	1.01135	1.00473	1.01812	**0.002**	1.05444	1.02892	1.08104	< 0.001	**17.55%**
TG, mmol/L	1.05386	1.02877	1.08051	< 0.001	1.01414	0.99021	1.03804	0.244	1.03916	1.00280	1.08051	0.032	26.77%
LDL, mmol/L	1.04737	1.01740	1.07798	0.004	0.99446	0.99103	0.99758	< 0.001	1.05321	1.02259	1.08450	0.002	−12.00%
TC, mmol/L	1.05390	1.02766	1.07975	< 0.001	0.99404	0.98772	1.00049	0.068	1.06022	1.03284	1.08813	< 0.001	−11.39%
HDL, mmol/L	1.05489	1.03018	1.08019	< 0.001	0.97016	0.94604	0.99547	0.014	1.08734	1.04946	1.12437	< 0.001	−56.69%
CRP, mg/L	1.05888	1.02790	1.08951	< 0.001	1.00034	0.99959	1.00123	0.388	1.05852	1.02721	1.08943	< 0.001	0.59%
U/C, mg/g	1.03198	1.00299	1.06433	0.030	1.02924	1.00009	1.06124	0.050	1.00266	1.00076	1.00464	0.004	91.55%
eGFR, mL/min per 1.73 m^2	1.04997	1.02401	1.07862	< 0.001	1.02173	1.01548	1.02850	**< 0.001**	1.02763	1.00338	1.05396	0.030	**44.09%**
BUN, mmol/L	1.04746	1.02221	1.07668	< 0.001	0.99723	0.99298	1.00175	0.202	1.05037	1.02563	1.07953	< 0.001	−5.98%
Uric acid, mmol/L	1.05229	1.02628	1.08173	< 0.001	1.02294	1.01818	1.02810	**< 0.001**	1.02869	1.00339	1.05637	0.030	**44.50%**
Bicarbonate, mmol/L	1.05330	1.02890	1.08058	< 0.001	1.00801	1.00458	1.01153	**< 0.001**	1.04493	1.02162	1.07113	0.002	**15.36%**
Total calcium, mmol/L	1.05394	1.02851	1.07950	< 0.001	1.00065	0.99946	1.00197	0.306	1.05326	1.02771	1.07903	< 0.001	1.24%
Phosphorus, mmol/L	1.05499	1.02983	1.08427	< 0.001	0.99932	0.99815	1.00024	0.138	1.05571	1.03033	1.08484	< 0.001	−1.27%
Sodium, mmol/L	1.05402	1.02847	1.08186	< 0.001	1.00114	0.99950	1.00296	0.174	1.05282	1.02798	1.08027	< 0.001	2.17%
Potassium, mmol/L	1.05363	1.02762	1.08063	< 0.001	0.99895	0.99767	0.99989	0.028	1.05474	1.02860	1.08187	< 0.001	−2.01%
Chloride, mmol/L	1.05336	1.02670	1.08183	< 0.001	1.00037	0.99990	1.00122	0.168	1.05297	1.02630	1.08120	< 0.001	0.71%
BMI, kg/m^2	1.06145	1.03201	1.09566	< 0.001	0.98844	0.98172	0.99587	0.002	1.07387	1.04177	1.10967	< 0.001	−19.50%
Female													
TG, mmol/L	1.07517	1.04336	1.11177	< 0.001	1.00859	0.97625	1.04091	0.598	1.06602	1.01943	1.11935	0.004	11.80%
LDL, mmol/L	1.06578	1.03064	1.10239	< 0.001	0.99274	0.98711	0.99806	0.010	1.07358	1.03900	1.11142	< 0.001	−11.44%
TC, mmol/L	1.07460	1.04229	1.11238	< 0.001	0.99496	0.98951	1.00063	0.084	1.08005	1.04585	1.11843	< 0.001	−7.02%
HDL, mmol/L	1.07615	1.04145	1.11141	< 0.001	0.98393	0.95783	1.01211	0.252	1.09373	1.04651	1.14244	< 0.001	−22.07%
CRP, mg/L	1.07504	1.03975	1.11224	< 0.001	1.00462	1.00221	1.00799	**< 0.001**	1.07010	1.03515	1.10632	< 0.001	**6.37%**
U/C, mg/g	1.02817	0.99811	1.05846	0.068	1.02334	0.99346	1.05278	0.138	1.00472	1.00246	1.00726	< 0.001	83.05%
eGFR, mL/min per 1.73 m^2	1.07530	1.04023	1.10879	< 0.001	1.02794	1.01982	1.03671	**< 0.001**	1.04607	1.01487	1.07768	0.006	**37.96%**
BUN, mmol/L	1.07408	1.04267	1.11106	< 0.001	0.99476	0.98904	1.00070	0.086	1.07974	1.04805	1.11506	< 0.001	−7.35%
Uric acid, mmol/L	1.07458	1.04200	1.11051	< 0.001	1.03329	1.02635	1.04025	**< 0.001**	1.03996	1.00949	1.07302	0.008	**45.53%**
Bicarbonate, mmol/L	1.07465	1.04288	1.11129	< 0.001	1.00899	1.00524	1.01333	**< 0.001**	1.06508	1.03335	1.10080	< 0.001	**12.43%**
Total calcium, mmol/L	1.07529	1.04157	1.11062	< 0.001	1.00080	0.99971	1.00219	0.158	1.07442	1.04111	1.11019	< 0.001	1.10%
Phosphorus, mmol/L	1.07560	1.04224	1.11086	< 0.001	0.99806	0.99643	0.99942	0.000	1.07768	1.04383	1.11246	< 0.001	−2.66%
Potassium, mmol/L	1.07391	1.03881	1.11217	< 0.001	1.00224	1.00068	1.00410	**0.002**	1.07151	1.03692	1.10858	< 0.001	**3.14%**
Sodium, mmol/L	1.07433	1.03972	1.11117	< 0.001	1.00401	1.00199	1.00646	**< 0.001**	1.07003	1.03558	1.10613	< 0.001	**5.58%**

Table 4 (continued)

	Total effect				Indirect effect				Direct effect				%mediated[b]
	OR	Lower 95% CI	Upper 95% CI	*P*-value	OR	Lower 95% CI	Upper 95% CI	*P*-value	OR	Lower 95% CI	Upper 95% CI	*P*-value	
Chloride, mmol/L	1.07323	1.03932	1.10937	< 0.001	1.00057	0.99989	1.00170	0.126	1.07261	1.03888	1.10836	< 0.001	0.81%

Abbreviations: BMI body mass index, *PIR* poverty-income ratio

[a] Odd ratios were adjusted for age (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American or other), education level (less than high school, high school or equivalent, or greater than high school); BMI (continuous), physical activity (never, moderate or vigorous), PIR (0–1.0,1.01–4.99 or 5.0), serum cotinine (> 10, LOD-10 or < LOD ng/mL), drinking status (< 12 dozen drinks/yr, ≥ 12 dozen drinks/yr); hypertension (yes or no), hypercholesterolemia (yes or no), diabetes (yes or no). This is not included in the adjusted variable when the variable itself computes least squares. This is not included in the adjusted variable when the variable itself computes mediation analysis

[b] The percentage mediated was calculated by log (indirect effect)/log (total effect)

Gender differences have multifaceted effects on AIP, with sex hormones playing a crucial role in modulating plasma lipid levels. Studies have shown disparities in plasma lipid levels between males and females, which may be attributed to the actions of sex hormones [12, 15, 31]. For instance, estrogen can elevate HDL-C levels, while testosterone may lead to an increase in LDL-C levels, potentially raising AIP [32]. However, as women age, their estrogen levels decline, which could affect their lipid metabolism and consequently impact AIP [33]. At the molecular level, gender-specific gene expression and hormone receptor activity may influence the expression of genes related to atherosclerosis, thereby affecting AIP, although current research in this area is still insufficient [34, 35]. In the pathogenesis of CKD, sex hormones exert distinct effects. Studies have indicated a correlation between male sex hormone levels and the progression of CKD, possibly accelerating renal disease development through pathways such as inflammation, apoptosis, and fibrosis. In contrast, estrogen exhibits anti-fibrotic and anti-apoptotic effects in the kidneys, potentially slowing down CKD progression. This also explains the findings of this study, indicating that elevated AIP levels may increase the risk of CKD, especially among males in the general U.S. population [36].

On the basis of the results of these mediation analyses, we can hypothesize some potential biological mechanisms explaining the gender differences between AIP and CKD. In males, uric acid changes may be partially explained in the AIP-CKD association, suggesting the importance of metabolic disorders in the pathogenesis of CKD in males. In addition, the contribution of eGFR, BMI, and bicarbonate levels suggests that renal function, body mass index, and acid–base balance may be associated with sex differences in AIP and CKD. Whereas in females, the association of uric acid changes with the prevalence of AIP and CKD may be influenced by the degree of metabolic disturbances in vivo, the contribution of eGFR, bicarbonate, CRP, sodium and potassium levels may be related to physiologic processes such as renal function, inflammatory response and electrolyte balance.

The possible mechanisms are as follows: (i) Uric acid is one of the independent risk factors for the development of CKD, which can damage the kidney through various pathways, such as inflammation, oxidative stress, and activation of the renin angiotensin system [37–39]; (ii) With the onset of CKD, eGFR decreases, leading to weakened renal regulation of fixed acid, decreased bicarbonate levels and metabolic acidosis, accelerating the development of CKD and increasing inflammatory state and mortality [40–43]; (iii) Several studies have identified BMI as an independent risk factor for CKD progression. Meta-analyses have shown that for every 1 kg/cm^2 increase in obesity, there is a 1.28-fold increase in the relative risk of developing low eGFR and a 1.51-fold increase in the risk of albuminuria. Obesity damages the kidneys and its associated complications include hypertension, insulin resistance, type 2 diabetes, and atherosclerotic dyslipidemia. These complications lead to renal damage and endothelial dysfunction through multiple pathways, such as inflammation, oxidative stress, increased RAAS and SNS activity, and other mechanisms, accelerating the development of CKD [44, 45]; (iv) CRP, as an indicator of inflammation, has an important role in the development of CKD, and persistent inflammation is a typical feature of the development of CKD, which forms a vicious circle with renal injury [1, 46]; (v) Sodium and potassium ion disorders accelerate the decline of eGFR and significantly increase the occurrence of CKD, mortality, hospitalization, and the need for renal replacement therapy, which seriously affects the long-term quality of patients' survival. These findings provide important clues for further research on the biological basis of the gender difference between AIP and CKD, and help us better understand the mechanism of the association [47, 48].

Our study has some limitations that need to be addressed in future research. Firstly, due to the cross-sectional nature of the NHANES data we used, lacking longitudinal follow-up studies, we can only preliminarily infer that higher AIP may correspond to a higher likelihood of CKD occurrence, but cannot establish a causal relationship between AIP and CKD. Therefore, further prospective cohort studies are needed to verify this association, especially with detailed analyses on different gender groups, to better understand the causal relationship between the two. Secondly, although we have adjusted for relevant confounding factors as much as possible, there may still be potential confounders that were not completely excluded, which could affect the causal relationship. Lastly, the NHANES database categorizes CKD simply as a single disease without distinguishing between primary and secondary forms. Different types of CKD exhibit significant differences in etiology and pathophysiological characteristics, which may affect the association between AIP and CKD. Future research should differentiate between different types of CKD and explore the stability of the association between AIP and each type of CKD to more accurately evaluate the impact of AIP on CKD.

Conclusions

In the general U.S. population, particularly males, we found that increased AIP levels were associated with an increased risk of developing CKD. However, cross-sectional studies were unable to determine causality,

and further research is needed to investigate the specific association between AIP and CKD and the mechanism of the role of gender factors. Future studies should emphasize gender differences as key variables affecting plasma Atherosclerotic Index and CKD occurrence to provide a more comprehensive and precise explanation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22087-7.

Supplementary Material 1

Acknowledgements
We would like to thank the NHANES data collection group and management for helping in developing this research utilizing NHANES data.

Authors' contributions
Jing Cui: Conceptualization, and Writing—original draft. Jing Gao: Writing—original draft, Software, and Validation. Shuang Liang: Software, Validation and Visualization. Guangyan Cai: Methodology and Visualization. Xiangmei Chen: Methodology and Visualization. Yong Wang: Resources, Project administration, and Writing—review and editing.

Funding
Not applicable.

Data availability
The data that were generated and analyzed in this study are available on the National Center for Health Statistics website (http://www.cdc.gov/nchs/nhanes/).

Declarations

Ethical approval and consent to participate
Institutional Review Board approval was waived as NHANES data is deidentified and publicly available. All the participants signed the informed consent before participating in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 29 June 2024 Accepted: 25 February 2025
Published online: 01 March 2025

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