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Inflammatory burden index (IBI) and body roundness index (BRI) in gallstone risk prediction: insights from NHANES 2017–2020

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Abstract

Background The Inflammatory Load Index (IBI) and Body Roundness Index (BRI) were employed to evaluate the systemic inflammatory status and body fat. This study aims to elucidate the association between IBI and the prevalence of gallstones, as well as to analyze the mediating role of BRI in this association.

Methods Data from the National Health and Nutrition Examination Survey (NHANES) (2017–2020) were utilized in our cross-sectional study. A total of 2598 participants aged ≥ 20 years were enrolled. The Boruta algorithm, a supervised classification feature selection method, is leveraged to identify the confounding variables most strongly associated with the prevalence of gallstones. Weighted multivariate logistic regression, restricted cubic splines (RCS), and subgroup analyses were employed to investigate the association between IBI and gallstones, assess the presence of a linear association, and evaluate the effect of IBI on gallstone risk across different populations. Finally, the mediating effect of BRI was examined.

Results In the fully adjusted model, when IBI was in the highest tertile, each unit increase in IBI (corresponding to an increase of 1 in the natural logarithm of IBI) was linked to a 110.8% higher prevalence of gallstones (OR = 2.108, 95% CI: 1.109–4.005; $P = 0.028$). The odds ratio for gallstones increased with higher IBI levels across unadjusted, partially adjusted, and fully adjusted models (P for trend < 0.05). This positive association was confirmed to be linear by the RCS curve (P for nonlinear = 0.887). Subgroup analysis indicated that the risk of gallstones was significantly elevated in individuals aged ≥ 60, females, and those with a Poverty-to-Income Ratio (PIR) ≥ 2 ($P < 0.05$). Mediation analysis revealed that IBI had a significant indirect effect on gallstone prevalence through BRI, with an effect size of 0.0129 (95% CI: 0.0121–0.0136; $P < 0.001$), and the mediation contributed to 33.24% of the total effect.

Conclusions This study demonstrates a significant linear positive relation of IBI to gallstone prevalence. Furthermore, BRI mediates the effect of IBI on gallstone risk. These findings provide a more precise inflammatory marker for gallstone prevention and treatment.

Trial registration Not applicable.

Keywords Inflammatory burden index, Body roundness index, Gallstones, Mediation analysis, NHANES

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Background

Gallstones are a prevalent and serious gastrointestinal disorder affecting populations worldwide. Approximately 6% of the global population is affected by gallstones, with the prevalence continuously rising [1]. This condition significantly impacts individuals' quality of life and overall health. Epidemiological evidence suggests that in America, around 10–15% of adults have gallstones [2], with even higher prevalence observed in certain high-risk groups, such as women, individuals with obesity, diabetes, liver diseases, and specific ethnic populations [3]. Gallstones can lead to severe abdominal pain and dyspepsia, and may also trigger more serious complications, such as cholecystitis, pancreatitis, and biliary infections [4]. Furthermore, a large cohort study has shown that gallstones are linked to a risen risk of liver and biliary tract cancers and serve as an independent risk factor for gallbladder cancer death [5]. The high prevalence of gallstones and their associated complications significantly increase both the medical burden on patients and the societal costs. Recent data indicates that in the United States, gallstone disease results in approximately 2.2 million outpatient and 1.2 million emergency department visits annually [6]. Therefore, an accurate assessment of the risk of gallstone onset and disease progression is crucial for early intervention.

Infection and inflammation are pivotal in the formation of gallstones. Cholesterol gallstones, the most prevalent type, are formed through chromatin exocytosis during neutrophil extracellular trap (NET) formation, which facilitates the accumulation of calcium or cholesterol crystals in the bile, thereby promoting the assembly process [7, 8]. Pigment stones, categorized as black and brown stones, represent another significant type of gallstones. Black stones arise from the breakdown of hemoglobin which leads to calcium bilirubin formation. Consequently, individuals experiencing hemolysis or suffering from inflammatory diseases such as Crohn's disease are more predisposed to black stones [9, 10]. In contrast, brown stones, comprising a mixture of calcium substrate, including calcium bilirubin, calcium phosphate, or palmitate, as well as cholesterol and bile, typically develop in the context of bacterial or parasitic infections [10, 11]. Therefore, individuals suffering from biliary stenosis or infected with bacteria or parasites have an elevated risk of developing brown stones. In summary, inflammatory processes and their associated immune responses are integral to the pathogenesis of various types of gallstones. Elevated levels of inflammatory cytokines have been positively linked to an increased risk of gallstone formation [12, 13]. The Inflammatory Burden Index (IBI), a composite measure integrating neutrophils, lymphocytes, and C-reactive protein (CRP) for chronic low-grade inflammation assessment, enables a more stable assessment of the inflammatory state and reflects the body's inflammatory condition more accurately. This index has been related to cancer risk and death, rheumatoid arthritis, osteoarthritis, and cardiovascular diseases [14–17]. An increased neutrophil count indicates persistent nonspecific inflammation, while a decreased lymphocyte count reflects impaired immune system function. Therefore, a higher neutrophil-to-lymphocyte ratio (NLR) signifies an imbalance between pro-inflammatory and anti-inflammatory systems, which suggests a worsening inflammatory state [16]. NLR has been proposed as a predictive marker for assessing the risk of cholecystitis and distinguishing between simple and severe cholecystitis [18]. Previous studies have demonstrated a significant association between hypersensitivity C-reactive protein (hs-CRP) levels and the likelihood of gallstone disease [19]. Persistent hs-CRP elevation typically indicates a chronic inflammatory process, which possibly leads to the damage of gallbladder mucosa, alterations in bile composition, and formation and deposition of cholesterol crystals, thereby increasing the risk of gallstone formation [20]. While CRP suggests the development of systemic inflammation, NLR may be indicative of immune system homeostasis. Therefore, integrating these two factors in the IBI may enhance the precision of gallstone risk assessment.

Moreover, obesity has been proven as a critical risk factor for gallstones. Obesity increases insulin resistance (IR) and disturbs various metabolic processes, which ultimately influences the development of gallstones [21]. Recent metabolomic studies [22] have further identified several metabolites associated with obesity and metabolic syndrome that lead to gallstone formation. Pertinent studies have demonstrated that higher levels of the proinflammatory adipokine visfatin are linked to the formation of cholesterol gallstones and inhibit neutrophil apoptosis, thereby raising lactone levels [9]. Therefore, individuals with diabetes, IR, or other metabolic disorders have a higher risk of developing cholesterol stones [10]. This also reflects the interplay between inflammation and obesity in the pathogenesis of gallstone disease. BRI, a tool for measuring body and visceral fat, reflects the distribution and degree of obesity [23]. Studies have demonstrated that BRI is a robust predictor of risks for colorectal cancer, metabolic syndrome, heart failure, and other diseases [24–26]. Furthermore, BRI has been shown to exhibit higher predictive accuracy for gallstone risk in comparison to Body Mass Index (BMI), and a higher BRI is linked to a greater likelihood of gallstones [21].

The National Health and Nutrition Examination Survey (NHANES) (www.cdc.gov/nchs/nhanes) represents a nationally representative cross-sectional study that evaluates the health and nutrition of both American children

and adults. Conducted biennially, NHANES mainly involves demographic, dietary, and health data via household interviews and physical examinations [27]. Furthermore, standardized medical examinations are performed at designated mobile examination centers, where biological samples are collected for analysis as well.

In summary, inflammation and obesity are intricately related, and their interplay should not be overlooked in the occurrence and progression of gallstones. IBI and BMI serve as comprehensive tools for evaluating these two factors. It is important to note that IBI primarily reflects neutrophil-mediated innate immune processes, while BRI is closely associated with cholesterol metabolism. The potential interplay between these two indices warrants further exploration, as they may collectively contribute to the susceptibility to cholesterol stones. Therefore, these indicators may play a suggestive role in the identification of gallstone types. The NHANES-based cross-sectional study aims to elucidate the association of IBI with gallstones and the mediating effect of BRI, providing valuable theoretical and data support for the clinical management and prevention strategies of gallstone disease.

Methods

Study design and study population

NHANES has received approval from the Institutional Review Board (IRB) of the National Center for Health Statistics (NCHS). The survey employs a sophisticated multi-stage probabilistic sampling design that integrates interview questionnaires, physical examinations, and laboratory tests. Written informed consent was obtained from every participant. In accordance with the policies of the National Institutes of Health (NIH), analyses conducted on de-identified data that do not involve direct interaction with participants are not considered human subject research and therefore exempt from IRB review [27].

This study utilized data from the 2017–2020 NHANES database, including adults aged 20 and older ($N = 9,232$). Among the original participants, there were 4,479 men and 4,753 women, with an average age of 51. Individuals with missing information on gallstones in the medical health questionnaire were initially excluded ($N = 22$). Subsequently, participants with missing data on the indices of IBI ($N = 1,373$) and Body Roundness Index (BRI) ($N = 377$) were excluded. Additionally, individuals with insufficient data on covariables were ostracized ($N = 2,055$). Those with incomplete weight-related data were also removed from the analysis ($N = 2,807$). Ultimately, 2,598 participants were eligible. The participant selection process is presented in Fig. 1.

Definition of gallstones

The presence of gallstone disease was self-reported by NHANES participants. Specifically, when respondents were asked by trained interviewers, "Has a doctor or other healthcare professional ever diagnosed you with gallstones?" Those who responded positively were confirmed to have gallstones, while those who answered negatively were deemed not to have the disease [20, 21].

Definition of IBI and BRI

Participants in the NHANES program provided fasting venous blood samples, and the results were analyzed using the Roche Cobas 6000 (c501 module) analyzer, adhering to international standards [28]. The IBI is derived from three indicators: neutrophil count, lymphocyte count, and CRP. Relevant data were retrieved from the "Laboratory Data" of NHANES. The formula for IBI was presented in Supplementary Material 1. A higher IBI score indicates a greater inflammatory burden, whereas a lower score reflects a lesser inflammatory burden.

The BRI was calculated using waist circumference (WC) and height data extracted from the "Body Measures" section of the NHANES "Examination Data." The formula for BRI can be found in Supplementary Material 1.

Definition of other variables

To comprehensively explore the potential association between IBI and gallstones, and to control for confounding factors, the study accounted for a variety of covariables: age, sex, race, poverty-to-income ratio (PIR), creatinine, blood urea nitrogen, triglycerides, total cholesterol, total bilirubin, uric acid, fasting blood glucose, hypertension, diabetes, kidney disease, fatty liver disease, coronary artery disease, asthma, cancer, smoking, alcohol consumption, sleep duration, physical activity, and dietary intake. Hypertension, diabetes, kidney disease, coronary artery disease, asthma, and cancer were categorized based on whether participants self-reported having been told by a healthcare professional that they had these conditions. Regarding alcohol consumption and smoking, participants who answered "yes" to the following questions were alcohol consumers: "Have you ever had at least one alcoholic drink in your lifetime, excluding small tastes or sips? By alcoholic drink, I mean a 12-ounce beer, a 5-ounce glass of wine, or 1.5 ounces of distilled spirits" [29]. Those who answered "yes" to having smoked at least 100 cigarettes in their lifetime were categorized into smokers [21]. The diagnosis of fatty liver disease was determined via vibration-controlled transient elastography (VCTE), a non-invasive, painless procedure that measures the Controlled Attenuation Parameter (CAP). CAP ≥ 274 dB/m denoted the presence of fatty liver disease, while CAP ≥ 302 dB/m meant serious fatty

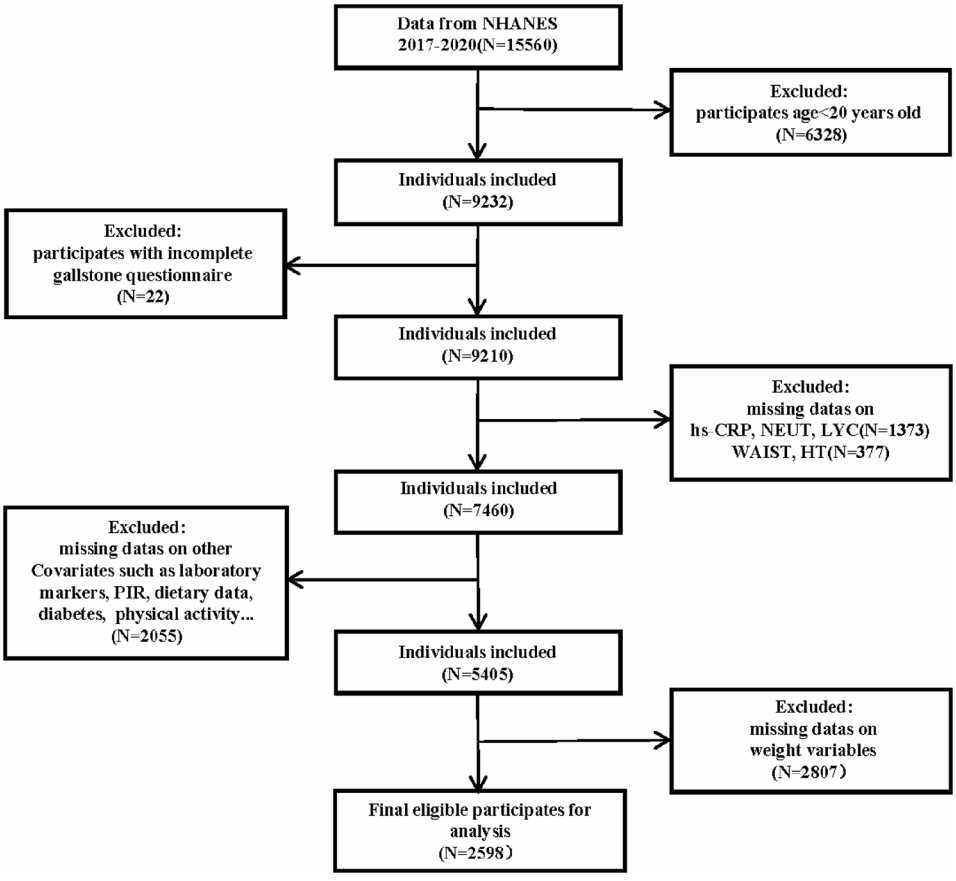

Fig. 1 Flowchart of participant selection. Notes: NHANES, National Health and Nutrition Examination Survey; hs-CRP: hypersensitivity c-reactive protein; NEUT, neutrophil count; LYC, lymphocyte count; HT, height; PIR, poverty-to-income ratio

liver disease [30]. Sleep duration was categorized based on self-reported normal sleep time on weekdays, with the following three categories based on previous research: < 7 h, 7–9 h, and > 9 h [31]. The PIR was stratified into two categories: < 2 and ≥ 2 [32]. Physical activity (PA) was assessed based on the type, frequency, and duration of activities, using the following formula for metabolic equivalent (MET)-minutes per week: PA(MET-min/wk)=MET× Frequency per week × Duration per activity. PA (MET-min/wk) = MET × Frequency per week × Duration per activity. A PA score of 0 indicates no participation in physical activity, while non-zero scores indicate constant or intermittent physical activity [33]. Participants were classified according to the U.S. adult physical activity guidelines: those who met the guidelines (≥ 600 MET-minutes/week, equivalent to 150 min of moderate-intensity or 75 min of vigorous-intensity activity/week) were classified as meeting the standard, while those who did not meet the threshold (< 600 MET-minutes/week) were classified as not meeting the standard [34]. Dietary intake data were based on participants' 24-hour dietary recall on the first day of the survey. Four racial groups were defined: Mexican American, Non-Hispanic Black, Non-Hispanic White, and Other [35].

Covariables screening

In this study, the Boruta algorithm was employed to screen covariables. Boruta, a feature selection method based on random forests, evaluates the relevance and independent contribution of each feature by generating shadow features, which are randomly permuted versions of the original features. The algorithm compares the importance scores of the original features with those of the shadow features. This approach minimizes the error of the random forest model and ultimately yields a subset of optimal features [36, 37].

Statistical analysis

All statistical analyses were undertaken via R 4.4.2. Variables with missing values exceeding 20% of the data were excluded, such as fasting blood sugar (FBS). The Kolmogorov-Smirnov test was applied to assess the normality of continuous variables. Data in a normal distribution were reported as mean ± standard deviation (SD), and intergroup comparisons were completed through

the t-test. Non-normally distributed data were expressed as median (interquartile range, IQR), with group comparisons performed through the Design-based Kruskal-Wallis test. Categorical variables were presented as frequencies and percentages, with group comparisons carried out via the chi-square test. IBI was regarded as an exposure factor. Given its non-normal distribution, IBI was transformed via the natural logarithm and denoted as In(IBI). The variable In(IBI) was subsequently divided into three tertiles (T1: IBI < 1.76, T2: 1.76 ≤ IBI < 5.94, and T3: IBI ≥ 5.94), with the first tertile (T1) serving as the reference group.The prevalence of gallstones was used as the outcome variable, and logistic regression analysis was conducted using the survey package to examine the association of IBI with the likelihood of gallstones. Three logistic regression models were constructed to adjust for different confounding factors. Model 1 had no adjustments for any confounders; Model 2 adjusted for age, sex, race, and PIR; and Model 3 incorporated the top 10 variables selected through the Boruta package, along with demographic information, to adjust for covariables most strongly affecting the outcome. To more precisely assess the association of IBI with gallstones, restricted cubic splines (RCS) were employed to fit the curves, clarifying whether the association was linear or nonlinear. Moreover, subgroup analyses were made to clarify the impact of characteristics like age, sex, and race (as considered in Model 3) on gallstone outcomes. Finally, mediation analysis was performed using the mediation package, and the bootstrap method was leveraged to estimate the confidence intervals of the mediation effects, determining the proportion of the total effect mediated by BRI. These statistical methods enabled a comprehensive investigation of the potential causal association between IBI and gallstones.

Results

Table 1 displays the baseline characteristics of 2,598 participants, including 2,339 non-gallstone patients and 259 gallstone patients. Unlike the non-gallstone group, the gallstone group showed a significantly elevated In(IBI), with a median value of 4 ($P = 0.004$). A similar result was observed for BRI levels ($P < 0.001$). Additionally, the proportion of females and individuals aged ≥ 40 was higher in the gallstone group ($P < 0.001$). Significant differences across groups were also noted for laboratory and disease-related variables, including blood creatinine, urine creatinine, triglycerides, kidney disease, hypertension, and diabetes ($P < 0.05$). In terms of dietary intake, the gallstone cohort exhibited a significantly lower intake of total protein and vitamin B6 in comparison to the non-gallstone cohort ($P < 0.001$). Furthermore, physical activity levels were notably decreased in the gallstone cohort ($P = 0.03$), which suggested a potential link of metabolism, diet, and exercise to the development of gallstones.

Figure 2 illustrates the feature selection results based on the Boruta algorithm. Variables identified as important features are marked in green, while those deemed unimportant are marked in red. After 500 iterations, the variables most strongly associated with the risk of gallstone development were: sex, total protein intake, total energy intake, age, blood creatinine, total fat intake, vitamin B6, vitamin B12, total sugar intake, and total carbohydrate intake. In contrast to the strongest or shadow features, some important variables, such as race and PIR, were excluded due to lower z-values, although these were retained in subsequent analyses based on previous research and clinical experience [38].

Table 2 shows the link of In (IBI) to the prevalence of gallstones. In the unadjusted model (Model 1), higher In (IBI) was markedly related to a risen prevalence of gallstones (OR = 1.252, 95% CI = 1.070–1.464, $P = 0.007$). In the partially adjusted model (Model 2), the positive relation of In(IBI) to gallstones remained significant (OR = 1.183, 95% CI = 1.001–1.396, $P = 0.048$). In the fully adjusted model (Model 3), in contrast to the lowest tertile of In(IBI), the prevalence of gallstones was markedly higher in the third tertile (OR = 2.108, 95% CI = 1.109–4.005, $P = 0.028$), with similar results found in the unadjusted and partially adjusted models. Furthermore, the trend test in Model 3 ($P = 0.02$) indicated that increasing In (IBI) was related to an elevated prevalence of gallstones, which aligned with our findings in Models 1 and 2.

RCS analysis results are detailed in Fig. 3. As In (IBI) rose, the prevalence of gallstones progressively grew. Overall, there was a significant linear positive association of In(IBI) with gallstones (P for overall = 0.005, P for nonlinear = 0.863).

Figure 4 illustrates the subgroup analysis results. In the female subgroup, In(IBI) was significantly positively linked to gallstone prevalence (T3: OR = 2.717, 95% CI (1.227, 6.016), P for trend = 0.02). Notably, in subgroups of people aged ≥ 60 and PIR ≥ 2, higher In(IBI) is significantly associated with a higher prevalence of gallstones ($P < 0.05$ for both). There existed no notable interaction effects in any subgroup (P for interaction > 0.05).

Figure 5; Table 3 explore the potential mediating effects of BRI on the association of IBI with gallstone development. In this analysis, IBI was considered the independent variable, BRI the mediator, and gallstones the dependent variable. It was revealed that IBI had a significant indirect effect on gallstone prevalence through BRI, with an indirect effect size of 0.0129 (95% CI: 0.0121–0.0136, $P < 0.001$), suggesting that BRI partially mediates the link of IBI to gallstones. Moreover, even after BRI was adjusted, gallstones and IBI continued to exhibit a

Table 1 Baseline characteristics of participants

Characteristic	Overall (*N* = 2598)	Non-stone formers (*n* = 259)	Stone formers (*n* = 2339)	Test of significance	*p*-value
ln(IBI)	3(1,8)	3(1,8)	4(2,12)	DBKW = 3.195	0.004
BRI	5.05(3.81,6.75)	4.94(3.69,6.54)	6.21(4.83,8.19)	DBKW = 6.020	< 0.001
Age				χ^2=11.108	< 0.001
<40	834(37%)	795(40%)	39(15%)		
40–59	915(35%)	817(35%)	98(41%)		
≥60	849(28%)	727(26%)	122(44%)		
Gender				χ^2=32.693	< 0.001
male	1288(50%)	1218(53%)	70(23%)		
female	1310(50%)	1121(47%)	189(77%)		
Race				χ^2=3.282	0.055
Mexican American	341(8.8%)	302(8.9%)	39(7.4%)		
Non-Hispanic White	957(65%)	847(65%)	110(72%)		
Non-Hispanic Black	637(11%)	599(12%)	38(4.4%)		
Other	663(15%)	591(15%)	72(17%)		
PIR				χ^2=0.137	0.714
<2	1112(30%)	1008(30%)	104(28%)		
≥2	1486(70%)	1331(70%)	155(72%)		
Diabetes	410(11%)	338(10.0%)	72(19%)	χ^2=18.379	< 0.001
Renal Disease	96(3.2%)	75(3.0%)	21(5.2%)	χ^2=5.027	0.034
Fatty Liver				χ^2=3.454	0.058
No	1445(57%)	1347(58%)	98(45%)		
Mild	385(15%)	338(15%)	47(20%)		
Severe	768(28%)	654(27%)	114(35%)		
Asthma	410(14%)	356(14%)	54(15%)	χ^2=0.002	0.958
Coronary Heart Disease	106(3.6%)	88(3.6%)	18(3.4%)	χ^2=0.027	0.872
Cancer	253(11%)	216(10%)	37(15%)	χ^2=2.537	0.124
Smoking	1114(43%)	989(42%)	125(50%)	χ^2=2.988	0.096
PA				χ^2=5.306	0.03
<600	898(29%)	780(28%)	118(39%)		
≥600	1700(71%)	1559(72%)	141(61%)		
Sleep duration				χ^2=0.704	0.461
<7	665(23%)	590(23%)	75(28%)		
7–9	1678(69%)	1522(69%)	156(63%)		
>9	255(8.0%)	227(7.8%)	28(9.5%)		
Drinking	2396(94%)	2153(94%)	243(95%)	χ^2=0.156	0.696
Hypertension	965(31%)	821(29%)	144(46%)	χ^2=8.220	0.008
UCREA	10,962(6,365,16,089)	11,050(6,542,16,177)	9,724(5,039,14,940)	DBKW=-2.329	0.029
BUN	5.00(3.93,6.07)	5.00(3.93,6.07)	5.00(4.28,6.07)	DBKW = 0.659	0.516
SCr	74(64,86)	75(64,87)	69(60,80)	DBKW=-3.982	< 0.001
TB	6.8(5.1,10.3)	6.8(5.1,10.3)	6.8(5.1,10.3)	DBKW = 0.245	0.808
TC	4.71(4.11,5.43)	4.71(4.09,5.43)	4.76(4.11,5.46)	DBKW = 0.430	0.671
TG	1.17(0.84,1.73)	1.15(0.82,1.71)	1.34(0.95,1.84)	DBKW = 2.575	0.017
BUA	315(262,369)	315(262,369)	315(268,375)	DBKW = 0.751	0.46
Total energy	2,063(1,512,2,742)	2,087(1,563,2,775)	1,760(1,294,2,355)	DBKW=-3.547	0.002
Total protein	77(54,104)	78(55,106)	63(44,92)	DBKW=-3.938	< 0.001
Total carbohydrate	230(164,311)	231(167,314)	212(140,296)	DBKW=-2.432	0.023
Total sugar	92(57,137)	92(57,137)	91(50,131)	DBKW=-0.442	0.662
Total fat	81(57,116)	83(59,117)	69(48,100)	DBKW=-2.617	0.015
Total water	2,797(2,041,3,792)	2,820(2,062,3,837)	2,667(1,806,3,540)	DBKW=-2.140	0.043
VA	491(265,768)	494(264,774)	460(265,695)	DBKW=-1.037	0.31
VB6	1.73(1.14,2.44)	1.77(1.17,2.49)	1.42(0.89,2.20)	DBKW=-5.067	< 0.001
VB12	3.6(2.0,5.7)	3.7(2.1,5.8)	3.2(1.5,4.9)	DBKW=-2.557	0.017

Table 1 (continued)

Characteristic	Overall (*N* = 2598)	Non-stone formers (*n* = 259)	Stone formers (*n* = 2339)	Test of significance	*p*-value
VC	45(19,103)	47(20,106)	36(15,74)	DBKW=-2.476	0.021
VD	2.9(1.1,5.3)	2.9(1.1,5.3)	2.7(0.9,5.6)	DBKW=-0.707	0.487

The Design-based KruskalWallis test is used for non-normal continuous variables; For categorical variables, the probability value was calculated using a weighted chi-square test. In(IBI), In-transformed inflammatory body index; BRI, body roundness index; PIR, poverty-to-income ratio; PA, physical activity; UCREA, urine creatinine; BUN, blood urea nitrogen; SCr, serum creatinine; TB, total bilirubin; TC, total cholesterol; TG, triglycerides; BUA, blood uric acid; VA, vitamin A; VB6, vitamin B6; VB12, vitamin B12; VC, vitamin C; VD, vitamin D

statistically significant association, with a direct effect size of 0.0258 (95% CI: 0.0237–0.0279, $P < 0.001$), suggesting that BRI has both direct and indirect effects on the occurrence of gallstones, with nearly 33.24% of the effect being mediated by BRI. Table 3 presents the mediation analysis results, including direct, indirect and total effects, as well as the mediation ratio.

Discussion

This study examined the association of gallstones with In (IBI) using data from the nationally representative NHANES. After stepwise adjustment for covariables, logistic regression analysis demonstrated a significant positive relation of high In(IBI) levels to the prevalence of gallstones, which remained consistent across unadjusted, partially adjusted, and fully adjusted models. Moreover, as In(IBI) increased, the prevalence of gallstones significantly increased, indicating that IBI is a risk factor for gallstones. The RCS analysis further clarified that the association between In(IBI) and gallstones is linear. Subgroup analysis revealed that the effects of In(IBI) on gallstones were more prominent in those aged ≥ 60, females, and those with PIR ≥ 2. Additionally, BRI partially mediated the positive association between IBI and gallstones.

Comparison with previous studies

Our findings demonstrate a significant positive association between IBI and gallstones, reflecting a critical link between systemic inflammatory status and the risk of gallstone development. To our knowledge, cohort studies have substantiated the notable relation of a greater likelihood of gallstones to higher levels of hs-CRP (trend $P < 0.001$) [14], which corroborates previous cross-sectional findings [39]. Our study indicates that in a fully adjusted weighted logistic regression model utilizing logarithmic conversion, a one-unit increase in IBI (OR = 2.108) significantly elevates the prevalence of gallstones in comparison to a one-unit increase in hs-CRP (OR = 1.29). This suggests that the IBI may serve as a more sensitive predictor of gallstone risk [39, 40]. Meanwhile, based on prior cross-sectional studies that proved the strong association between BRI and gallstone risk [21], our study further revealed that BRI, as an intermediary indicator, partially mediates the positive association between IBI and gallstone risk.

IBI and gallstones

This result suggests an important link between systemic inflammatory status and the risk of gallstones. Gallstones have been shown to be associated with various mechanisms, including bile supersaturation, cholesterol accumulation, genetic factors, gut microbiota dysbiosis, and gallbladder motility dysfunction [41]. Immune-mediated inflammation plays a role in the downstream stages of the pathogenesis of gallstones [12, 42]. Relevant studies have indicated that circulating inflammatory proteins are significantly linked to the inflammatory proteins measured in bile. Elevated serum and bile levels of inflammatory factors such as C-C motif chemokine ligand 20(CCL20), CRP, C-X-C motif Chemokine ligand 8(CXCL8), 10(CXCL10), resistin, and Serum amyloid A(SAA) in gallstone patients have been linked to poor prognosis. These findings suggest that using blood-based inflammatory markers could better reflect the association between inflammation and the risk of gallstones [43]. Some studies have also stratified gallstone patients based on optimal combinations of circulating inflammatory proteins to guide the prioritization of cholecystectomy [44]. Lymphocytes, dendritic cells, neutrophils, and/or monocytes are chemotactically attracted by CCL20, CXCL8, CXCL10, and SAA, exerting effects in the pathogenesis of gallstones [45, 46]. Specifically, Th1-mediated immune responses are mediated by chemokines (CCL20, CXCL8, CXCL10) that bind to the chemokine receptor-3 (CXCR3) [46, 47]. SAA exerts chemotactic effects on neutrophils and mast cells by binding and activating surface receptors such as Toll-like receptors 2 (TLR2), 4 (TLR4), formyl peptide receptor-like 1 (FPRL1), class B scavenger receptor CD36, and ATP receptor P2X [48]. Furthermore, SAA influences CXCL8 production and activates inflammasomes (NLRP3), triggering immune cascades that extend leukocyte release time, thereby causing chronic inflammation [49–51]. Thus, the IBI, composed of CRP, neutrophil count, and lymphocyte count, more comprehensively reflects the immune-mediated inflammatory effects on gallstones compared to single circulating inflammatory markers.

The mediating role of BRI in gallstone development

A high BRI indicates severe abnormalities in body fat and visceral fat distribution, often due to lipid metabolism disorders. Previous studies have confirmed that high BRI

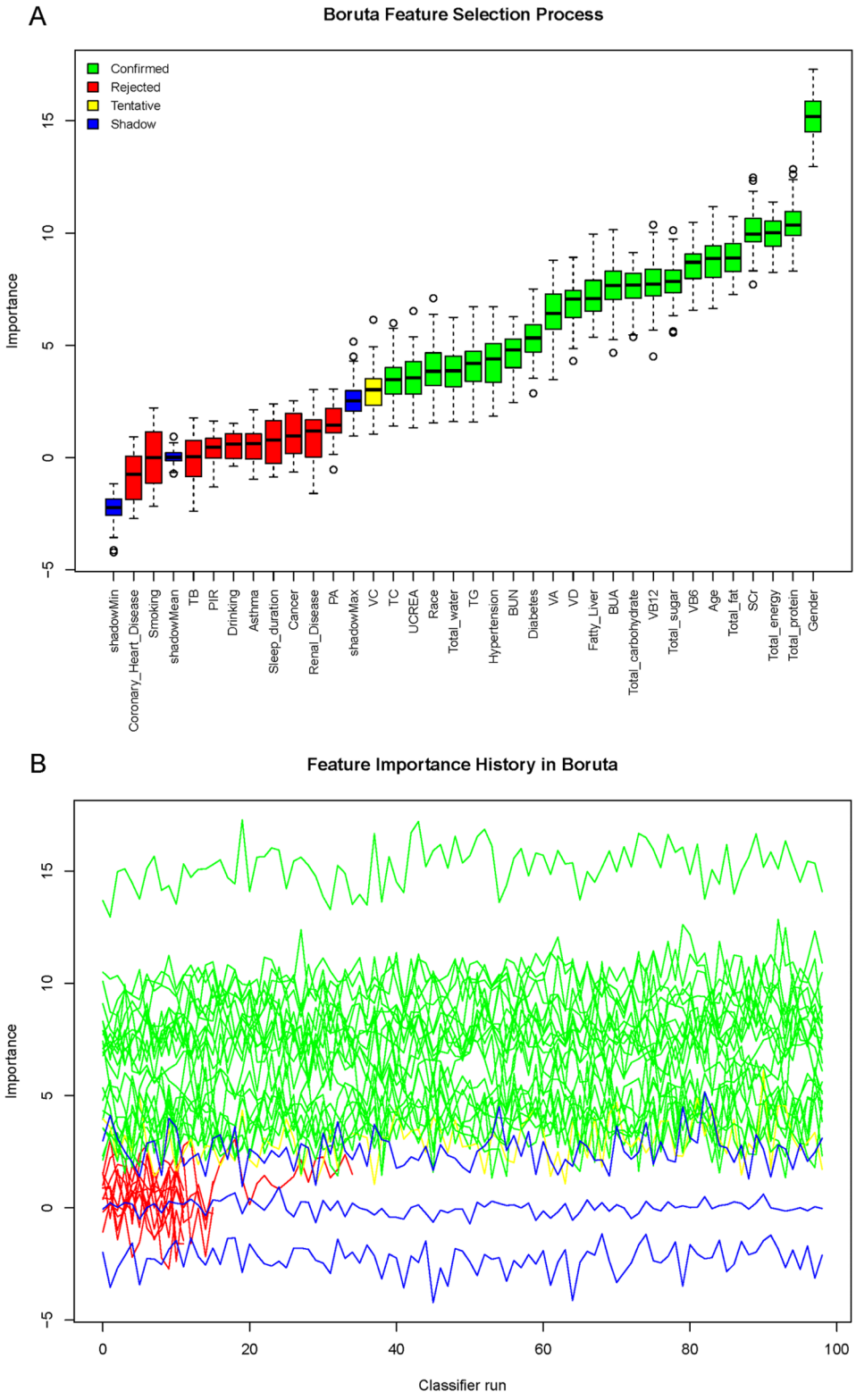

Fig. 2 Feature selection results based on the Boruta algorithm. Notes: SCr, serum creatinine; VB6, vitamin B6; VB12, vitamin B12; BUA, blood uric acid; VD, vitamin D; VA: vitamin A; BUN: blood urea nitrogen; TG, Triglycerides; UCREA, urine creatinine; TC, Total Cholesterol; VC, vitamin C; PA, physical activity; PIR, poverty-to-income ratio; TB, total bilirubin

Table 2 Logistic regression analysis of the association between IBI with gallstones

	Model 1			Model 2			Model 3		
	OR	**95%CI**	***P***	**OR**	**95%CI**	***P***	**OR**	**95%CI**	***P***
ln(IBI)	1.252	1.070, 1.464	0.007	1.183	1.001, 1.396	0.048	1.167	0.972, 1.401	0.088
Categories									
T1	—	—		—	—		—	—	
T2	1.679	0.934, 3.017	0.08	1.663	0.892, 3.100	0.102	1.689	0.844, 3.381	0.12
T3	2.495	1.424, 4.371	0.003	2.159	1.229, 3.791	0.01	2.108	1.109, 4.005	0.028
P for trend	1.567	1.206, 2.037	0.002	1.448	1.120, 1.871	0.007	1.426	1.073, 1.896	0.02

OR, Odds Ratio, CI, confidence interval. Model 1 was crude model; Model 2 was adjusted for age, race, gender, poverty-income ratio; Model 3 was adjusted for age, race, gender, poverty-income ratio, Total protein, Total energy, SCr, Total fat, VB6, Total sugar, VB12, Total carbohydrate

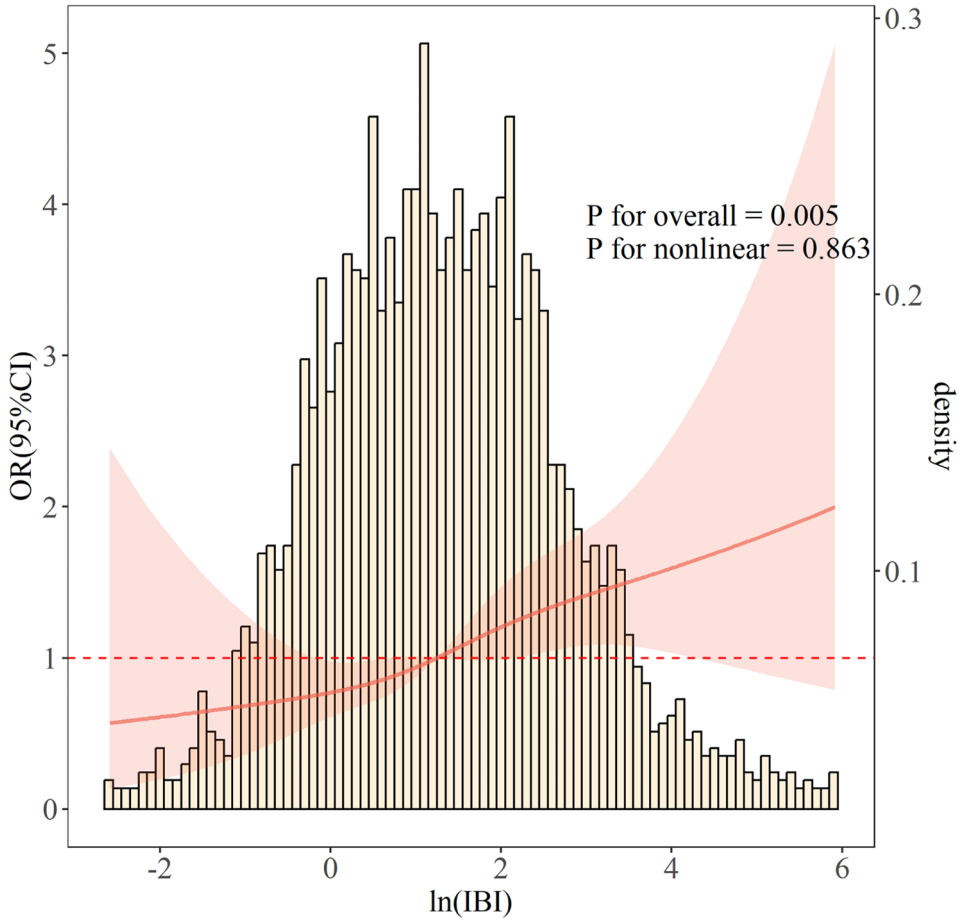

Fig. 3 Restrictive cubic spline analysis for the association between IBI and gallstones. Notes: In (IBI), In-transformed inflammatory body index; OR, odds ratios; CI, confidence intervals

is a significant risk factor for gallstones [23]. Our study found that BRI partially mediates the effect of IBI on gallstone prevalence. This suggests a potential interrelation among inflammation, lipid metabolism, and obesity in the pathological process of gallstone formation. Experimental studies also show that serum inflammatory markers such as SAA and Interleukin-1β (IL-1β) accelerate low-density lipoprotein (LDL) transcytosis through the nuclear transcription factor-κB/caveolin-1/cavin-1 axis, leading to elevated arterial LDL levels [52]. Moreover, high levels of SAA can displace apolipoproteinA-I (apoA-I) in high-density lipoprotein (HDL), altering the remodeling pattern of HDL and affecting its function [53]. Specific inflammatory chemokines (e.g., CXCL1, CXCL2, CXCL16) increase macrophage uptake of oxidized low-density lipoprotein (oxLDL), promoting foam cell formation, lipid accumulation in the vasculature, and plaque development [54]. Therefore, circulating inflammatory proteins profoundly affect the various intermediates of blood lipid metabolism, resulting in abnormal fat

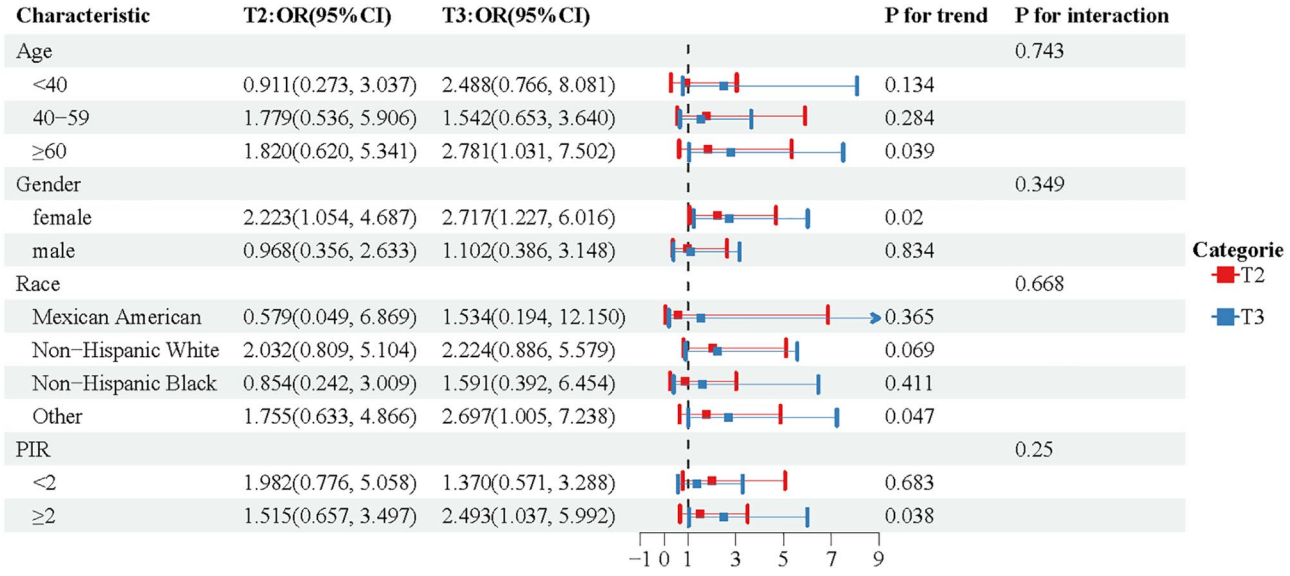

Fig. 4 Subgroup analysis of the association between IBI and gallstones. Notes: PIR, poverty-to-income ratio; OR, odds ratios; CI, confidence intervals. T2, the second tertile; T3, the third tertile

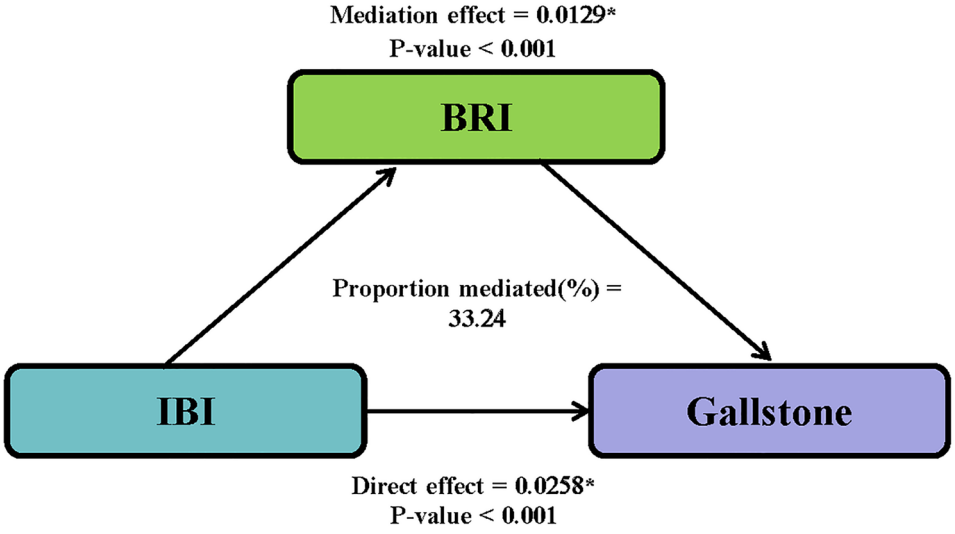

Fig. 5 The mediating role of BRI in the association between IBI and gallstones. Notes: IBI, inflammatory burden index; BRI, body roundness index

Table 3 The mediating role of BRI in the association between IBI and gallstones

	Estimate	95%CI lower	95%CI upper	*P*-value
Total effect	0.0387	0.0366	0.0409	< 0.001
Mediation effect	0.0129	0.0121	0.0136	< 0.001
Direct effect	0.0258	0.0237	0.0279	< 0.001
Proportion mediated	0.3324	0.3090	0.3580	< 0.001

distribution throughout the body. Simultaneously, weight gain and obesity can transform the phenotype of white adipose tissue (WAT), leading to macrophage-dominated immune cell infiltration and cytokine secretion, ultimately initiating inflammatory signaling cascades [55, 56]. In contrast, this process also impairs the metabolic function of adipose tissue, leading to glucose intolerance and IR [56–59], mechanisms closely related to endoplasmic reticulum stress, hypoxia, and programmed cell death [60–62]. This partially explains the complex bidirectional interaction between inflammation and obesity reflected by IBI and BRI, which exerts a positive association with gallstone formation.

Interpretation of subgroup analysis results

Subgroup analysis revealed that the risk of gallstones is higher in women, with an overall odds ratio (OR) more than twice that observed in men. Moreover, for each unit of increase in the In (IBI) value within the third quartile, the OR rose by 1.717 times, which is consistent with

prior literature [3]. The mechanism may involve more estrogen secretion, which upregulates the expression of intestinal sterol influx transporter Niemann-Pick C1-like 1 (NPC1L1) via the estrogen receptor 1 (ESR1) pathway, thereby promoting intestinal cholesterol absorption. This effect is also mediated by the G protein-coupled estrogen receptor 30 (GPR30) [63]. GPR30 triggers swift cellular signaling cascades stimulated by estrogen and facilitates the transcriptional control of genes, thus affecting gene expression in response to estrogen [63–65]. Furthermore, it collaborates with ESR1 to manage the liver's metabolism of cholesterol and bile salts [63, 65]. Based on the findings of the sex subgroup analysis, it is recommended that female patients, particularly those of reproductive age or using estrogen-containing medications, adopt preventive measures such as dietary modifications and routine medical examinations. Moreover, men need to improve their lifestyles through smoking cessation, alcohol moderation, and weight management, to mitigate chronic inflammatory states and ultimately prevent gallstone formation. The prevalence of gallstones is markedly higher among people aged ≥ 60 and those with a PIR ≥ 2. Aging is often related to alterations in gallbladder function, including decreased efficiency of gallbladder emptying and changes in bile composition. Furthermore, the incidence of chronic inflammation may increase with advancing age. Family income levels may directly influence eating habits, health awareness, and access to medical resources. Low-income families may consume diets high in fat and sugar, which is associated with a higher risk of gallstones. However, due to the lack of definitive studies, the relationship between these factors and gallstone prevalence remains inconclusive.

Advantages of our research

Our study is the first to prove a significant positive association between IBI and gallstones. To our knowledge, this study is the first to demonstrate a significant association between IBI and the prevalence of gallstones. It represents the inaugural application of IBI as a composite indicator of both inflammation and immune system status of gallstone disease, and IBI has been shown to be more accurate and sensitive than individual indicators of inflammation. Leveraging a large sample size, this study comprehensively considered potential confounding factors and constructed a reliable logistic regression model after systematical covariable selection enabled by machine learning algorithms, thereby leading to a compelling conclusion. Based on this, mediation analysis was employed to investigate the potential mediating role of BRI in the association between IBI and gallstone risk. This analysis reveals the direct association between inflammation and gallstone formation, as well as the indirect impact of obesity on the inflammatory processes that bear on the formation of gallstones. These findings underscore the necessity for comprehensive management of inflammation and body fat in the prevention and treatment of gallstones. Furthermore, the subgroup analysis indicated that IBI exerts a more pronounced effect on the elevated risk of gallstones in specific populations. Therefore, gallstone management and prevention strategies could be more effectively tailored.

Limitations of our research

Despite its strengths, our study has several limitations. First, its cross-sectional design precludes causal inferences due to the absence of longitudinal data. Second, although many potential covariables were considered, some may have been overlooked. Additionally, the reliance on questionnaire data, particularly the self-reported gallstone status of NHANES participants, possibly leads to recall and reporting bias, and the lack of objective imaging data, such as ultrasound, for confirming the diagnosis of gallstones, may introduce bias into our results. Furthermore, the evaluation of gallstone prevalence was based solely on the presence of gallstones, which limited our ability to assess the details of participants' symptoms and prevented us from drawing conclusions regarding the effects of IBI on the variability of gallstone status. Lastly, as our study population was derived only from NHANES participants from the United States, caution is warranted when applying these findings to other ethnicities and populations.

Conclusion

Our study demonstrated a significant linear positive link of IBI to gallstone prevalence. Furthermore, BRI partially mediates the positive effect of IBI on gallstone prevalence. The foregoing results suggest that IBI could be incorporated into routine health assessments, particularly for high-risk populations, including women, old adults, economically disadvantaged individuals, and those with low physical activity levels. Such integration may facilitate early prevention and improve gallstone management.

It is hoped that future longitudinal cohort studies incorporate imaging techniques and fully integrate patients' symptoms to ultimately elucidate the causal relationship between IBI and gallstone prevalence and to develop accurate models for predicting gallstone risk. Moreover, future research may examine the predictive roles of IBI and BRI in identifying gallstone types. Understanding the biological mechanisms underlying the effects of inflammation and obesity on gallstone formation is also crucial for future investigations.

Abbreviations

IBI	Inflammatory Burden Index
BRI	Body Roundness Index

RCS	Restrictive Cubic Splines
CRP	C-Reactive Protein
hs-CRP	hypersensitivity C-Reactive Protein
NLR	Neutrophil-to-Lymphocyte Ratio
NET	Neutrophil Extracellular Trap
BMI	Body Mass Index
PIR	Poverty-to-Income Ratio
WC	Waist Circumference
VCTE	Vibration-controlled Transient Elastography
CAP	Controlled Attenuation Parameter
MET	Metabolic Equivalent
PA	Physical Activity
UCREA	Urine Creatinine
BUN	Blood Urea Nitrogen
SCr	Serum Creatinine
TB	Total Bilirubin
TC	Total Cholesterol
TG	Triglycerides
BUA	Blood Uric Acid
VA	Vitamin A
VB6	Vitamin B6
VB12	Vitamin B12
VC	Vitamin C
VD	Vitamin D
FBS	Fasting Blood Sugar
CCL	C-C motif Chemokine ligand
CXCL	C-X-C motif Chemokine ligand
SAA	Serum Amyloid A
CXCR	C-X-C motif Chemokine Receptor
TLR	Toll-Like Receptors
FPRL1	Formyl Peptide Receptor-Like 1
NLRP3	Activates Inflammasomes
IL-1β	Interleukin-1β
LDL	Low-Density Lipoprotein
oxLDL	oxidized Low-Density Lipoprotein
ApoA-I	ApolipoproteinA-I
HDL	High-Density Lipoprotein
WAT	White Adipose Tissue
NPC1L1	Niemann-Pick C1-like 1
ESR1	estrogen receptor 1
GPR30	G protein-coupled receptor 30
SD	Standard Deviation
IQR	Interquartile Range
Cis	Confidence Intervals
Ors	Odds Ratios
NHANES	National Health and Nutrition Examination Survey
IRB	Institutional Review Board
NCHS	National Center for Health Statistics
NIH	National Institutes of Health

Supplementary Information

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Supplementary Material 1

Author contributions

All authors contributed to the study conception and design. Writing - original draft preparation: [Yuting Gu]; Writing - review and editing: [Yuting Gu，Zhanyi Zhou，Xuan Zhao，Xiaolu Ye]; Conceptualization: [Yuting Gu，Zhanyi Zhou]; Methodology: [Yuting Gu，Zhanyi Zhou]; Formal analysis and investigation: [Yuting Gu，Zhanyi Zhou，Xuan Zhao，Xiaolu Ye，Keyi Qin，Jiahui Liu, Xiao Zhang]; Funding acquisition: [Yunxi Ji]; Resources: [Yunxi Ji]; Supervision: [Yunxi Ji], and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

This study utilized data from the 2017-2020 NHANES database, it approved by the Institutional Review Board (IRB) of the National Center for Health Statistics (NCHS).

Declarations

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Competing interests

The authors declare no competing interests.

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