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Association between oxidative balance score and gallstone disease: a population-based study from NHANES

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Background: Oxidative stress has been reported to participant in the pathogenesis of gallstones. Oxidative balance score (OBS) represents pro-oxidant and antioxidant exposures to diet and lifestyle, closely associated with multiple metabolic disorders. However, the relationship between OBS and gallstones remains unclear.

Methods: This study analyzed cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) 2017–2020. OBS was calculated based on the 24-h recall interviews or questionnaires. We used weighted logistic regression, restricted cubic splines (RCS), weighted quantile sum (WQS) regression and the Bayesian kernel machine regression (BKMR) model to identify the relationship between OBS and gallstones. Subgroup analysis and sensitivity analysis were used to explore potential heterogeneity and stability of the results. Mediation analysis was performed to assess the mediating effects of serum lipid in the association between OBS and gallstones.

Results: A total of 7,618 participants were finally included in this study. Weighted logistics regression showed that total OBS was associated with gallstones risk (OR = 0.98, $p = 0.03$), particularly in individuals who were under 60 years old, Hispanic, educated below high school, non-smokers, had hypertension or malignancy. Dietary and lifestyle OBS independently contribute to the protection against gallstones. RCS analysis indicated a non-linear relationship between OBS and gallstones ($p = 0.03$). WQS and BKMR model identified that BMI, vitamin E, vitamin B6, magnesium and carotene played relatively important role among 20 components. Mediation analysis showed serum TG and HDL as mediators of the association between OBS and gallstones.

Conclusion: Higher OBS or increased oxidative balance are positively associated with reduction of gallstone risk. This findings provide valuable insights for surveillance and interventions targeting for antioxidant-rich diet and lifestyle for gallstone disease.

KEYWORDS

oxidative balance score, diet, lifestyle, gallstones, NHANES

Introduction

Cholelithiasis or gallstone disease is a common digestive disease and causes significant health care burden worldwide. The prevalence of gallstones is approximately 10–15% in adult population, which is usually underestimated as about 70% of patients with cholelithiasis are asymptomatic (1). About 10–20% of patients have varying degrees of abdominal symptoms or even develop severe complications (2), such as gallstone ileus especially in the elderly (3). Gallstones are traditionally classified as cholesterol, pigment, or mixed stones based on their composition. The mechanism of gallstone formation has not been well understood, involving multiple factors. Disrupted cholesterol homeostasis is the primary cause of cholesterol gallstone formation and depends largely on genetic predisposition, while pigment gallstones are the integrated consequences of hepatic hypersecretion of bilirubin, bile stasis, and bacterial infection (4). Besides, age, female, ethnic background, dietary or lifestyle habits, bariatric surgery-induced rapid weight loss are the modifiable risk factors, particularly in the development of cholesterol gallstones (1, 5, 6).

Oxidative stress or imbalance plays an important role in multiple physiological processes and has been identified to participate in the nucleation and deposition of gallstones (7). Abnormal oxidative stress may induce dysfunction of lipid metabolism through affecting metabolism-related organelles and leading to cellular damage, lipid peroxidation, and mitochondrial dysfunction, etc (8). In addition, Sanikidze et al. (7) revealed the existence of oxidized bilirubin free radical in pigmented gallstones using electron paramagnetic resonance, acting as a key driver for gallstone formation. Besides maintained mainly by endogenous enzymatic mechanisms, the pro-oxidant/antioxidant balance is also affected by exogenous factors, including diet and lifestyle (9). Oxidative balance score (OBS) is a novel concept to assess pro-oxidant and antioxidant exposures in individuals, which was composed of dietary intakes and lifestyles (9, 10). Higher OBS represents a stronger antioxidant capacity within the body. Several studies reported that OBS is significantly associated with metabolic disorders (11), cardiovascular diseases (12), chronic disease (13, 14), or malignant disease (15). However, the potential association between OBS and gallstones remains unclear. The joint and independent effects of OBS components on gallstones should be evaluated to comprehensively reveal the role of pro-oxidant and antioxidant balance adjusted by dietary diet or lifestyle in the pathogenesis of gallstones, and provide evidence for gallstone prevention through maintaining antioxidant-rich diet or lifestyle.

Therefore, we aimed to investigate the association between dietary and lifestyle integrated OBS and all types of gallstones incidence in the general US population from the National Health and Nutrition Examination Survey (NHANES) 2017 to March 2020 cycle to provide further evidence for the occurrence of gallstones.

Materials and methods

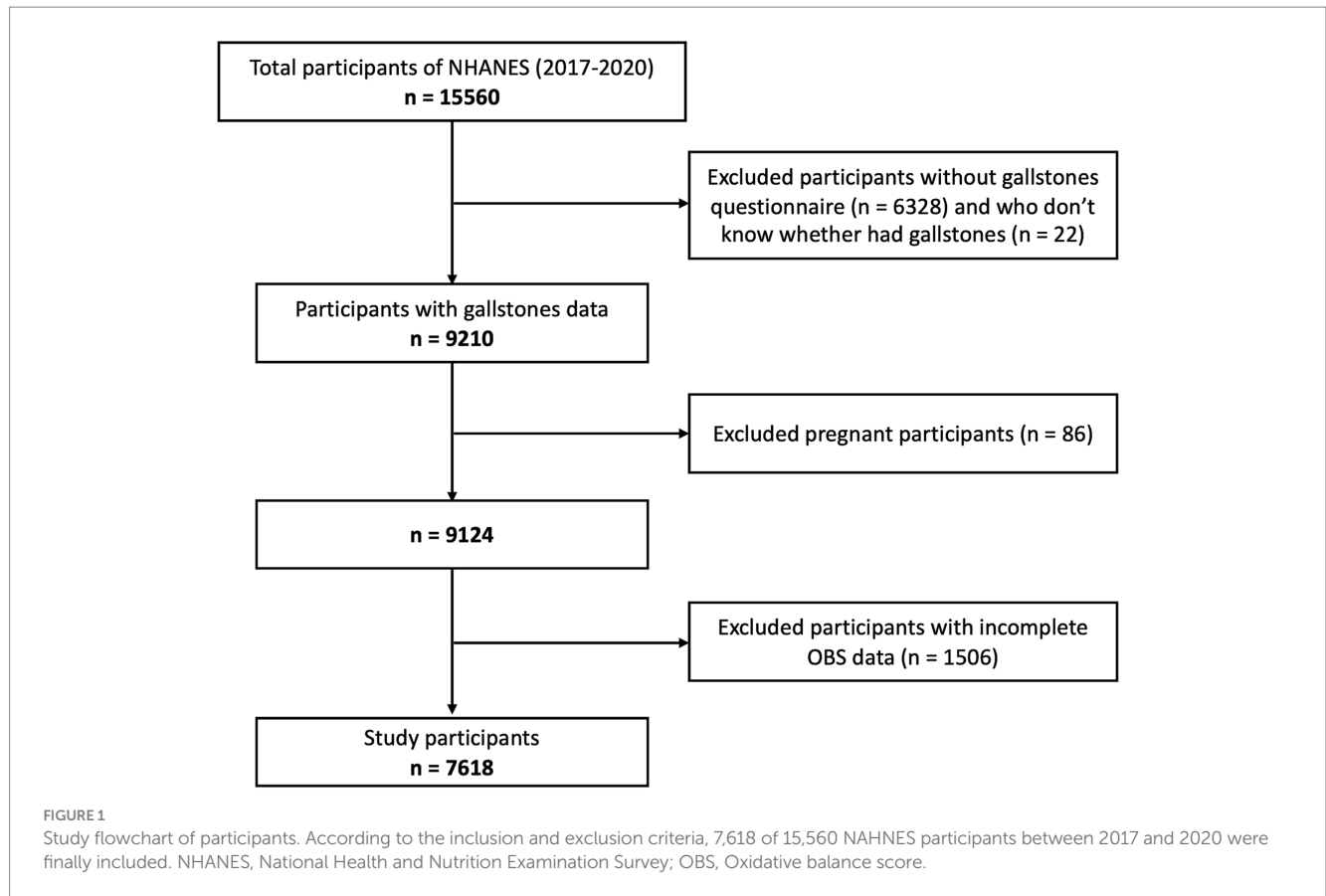
Study design and participants

All data were obtained from NHANES 2017–March 2020, a nationally population-based survey conducted by the National Center for Health Statistics (NCHS) of the centers to evaluate the nutritional status and health of adults and children in the US. As a large-scale, national study, the rigorous stratified, multistage probability sampling method ensures the comprehensive representativeness and diversity of the participants, which has superior performance in the assessment of risk factors. Initially, 9,232 of 15,560 individuals completed the questionnaire of whether they had gallstones. As is shown in Figure 1, 86 pregnant participants, 22 participants with incomplete gallstone questionnaires, 1,506 participants with incomplete data of OBS were excluded. Finally, 7,618 participants were included in this study, who were all ≥ 20 years old. The National Center for Health Statistics Ethics Review Board approved the protocol. Written informed consent was obtained from all participants.

Oxidative balance score

OBS is an index representing overall oxidative balance status based on 16 dietary nutrients (dietary fiber, carotene, riboflavin, niacin, vitamin B6, vitamin B12, vitamin C, vitamin E, total folate, calcium, magnesium, zinc, copper, selenium, total fat, iron) and 4 lifestyle indicators (physical activity, alcohol intake, cotinine and body mass index). The calculation of OBS was referred to previous studies (16, 17), which is illustrated in Supplementary Table S1. A total of 16 nutrients and alcohol intake were collected from two 24-h total dietary nutrient intakes files. NHANES participants were performed two 24-h dietary recall interviews. The first dietary recall was collected in-person during the NHANES visit, and the second recall was assessed through telephone follow-up 3 to 10 days later. Daily aggregates of food energy, nutrients, and food components from all foods were calculated using the U.S. Department of Agriculture (USDA)'s Food and Nutrient Database for Dietary Studies 2017–2018 and 2019–2020. We used the average of the two 24-h intakes of each nutrient to calculate the OBS (if only one 24-h record was available, this one-day value was used instead of the average). Physical activity was assessed derived from the questionnaire data using metabolic equivalent of task (MET) scores, which were calculated as NHANES suggested, including walking, bicycling, moderate and vigorous activity. Vigorous work-related and leisure-time activity were both assigned with a score coefficient of 8.0, while moderate work-related and leisure-time activity and walking or bicycling for transportation were assigned with a score coefficient of 4.0. Smoking was estimated by serum cotinine, which was measured by an isotope dilution-high performance liquid chromatography/atmospheric pressure chemical ionization tandem mass spectrometry (ID HPLC-APCI MS/MS) method. Body mass index (BMI) was collected from body measures and calculated as weight in kilograms divided by height in meters square. These components were divided into three groups by their sex-specific tertiles. Antioxidants (dietary fiber, carotene, riboflavin, niacin, vitamin B6, vitamin B12, vitamin C, vitamin E, total folate, calcium, magnesium, zinc, copper, selenium and physical activity) were assigned points from 0 to 2 for tertile groups 1 to 3 respectively,

Abbreviations: OBS, oxidative balance score; NHANES, National Health and Nutrition Examination Survey; RCS, restricted cubic splines; WQS, weighted quantile sum; BKMR, Bayesian kernel machine regression; BMI, body mass index; OR, odds ratio; CI, confidence interval; TC, cholesterol; TG, triglyceride; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.



and pro-oxidants (total fat, iron, cotinine, alcohol intake, and BMI) were assigned points from 0 to 2 for tertile group 3 to 1 inversely. The total OBS was the sum of the antioxidant and pro-oxidant components, ranged from 0 to 40 points. Higher points indicate increased antioxidant levels.

Outcome variables

Gallstones were determined by the medical history questionnaire. The positive response to the question “Has the doctor ever said you have gallstones?” was used to define gallstones. Conversely, the “no” response was defined as non-gallstones. Participants who refused to answer or do not know were excluded from our analysis.

Covariates

Demographic data including age, gender, race/ethnicity, educational level, smoking status were collected. Race/ethnicity was categorized as Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, or Other. Educational level was categorized as less than high school, high school, and more than high school. Comorbidity condition including hypertension, diabetes, coronary heart disease, malignant disease was recorded respectively. The definition of hypertension was required to meet one of these three criteria: (i) the mean systolic blood pressure ≥ 140 mmHg and / or diastolic blood pressure ≥ 90 mmHg measured 3 times on the same day if some blood

pressure measurement data are missing, the value or average of the available measurement data was used; (ii) participants who take antihypertensive medication currently; (iii) self-reported hypertension in the questionnaire data. The definition of diabetes also needs to meet one of these criteria: (i) the glycated hemoglobin A1c (HbA1c) cut point of $\geq 6.5\%$; (ii) the FBG cut point of ≥ 126 mg/dL; (iii) participants who reported the diagnosis of diabetes or currently taking insulin or anti-diabetes drugs in the questionnaire date. The definition of coronary heart disease and malignant disease was both based on the medical history questionnaire. Serum parameters were extracted from laboratory data of NHANES, including total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, and fast blood glucose. Dietary inflammatory index (DII) was calculated by R package “dietaryindex” based on dietary intake data to reflecting overall dietary inflammatory potential as previously reported (18, 19). The triglyceride-glucose (TyG) index, a novel indicator of high atherosclerotic cardiovascular diseases risks, was calculated as $\text{Ln}[\text{fasting triglycerides (mg/dl)} \times \text{fasting glucose (mg/dl)}^2]$ (20).

According to previous literature, directed acyclic graph (DAG) was illustrated to show the relation among OBS, gallstones and potential confounders, which included age, gender, race/ethnicity, education, comorbidities, as shown in [Supplementary Figure 1](#).

Statistical analysis

All analyses were conducted in accordance with NHANES analysis and reporting criteria (21), and sample weights, clusters and

stratification were all considered. The appropriate survey weight is based on the variable of interest that was collected on the smallest number of respondents (21). Multiple imputations were used for missing covariates including smoking status, comorbidities, and serum lipid levels. We applied the R “jomo” package to generate 10 imputed datasets after a burn-in of 500 iterations and 100 updates to ensure stochastic independence between imputed datasets, as described previously (22, 23).

Continuous variables are presented as mean (standard deviation) if they meet normal distribution or median (interquartile ranges) if not. Differences among different groups were compared using the weighted univariate linear regression and the Kruskal-Wallis test for normal continuous and nonnormal continuous variables, respectively. Categorical data were presented as frequencies (weighted percentages) and compared with chi-squared test.

Survey-weighted multiple logistic regression analysis was performed to investigate the association between OBS and gallstones. OBS was converted to a categorical variable by quartile and computed *p*-value for trend. Another three models for covariate adjustments were constructed to evaluate potential differences in the confounding effects. Model 2 was adjusted for age, gender, race/ethnicity and educational level. Model 3 was adjusted for the variables in Model 2 plus comorbidities. Model 4 was adjusted for the variables in Model 3 plus triglyceride.

To assess the effects of multiple components in OBS on gallstones, weighted quantile sum (WQS) regression model was used as reported previously (24–26). It can identify the contribution of each dietary or lifestyle components on the occurrence of gallstones. Participants were randomly divided into training (60%) and validation (40%) sets, and 1,000 bootstrap iterations on the training set were performed for WQS modeling. The R package “wqs” was used for WQS analysis.

Bayesian kernel machine regression (BKMR) model analysis was performed to examine the combined effect of individual component in OBS on predicted gallstone risk based on Gaussian process regression. As described previously (27), the posterior inclusion probability (PIP) was calculated to reflect the probability of overall OBS and specific component, respectively. Exposure variables with larger PIP values have more importance for the overall impact of gallstone risk. The BKMR model estimates were established after 20,000 iterations. The BKMR analysis was performed using R “bkmr” package.

We also used restricted cubic splines (RCS) models to explore the potential nonlinear associations between OBS and the prevalence of gallstones. Then, mediation effect analysis was performed to demonstrate the role of serum lipid levels in the relation between OBS and gallstones by using R package “mediation.”

In addition, sensitivity analysis was conducted to further examine the robustness of the findings. Firstly, as described above, using survey-weighted multiple logistic regression, WQS regression and BKMR model, the association between OBS and gallstones was assessed with and without the adjustment for possible confounding effects, and the single or joint effects of OBS components on the gallstones were also studied. Secondly, subgroup analyses and interaction tests were carried out to investigate whether different subgroups showed consistent trends with the overall population, and explore the effects and interactions of the covariates including age, gender, race/ethnicity, education and comorbidities. Thirdly, as OBS contains dietary and lifestyle components, we evaluated the

impacts of dietary OBS and lifestyle OBS on gallstone disease respectively, in order to provide a more specific direction for gallstones prevention.

The $p < 0.05$ was considered statistically significant. All statistical analysis was performed by using R (version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

Study participants and baseline characteristics

In total, 15,560 participants were identified in NHANES 2017–2020. According to the inclusion criteria shown in Figure 1, 7,618 participants were finally included in this study, of whom 833 had gallstones. As listed in Table 1, there were significant differences between the gallstones group and non-gallstones group in terms of age, gender, race, education and smoking status. And individuals with gallstones had higher proportions with hypertension, diabetes, coronary heart disease and malignant disease. Serum cholesterol, triglyceride, high density lipoprotein-cholesterol and fasting blood glucose in gallstones group were more increased than those in non-gallstone group. Moreover, the metabolic risk index, triglyceride-glucose (TyG) values, were also significantly higher in gallstones group compared with non-gallstone group. From dietary data, individuals with gallstones had higher DII scores, which serves as a comprehensive index for dietary inflammation. Similarly, OBS in gallstone group was significantly lower than that in non-gallstone group (19.68 ± 6.61 vs. 20.48 ± 6.28 , $p = 0.029$).

Association of OBS with gallstones

In logistics regression analysis, participants were grouped according to quantiles of OBS (Q1: 0–25%; Q2: 25–50%; Q3: 50–75%; Q4: 75–100%). Table 2 shows the association between total OBS and gallstones. As compared with the lowest quartile (Q1), the unadjusted model showed that higher OBS in Q2 and Q4 group were associated with lower gallstones risks. After adjusting for sociodemographic covariates and comorbidities in Model 2, Model 3 and Model 4, the Q2 and Q4 group of total OBS maintained a significant association with lower gallstones risks.

As OBS contains dietary and lifestyle components, we studied the association between dietary OBS, lifestyle OBS and gallstone risks, respectively, (Table 2). The unadjusted model showed that dietary OBS in Q2 and Q3 group and lifestyle OBS in Q2, Q3 and Q4 group were associated with lower gallstones risks. And after adjusting for sociodemographic covariates and comorbidities, dietary and lifestyle OBS both in Q2 group remained significantly associated with lower risk of gallstones.

Then we analyzed the association between each components in OBS and gallstones risks, respectively. As shown in Figure 2, there were significant correlation between most components and gallstone risks, while after adjusting for sociodemographic covariates, niacin (Q2), total folate (Q3), magnesium (Q2), physical activity (Q3), BMI (Q2, Q3, Q4), alcohol intake (Q4) remained associated with decreased risk of gallstones.

TABLE 1 Baseline characteristics of included participants.

Characteristics	Overall	Gallstones	No gallstones	P-value
Unweighted number	7,618	833	6,785	
Weighted number	237842359.48	25906309.27	211936050.22	
Age, mean (SD), years	48.62 (17.45)	58.07 (15.80)	47.46 (17.29)	<0.001
Gender, %				<0.001
Male	48.6	27.6	51.2	
Female	51.4	72.4	48.8	
Race/ethnicity, %				0.002
Hispanic	16.0	15.7	16.0	
Non-Hispanic White	62.4	66.8	61.9	
Non-Hispanic Black	11.6	7.9	12.0	
Non-Hispanic Asian	5.9	2.9	6.3	
Other	4.1	6.7	3.8	
Education, %				0.010
< High school	10.3	10.4	10.3	
High school	27.6	32.5	27.0	
> High school	62.0	57.1	62.7	
Smoking, %	42.6	47.1	42.0	0.026
Hypertension, %	42.7	62.0	40.3	<0.001
Diabetes, %	15.0	25.5	13.7	<0.001
Coronary heart disease, %	5.6	9.6	5.1	<0.001
Malignant disease, %	11.3	18.5	10.4	<0.001
BMI, mean (SD), kg/m ²	29.75 (7.18)	33.21 (8.56)	29.33 (6.88)	<0.001
TC, mean (SD), mmol/L	4.87 (1.05)	4.85 (1.04)	4.87 (1.05)	0.782
TG, mean (SD), mmol/L	1.60 (1.13)	1.72 (1.01)	1.59 (1.14)	0.024
LDL-C, mean (SD), mmol/L	2.81 (0.94)	2.79 (0.96)	2.82 (0.93)	0.636
HDL-C, mean (SD), mmol/L	1.40 (0.46)	1.36 (0.44)	1.41 (0.46)	0.069
FBG, mean (SD), mg/dl	108.99 (34.76)	115.13 (35.68)	108.23 (34.57)	<0.001
TyG, mean (SD)	8.73 (0.70)	8.90 (0.64)	8.71 (0.71)	<0.001
DII, mean (SD)	1.15 (1.70)	1.42 (1.69)	1.12 (1.70)	0.001
Total OBS, mean (SD)	20.39 (6.32)	19.68 (6.61)	20.48 (6.28)	0.029

BMI, body mass index; TC, cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; FBG, fasting plasma glucose; TyG, triglyceride-glucose index, $TyG = \ln(TG \text{ (mg/dl)} * FBG \text{ (mg/dl)} / 2)$; DII, dietary inflammatory index; OBS, oxidative balance score. Data were weighted estimate. Continuous data are presented as mean (SD). Categorical data are presented as weighted percentage (%).

Furthermore, restricted cubic spline curves (Figure 3A) visualized the non-linear relationship between the OBS and gallstones (overall $p = 0.0003$, nonlinear $p = 0.03$). Under the premise of the total OBS below 19.92, a lower OBS was associated with increased risk of gallstone disease, whereas gallstone risk remained stable when the OBS exceeded 19.92.

Sub-analysis in the association of OBS with gallstones

Subgroup analyses were performed to examine whether the relationship between OBS and gallstones was influenced by covariables. As illustrated in Figure 4, after controlling for selected confounding factors, increased total OBS exhibited a significant

association with a higher risk of gallstones in participants who were under 60 years old, Hispanic, educated below high school, non-smokers, had hypertension or malignancy.

The interaction between malignancy and the relationship between OBS and gallstone was significant (P for interaction = 0.008). Among the other subgroups, there were no significant interactions between OBS and gallstone incidence (P for interaction >0.05).

WQS and BKMR analysis on the relation of overall OBS components and gallstones

WQS regression analysis indicated a negative association between 20 OBS components and gallstones risk (OR = 2.21, 95% CI 1.84–2.66, $p < 0.001$). Figure 3B showed the estimated weights of each OBS

TABLE 2 Logistics regression analysis of the association between OBS and gallstones risks.

	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
OBS	0.98 (0.96–1.00)	0.030	0.99 (0.97–1.00)	0.12	0.99 (0.97–1.01)	0.2	0.99 (0.97–1.01)	0.2
Q1 (3.0–13.9)	–	–	–	–	–	–	–	–
Q2 (14.0–19.9)	0.71 (0.55–0.92)	0.012	0.72 (0.56–0.91)	0.009	0.73 (0.57–0.94)	0.019	0.72 (0.56–0.94)	0.018
Q3 (20.0–24.9)	0.78 (0.60–1.02)	0.065	0.79 (0.60–1.05)	0.10	0.83 (0.63–1.09)	0.2	0.82 (0.62–1.09)	0.2
Q4 (25.0–36.0)	0.65 (0.49–0.85)	0.003	0.69 (0.52–0.92)	0.015	0.72 (0.55–0.96)	0.026	0.72 (0.55–0.95)	0.023
Dietary OBS	0.99 (0.97–1.01)	0.200	0.99 (0.97–1.01)	0.4	0.99 (0.97–1.01)	0.4	0.99 (0.97–1.01)	0.4
Q1 (2.0–9.9)	–	–	–	–	–	–	–	–
Q2 (10.0–14.9)	0.77 (0.62–0.96)	0.023	0.72 (0.54–0.96)	0.030	0.73 (0.54–0.99)	0.045	0.73 (0.53–1.00)	0.052
Q3 (15.0–19.9)	0.78 (0.59–1.02)	0.066	0.78 (0.57–1.07)	0.11	0.80 (0.57–1.11)	0.15	0.80 (0.56–1.13)	0.200
Q4 (20.0–29.0)	0.87 (0.63–1.20)	0.400	0.93 (0.65–1.35)	0.700	0.96 (0.65–1.40)	0.800	0.95 (0.64–1.42)	0.800
Lifestyle OBS	0.87 (0.81–0.93)	<0.001	0.89 (0.80–0.99)	0.041	0.91 (0.81–1.02)	0.084	0.91 (0.81–1.03)	0.11
Q1 (0–2.9)	–	–	–	–	–	–	–	–
Q2 (3.0–3.9)	0.66 (0.49–0.88)	0.007	0.66 (0.47–0.92)	0.021	0.69 (0.48–0.99)	0.045	0.69 (0.47–1.02)	0.061
Q3 (4.0–5.9)	0.72 (0.51–1.00)	0.053	0.81 (0.53–1.25)	0.300	0.86 (0.52–1.41)	0.500	0.87 (0.52–1.46)	0.500
Q4 (6.0–8.0)	0.45 (0.26–0.79)	0.007	0.56 (0.28–1.13)	0.100	0.61 (0.29–1.31)	0.200	0.62 (0.28–1.41)	0.200

OR, odds ratio; CI, confidence interval; OBS, oxidative balance score. Model 1 had no covariate-adjusted. Model 2 adjusted age, gender, race, educational level. Model 3 adjusted age, gender, race, educational level, hypertension, diabetes, coronary heart disease, malignancy. Values are weighted OR (95% CI).

components for the WQS model, in which the top three highest weighted components in the WQS model were BMI (46.1%), vitamin E (30.5%), and carotene (13.9%).

Through correlation analysis, there were several significant correlations among 20 components in OBS, as shown in Figure 3C. We further applied the BKMR model to analyze the joint effect of OBS components on the risk of gallstones, which indicated a positive association between total OBS and gallstones (Figure 3D). Compared to all OBS components at the 50th percentile, the risk of gallstones significantly increased when OBS components were at the 55th percentile or above, and significantly decreased when all OBS components were at the 45th percentile or lower. The top three highest PIP values generated from the BKMR model were BMI (1.0), magnesium (0.0246), vitamin B6 (0.0178). Consistently, the estimated univariate exposure-response function of each component was demonstrated in Supplementary Figure 2, BMI was positively correlated with gallstone risk when the other components were fixed at the median.

Mediation analysis of serum lipid on the association between OBS and gallstones

We further evaluated whether serum lipid levels mediate the association between OBS and gallstones. As shown in Figure 5, the mediating effect of TG and HDL on the association was 3.3% and 19.55%, respectively, and there were no significant mediating effects of serum TC and LDL. And moreover, TG (OR = 1.09, 95% CI 1.01–1.18, $p = 0.022$) and HDL (OR = 0.80, 95% CI 0.62–1.03, $p = 0.077$) were correlated with gallstone risks. Serum TG levels were negatively associated with OBS, which were, respectively, 1.60 (1.08), 1.70 (1.23), 1.58 (1.13), 1.53 (1.06) in Q1 to Q4 group of total OBS ($p = 0.002$).

Serum HDL levels were positively associated with OBS, which were, respectively, 1.36 (0.48), 1.38 (0.46), 1.41 (0.46), 1.44 (0.44) in Q1 to Q4 group of total OBS ($p = 0.008$).

Discussion

This cross-sectional study revealed a significant and non-linear relationship between OBS and gallstones risk in US general population. Higher dietary and lifestyle OBS, indicating increased antioxidant levels, was associated with lower gallstones risk. BMI, vitamin E, vitamin B6, magnesium and carotene were identified as having relatively important role in WQS and BKMR model. Serum TG and HDL levels were further identified as partially mediating the association between OBS and gallstones.

OBS represents an individual's oxidative stress status and has been reported to have associated with metabolic diseases (11, 28, 29) or inflammatory condition (12, 30). Until now, there has no study about OBS and gallstone disease. From the perspective of oxidative stress, there were some evidence about the role of oxidative stress in pathogenesis of gallstones. Metagenomic sequencing of bile from gallstone patients showed significantly enriched pathways related to glycerophospholipid and glutathione metabolism, which are involved in inflammation and oxidative stress responses (31). The oxidative stress marker 8-OH-dG, was found to significantly increased at plasma and DNA level in patients with cholelithiasis (32). Kuba et al. (33) reported that a microsomal enzyme, Elov16, can regulate fatty acid metabolism and hepatic oxidative stress, leading to increased formation of cholesterol crystals. Additionally, it was proved that oxidized bilirubin free radical existed in the gallstones using electron paramagnetic resonance technique, which promoted stone nucleation and deposition (7). These observations suggested that oxidative stress

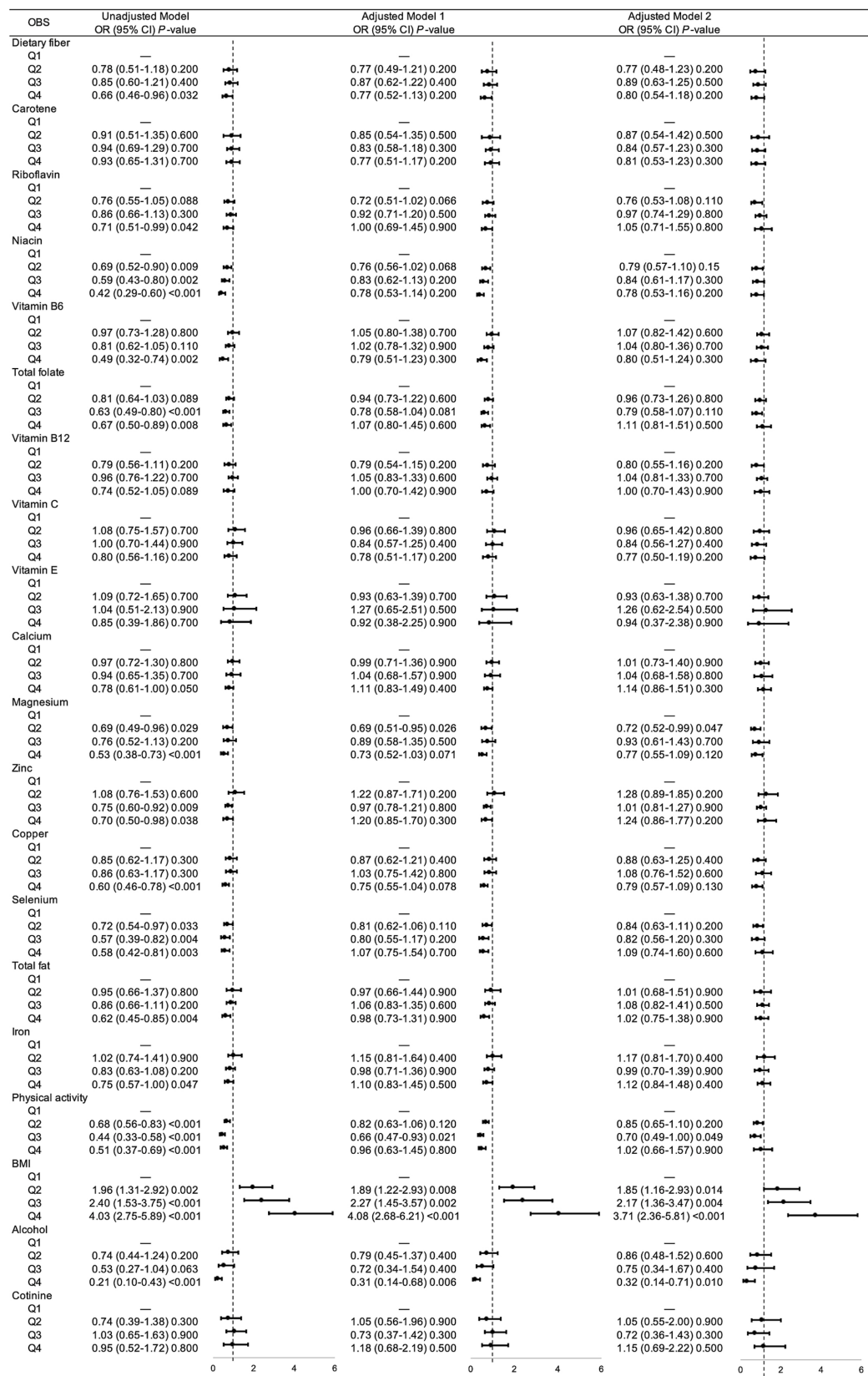


FIGURE 2 Unadjusted and adjusted associations between 20 OBS components and gallstones. Adjusted model = multivariable logistic regression model. Adjusted model 1 was multivariable logistic regression model adjusted age, gender, race, educational level. Adjusted model 2 was multivariable logistic regression model adjusted age, gender, race, educational level, hypertension, diabetes, coronary heart disease, malignancy. OR, odds ratio; CI, confidence interval; OBS, oxidative balance score; BMI, body mass index.

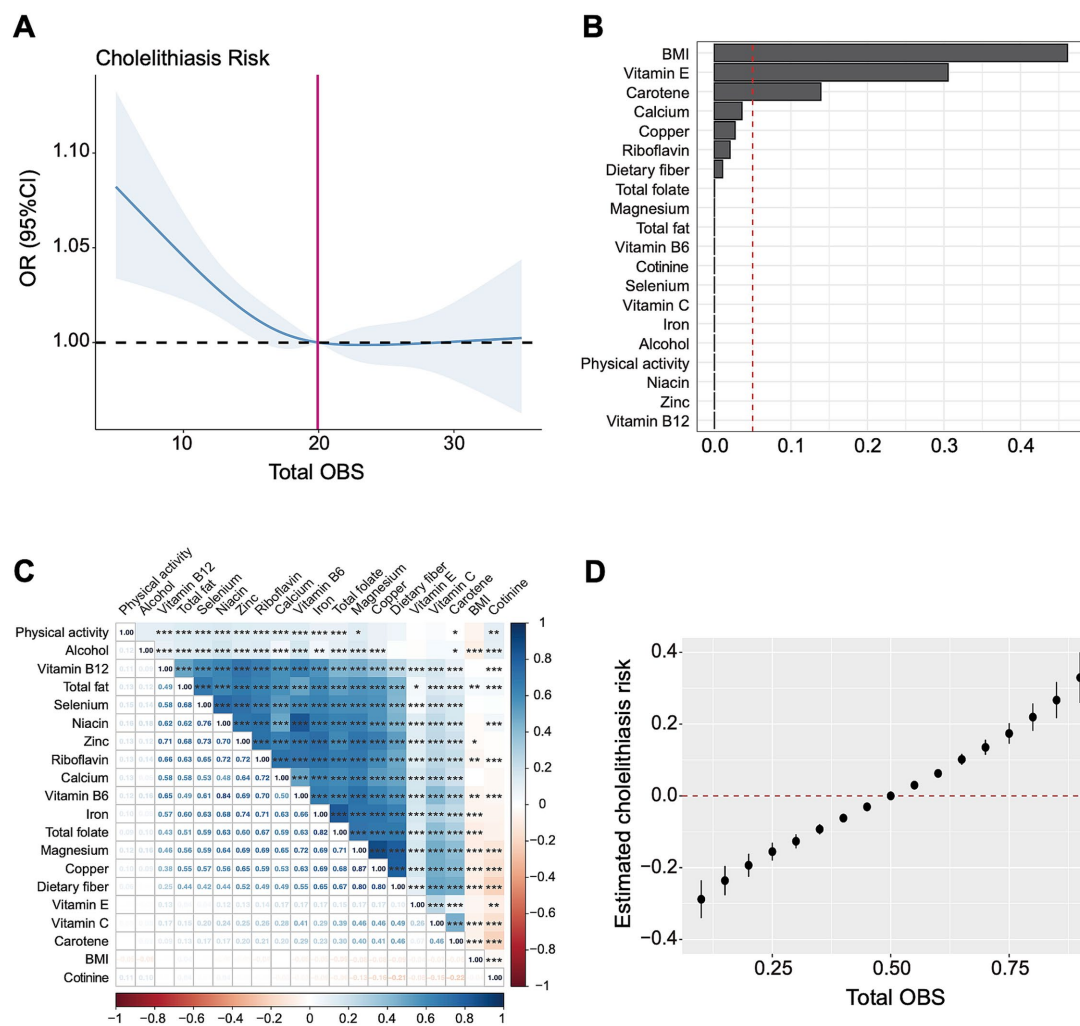


FIGURE 3 The association between OBS and gallstones based on RCS, WQS, and BKMR analysis. **(A)** Restricted cubic spline analysis revealed the non-linear relationship between OBS and gallstones. **(B)** The WQS model showed estimated weighted values of 20 OBS components for gallstones risk. **(C)** Matrix heatmap of correlations among 20 components in OBS. **(D)** The BKMR model showed the joint effect (95% CI) of OBS components on gallstones when all components were at particular percentiles compared with all components at their 50th percentile. The BKMR model was adjusted for age, gender, race/ethnicity and educational level. OR, odds ratio; CI, confidence interval; OBS, oxidative balance score; BMI, body mass index.

is closely related to the development of gallstones, which were consistent with our findings that the index of anti-oxidant capacity, OBS, was strongly associated with gallstones.

Specifically, OBS was derived from multiple dietary and lifestyle components. Our results showed dietary OBS and lifestyle OBS were both associated with gallstones risk. A Iranian case-control study demonstrated that higher dietary total antioxidant capacity had lower risk for gallstone disease (34), which is consistent with our results. Previous studies have proved several dietary nutrients exert anti-oxidative functions and protective effect on gallstone disease. Vitamin E, as an antioxidant, might suppress the gallstone formation. A cross-sectional study from Germany revealed that low proportions of gallstone disease were observed in the top tertile of plasma α -tocopherol/cholesterol ratio group (35). The reduction of oxidative stress after vitamin E supplementation may improve lipid metabolism via gene expression regulation, involving in the cholesterol synthesis pathway, lipid transport, lipogenesis, and mitochondrial biogenesis (36, 37). B vitamins, especially vitamin B6, have been identified in

relation to hypercholesterolemia or calculus of kidney (38), which partially supports our findings. Previous studies and our results both found magnesium intake had negative association with gallstones risk (39, 40). Magnesium may alter biliary cholesterol saturation and enhance gallbladder emptying, and lack of magnesium has been found to increase levels of triglycerides and decreasing levels of HDL-C in the bloodstream simultaneously, which can explain our serum lipid changes (39, 41). In addition, different dietary habits have been proved to affect biliary microbial composition and gallstone development (42). On the other hand, in our study, obesity is the most significant risk factor associated with gallstones. Obesity is a current health problem globally and is a recognized risk factor for the development of metabolic comorbidities, and normal BMI can promote the maintenance of a proper nutritional status (43). The abnormalities of adipocyte function and adipocytokines contributed to the local and systemic inflammation responses and increased oxidative stress in the context of obesity (44). Mechanistically, lipid metabolism can be regulated by inflammatory pathways, oxidative stress or gut

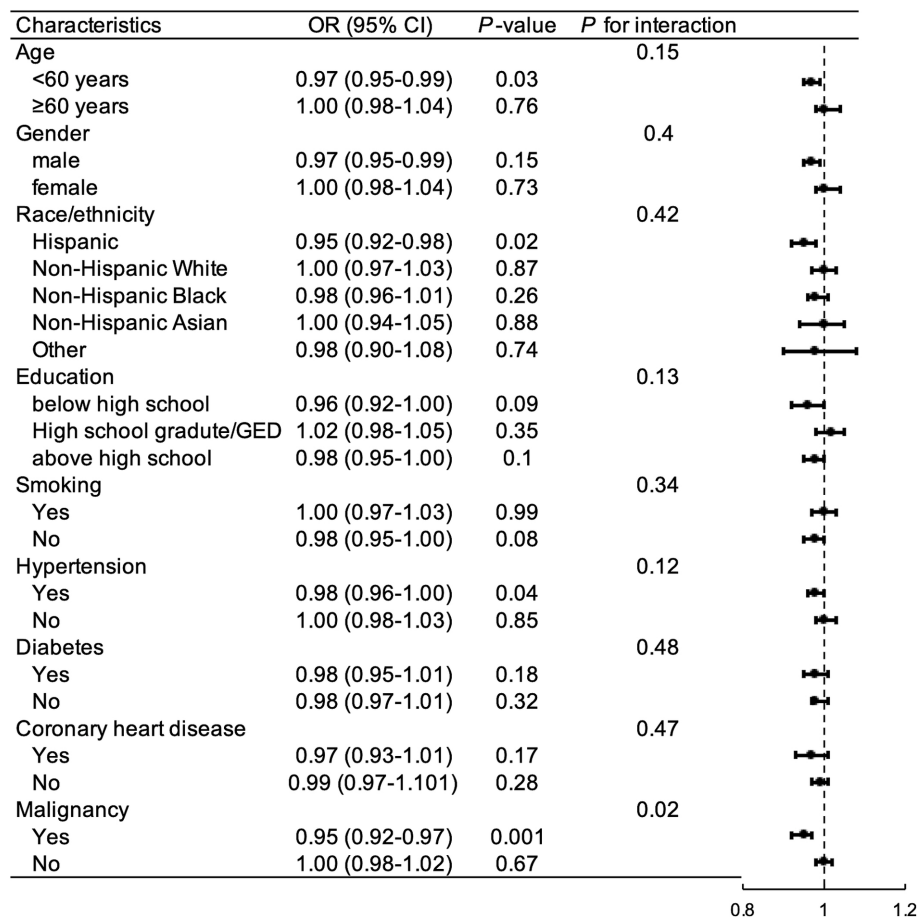


FIGURE 4 Subgroup and interaction analysis to assess the association between OBS and gallstones. OR, odds ratio; CI, confidence interval; GED, general educational development; OBS, oxidative balance score.

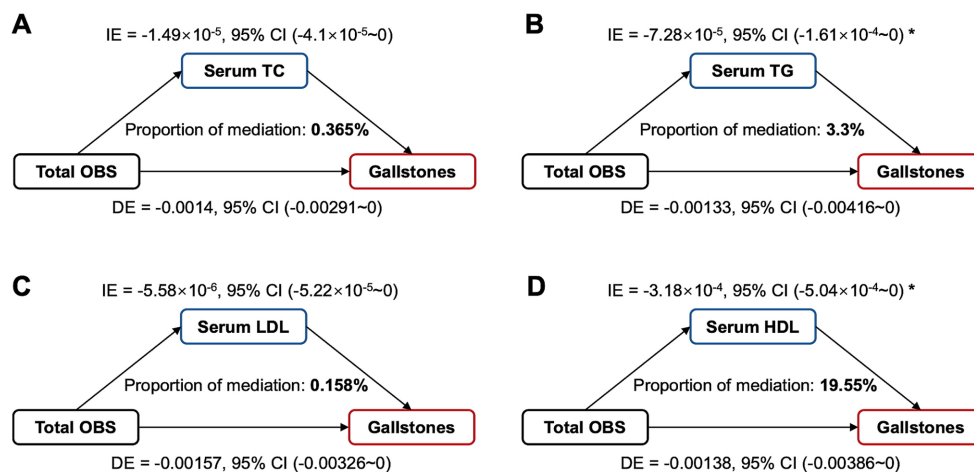


FIGURE 5 Estimated proportion of the association between total OBS and gallstones mediated by serum lipid levels. (A) TC, cholesterol; (B) TG, triglyceride; (C) LDL, low-density lipoprotein cholesterol; (D) HDL, high-density lipoprotein cholesterol; Mediation analysis adjusted age, gender, race, educational level, hypertension, diabetes, coronary heart disease. OBS, oxidative balance score; IE, indirect effect; DE, direct effect; Proportion of mediation = $IE / (DE + IE)$; * $p < 0.05$.

dysbiosis, which are always accompanied by obesity (45, 46). Multiple proteins in bile samples, regulating the inflammatory and metabolic processes, were proved to have differential expression between the obese and non-obese individuals (47). Increased cholesterol supersaturation and nucleating factors in bile promote the formation of gallstones, especially cholesterol stones. Moreover, obesity also causes abnormalities in gastrointestinal hormones secretion. For example, ghrelin, mainly produced by the gastric fundus, has been generally regarded as a key regulator on obesity (48). Previous studies revealed that ghrelin might had a potential role on glucose regulation and was associated with gallstone disease (48, 49).

The subgroup analysis showed differences in the association between OBS and gallstones across population characteristics. Individuals aged <60 years appeared to be more sensitive to OBS on gallstone than older participants (≥ 60 years). Young population tend to have unhealthy dietary and lifestyle habits compare to the elderly, so OBS increase may be particularly beneficial to these young participants. And the elderly are more likely to have metabolic disorders, making it difficult to increase antioxidant capacity simply through improving exogenous diet and lifestyle. Our results also indicated that Hispanic and individuals with lower education level were more susceptible to the effects of OBS on gallstones. Epidemiological studies have shown gallstones affected up to 30% of Hispanic populations in Central and South America, for which genetic factors can account predominantly (50). In addition, gallstone risks in participants with metabolic or malignant comorbidities are more prone to be influenced by OBS. Previous studies showed that gallstone disease was significantly related with cardiometabolic risks (28), metabolic syndrome (OR 1.31, $p = 0.02$) (51) and malignancy (OR 1.3, $p < 0.001$) (52). Nutrients metabolism can affected cholesterol metabolism and cardiometabolic disease risks by oxidative stress related pathway (53). These might partially explain why gallstones risk in patients with metabolic diseases is relatively significantly affected by OBS compared with those without metabolic comorbidities.

Furthermore, serum TG and HDL partially mediated the association between OBS and gallstones in our study, which suggested that serum TG and HDL levels might be influenced by oxidative stress and can be regarded as key indicators in clinical monitoring of gallstones. As for HDL, the interaction of HDL and oxidative stress is always bi-directional and multifactorial. HDL has been demonstrated to possess anti-oxidant activity and can mediate the inhibition of LDL oxidation, and in return, increased oxidative stress may affect the structural state of HDL-C (54–57). Furlong et al. (58) reported that HDL-related enzyme paraoxonase-3 knockout mice exhibited susceptible to gallstone formation and metabolic dysfunction through regulation of oxidative stress and inflammatory response. Thus HDL may serve as a reflection of oxidative capacity or partially exert its antioxidant activity. And for TG, recent study revealed that chronic oxidative stress induces TG accumulation by regulating the expression of lipopolysaccharide-binding protein and lipid-redox homeostasis (59). Zhang et al. (60) reported that peroxisome proliferator-activated receptor (PPAR) α signaling pathway, involved in oxidative stress and inflammatory response, plays an important role in the synthesis of TG. The relationship between oxidative stress and lipid metabolism may partly explains the association between OBS and gallstones.

From this study, we hope the OBS can provide great practical value for gallstone assessment in clinical work. First, considering its convenience and cost-effectiveness, the OBS can be used as a

preliminary evaluation for gallstone risk in the healthy check-ups. From our results, it is recommended that consequent examinations (e.g., the abdominal ultrasound) should be arranged to screen for gallstones for the individuals with the OBS below 19.92 or lower. Besides, as for the patients with gallstones or high gallstones risks (e.g., low OBS, hyperlipidemia, etc.), the measurement of OBS can provide a more accurate strategy for improving or preventing the gallstones, including specific daily food adjustments, quantified exercise intensity and weight management regimen.

To our knowledge, this is the first study to comprehensively analyze the association between OBS and gallstones through multiple statistical models. We minimize confounding bias via adjustment for multiple covariates and subgroup and interaction analysis. Then we investigated the relationship between each component of OBS and gallstones risk to reflect the most critical factors in OBS. Moreover, mediation analysis in this study found that serum lipid may plays a mediating role between OBS and gallstones, which indicates the potential relation among lipid metabolism, oxidative stress and cholelithiasis and also provides theoretical evidence for clinical surveillance.

This study also has some limitations. Firstly, gallstone compositions were not available in the NHANES data, so the role of OBS in gallstones with different compositions is not clear. And there are also other potential confounding factors that have not been assessed in this study, for instance, patients with genetic predisposition, bariatric surgery-induced rapid weight loss, or hematological disorders, may predispose to gallstones. Secondly, despite thorough sensitivity analysis in this study, the selection bias still remains because of the exclusion of participants with missing data. Thirdly, recall bias was inevitable as comorbidities and OBS data were acquired from questionnaire. And the cross-sectional characteristics of this study cannot evaluate the causal relations between OBS and gallstones. Thus more prospective cohort studies are required to validate the role of OBS in gallstone disease.

In conclusion, increased oxidative balance, as evidenced by a higher OBS, are positively associated with reduction of gallstone risk. These findings highlight the previously unknown associations between dietary and lifestyle oxidative levels and gallstones in the general population. Surveillance for serum lipid or nutrients and early interventions targeting for antioxidant-rich diets or lifestyles may be helpful for gallstone prevention. Further prospective and experimental studies are warranted to confirm causal relationship and potential mechanisms.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: <https://www.cdc.gov/nchs/nhanes/>.

Ethics statement

The studies involving humans were approved by the Ethics Review Committee of the National Center for Health Statistics. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation

in this study was provided by the participants' legal guardians/next of kin.

Author contributions

MZ: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft. AY: Funding acquisition, Supervision, Writing – review & editing.

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References

- Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver*. (2012) 6:172–87. doi: 10.5009/gnl.2012.6.2.172
- Dahiya DS, Facciorusso A, Chandan S, Sohail AH, Gangwani MK, Franchellucci G, et al. Understanding evidence-based clinical practice guidelines for cholelithiasis 2021. *Hepatobiliary Surg Nutr*. (2024) 13:352–5. doi: 10.21037/hbsn-24-25
- Mulita F, Tchabashvili L, Bousis D, Kehagias D, Kaplanis C, Liolis E, et al. Gallstone ileus: a rare cause of small intestine obstruction. *Clin Case Rep*. (2021) 9:e04924. doi: 10.1002/ccr3.4924
- Lammert F, Gurusamy K, Ko CW, Miquel JF, Méndez-Sánchez N, Portincasa P, et al. Gallstones. *Nat Rev Dis Primers*. (2016) 2:16024. doi: 10.1038/nrdp.2016.24
- Kehagias I, Bellou A, Kehagias D, Markopoulos G, Amanatidis T, Alexandrou A, et al. Long-term (11 + years) efficacy of sleeve gastrectomy as a stand-alone bariatric procedure: a single-center retrospective observational study. *Langenbeck's Arch Surg*. (2022) 408:4. doi: 10.1007/s00423-022-02734-y
- Haal S, Guman MSS, Boerlage TCC, Acherman Y, de Brauw M, Bruin S, et al. Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery (UPGRADE): a multicentre, double-blind, randomised, placebo-controlled superiority trial. *Lancet. Gastroenterol Hepatol*. (2021) 160:S–67. doi: 10.1016/S0016-5085(21)00902-1
- Sanikidze T, Chikvaizde E. Role of the free radicals in mechanisms of gallstone formation: an EPR study. *Radiat Prot Dosim*. (2016) 172:317–24. doi: 10.1093/rpd/ncw237
- Arroyave-Ospina JC, Wu Z, Geng Y, Moshage H. Role of oxidative stress in the pathogenesis of non-alcoholic fatty liver disease: implications for prevention and therapy. *Antioxidants*. (2021) 10:174. doi: 10.3390/antiox10020174
- Goodman M, Bostick RM, Dash C, Flanders WD, Mandel JS. Hypothesis: oxidative stress score as a combined measure of pro-oxidant and antioxidant exposures. *Ann Epidemiol*. (2007) 17:394–9. doi: 10.1016/j.annepidem.2007.01.034
- Lakkur S, Bostick RM, Roblin D, Ndirangu M, Okosun I, Annor F, et al. Oxidative balance score and oxidative stress biomarkers in a study of whites, African Americans, and African immigrants. *Biomarkers*. (2014) 19:471–80. doi: 10.3109/1354750X.2014.937361
- Kong X, Gao X, Wang W. Oxidative balance score and associations with dyslipidemia and mortality among US adults: a mortality follow-up study of a cross-sectional cohort. *JPEN J Parenter Enteral Nutr*. (2024) 48:735–45. doi: 10.1002/jpen.2661

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2025.1539969/full#supplementary-material>

- Chen K, Li S, Xie Z, Liu Y, Li Y, Mai J, et al. Association between oxidative balance score, systemic inflammatory response index, and cardiovascular disease risk: a cross-sectional analysis based on NHANES 2007–2018 data. *Front Nutr*. (2024) 11:1374992. doi: 10.3389/fnut.2024.1374992
- Wen H, Li X, Chen J, Li Y, Yang N, Tan N. Association of oxidative balance score with chronic kidney disease: NHANES 1999–2018. *Front Endocrinol*. (2024) 15:1396465. doi: 10.3389/fendo.2024.1396465
- Li F, Chang Y, Wang Z, Wang Z, Zhao Q, Han X, et al. Antioxidant insights: investigating the protective role of oxidative balance in inflammatory bowel disease. *Front Endocrinol*. (2024) 15:1386142. doi: 10.3389/fendo.2024.1386142
- Gu H, Li B, Xiang L, Xu Z, Tang Y, Zhu Z, et al. Association between oxidative stress exposure and colorectal cancer risk in 98,395 participants: results from a prospective study. *Front Nutr*. (2023) 10:1284066. doi: 10.3389/fnut.2023.1284066
- Tan Z, Wu Y, Meng Y, Liu C, Deng B, Zhen J, et al. Trends in oxidative balance score and prevalence of metabolic dysfunction-associated Steatotic liver disease in the United States: National Health and nutrition examination Survey 2001 to 2018. *Nutrients*. (2023) 15:4931. doi: 10.3390/nu15234931
- Zhang W, Peng S-F, Chen L, Chen H-M, Cheng X-E, Tang Y-H. Association between the oxidative balance score and telomere length from the National Health and nutrition examination Survey 1999–2002. *Oxidative Med Cell Longev*. (2022) 2022:1–11. doi: 10.1155/2022/1345071
- Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr*. (2014) 17:1689–96. doi: 10.1017/S1368980013002115
- Zhang C, Zhang Z, Li J, Deng L, Geng J, Jin K, et al. Association between dietary inflammatory index and serum klotho concentration among adults in the United States. *BMC Geriatr*. (2022) 22:528. doi: 10.1186/s12877-022-03228-8
- Ding X, Wang X, Wu J, Zhang M, Cui M. Triglyceride-glucose index and the incidence of atherosclerotic cardiovascular diseases: a meta-analysis of cohort studies. *Cardiovasc Diabetol*. (2021) 20:76. doi: 10.1186/s12933-021-01268-9
- Akinbami LJ, Chen T-C, Davy O. Prepandemic file: sample design, estimation, and analytic guidelines. *Vital Health Stat*. (2022) 1:190
- Muntner P, Hardy ST, Fine LJ, Jaeger BC, Wozniak G, Levitan EB, et al. Trends in blood pressure control among US adults with hypertension, 1999–2000 to 2017–2018. *JAMA*. (2020) 324:1190–200. doi: 10.1001/jama.2020.14545

23. Quartagno GM, Carpenter JR. Jomo: a flexible package for two-level joint modelling multiple imputation. *R J.* (2020) 11:28. doi: 10.32614/RJ-2019-028
24. Gennings C, Curtin P, Bello G, Wright R, Arora M, Austin C. Lagged WQS regression for mixtures with many components. *Environ Res.* (2020) 186:109529. doi: 10.1016/j.envres.2020.109529
25. Wu M, Liu M, Zhang Y, Wu J, Gao M, Huang F, et al. Serum HDL partially mediates the association between exposure to volatile organic compounds and kidney stones: a nationally representative cross-sectional study from NHANES. *Sci Total Environ.* (2024) 907:167915. doi: 10.1016/j.scitotenv.2023.167915
26. Ma J, Li P, Jiang Y, Yang X, Luo Y, Tao L, et al. The association between dietary nutrient intake and acceleration of aging: evidence from NHANES. *Nutrients.* (2024) 16:635. doi: 10.3390/nu16111635
27. Tang W, Zhan W, Wei M, Chen Q. Associations between different dietary vitamins and the risk of obesity in children and adolescents: a machine learning approach. *Front Endocrinol.* (2021) 12:816975. doi: 10.3389/fendo.2021.816975
28. Lai Q, Ye L, Luo J, Zhang C, Wu Q, Shao Y. The cross-sectional correlation between the oxidative balance score and cardiometabolic risk factors and its potential correlation with longitudinal mortality in patients with cardiometabolic risk factors. *BMC Public Health.* (2024) 24:1452. doi: 10.1186/s12889-024-18967-z
29. Lu Y, Wang M, Bao J, Chen D, Jiang H. Association between oxidative balance score and metabolic syndrome and its components in US adults: a cross-sectional study from NHANES 2011–2018. *Front Nutr.* (2024) 11:1375060. doi: 10.3389/fnut.2024.1375060
30. Nanri H, Hara M, Nishida Y, Shimano C, Higaki Y, Tanaka K. Association between oxidative balance score and inflammatory markers in middle-aged and older Japanese people. *Am J Hum Biol.* (2024) 36:e24059. doi: 10.1002/ajhb.24059
31. Shen H, Ye F, Xie L, Yang J, Li Z, Xu P, et al. Metagenomic sequencing of bile from gallstone patients to identify different microbial community patterns and novel biliary bacteria. *Sci Rep.* (2015) 5:17450. doi: 10.1038/srep17450
32. Singh N, Kazim SN, Sultana R, Tiwari D, Borkotoky R, Kakati S, et al. Oxidative stress and deregulations in base excision repair pathway as contributors to gallbladder anomalies and carcinoma - a study involving north-east Indian population. *Free Radic Res.* (2019) 53:473–85. doi: 10.1080/10715762.2019.1606423
33. Kuba M, Matsuzaka T, Matsumori R, Saito R, Kaga N, Taka H, et al. Absence of Elov6 attenuates steatohepatitis but promotes gallstone formation in a lithogenic diet-fed Ldlr(−/−) mouse model. *Sci Rep.* (2015) 5:17604. doi: 10.1038/srep17604
34. Saadati S, Salehi-sahlabadi A, Hosseini-Oskouie F, Aghamohammadi V, Ramezani M, Askari B, et al. Dietary Total antioxidant capacity and risk of gall stone: a case-control study. *Int J Prev Med.* (2021) 12:178. doi: 10.4103/ijpvm.IJPVM_245_20
35. Waniek S, di Giuseppe R, Esatbeyoglu T, Ratjen I, Enderle J, Jacobs G, et al. Association of Circulating Vitamin E (α - and γ -tocopherol) levels with gallstone disease. *Nutrients.* (2018) 10:133. doi: 10.3390/nu10020133
36. Landrier J-F, Gouranton E, Reboul E, Cardinault N, el Yazidi C, Malezet-Desmouilins C, et al. Vitamin E decreases endogenous cholesterol synthesis and apo-AI-mediated cholesterol secretion in Caco-2 cells. *J Nutr Biochem.* (2010) 21:1207–13. doi: 10.1016/j.jnutbio.2009.10.008
37. Alcalá M, Sánchez-Vera I, Sevillano J, Herrero L, Serra D, Ramos MP, et al. Vitamin E reduces adipose tissue fibrosis, inflammation, and oxidative stress and improves metabolic profile in obesity. *Obesity (Silver Spring).* (2015) 23:1598–606. doi: 10.1002/oby.21135
38. Wang L, Li X, Montazeri A, MacFarlane AJ, Momoli F, Duthie S, et al. Phenome-wide association study of genetically predicted B vitamins and homocysteine biomarkers with multiple health and disease outcomes: analysis of the UK biobank. *Am J Clin Nutr.* (2023) 117:564–75. doi: 10.1016/j.ajcnut.2023.01.005
39. du W, Yan C, Wang Y, Song C, Li Y, Tian Z, et al. Association between dietary magnesium intake and gallstones: the mediating role of atherogenic index of plasma. *Lipids Health Dis.* (2024) 23:82. doi: 10.1186/s12944-024-02074-4
40. Tsai C-J, Leitzmann MF, Willett WC, Giovannucci EL. Long-term effect of magnesium consumption on the risk of symptomatic gallstone disease among men. *Am J Gastroenterol.* (2008) 103:375–82. doi: 10.1111/j.1572-0241.2007.01696.x
41. Ko CW. Magnesium: does a mineral prevent gallstones? *Am J Gastroenterol.* (2008) 103:383–5. doi: 10.1111/j.1572-0241.2007.01690.x
42. Gutiérrez-Díaz I, Molinero N, Cabrera A, Rodríguez JI, Margolles A, Delgado S, et al. Diet: cause or consequence of the microbial profile of Cholelithiasis disease? *Nutrients.* (2018) 10:1307. doi: 10.3390/nu10091307
43. Mulita F, Lampropoulos C, Kehagias D, Verras GI, Tchabashvili L, Kaplanis C, et al. Long-term nutritional deficiencies following sleeve gastrectomy: a 6-year single-Centre retrospective study. *Prz Menopauzalny.* (2021) 20:170–6. doi: 10.5114/pm.2021.110954
44. Codoñer-Franch P, Valls-Bellés V, Arilla-Codoñer A, Alonso-Iglesias E. Oxidant mechanisms in childhood obesity: the link between inflammation and oxidative stress. *Transl Res.* (2011) 158:369–84. doi: 10.1016/j.trsl.2011.08.004
45. Wang HH, Portincasa P, Liu M, Wang DQH. Effects of biliary phospholipids on cholesterol crystallization and growth in gallstone formation. *Adv Ther.* (2023) 40:743–68. doi: 10.1007/s12325-022-02407-8
46. Cortés VA, Barrera F, Nervi F. Pathophysiological connections between gallstone disease, insulin resistance, and obesity. *Obes Rev.* (2020) 21:e12983. doi: 10.1111/obr.12983
47. Chen M-Z, Xie P, Wu X-C, Tan ZH, Qian H, Ma ZH, et al. Comparison of biliary protein spectrum in gallstone patients with obesity and those with normal body weight. *Hepatobiliary Pancreat Dis Int.* (2024) 23:385–92. doi: 10.1016/j.hbpd.2023.11.007
48. Kehagias D, Georgopoulos N, Habeos I, Lampropoulos C, Mulita F, Kehagias I. The role of the gastric fundus in glycemic control. *Hormones.* (2023) 22:151–63. doi: 10.1007/s42000-023-00429-7
49. Villarreal D, Pradhan G, Zhou Y, Xue B, Sun Y. Diverse and complementary effects of ghrelin and Obestatin. *Biomol Ther.* (2022) 12:517. doi: 10.3390/biom12040517
50. Krawczyk M, Miquel JF, Stokes CS, Zuniga S, Hampe J, Mittal B, et al. Genetics of biliary lithiasis from an ethnic perspective. *Clin Res Hepatol Gastroenterol.* (2013) 37:119–25. doi: 10.1016/j.clinre.2012.09.002
51. Hung M-C, Chen C-F, Tsou M-T, Lin H-H, Hwang L-C, Hsu C-P. Relationship between gallstone disease and Cardiometabolic risk factors in elderly people with non-alcoholic fatty liver disease. *Diabetes Metab Syndr Obes.* (2020) 13:3579–85. doi: 10.2147/DMSO.S266947
52. Higashizono K, Nakatani E, Hawke P, Fujimoto S, Oba N. Risk factors for gallstone disease onset in Japan: findings from the Shizuoka study, a population-based cohort study. *PLoS One.* (2022) 17:e0274659. doi: 10.1371/journal.pone.0274659
53. Butcko AJ, Putman AK, Mottillo EP. The intersection of genetic factors, aberrant nutrient metabolism and oxidative stress in the progression of Cardiometabolic disease. *Antioxidants.* (2024) 13:87. doi: 10.3390/antiox13010087
54. Bandeali S, Farmer J. High-density lipoprotein and atherosclerosis: the role of antioxidant activity. *Curr Atheroscler Rep.* (2012) 14:101–7. doi: 10.1007/s11883-012-0235-2
55. Karabacak M, Uysal BA, Turkdogan AK. Alteration in serum oxidative stress balance in patients with different circulating high-density lipoprotein cholesterol levels. *Rev Port Cardiol.* (2022) 41:833–9. doi: 10.1016/j.repc.2021.06.022
56. Denimal D. Antioxidant and anti-inflammatory functions of high-density lipoprotein in type 1 and type 2 diabetes. *Antioxidants.* (2023) 13:57. doi: 10.3390/antiox13050616
57. Zheng J, Hong BV, Agus JK, Tang X, Klebaner NR, Chen S, et al. Lutein and zeaxanthin enhance, whereas oxidation, Fructosylation, and low pH damage high-density lipoprotein biological functionality. *Antioxidants.* (2024) 13:616. doi: 10.3390/antiox13050616
58. Furlong CE, Marsillach J, Jarvik GP, Costa LG. Paraoxonases-1, -2 and -3: what are their functions? *Chem Biol Interact.* (2016) 259:51–62. doi: 10.1016/j.cbi.2016.05.036
59. Zhang Q, Shen X, Yuan X, Huang J, Zhu Y, Zhu T, et al. Lipopolysaccharide binding protein resists hepatic oxidative stress by regulating lipid droplet homeostasis. *Nat Commun.* (2024) 15:3213. doi: 10.1038/s41467-024-47553-5
60. Zhang W, Sun Y, Liu W, Dong J, Chen J. SIRT1 mediates the role of RNA-binding protein KQ1 5 in the synthesis of triglycerides in non-alcoholic fatty liver disease mice via the PPAR α /fox O1 signaling pathway. *Int J Mol Med.* (2019) 43:1271–80. doi: 10.3892/ijmm.2019.4059