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The association between dietary acid load and risk of gallstone: a case-control study

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Abstract

Background and aim While dietary factors are known to influence gallstone disease (GD), the specific role of dietary acid load (DAL) remains unclear. This study aimed to explore the relationship between DAL and GD risk using a case-control design.

Methods The study included 189 adults with newly diagnosed GD and 342 controls. Anthropometric data were collected, and DAL was calculated using the potential renal acid load (PRAL) and net endogenous acid production (NEAP) indices. Multivariable logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI), adjusting for confounders.

Results Participants in the higher tertiles of both PRAL and NEAP scores showed notably elevated grain consumption and reduced intake of vegetables and fruits ($P < 0.001$). Conversely, an inverse relationship was observed between NEAP scores and intake of legumes, nuts, and seeds ($P = 0.044$). After adjustment for confounders, the risk of GD was 25% higher in the second tertile (OR: 1.25; 95% CI: 0.9, 2.3) and 51% higher in the third tertile (OR: 1.51; 95% CI: 0.54, 1.36) of PRAL compared to the first tertile (*P trend* = *0.023*). A similar trend was seen for NEAP, with a 19% increased risk in the second tertile (OR: 1.19; 95% CI: 0.78, 1.84) and 48% in the third tertile (OR: 1.48; 95% CI: 0.9, 2.3) relative to the first tertile.

Conclusions Higher dietary acid load is associated with an increased risk of GD. Further studies are needed to confirm these findings and elucidate underlying mechanisms.

Keywords Gallstone, Dietary acid load, PRAL, NEAP

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Introduction

Gallstone Disease (GD) is one of the most prevalent and the second most costly gastrointestinal disorders, imposing a significant financial burden on healthcare systems worldwide [1]. Cholesterol stones account for 80–90% of all gallstones, while mixed and pigment stones are less common [2]. The prevalence of GD is approximately 15% in the U.S., 9–21% in Europe, and 10% in Asian populations, with increasing trends globally [3–5]. In Iran, GD is less common among middle-aged adults but increases significantly with age, affecting 12.5% of men and 24.6% of women over the age of 50 [6]. Known predisposing factors for GD include female gender, pregnancy, obesity, sedentary lifestyle, dyslipidemia, type 2 diabetes, high cholesterol, high-carbohydrate diet, rapid weight loss, and family history [7].

The relationship between dietary patterns and GD has been extensively studied, with numerous reports highlighting the role of diet in the formation of gallstones [8, 9]. Recently, there has been growing attention on how specific dietary factors influence GD risk. As a preventable condition, GD is less common among individuals who maintain a healthy lifestyle. For example, maintaining a normal body weight and consuming unsaturated fats, fiber, vegetables, and fruits are known to have a protective effect against gallstones. In contrast, diets high in fast food, saturated fats, and refined sugars are associated with an increased risk of developing gallstones [8, 9].

Diet composition also plays a crucial role in influencing the body's acid-base balance by providing acid or base precursors. Protein-rich diets, such as those containing meat, cheese, and eggs, tend to increase acid production, while the intake of vegetables and fruits has an alkalizing effect [23]. Dietary acid load (DAL), as measured by indices like potential renal acid load (PRAL) and net endogenous acid production (NEAP), is associated with metabolic acidosis, inflammation, and tissue damage [10–13]. PRAL reflects the acid or base production capacity of food, considering factors like sulfur-containing minerals (e.g., potassium, calcium, and magnesium) and protein metabolism [14]. Both PRAL and NEAP are considered reliable measures of DAL due to their correlation with 24-hour net uric acid excretion (NAE), and higher PRAL values are linked to a more acidic diet and lower urine pH [15].

Additionally, previous studies have shown that DAL is positively associated with an increased risk of various conditions, including non-alcoholic fatty liver disease, inflammation, insulin resistance, and type 2 diabetes—all of which are closely related to GD or considered risk factors for it [16–19]. However, limited research has been conducted on the relationship between DAL and the risk of GD. Given this knowledge gap, the present study was designed as a case-control investigation to test the hypothesis that higher dietary acidity is associated with an increased risk of gallstones.

Methods and materials

Study design

The present case-control study was performed on the new cases of GD ($n = 189$) and healthy controls ($n = 342$). The study protocol was approved by the Ethics Committee of the Research Institute of Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences (IR.SBMU.RIGLD.REC.1396.159). Patients were recruited from the Research Institute of Gastrointestinal and Liver Diseases of Taleghani Hospital associated with Shahid Beheshti University of Medical Sciences in Tehran, Iran. Informed written consent was acquired from all participants.

Participants

Details of the selection of case and control subjects have been described elsewhere [20]. Briefly, the inclusion criteria for the study were: patients diagnosed with GD within the past month, aged 18 years or older, and willing to participate. The control group consisted of individuals without a history of GD, selected from patients referred to other departments of the hospital. Exclusion criteria included lactating or pregnant women, as well as individuals with a history of cancer, autoimmune diseases, inflammatory or infectious conditions, or other acute illnesses. The flowchart of study enrollment is displayed in Fig. 1.

Assuming that the minimum correlation coefficient between the two variables is 0.3 ($r = 0.3$), the difference of this correlation coefficient from zero is significant, if the probability is 95% and the power is 90%. On this basis and by considering the equation presented by Park et al. [21], a minimum sample size of 160 people was calculated for this study, and twice this number was considered for the control group. In order to anticipate attrition and to have greater accuracy and calculate the effect size, the present study was conducted on 531 sample populations.

Socio-demographic, anthropometrics and physical activity

Trained interviewers collected socio-demographic data including age, alcohol and tobacco use, and medical history. A digital scale (Soehnle, Berlin, Germany) with an accuracy of 100 g was used for weight measurement. Height without footwear was assessed using a portable non-elastic measuring device and rounded to the nearest 0.5 cm. Body mass index (BMI) was determined by dividing weight in kilograms by the square of height in meters. Physical activity was calculated based on metabolic equivalent hours per day (MET-h/day) using a classified questionnaire measuring the frequency and intensity of activity, from rest and sleep to vigorous activity [22, 23].

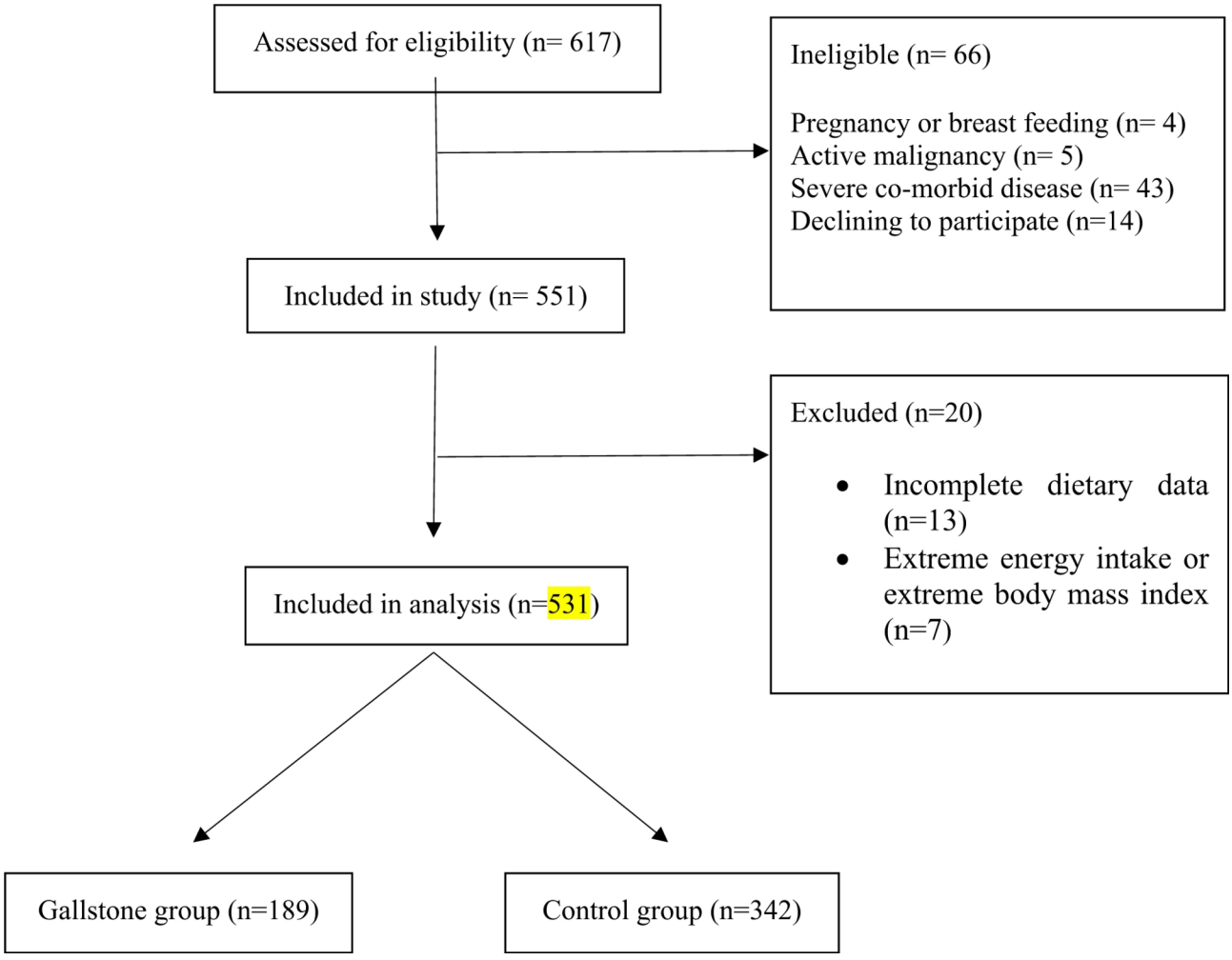

Fig. 1 Flow chart of study enrollment

Dietary intake assessment and dietary acid load calculation

Data on the dietary intake of cases (prior to GD diagnosis) and controls (prior to hospital admission), during the previous year, were collected using a food frequency questionnaire (FFQ) consisting of 168 items [24]. In face-to-face interviews, well-trained dietitians assessed the frequency of consumption (daily, weekly, or monthly) for each food item based on household measurements, and the values were subsequently converted to grams. The collected data were then analyzed using Nutritionist IV software.

The dietary acid load was calculated based on PRAL and NEAP scores, according to the subsequent formula:

PRAL (mEq/d) = 0.4888 × dietary protein (g /d) + 0.0366 × dietary phosphorus (mg/d) – 0.0205 × dietary potassium (mg/d) – 0.0125 × calcium (mg/d) – 0.0263 × magnesium (mg/d) [25].

NEAP (mEq/d) = 54.5 × protein intake (g/d) / potassium intake (mEq/d) – 10.2 [26].

Statistical analysis

Means ± standard deviation for continuous variables and number (percentages) for categorical variables across the tertiles of PRAL and NEAP were determined using the general linear model and the chi-square test, respectively, and P–value for the trend of GD risk was assessed. The association between the tertiles of PRAL and NEAP with the odds of GD was calculated using logistic regression with adjustment for potential confounders including age, sex, physical activity, energy intake, BMI, smoking, and alcohol consumption. *P* values less than 0.05 were deemed statistically significant. All statistical analyses were conducted using SPSS software version 19 (SPSS Inc., Chicago, Illinois).

Results

A detailed comparison of the primary characteristics between cases and controls has been described elsewhere [20]. The general characteristics of study subjects and their dietary intakes across the tertiles of PRAL and

Table 1 Baseline characteristics of study participants by tertile of dietary acid load

	PRAL (mEq/day)				NEAP (mEq/day)			
	Tertile 1 (*n* = 177)	**Tertile 2 (*n* = 177)**	**Tertile 3 (*n* = 177)**	***P* value**	**Tertile 1 (*n* = 177)**	**Tertile 2 (*n* = 177)**	**Tertile 3 (*n* = 177)**	***P* value**
Cases, n (%)	55 (29)	63 (33)	71 (38)	0.047	53 (28)	64 (34)	72 (38)	0.046
Men, n (%)	42 (24)	70 (40)	90 (51)	< 0.001	43 (24)	75 (43)	84 (47)	< 0.001
Age (y)	52.1 ± 12.4	54.1 ± 12.4	52.3 ± 14.8	0.287	52.6 ± 12.3	54.3 ± 12.8	51.8 ± 14.5	0.198
Alcohol drinker	2 (1)	5 (3)	6 (3.5)	0.359	2 (1)	6 (3.5)	5 (3)	0.356
Smoker, %	14 (8)	31 (17)	33 (19)	0.007	16 (9)	31 (18)	31 (18)	0.034
IPAQ level, %	125 (71)	42 (24)	10 (5)	0.001	124 (70)	44 (25)	9 (5)	0.001
1	125 (71)	50 (28)	2 (1)		124 (70)	49 (28)	3 (2)	
2	150 (85)	23 (13)	4 (2)		152 (85)	22 (13)	4 (2)	
3								
Weight, kg	73.6 ± 12.7	73.2 ± 12.1	72.9 ± 15.4	0.886	73.2 ± 12.8	74.3 ± 12.7	72.3 ± 14.9	0.388
Height, cm	163.5 ± 8.8	164.8 ± 8.6	165.8 ± 8.8	0.039	163.6 ± 9.3	165.5 ± 8.2	165.1 ± 8.7	0.100
BMI, kg/m^2	27.5 ± 4.1	26.9 ± 3.9	26.4 ± 4.9	0.060	27.3 ± 3.8	27.1 ± 4.4	26.4 ± 4.7	0.153

The results are described as mean ± standard deviation (ANOVA test) or number (%) (Chi-square test).

Abbreviations: PRAL: potential renal acid load, NEAP: net endogenous acid production, BMI: body mass index

Table 2 Dietary intakes of patients across tertiles of dietary acid-base load

	PRAL (mEq/day)				NEAP (mEq/day)			
	Tertile 1 (*n* = 177)	**Tertile 2 (*n* = 177)**	**Tertile 3 (*n* = 177)**	***P* value**	**Tertile 1 (*n* = 177)**	**Tertile 2 (*n* = 177)**	**Tertile 3 (*n* = 177)**	***P* value**
Calorie (Kcal/d)	2357 ± 561	2216 ± 567	2524 ± 709	< 0.001	2367 ± 584	2305 ± 560	2419 ± 721	0.244
Carbohydrate (g/d)	306 ± 90	275 ± 86	313 ± 119	0.001	305 ± 92	295 ± 97	293 ± 112	0.469
Protein (g/d)	70 ± 19	70 ± 20	83 ± 26	< 0.001	70 ± 19	76 ± 22	77 ± 26	0.005
Fat (g/d)	110 ± 41	102 ± 38	117 ± 42	0.003	110 ± 40	109 ± 43	111 ± 38	0.955
Phosphorous (mg/d)	1322 ± 414	1265 ± 385	1467 ± 559	< 0.001	1348 ± 422	1398 ± 472	1308 ± 498	0.193
Potassium (mg/d)	3982 ± 1067	3172 ± 879	3064 ± 1127	< 0.001	3992 ± 1068	3466 ± 964	2769 ± 929	< 0.001
Calcium (mg/d)	918 ± 303	850 ± 306	862 ± 335	0.095	935 ± 304	903 ± 298	793 ± 328	< 0.001
Magnesium (mg/d)	382 ± 119	334 ± 108	369 ± 154	0.001	385 ± 124	368 ± 122	331 ± 137	< 0.001
Food groups								
Grains (g/d)	334 ± 158	372 ± 181	476 ± 276	< 0.001	340 ± 163	375 ± 166	466 ± 287	< 0.001
Whole grains (g/d)	37 ± 44	40 ± 48	45 ± 68	0.304	38 ± 46	40 ± 49	43 ± 65	0.620
Refined grains (g/d)	281 ± 156	315 ± 173	412 ± 273	< 0.001	284 ± 159	317 ± 163	407 ± 280	< 0.001
Fruits (g/d)	506 ± 281	355 ± 194	293 ± 195	< 0.001	502 ± 283	359 ± 199	293 ± 84	< 0.001
Vegetables (g/d)	416 ± 234	325 ± 191	277 ± 187	< 0.001	407 ± 236	355 ± 216	258 ± 150	< 0.001
Red meat (g/d)	26 ± 22	27 ± 34	29 ± 30	0.711	27 ± 22	27 ± 29	29 ± 34	0.791
Dairy products (g/d)	317 ± 212	296 ± 259	312 ± 219	0.673	320 ± 214	304 ± 193	300 ± 277	0.689
Legumes and nuts (g/d)	72 ± 48	65 ± 47	64 ± 48	0.208	72 ± 46	69 ± 47	60 ± 45	0.044
protein to potassium ratio	0.69 ± 0.09	0.86 ± 0.07	1.15 ± 0.27	< 0.001	0.69 ± 0.09	0.87 ± 0.06	1.15 ± 0.27	< 0.001
Animal protein to potassium ratio	0.36 ± 0.14	0.49 ± 0.4	0.62 ± 0.31	< 0.001	0.36 ± 0.15	0.45 ± 0.17	0.66 ± 0.45	< 0.001
Plant protein to potassium ratio	0.35 ± 0.14	0.43 ± 0.25	0.50 ± 0.23	< 0.001	0.35 ± 0.14	0.39 ± 0.17	0.53 ± 0.28	< 0.001

Abbreviations: PRAL: potential renal acid load, NEAP: net endogenous acid production

The results are described as mean ± standard deviation using ANOVA test

NEAP are summarized in Table 1. The number of cases was substantially more throughout the DALs tertiles. Subjects were more likely to be female ($P < 0.05$) whereas the percentage of male cases increased across the PRAL and NEAP tertiles. Generally, patients with GD were less physically active ($P < 0.05$) compared to the controls. Unlike the number of alcohol drinkers, the number of smokers increased across tertiles of DALs. No difference was found in the mean age and BMI of the participants among the DALs tertiles. Mean NEAP and PRAL values in patients with GD were significantly higher as compared with controls (60.7 ± 24.2 mEq/d vs. 55.6 ± 13.9, $P = 0.008$ and − 5.5 ± 14.5 mEq/d vs. -4 ± 12.3, $P = 0.021$ respectively).

Table 2 summarizes the dietary intakes of cases and controls. Total calorie intake and also the consumption of macronutrients, including carbohydrates, proteins, and fats, increased significantly across the tertiles of PRAL, while energy and macronutrient intake exposed no significant difference, except for dietary protein, which

Table 3 Odds and 95% confidence interval for occurrence of the gallstone in each tertile categories of DAL

	Tertiles of dietary acid load			*P* trend
PRAL	**T1 (< -11.2)**	**T2 (-11.2-0.56)**	**T3 (0.56 ≤)**	
No. of cases	55	63	71	0.047
Model 1	ref	0.9 (0.57, 1.4)	1.2 (0.8, 1.86)	0.089
Model 2	ref	1.03 (0.99, 1.04)	1.18 (0.48, 1.2)	0.047
Model 3	ref	1.25 (0.9, 2.3)	1.51 (0.54, 1.36)	0.023
NEAP	**T1 (< 48.7)**	**T2 (48.7–59.9)**	**T3 (59.9 ≤)**	
No. of cases	53	64	72	0.046
Model 1	ref	0.95 (0.43, 1.1)	1.17 (0.7, 2.9)	0.082
Model 2	ref	1.2 (0.8, 1.9)	1.39 (0.89, 2.1)	0.045
Model 3	ref	1.19 (0.78, 1.84)	1.48 (0.9, 2.3)	0.037

Based on multiple logistic regression model.

Model 1: crude

Model 2: adjusted for age and sex

Model 3: additionally adjusted for energy intake, BMI, physical activity, smoking, alcohol

increased significantly across the tertiles. Consumption of micronutrients involved in the acid load of the diet varied significantly across the tertiles of DAL, except for calcium in PRAL and phosphorus in NEAP.

The comparison of food groups' consumption also disclosed substantial differences in the intake of vegetables, fruits, legumes, and nuts (only between NEAP tertiles). The ratio of animal protein to potassium and the ratio of vegetable protein to potassium, in both NEAP and PRAL tertiles, showed a significant increase. Table 3 outlines OR and 95% CIs for crude and adjusted models for gallstone. The crude model failed to show any significant association between the odds of GD and PRAL (*P trend = 0.089*) and NEAP (*P trend = 0.082*).

Age- and sex-adjustment significantly increased the risk of gallstones (*P trend: 0.047*) in the second (OR: 1.03; 95% CI: 0.99, 1.04) and third (OR: 1.18; 95% CI: 0.48, 1.2) tertiles of PRAL. Also, compared with those who were in the first tertile, the risk of GD was 25% (OR: 1.25; 95% CI: 0.9, 2.3) and 51% higher (OR: 1.51; 95% CI: 0.54, 1.36) in the second and third tertiles of PRAL, respectively, after adjustment of all the confounders (*P trend: 0.023*). Similarly, a higher NEAP was associated with an increased risk of gallstones. Compared with the first tertile of NEAP, the risk of gallstones showed an increase in the risk of GD by 19% (OR: 1.19; 95% CI: 0.78, 1.84) and 48% (OR: 1.48; CI: 0.9, 2.3), respectively, in the second and third tertiles, after adjustment of all confounders (*P trend: 0.037*).

Discussion

This case-control study found a direct association between dietary PRAL and NEAP scores and an increased risk of gallstones. Additionally, a significant inverse relationship was observed between the intake of legumes, nuts, and seeds and the NEAP score. Participants with higher PRAL and NEAP scores tended to consume more grains and fewer fruits and vegetables. While the relationship between DAL and various gastrointestinal disorders has been widely studied [17, 27, 28], his is the first study, to our knowledge, to investigate the association between DAL and the risk of GD.

Several factors, such as obesity, insulin resistance, inflammation, and gut microbiota, directly or indirectly contribute to the formation of gallstones [29]. Consistent with prior studies, our findings indicate that increased grain intake is associated with higher dietary acid load [18, 30]. Previously, in the study of Konner et al. [31], grains were considered as acid-yielding food, and Scialla et al. [32] also mentioned cereals as acid-inducing food. However, the type of grain - refined versus whole - is important in this context. In the present study, there was a significant difference in refined grain intake between NEAP and PRAL diets, but there was no difference in whole grains, which is of course due to the lack of availability and accessibility of whole grains in our culture. Grain consumption has been linked to increased insulin resistance [33], which in turn is a known risk factor for gallstones [34]. Furthermore, acidosis may increase magnesium secretion, which in turn can lead to insulin resistance [18]. Additionally, high-carbohydrate, low-fat diets may also impair cholecystokinin (CCK) secretion, leading to reduced gallbladder motility and bile supersaturation, further increasing the risk of gallstone formation [29].

Moreover, gallstones and metabolic syndrome share several common risk factors, such as obesity, dyslipidemia, and hyperglycemia [35]. Previous studies have demonstrated that dietary acid load is linked to these risk factors [36, 37], suggesting that an increase in dietary acid load may contribute to a higher risk of gallstones. Indeed, our findings support this hypothesis.

A significant effect of high dietary acid load is the induction of a pro-inflammatory state [38], which is a known risk factor for GD [39]. Previous studies have shown a direct association between dietary acid load (i.e., higher PRAL) and increased levels of inflammatory markers, such as C-reactive protein (CRP) [40]. Similar associations have been also observed in other populations [38, 41]. Though the precise mechanism is not fully understood, research suggests that acidosis-induced tissue damage may increase the expression of inflammatory molecules (e.g., nitric oxide synthases) and enzymes (e.g., myeloperoxidase) while reducing the activity of antioxidants like glutathione [40, 42, 43]. In addition, metabolic acidosis can stimulate the release of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α) and interleukin-6, while inhibiting anti-inflammatory cytokines like interleukin-10 [44]. Acidosis catalyzes these

reactions by increasing the formation of free radicals by H^+-dependent reactions [45]. Inflammation by tissue damage and stimulating the gallbladder and bile duct increases the risk of gallstones [27, 46].

The current study also found that higher red meat intake was associated with an increased dietary acid load and a higher risk of gallstones. This is consistent with previous research, which has shown that red meat consumption can promote inflammation and elevate the risk of GD [39]. Similarly, earlier studies have reported a direct relationship between red meat intake and DAL [31, 32]. In one multiethnic cohort study, higher red meat consumption was linked to an increased risk of GD, potentially due to the high cholesterol and saturated fat content in red meat [47]. Another key finding of this study was the significant association between a decrease in fruit and vegetable intake and an increase in PRAL and NEAP, which heightened the risk of GD. This is consistent with previous research, including a meta-analysis, which found that higher consumption of fruits and vegetables was linked to a reduced risk of GD [48]. Similarly, another study demonstrated that diets rich in fruits and vegetables lowered the risk of GD [49]. The protective effects of fruits and vegetables are mainly attributed to their high fiber content [47].

This study possesses several strengths. It is the first investigation to explore the relationship between DAL, NEAP, and GD within a case-control framework. The study's strength is bolstered by its substantial sample size and the meticulous consideration of diverse confounding variables, enhancing the reliability of the results. Furthermore, dietary intake was evaluated through a dependable and validated FFQ, and two distinct dietary acid load indices (PRAL and NEAP) were utilized, offering a comprehensive perspective on the acid load present in the diet. However, the study has some limitations. The cross-sectional design limits our ability to establish a causal relationship between dietary acid load and gallstone formation. Future longitudinal studies are needed to confirm these findings. Additionally, FFQs are subject to recall bias, and over- or under-reporting of food intake is inevitable. Not all potential confounders could be controlled in the analysis. Diseases such as nonalcoholic fatty liver disease, insulin resistance, and type 2 diabetes, which share risk factors with GD and could confound the relationship between DAL and GD, were not measured due to budget constraints. Finally, the timeframe required for a high-acid-load diet to lead to gallstone formation was not examined in this study, necessitating further investigation through longitudinal or experimental studies.

Conclusion

In conclusion, the findings of the present study confirmed the study hypothesis that the risk of GD increases with increasing dietary acid load, as measured by PRAL and NEAP scores. Dietary acid load also appears to be inversely related to intake of fruits, vegetables, legumes, nuts, and seeds, and directly related to grains and meat. However, further research is needed to explore the underlying pathophysiological mechanisms and confirm these findings.

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Author contributions
Conceptualization, ZY and AH; Formal analysis, ZY; Methodology, ZK, MG, and AS; Project administration, ZK and AH; Writing– original draft, ZK, DF and ZY; Writing– review & editing, DF, ZY and AH. All authors read and approved.

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Data availability
The datasets analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Research Institute of Gastroenterology and Liver Diseases Ethics Committee, Shahid Beheshti University of Medical Sciences (IR.SBMU.RIGLD.REC.1396.159). Informed written consents were obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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