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# DIET AND LIFESTYLE FACTORS ASSOCIATED WITH THE RISK OF GALLSTONE DISEASE: A REVIEW OF THE CURRENT LITERATURE

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## ABSTRACT

**Background:** Gallstone disease (GSD) is a prevalent gastrointestinal disorder, particularly in developed countries, with a global adult prevalence ranging between 10% and 20%. Although often asymptomatic, GSD may lead to serious complications including acute pancreatitis, cholecystitis, and biliary obstruction.

**Aim:** This review aims to summarize current evidence on dietary and lifestyle factors associated with the risk of gallstone disease and explore modifiable risk factors relevant for prevention.

**Material and Methods:** A narrative review of recent literature was conducted using peer-reviewed articles published in PubMed and Google Scholar. Prospective cohort studies, meta-analyses, and Mendelian randomization analyses were included to evaluate associations between dietary patterns, lifestyle behaviors, and gallstone disease risk.

**Results:** High intake of ultra-processed foods, sugar-sweetened beverages, and refined carbohydrates was consistently associated with an increased risk of GSD. Conversely, plant-based diets emphasizing whole and minimally processed foods, high fruit and vegetable consumption, and anti-inflammatory dietary patterns showed protective effects. Vegetarian diets appeared particularly beneficial for women. Additionally, obesity, type 2 diabetes, and smoking were confirmed as causal risk factors, while moderate coffee consumption may reduce GSD risk. Rapid weight loss and weight cycling were also identified as risk enhancers. Additionally, increased physical activity appears to reduce the risk of GSD.

**Conclusions:** The findings highlight the importance of dietary quality and healthy lifestyle choices in the prevention of gallstone disease. Modifiable factors such as diet composition, physical activity, and body weight management play a pivotal role in reducing GSD incidence. Preventive strategies should focus on long-term adherence to plant-based, low-processed diets and healthy lifestyle practices.

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## KEYWORDS

Gallstone Disease, Cholelithiasis, Diet, Lifestyle, Physical Activity, Risk Factors

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### Introduction and Purpose

Gallstone disease (GSD) is one of the most common disorders of the gastrointestinal tract, representing a significant health problem, especially in developed countries. Its prevalence ranges between 10% and 20% among adults [1].

GSD comprises a spectrum of conditions, ranging from asymptomatic gallbladder stones to severe manifestations such as acute biliary pancreatitis, including biliary colic, cholecystitis, obstructive jaundice, and acute biliary cholangitis. The overall prognosis is generally favorable, with a mortality rate of less than 0.5% associated with uncomplicated gallbladder stones. However, in cases of severe acute pancreatitis, the mortality rate may increase substantially, reaching 20% to 50% [2].

Despite the fact that only half of the people with documented GSD ever experience symptoms requiring treatment, cholelithiasis represents the leading cause of hospital admissions [3].

GSD is defined by the formation of solid deposits or calculi within the gallbladder and biliary tract. Under normal physiological conditions, the gallbladder functions as a reservoir for bile, releasing it into the small intestine as needed to facilitate the digestive process. Gallstones may form when there is an excess of cholesterol or bilirubin in the bile, when gallbladder motility is compromised, or when bile flow is otherwise obstructed. Gallstones are classified based on their chemical composition into two principal categories: cholesterol-rich stones, which are most commonly associated with individuals adhering to Western dietary and lifestyle patterns; and pigment stones, which primarily consist of bile pigments [4].

Contemporary research has increasingly focused on modifiable risk factors associated with gallstone formation, reflecting a shift toward preventive strategies. Healthy lifestyle including regular physical activity and an appropriate diet are supposed to be the most important measures for the prevention of GSD [5].

Therefore, the association between diet, lifestyle and the risk of gallstone disease has been examined in this study.

### **Materials and Methods**

A comprehensive literature review was conducted using the PubMed and Google Scholar databases and following keywords: gallstone disease, cholelithiasis, diet, lifestyle, physical activity, risk factors, prevention. The inclusion criteria were original research articles, reviews and meta-analysis with date of publication from 2010 to 2025. Articles not available in English and those which do not provide full-text access. The findings were analyzed and synthesized to provide the comprehensive overview of the current state of knowledge of the topic.

### **Description of the current state of knowledge**

#### **Epidemiology of GSD**

Gallstone disease (GSD) remains a significant global health concern, with its prevalence and incidence varying across different populations and regions. A comprehensive systematic review and meta-analysis encompassing 115 studies with over 32 million participants estimated the global pooled prevalence of gallstones at 6.1% (95% CI: 5.6–6.5). The prevalence was notably higher in females (7.6%) compared to males (5.4%) and increased with advancing age. Geographically, South America exhibited the highest prevalence at 11.2%, while Asia reported a lower prevalence of 5.1% [6].

The incidence of gallstones has shown an increasing trend globally. Data from the Global Burden of Disease Study 2019 indicated a rapid rise in the incidence of gallbladder and biliary diseases from 1990 to 2019, particularly among individuals aged 25–49 years. This increase correlates with the rising prevalence of high body mass index (BMI) and associated metabolic disorders. Obesity, in particular, has been identified as a major risk factor, with studies demonstrating a positive association between increased BMI and the risk of gallstone formation [7,8].

In the United States, gallstone disease imposes a substantial healthcare burden. As of 2019, GSD accounted for approximately 2.2 million ambulatory care visits, 1.2 million emergency department visits, 625,000 hospital discharges, and 2,000 deaths annually. Women exhibited higher medical care utilization rates for GSD, while mortality rates were higher among men. Hispanics had higher ambulatory care visit and hospital discharge rates compared to Whites, whereas Blacks had lower ambulatory care visit and mortality rates [9].

Pregnancy is another period associated with an increased risk of gallstone formation. A systematic review and meta-analysis reported a global prevalence of gallstones during pregnancy at 3.6% (95% CI: 1.9–6.7%), with the highest prevalence observed in the Americas at 6.8% [10].

Overall, the epidemiology of GSD underscores the influence of demographic factors such as age and sex, as well as modifiable risk factors including obesity and metabolic health. The rising incidence, particularly among younger populations, highlights the need for targeted public health interventions focusing on lifestyle modifications and early detection strategies.

#### **Pathophysiology of gallstones**

The formation of gallstones is a multifactorial process involving complex interactions between genetic predisposition, metabolic factors, and alterations in bile composition. A primary mechanism is the hepatic hypersecretion of cholesterol, leading to bile supersaturation and subsequent precipitation of cholesterol crystals [11]. This process is exacerbated by impaired gallbladder motility, which promotes bile stasis and facilitates stone formation. Genetic factors also play a significant role; mutations in genes such as ABCG5 and ABCG8, which are involved in cholesterol transport, have been associated with increased susceptibility to cholesterol gallstones [12].

Additionally, the gut microbiota has emerged as a contributing factor in cholelithogenesis. Alterations in the gastrointestinal microbiome can influence bile acid metabolism and promote conditions favorable to gallstone formation [13].

Moreover, metabolic disorders like insulin resistance and obesity are supposed to increase cholesterol secretion and decreased bile acid synthesis, further contributing to the lithogenic environment. Understanding these interconnected mechanisms is crucial for developing targeted prevention and treatment strategies for gallstone disease [14].

### Dietary and Lifestyle Factors Associated with Gallstone Disease

Researchers led by Eugenia Uche-Anya conducted a study on 44,149 males in the Health Professionals' Follow-up Study (HPFS: 1986-2022), 71,145 females in the Nurses' Health Study (NHS: 1986-2021), and 90,932 females in the NHS II (1991-2021). Dietary intake was assessed every four years using validated semiquantitative food frequency questionnaires, which were utilized to identify the consumption of ultra-processed foods (UPFs). Data from these three large-scale prospective cohort studies demonstrate a positive, dose-dependent association between UPF consumption and the risk of incident gallstone disease. Specifically, each additional daily serving of UPFs was associated with a 2.8% increase in gallstone disease risk. Subgroup analyses indicate that this association is primarily driven by the intake of sugar-sweetened beverages, artificially sweetened beverages, and other non-alcoholic UPF items containing artificial sweeteners [15]. In another study, researchers examined the influence of dietary quality indicators on GSD. Adopting diets that are anti-inflammatory and align with established healthy eating indices may reduce the risk of gallstone formation. These dietary modifications could serve as a non-invasive strategy to mitigate gallstone disease, potentially reducing the need for surgical interventions such as cholecystectomy [16].

Li et al. examined the correlation between plant-based diet quality and the risk of gallstone disease in adults. It found that a higher unhealthy plant-based diet index (uPDI) — rich in refined grains, sugary drinks, and processed plant foods — was significantly associated with an increased risk of gallstones (OR = 1.53). In contrast, the healthy plant-based diet index (hPDI) and overall PDI showed no significant associations. These findings indicate that the nutritional quality of plant-based diets plays a more critical role in gallstone disease risk than plant-based dietary adherence alone. Only plant-based diets that emphasize whole, minimally processed foods may confer protective effects against the development of gallstone disease [17].

The prospective cohort study by Chang et al. also investigated the association between vegetarian diets and the risk of symptomatic GDS among adults. After 29,295 person-years of follow-up researchers found that women adhering to a vegetarian diet had a significantly lower risk of developing symptomatic GSD compared to nonvegetarian women. Notably, nonvegetarian women with hypercholesterolemia exhibited a markedly increased risk compared to vegetarian women with normal cholesterol levels. These findings suggest that a vegetarian diet may confer protective effects against GSD in women, potentially through mechanisms involving cholesterol reduction [18].

The prospective cohort study conducted by Nordenvall et al. took the investigation a step further and examined the association between fruit and vegetable consumption and the risk of cholecystectomy, a proxy for GSD. Data were collected from over 70,000 participants in the Swedish Mammography Cohort and the Cohort of Swedish Men over a follow-up period of up to 20 years. The results demonstrated that higher intake of fruits and vegetables was significantly associated with a reduced risk of cholecystectomy. This inverse association remained robust after adjustment for confounding variables such as age, BMI, physical activity, and other dietary factors. The findings suggest that a diet rich in fruits and vegetables may have a protective effect against gallstone formation. These results support dietary recommendations emphasizing plant-based foods for gallbladder disease prevention [19].

Bin et al. performed a study to examine the relationship between dietary vitamin D intake (D<sub>2</sub> + D<sub>3</sub>) and the occurrence of gallstones in adult US residents. The analysis was based on data from the National Health and Nutrition Examination Survey (NHANES) from 2017–2020, including 6,873 participants. In the unadjusted model, a positive correlation was observed between vitamin D intake and the presence of gallstones (OR: 1.11; 95% CI: 1.05–1.17;  $p < 0.001$ ). However, after adjusting for confounding variables, the association was no longer statistically significant. Quartile analysis of vitamin D intake showed an increased risk of gallstones in higher intake groups, but after controlling for confounders, these differences were not statistically significant [20].

Furthermore Yuan et al. conducted a study aimed to investigate the causal effects of obesity, type 2 diabetes, and selected lifestyle factors (smoking initiation, alcohol consumption, coffee intake) on the risk of gallstone disease using Mendelian randomization. The study provides evidence for a causal role of obesity, type 2 diabetes, and smoking in increasing gallstone disease risk. Coffee intake may have a protective effect, while alcohol consumption does not appear to influence risk significantly. These findings highlight the importance of modifiable risk factors in the prevention of gallstone disease [21].

Among dietary factors, a short-term intake of a high-cholesterol diet and the consumption of high-carbohydrate foods have been associated with an elevated risk of developing gallstones. In regions with high prevalence rates, the consumption of legumes appears to have a protective effect. Similarly, the intake of unsaturated fats, coffee, and moderate amounts of alcohol is linked to a reduced risk. Physical activity has also

been shown to lower the likelihood of symptomatic gallstone disease in both men and women, regardless of weight loss. Conversely, rapid weight loss and repeated cycles of weight gain and loss significantly increase the risk of gallstone formation. Therefore, it is recommended that weight reduction should not exceed 1.5 kilograms per week [22].

In another Mendelian randomization study Zhou et al. tried to explain the causal relationships between behavioral determinants and gallstone disease susceptibility in populations of European descent. Drawing upon extensive datasets from the UK Biobank and FinnGen cohorts, their analysis demonstrated that genetically predicted adiposity, type 2 diabetes mellitus, and smoking initiation significantly elevate the risk of gallstone formation. In contrast, genetically inferred higher levels of physical activity and coffee consumption were associated with a decreased risk. These findings substantiate the role of modifiable lifestyle factors in the pathogenesis of gallstone disease and underscore the importance of targeted preventative interventions emphasizing weight control, smoking avoidance, and increased physical exercise [23].

Xie et al. utilized large-scale genome-wide association study (GWAS) data to identify a potential causal inverse relationship between dried fruit intake and the risk of cholelithiasis. Dried fruits, rich in dietary fiber, may modulate cholesterol and bile acid metabolism, suggesting a potential protective mechanism. These findings support the potential role of dietary dried fruit consumption in cholelithiasis prevention. Further clinical studies and investigations across diverse populations are warranted to validate and extend these results [24].

Lastly, the study conducted by Neshatbini Tehrani et al. investigated the association between dietary fiber intake and the risk of gallstone disease (GSD) using a case-control design. The research included 189 patients diagnosed with GSD and 342 age-matched control subjects. Dietary intake was assessed using a validated food frequency questionnaire. The analysis revealed a significant inverse association between total dietary fiber intake - as well as both soluble and insoluble fiber - and the risk of GSD. Notably, the protective effect of higher fiber consumption was more pronounced among individuals who were overweight or obese. These findings suggest that increased dietary fiber intake may serve as a potential preventive strategy against gallstone formation [25].

### **Physical activity and GSD**

Some research highlights the role of physical activity in reducing gallstone risk, noting that regular exercise can improve gallbladder motility and bile composition [26].

The study conducted by Wirth et al. examined the impact of physical activity on the development of gallstones. Using data from two large prospective cohorts, the researchers found that higher levels of regular physical activity were significantly associated with a reduced risk of symptomatic gallstone disease. This protective effect was independent of other lifestyle factors such as diet and smoking. The findings support the role of physical activity as a key modifiable factor in preventing gallstone formation [27].

The narrative review synthesized findings from 15 studies, including 12 cohort studies and 3 Mendelian randomization analyses, to examine the relationship between physical activity and gallstone disease. The review identified a consistent inverse association between physical activity and the risk of developing cholelithiasis, suggesting that increased physical activity may reduce the risk of gallstone formation. Notably, Mendelian randomization analyses provided evidence supporting a causal relationship between physical activity and reduced gallstone risk, independent of other lifestyle factors. The review underscores the potential of physical activity as a modifiable risk factor for cholelithiasis and advocates for further research to establish definitive guidelines for prevention through lifestyle modification [28].

### **Risk prediction models of GSD**

The analysis conducted by Gao et al. utilizing data from the National Health and Nutrition Examination Survey (NHANES) 2017–2020 encompassing 6,084 participants aged 20 years and older, reveals that Relative Fat Mass (RFM) is a robust and independent risk factor for gallstones. RFM outperforms traditional anthropometric indices in predicting this condition. The proposed predictive model may serve as a valuable tool in identifying individuals at elevated risk, facilitating targeted preventive measures, particularly in populations with high prevalence of obesity and metabolic disorders [29].

Another study conducted within the framework of the NHANES from 2017 to 2020 found that the Cardiometabolic Index (CMI) is a strong and independent risk factor for the development of GSD among U.S. adults. This index demonstrates superior predictive capability compared to traditional metrics such as Body Mass Index (BMI) and Waist Circumference (WC). Due to its high diagnostic value, CMI could serve as an

effective tool for identifying individuals at elevated risk, thereby facilitating targeted preventive measures, particularly in populations with a high prevalence of obesity and metabolic disorders [30].

In a study conducted by Yu et al. a predictive model for GSD risk was developed and validated using data from 96,426 participants across four hospitals in China. Two models were created: a comprehensive model incorporating all significant risk factors, and a simplified model that included only sex, age, BMI, presence of gallbladder polyps, and hepatic steatosis. Both models demonstrated high predictive capability and clinical utility. Due to its reduced number of variables, the simplified model may be more practical for daily clinical practice, enabling effective identification of individuals at elevated risk and facilitating appropriate preventive measures [31].

### Research Perspectives and Limitations

While current evidence highlights the beneficial effects of diet and physical activity on gallstone disease risk, several limitations remain in the existing literature. Most studies are observational, which limits the ability to infer causality due to potential confounding and bias, especially with reliance on self-reported lifestyle data. The variability in physical activity measurement and dietary assessment methods further complicates data synthesis across populations [28]. To address these issues, well-designed randomized controlled trials are essential for establishing causal links and testing specific lifestyle interventions [32]. Additionally, there is growing interest in understanding the role of gut microbiota in bile acid metabolism and gallstone pathogenesis, which could uncover novel preventive targets [33]. Future research should also explore genetic and socio-cultural factors influencing GSD risk across diverse populations to enable personalized prevention strategies [34]. Longitudinal cohort studies tracking lifestyle behaviors over extended periods are warranted to clarify long-term effects on gallstone development and progression.

### Conclusions

In summary, current evidence strongly suggests that modifiable dietary and lifestyle factors play a significant role in the development and prevention of gallstone disease. Diets high in ultra-processed foods, refined carbohydrates, and added sugars are associated with an increased risk, whereas plant-based diets rich in whole, minimally processed foods, fruits, and vegetables appear protective. Specific dietary patterns such as vegetarian and anti-inflammatory diets may reduce the need for surgical interventions like cholecystectomy. Additionally, lifestyle-related factors such as obesity, type 2 diabetes, and smoking have been shown to causally increase the risk of GSD. These findings underscore the importance of preventive strategies centered around nutrition and healthy living. Further longitudinal and interventional studies are warranted to refine dietary guidelines for gallstone disease prevention.

### Disclosure and Supporting Statements

#### Disclosure

The authors declare no conflicts of interest.

#### Supplementary Materials

Supplementary questionnaires, raw datasets, and statistical syntax are available upon request from the corresponding author.

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