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Association between Atherogenic index of plasma and gallstones in the United States adults: A cross-sectional analysis of NHANES 2017–2020

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ABSTRACT

Background: Although substantial evidence suggests an association between dyslipidemia as an isolated factor and gallstones, research on the Atherogenic Index of Plasma (AIP) and gallstones remains limited.
Methods: A total of 3557 eligible adults from the United States were selected for cross-sectional analysis using the 2017–2020 National Health and Nutrition Examination Survey database. Logistic regression was employed to evaluate the association between AIP gallstones. Restricted cubic spline (RCS) analysis and threshold effect analysis were conducted to explore potential non-linear relationship.
Results: The study found a positive association between higher AIP levels and higher odds of gallstones. In the fully adjusted logistic regression model, each 1-unit increase in AIP was associated with 59 % higher odds of gallstones (OR = 1.59, 95 % CI: 1.06, 2.38). Compared to the lowest quartile of AIP, the highest quartile showed 82 % higher odds of gallstones (OR = 1.82, 95 % CI: 1.23, 2.69). RCS analysis revealed a non-linear relationship between AIP and gallstones, with threshold effect analysis identifying a turning point at −0.13, where AIP had a positive correlation with gallstones before this threshold.
Conclusion: Higher AIP is positively correlated with higher odds of gallstones, showing a non-linear relationship. As AIP increases, the odds of gallstones also rise, but this relationship is no longer observed beyond a certain threshold. It is recommended to maintain appropriate AIP levels to reduce the incidence of gallstones.

1. Introduction

Gallstones are a prevalent digestive system disorder and are common worldwide. The prevalence of gallstones among Western adults is approximately 10–20 % (Portincasa et al., 2019), while in Asian populations, it is also around 10–20 % (Yu et al., 2022). In recent years, the incidence of gallstones has increased due to changes in dietary patterns and advancements in diagnostic technologies (Choi et al., 2022b). Most gallstones initially exhibit no significant clinical symptoms and are often discovered incidentally during routine examinations (Sun et al., 2022). However, about 3 %–8 % of patients may develop severe complications such as cholecystitis, gallstone ileus, pancreatitis, empyema, and gallbladder perforation (Sadri et al., 2022).The formation of gallstones is influenced by various factors, including sex, obesity, metabolic syndrome, pregnancy, insulin resistance, diabetes, and unhealthy lifestyle habits (Nauck et al., 2019; Frost et al., 2021). Among these, dyslipidemia is considered a significant risk factor for gallstones and is observed in more than 50 % of patients with gallstones (Kim et al., 2019; Pooria et al., 2022). Dyslipidemia associated with diabetes typically manifests as elevated triglyceride (TG) levels and reduced high-density lipoprotein cholesterol (HDL—C) levels (Choi et al., 2022a). Additionally, other types of dyslipidemia include increased levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) (Wang et al., 2022a, 2022b, 2022c).

Atherogenic Index of Plasma (AIP), first proposed by Dobiá and Frohlich, is an indicator used to assess atherosclerosis risk (Fernández-Macías et al., 2019). It is calculated as log10(TG/HDL-C), reflecting levels of TG and HDL-C and serving as a strong predictor of dyslipidemia (Shin et al., 2022). Although the close association between elevated TG and reduced HDL-C levels with gallstones is widely recognized, there is a

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paucity of studies systematically investigating the relationship between the AIP and gallstones. Moreover, the non-linear relationship between AIP and gallstones has yet to be clearly defined. Therefore, this study, based on data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2017 and 2020 in the United States, uses a cross-sectional design to examine the possible role of AIP in predicting gallstones.

2. Materials and methods

2.1. Study population

Data for this study were obtained from the NHANES database, which employs a stratified, multistage sampling design and includes demographic data, dietary records, laboratory test results, and questionnaire information. We analyzed data from 15,560 participants collected between 2017 and 2020. To ensure the accuracy and completeness of the analysis, we excluded individuals who were under the age of 20 and those lacking data on gallstone status, TG, HDL—C, education level, marital status, hypertension, diabetes, asthma, smoking, and cancer-related information. Ultimately, 3557 participants met all inclusion criteria and were included in the final analysis (Fig. 1). NHANES is an anonymized, publicly available dataset approved by the Ethics Review Board of the National Center for Health Statistics. The dataset adheres to ethical standards and follows guidelines designed to ensure the safety and privacy of participants, with written informed consent obtained from all participants. Therefore, no additional ethical review was required.

2.2. Exposure and Outcome Variables

In this study, the AIP was defined as the logarithmic transformation of the ratio of TG to HDL—C, calculated using the formula: AIP = log[TG (mmol/L) / HDL-C (mmol/L)]. Participants were categorized into four quartiles based on their AIP values: Q1 (−1.252 to −0.342), Q2 (−0.343 to −0.115), Q3 (−0.116 to 0.108), and Q4 (0.109 to 1.607).

The outcome variable was the presence of gallstones. In a survey conducted by trained professional interviewers, participants were asked the following question: “Has a doctor or other healthcare professional ever diagnosed you with gallstones?” Those who responded affirmatively were classified as having gallstones, while those who responded negatively were not. This straightforward and practical approach has been widely used in previous studies (Wang et al., 2023a, 2023b; Du et al., 2024; Zhang et al., 2024a, 2024b).

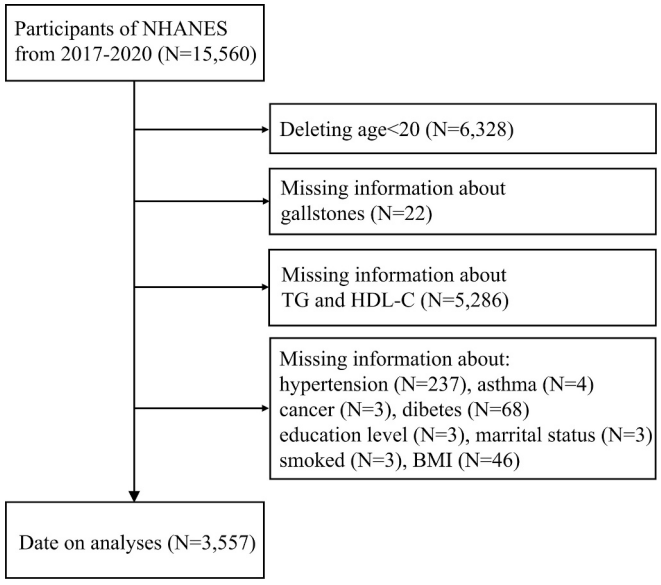

Fig. 1. The flowchart of participants selection from NHANES 2017–2020 among United States adults. Abbreviations: TG, triglycerides; HDL—C, high-density lipoprotein cholesterol; BMI, body mass index; NHANES, National Health and nutrition examination survey

2.3. Covariates

This study included multiple potential covariates that may influence the relationship between AIP and gallstones. These covariates encompassed: age, sex, race, education level, marital status, poverty income ratio (PIR), physical activity, smoking status, alcohol consumption, as well as health conditions including hypertension, diabetes, cardiovascular disease, asthma, cancer, TC, aspartate aminotransferase(AST), alanine aminotransferase(ALT). Dietary information was obtained on total energy (kcal), total sugar (g), total fat (g), total water (g), vitamin C (mg), and caffeine(mg) intake. Smoking status was categorized into non-smokers, former smokers, and current smokers. Alcohol consumption was classified based on responses to the questionnaire item “Have you ever had a drink of any kind of alcohol?” Those who answered ‘yes’ were classified as drinkers. Diabetes was defined as fasting blood glucose ≥7.0 mmol/L, or hemoglobin A1c ≥6.5 %, or a history of diabetes diagnosis and currently receiving hypoglycemic or insulin treatment (Zhou et al., 2021; Y. Wang et al., 2022). Cardiovascular disease was identified based on affirmative responses to the questionnaire item “Have you ever been informed by a doctor that you have congestive heart failure, coronary artery disease, angina, or a myocardial infarction?”. Hypertension was defined as an average systolic blood pressure exceeding 140 mmHg or an average diastolic blood pressure exceeding 90 mmHg, or a diagnosis of hypertension and currently taking antihypertensive medication (Beaney et al., 2019). Physical activity was determined through questionnaire and calculation, categorized based on whether vigorous activity exceeded 75 min per week or moderate activity exceeded 150 min per week, into: mild, moderate, vigorous, and unclear (Hubbard et al., 2019). Asthma and cancer were determined based on affirmative responses in the questionnaire. Additionally, existing research indicates that the Waist-to-Weight Index (WWI), a novel obesity metric calculated as waist circumference (WC) in centimeters (cm) divided by the square root of weight (kg), provides a more accurate assessment of obesity and is associated with gallstones. Therefore, it was included as a covariate in this study (Ye et al., 2023; J. Zhang et al., 2024). Dietary information was derived from 24-h dietary recall questionnaires and analyzed as the average of two 24-h intake measures. All biochemical indicators were measured using an automated biochemical analyzer following a fasting period of at least 8 h.

2.4. Handling of Missing Data

In this study, two strategies were employed to address missing data for covariates. For continuous variables with substantial missing data, these variables were converted into categorical variables, with participants having missing values classified into an “Unknown” category. For variables with minimal missing data, multiple imputation methods were used to enhance data completeness and analytical accuracy. Detailed measurement methods for all variables can be accessed free of charge on the NHANES website (https://www.cdc.gov/nchs/nhanes).

2.5. Statistical Analysis Methods

For normally distributed continuous variables, results are presented as mean ± standard deviation, and differences between covariates were assessed using chi-square tests or *t*-tests. Logistic regression was used to examine the relationship between AIP and gallstones. Model 1: No covariate adjustments. Model 2: Adjustments for age, gender, and race. Model 3: Further adjustments for all covariates. After transforming AIP from a continuous variable to a quartile categorical variable, trend tests

were performed to explore its association with gallstones. Additionally, restricted cubic spline (RCS) analysis was used to assess the non-linear relationship between AIP and gallstones. Further, a two-stage linear regression model was used to analyze the threshold effect of AIP on gallstones. *P* value <0.05 was considered statistically significant in all analyses. Statistical analyses were performed using Empower software (version 5.0) and R (version 4.2.0).

3. Results

3.1. Baseline Characteristics of participants

The study included 3557 participants, 48.9 % male and 51.1 % female, with a mean age of 51.1 ± 17.4 years (Table 1). The mean AIP was −0.109 ± 0.331 and the prevalence of gallstones was 10.7 %. The average age of participants with gallstones was 58.4 ± 15.3 years, compared with 50.2 ± 17.4 years for those without gallstones. Compared to participants without gallstones, those with gallstones were generally older, more likely to be female, non-Hispanic White, and alcohol consumers, and had a higher prevalence of comorbidities such as hypertension, diabetes, asthma, heart disease, and cancer ($p < 0.05$). Additionally, participants with gallstones had higher WWI and AIP values, along with lower energy and fluid intake ($p < 0.05$).

3.2. Associations between AIP and gallstones

Logistic regression analysis showed a significant positive association between AIP and the odds of gallstones in unadjusted, partially adjusted and fully adjusted models (Table 2). In the fully adjusted model, this association remained robust (OR = 1.59; 95 % CI: 1.06–2.38), meaning that each unit increase in AIP was associated with 59 % higher odds of gallstones. In addition, in the fully adjusted model, the odds of gallstones were 82 % higher for participants in the fourth quartile of AIP compared to those in the first quartile (OR = 1.82; 95 % CI: 1.23–2.69). Moreover, the OR of gallstones increased with increasing AIP in each model (*p* for trend < 0.05).

RCS analysis showed a significant overall trend (*p* for overall = 0.006) and a non-linear association (p for non-linear = 0.043) between AIP and the odds of gallstones (Fig. 2). Further threshold effect analysis identified an inflection point for AIP at −0.13 (Table 3). Results from piecewise linear regression models showed that when AIP was below −0.13, each unit increase in AIP was associated with 243 % higher odds in gallstones (OR = 3.43, 95 % CI = 1.42–8.33, $p = 0.0064$). However, when the AIP was greater than −0.13, the odds of gallstones did not increase with increasing AIP (OR = 0.99, 95 % CI = 0.52–1.86, $p = 0.9700$).

4. Discussion

In this cross-sectional study of 3557 US adults, a significant association was observed between higher AIP and higher odds of gallstones, which remained significant after adjustment for all covariates. This suggests that an elevated AIP may increase the odds of gallstone formation. RCS analysis revealed a non-linear relationship and a threshold effect between AIP and gallstones. These findings underscore the potential importance of AIP in the assessment and management of gallstones.

To our knowledge, this is the first study to investigate the association between AIP and the odds of gallstone disease. Previous studies have primarily focused on the relationship between obesity or individual lipid parameters and gallstones. A cross-sectional study of 6848 US adults showed that increases in obesity measures such as waist circumference (WC), body mass index (BMI), waist-to-height ratio (WtHR), and abdominal visceral fat index (AVI) were associated with an increased risk of gallstones (J. Zhang et al., 2024). A prospective study from the UK reported an 8 % increase in the risk of gallstones for each unit increase in BMI (Banim et al., 2011). Additionally, research has shown that obese children are four times more likely to develop gallstones than their non-obese counterparts (Herman and Siegel, 2010). A study of 3190 Taiwan participants found that the association between gallstones and metabolic syndrome, as well as obesity, was more pronounced in individuals under the age of 50 (Su et al., 2019). Obesity is often associated with

Table 1
Distribution of selected characteristics of the United States adults from NHANES 2017–2020 ($n = 3557$).

Characteristics	Non-Gallstones	Gallstones	*P*-value
	N = 3176 (89.3 %)	*N* = 381 (10.7 %)	
Age, year	50.2 ± 17.4	58.4 ± 15.3	<0.001
PIR	2.6 ± 1.5	2.6 ± 1.4	0.447
ALT (U/L)	22.4 ± 20.2	21.6 ± 14.2	0.450
AST (U/L)	22.1 ± 15.6	21.1 ± 10.2	0.226
TC (mmol/L)	4.8 ± 1.1	4.7 ± 1.2	0.324
Total Energy (kcal)	2055.9 ± 831.4	1905.1 ± 779.0	<0.001
Total Sugar (g)	101.0 ± 62.4	100.4 ± 71.9	0.475
Total Fat (g)	83.5 ± 39.3	79.6 ± 38.5	0.052
Vitamin C (mg)	77.7 ± 77.3	75.0 ± 89.3	0.185
Coffee (mg)	140.3 ± 195.5	140.8 ± 146.9	0.378
Total Water (g)	2776.0 ± 1264.6	2692.0 ± 1273.6	0.044
WWI	11.1 ± 0.9	11.5 ± 0.7	<0.001
AIP	−0.117 ± 0.334	−0.044 ± 0.301	<0.001
Gender, n(%)			<0.001
Male	1634 (51.5)	106 (27.8)	
Female	1542 (48.5)	275 (72.2)	
Race, n(%)			<0.001
Mexican American	398 (12.5)	52 (13.6)	
Other Hispanic	305 (9.6)	48 (12.6)	
Non-Hispanic White	1083 (34.1)	157 (41.2)	
Non-Hispanic Black	832 (26.2)	65 (17.1)	
Other Race	558 (17.6)	59 (15.5)	
Education level, n(%)			0.707
Less than high school	589 (18.5)	76 (20.0)	
High school	761 (24.0)	94 (24.6)	
More than high school	1826 (57.5)	211 (55.4)	
Marital status, n(%)			0.814
Live with partner	1864 (58.7)	226 (59.3)	
Live alone	1312 (41.3)	155 (40.7)	
Alcohol, n(%)			0.038
No	265 (8.4)	30 (7.9)	
Yes	2796 (88.0)	327 (85.8)	
Unclear	115 (3.6)	24 (6.3)	
Smoked, n(%)			<0.001
Non-smoker	1811 (57.0)	206 (54.1)	
Former-smoker	751 (23.7)	121 (31.7)	
Current-smoker	614 (19.3)	54 (14.2)	
Activity, n(%)			0.594
Mild	1645 (51.8)	209 (54.9)	
Moderate	232 (7.3)	30 (7.9)	
Vigorous	1283 (40.4)	140 (36.7)	
Unclear	16 (0.5)	2 (0.5)	
Hypertension, n(%)			<0.001
Yes	1456 (45.8)	241 (63.3)	
No	1720 (54.2)	140 (36.7)	
Diabetes, n(%)			<0.001
Yes	685 (21.6)	154 (40.4)	
No	2491 (78.4)	227 (59.6)	
Asthma, n(%)			<0.001
Yes	490 (15.4)	84 (22.1)	
No	2686 (84.6)	297 (77.9)	
Heart Disease, n(%)			<0.001
Yes	274 (8.6)	69 (18.1)	
No	2902 (91.4)	312 (81.9)	
Cancer, n(%)			<0.001
Yes	306 (9.6)	69 (18.1)	
No	2870 (90.4)	312 (81.9)	

Notes: Mean ± SD for continuous variables: the *P*-value was calculated by the weighted linear regression model; (%) for categorical variables: the *P*-value was calculated by the weighted chi-square test.
Abbreviations: PIR, poverty income ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; WWI, Waist-to-Weight Index; AIP, atherogenic index of plasma.

Table 2
Logistic regression analysis on the association between the Atherogenic Index of Plasma and gallstones in the United States adults from NHANES 2017–2020.

Exposure	Model 1 [OR(95 %CI)]	Model 2 [OR(95 %CI)]	Model 3 [OR(95 %CI)]
AIP (continuous)	1.92 (1.40, 2.63)	2.20 (1.55, 3.12)	1.59 (1.06, 2.38)
AIP (quartiles)			
Q1(−1.252 - -0.342)	1.00	1.00	1.00
Q2(−0.343 - -0.115)	1.96 (1.39, 2.77)	1.99 (1.40, 2.83)	1.72 (1.20, 2.48)
Q3(−0.116–0.108)	2.21 (1.57, 3.10)	2.13 (1.50, 3.02)	1.74 (1.20, 2.52)
Q4(0.109–1.607)	2.32 (1.65, 3.25)	2.47 (1.73, 3.52)	1.82 (1.23, 2.69)
P for trend	<0.0001	<0.0001	0.0084

Model 1: No covariate adjustments.
Model 2: Adjusted for age, gender, and race.
Model 3: Adjusted for age, sex, race, education level, marital status, poverty income ratio (PIR), physical activity, smoking status, alcohol consumption, hypertension, diabetes, cardiovascular disease, asthma, cancer, total cholesterol (TC), energy intake, total sugar, total fat, total water, vitamin C, caffeine, and waist-to-weight Index (WWI).
Abbreviations: AIP, atherogenic index of plasma; OR, odds ratio; CI, confidence interval.

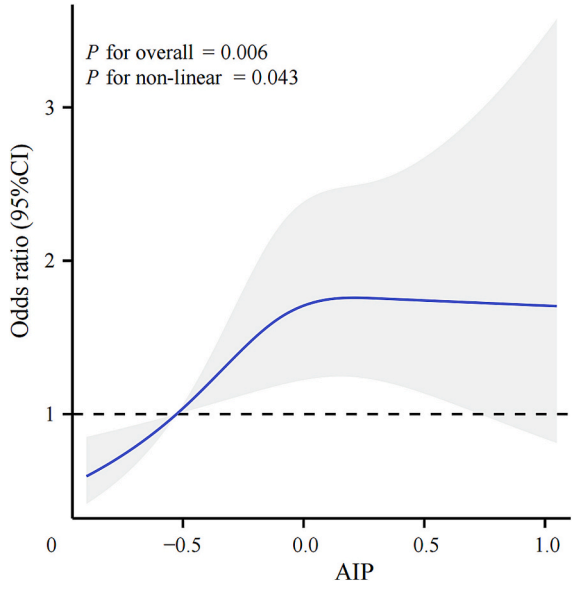

Fig. 2. Non-linear relationship between the Atherogenic Index of Plasma and the odds of gallstones in the United States adults from NHANES 2017–2020. Notes: Adjusted for age, sex, race, education level, marital status, poverty income ratio (PIR), physical activity, smoking status, alcohol consumption, hypertension, diabetes, cardiovascular disease, asthma, cancer, total cholesterol (TC), energy intake, total sugar, total fat, total water, vitamin C, caffeine, and waist-to-weight Index (WWI). Abbreviations: AIP, atherogenic index of plasma; CI, confidence interval

dyslipidemia (Michalczyk et al., 2017; Mu et al., 2019). Research by Habiba and Fadima demonstrated a significant difference in BMI between participants with and without dyslipidemia, with a higher proportion of participants with a normal BMI among those without dyslipidemia (43.6 % vs. 26.7 %) (Ali et al., 2022). Previous studies have shown a strong association between dyslipidemia and gallstones.

The AIP was introduced by Dobiásová and Frohlich in 2001 as an improved lipid parameter reflecting the state of lipid metabolism (Yu et al., 2023). An abnormal AIP typically indicates dyslipidaemia, characterized by elevated TG, reduced HDL—C, and an increased LDL-C. Elevated AIP has been associated not only with cardiovascular disease but also with an increased risk of several other conditions, such as

Table 3
Threshold effect analysis of the Atherogenic Index of Plasma on gallstones using a two-piecewise linear regression model in the United States adults from NHANES 2017–2020.

Gallstones	Adjust OR (95 % CI)	*P*-value
AIP		
Fitting by standard linear model	1.59 (1.06, 2.38)	0.0243
Fitting by two-piecewise linear model		
Inflection point	−0.13	
< −0.13	3.43 (1.42, 8.33)	0.0064
> −0.13	0.99 (0.52, 1.86)	0.9700
Log-likelihood ratio	0.047	

Notes: Adjusted for age, sex, race, education level, marital status, poverty income ratio (PIR), physical activity, smoking status, alcohol consumption, hypertension, diabetes, cardiovascular disease, asthma, cancer, total cholesterol (TC), energy intake, total sugar, total fat, total water, vitamin C, caffeine, and waist-to-weight Index (WWI).
Abbreviations: AIP, atherogenic index of plasma; OR, odds ratio; CI, confidence interval.

diabetes and obesity (Shin et al., 2022; Yin et al., 2023). However, there is currently limited research exploring the relationship between AIP and gallstones. A prospective cross-sectional study by Sikandar and Zarbakht found that patients with gallstones had higher serum TG levels and lower HDL-C levels (Hayat et al., 2019), which is consistent with our findings. Helene emphasized the importance of the relationship between blood lipids and plasma lipoprotein cholesterol levels in gallstones (Gellert-Kristensen et al., 2019). In addition, several studies have reported a positive association between hyperlipidaemia and gallstones (Zanlungo and Rigotti, 2009; Grigor'eva et al., 2010). Conversely, other studies have shown different results. An epidemiological study found no significant difference in lipid profiles between gallstone patients and controls (Méndez-Sánchez et al., 2004). Regarding the relationship between lipids and gallstones, Atamanalp et al. found that elevated LDL-C levels were associated with an increased risk of gallstones, whereas low HDL-C levels did not show a significant association (Atamanalp et al., 2013). On the other hand, Andreotti et al. reported that high TG levels and low HDL-C levels were significantly associated with gallstone risk, whereas LDL-C levels showed a negative association with gallstone risk (Andreotti et al., 2008). Unlike previous studies, we analyzed the relationship between HDL-C and TG in combination with gallstones.

Several potential mechanisms may explain the positive association between AIP and gallstones. First, dyslipidaemia can lead to metabolic abnormalities, including dysfunction of key metabolic organs such as the liver and gallbladder (Chen et al., 2022). For example, excessive bile secretion by the liver combined with slowed intestinal motility can lead to cholesterol supersaturation in the bile, resulting in the formation of cholesterol monohydrate crystals and ultimately macroscopic gallstones (H. H. Wang et al., 2023). Secondly, hyperlipidaemia can exacerbate insulin resistance, leading to inactivation of the FoxO1 transcription factor. This inactivation increases the expression of the cholesterol transporters ABCG5/G8, promoting excessive cholesterol secretion into the bile and thereby increasing the risk of gallstone formation (Yu et al., 2019). Thirdly, dyslipidaemia can reduce the level of phospholipids in the bile secreted by the liver, significantly reducing the solubility of cholesterol in the bile. This facilitates the rapid nucleation and crystallisation of cholesterol, contributing to the formation of solid, needle-like cholesterol crystals and stones in the bile ducts and gallbladder (H. H. Wang et al., 2022).

Compared to previous studies, our research offers several advantages. First, it is based on the NHANES database, which provides the benefits of a large sample size and reliable data. Second, as the first study to examine the relationship between AIP and gallstones through adjustment for multiple confounding factors, it offers a novel perspective on the prevention of gallstones. Third, using threshold effect analysis, we identified a point of inflection in the relationship between AIP

and gallstones. However, there are several limitations to this study. First, the diagnosis of gallstones was based solely on self-reported data from the health questionnaire, lacking more precise diagnostic imaging, which may introduce recall bias. Second, due to the cross-sectional design, causal relationships between AIP and gallstones cannot be established, and prospective studies are needed for further validation. Additionally, due to data limitations, some participants were excluded from the analysis. Future research should aim to collect more comprehensive and larger-scale data to enhance the generalizability and reliability of the findings.

5. Conclusion

The results of this study indicate a positive and non-linear relationship between higher AIP and higher odds of gallstone disease. Maintaining appropriate AIP levels may help to reduce the incidence of gallstones. These findings provide new theoretical foundations and potential intervention strategies for the prevention and treatment of gallstones. Future research should delve into the mechanisms by which AIP acts as a risk factor for gallstones and explore its potential applications in clinical practice.

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Institutional review board statement

This study, approved by the Research Ethics Review Board of the National Center for Health Statistics, adheres to the Declaration of Helsinki; all participants provided written informed consent, and no additional local ethical approvals were required due to the data's openness and originality.

Informed consent statement

Not applicable as this study involves secondary analysis of data.

CRediT authorship contribution statement

Shuang Yang: Writing – original draft, Validation, Data curation, Conceptualization. **Jianhui Song:** Writing – review & editing, Validation, Conceptualization. **Zhengbo Yang:** Methodology, Formal analysis. **Nanbo Li:** Software, Investigation. **Ju Wu:** Supervision, Project administration, Funding acquisition. **Shuangshuang Hou:** Visualization, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data files are publicly available through the National Center for Health Statistics (NCHS).

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