

RISK FACTOR OF DIETARY HABITS WITH CHOLELITHIASIS

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ABSTRACT

Cholelithiasis affects 10-15% of the adult population. There are four main factors commonly associated with cholelithiasis abbreviated as "4F" namely female, forty, fertile and fat. However, the relationship between dietary habits as a risk factor of cholelithiasis has not been explained. The aim of the study was to determine the association between dietary habits and cholelithiasis. This study used a systematic review design with a comprehensive search of PubMed, Scopus, ScienceDirect, SpringerLink, and SAGE published from 2017 to 2021. Five studies (three prospective cohorts and two case-control studies) were included. The overall analysis of studies reported a significant risk factor of cholelithiasis in high intake of animal fats, meat, and fried foods and significant protection against cholelithiasis in high intake of fruits, nuts, fish, MUFA/SFA, n-3 FA/omega-3 fatty acids, and vegetables. Healthy dietary habits characterized by high intake in vegetables, fruits, fish, MUFA/SFA, n-3 FA/omega-3 fatty acids, and nuts will lower the risk of cholelithiasis.

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INTRODUCTION

Cholelithiasis or gallstones are stones that are formed from cholesterol, bilirubin, or bile. The stone hardens and forms in the gallbladder.¹ The gallbladder stores bile which is secreted under certain conditions. There are 6% of men and 9% of women have gallstones in the United States, most cases appear without any signs or symptoms.¹ In developing countries, such as Indonesia, it is estimated that 10-15% of the adult population has gallstones.² Asymptomatic gallstones are usually found incidentally and 1% to 2% of cases becomes symptomatic or get

complication in a year.¹ However, in ± 15 years, these asymptomatic gallstones will develop symptoms in about 20% of cases when not followed up regularly. Cholecystitis, cholangitis, choledocholithiasis, gallstone pancreatitis, and cholangiocarcinoma can occur as complications of enlargement of these gallstones.¹

The incidence of cholelithiasis is associated with 4 main factors commonly abbreviated as "4F", namely female, forty (aged 40 years and over), fertile (in the fertile period), and fat (obesity). In general, the risk factors for cholelithiasis are present during pregnancy

(progesterone suppresses gallbladder contractility that triggers stasis), obesity, genetics, certain medications (estrogens, fibrates, somatostatin analogs), gallbladder stasis, in women, metabolic syndrome, drastic decrement of weight, prolonged fasting, surgery of biliary system, Crohn's disease, and bowel resection.³

Usually, patients with gallstone symptoms present with nausea and vomiting, and pain in the upper right abdomen or in the right scapula or middle back which radiates from the epigastric area after eating fatty or spicy foods.³ Fatty foods are one of the causes of gallbladder contractions. After eating fatty foods, the intense and dull pain will occur in an hour and last from 1 to 5 hours. However, the relationship with food is not universal and still needs further investigation.¹

MATERIALS AND METHODS

Search strategy, inclusion criteria, and data extraction

This study used a systematic design that is a qualitative study with research questions using the SPIDER method (Sample, Phenomenon of Interest, Design, Evaluation, Research type) as shown in Table 1.

This study followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guideline. The study systematically identified all potential English articles relevant by searching in computerized electronic databases: PubMed, Scopus, ScienceDirect, SpringerLink, SAGE published from 2017 to 2021. The search terms used MeSH (Medical Subject

Headings) terms with the following keywords: (("Feeding behavior") OR ("diet") OR ("nutrients") OR ("meals")) AND (("Cholelithiasis") OR ("Gallstones")). This research was limited to human studies.

The inclusion criteria for eligible studies were case control studies (retrospective studies), clinical trials, and cohort studies that reported a measurable association between dietary habits and cholelithiasis conducted in populations of men and women aged ≥ 30 years. Dietary habits were measured in the form of quality, frequency, and type of food consumed. Evaluations for cholelithiasis were based on history, medical records, laboratory examinations, USG, BOF, ERCP, MRCP, PTC, and CT scans.

Three reviewers (AN, NW, and RT) independently extracted data from all the studies that meet inclusion criteria. The data were extracted from the original article based on: title, author, year, research location, study design, subject, age of subjects, sample size, type of diet, cholelithiasis indicators, and outcomes.

Assessment of methodological quality

Three reviewers (AN, NW, and RT) independently evaluated the methodological quality of the included studies using the Joanna Briggs Institute (JBI) Critical Appraisal instrument to assess the risk of bias in observational studies. The JBI instrument consists of 10 questions for case control studies and 11 questions for cohort studies with one point for each question. A journal is considered eligible if it has a point of at least 50% of the total questions.

Table 1. SPIDER framework for searching research question

| SPIDER Framework | Search Term |
|------------------------|--------------------------------------|
| Sample | Men and women aged ≥ 30 years |
| Phenomenon of Interest | Dietary habits |
| Design | Case-control, Clinical trial, Cohort |
| Evaluation | Cholelithiasis |
| Research type | Analytic Study |

RESULTS

In our search from all the journal databases used, the total number of journals was 1419 journals with 117 duplicate journals so the total number of journals to be identified was 1302. After reviewing and analyzing the inclusion and exclusion criteria, we

identified 5 journals as potentially relevant for the analysis and after reviewing the study methodology with Joanna Briggs Institute critical appraisal, the journals used in the study were 5 journals with prospective cohort and case control study design. Overall, a total of 5 journals were finally included in the systematic review (Figure 1).

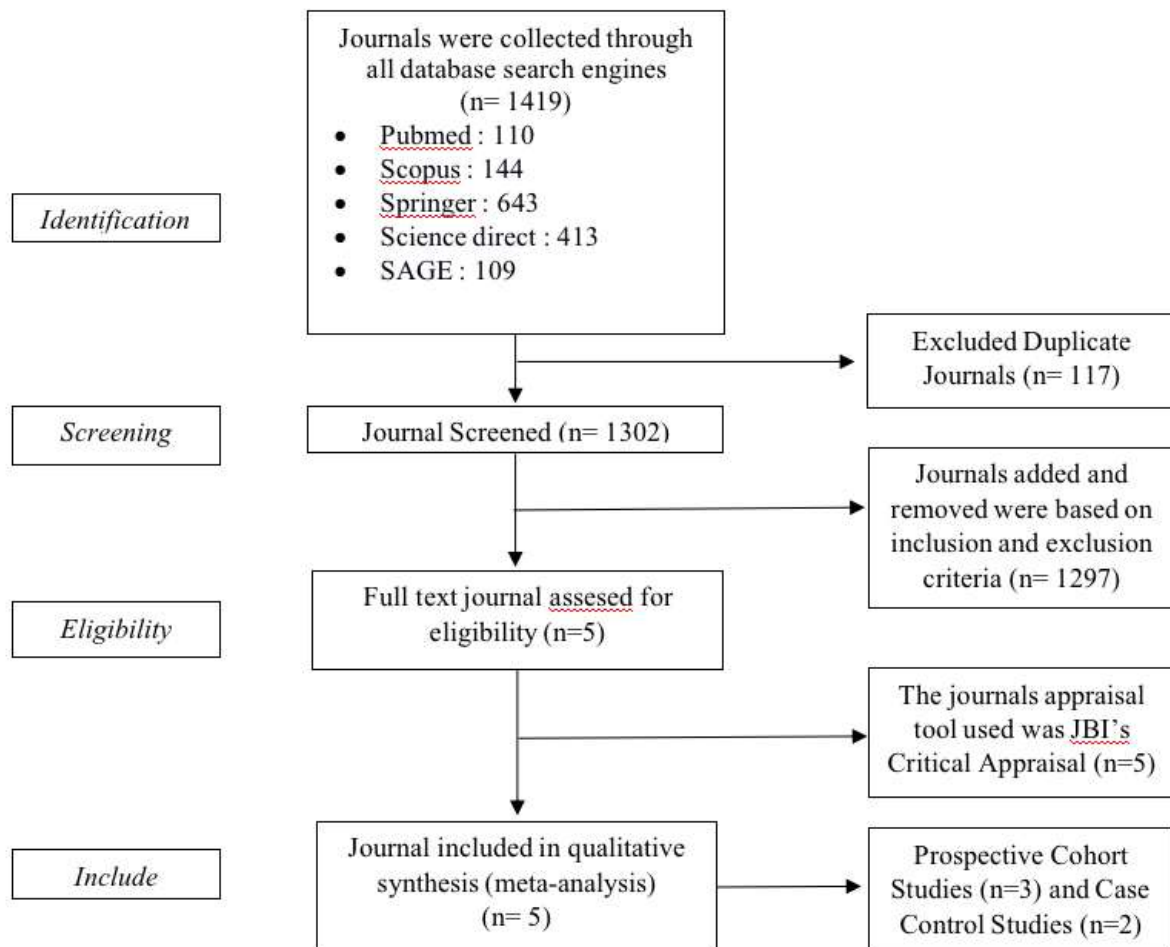


Figure 1. PRISMA flow diagram for search strategy

Table 2. Journal resume

| Author /Studi | Study Design | Population (n) | Population Characteristic | Age | Dietary habits | Outcomes |
|---------------------------------|--------------------------|---|--|---|---|--|
| Wirth <i>et al.</i> , 2018 | Prospective Cohort Study | 43,635 | Male without symptomatic gallstone and diabetes | 40 - 75 years old | High quality diet recommendation based on the alternate Mediterranean (aMed), Alternate Healthy Eating Index (AHEI-2010), and Dietary Approaches to Stop Hypertension (DASH) assessment | Increased diet-quality scores based on aMed, AHEI-2010, and DASH decrease the incidence of symptomatic cholelithiasis |
| Wirt <i>et al.</i> , 2020 | Prospective Cohort Study | Female : 60,768 Male : 40,744 | Female and male without gallstone disease and diabetes | Female : 30 - 55 years old Male : 40-75 years old | A healthy diet is defined using the Alternate Healthy Eating Index (AHEI-2010). Participants considered consuming a healthy diet if the AHEI-2010 scores upper 2 quintiles | AHEI-2010 scores upper 2 quintiles reduce the risk of cholelithiasis in women by 8% and men by 11% |
| Figueiredo <i>et al.</i> , 2017 | Prospective Cohort Study | 144,409 | Female and male from five different ethnics without gallbladder disease | 45-75 years old | Dietary and nutritional factors (red meat, fruits, vegetables, fiber, saturated fat, cholesterol, and carbohydrates, etc.) and alcohol consumption | Increasing the intake of vegetables, fruits, and high fiber foods can reduce the risk of gallbladder disease Increasing the intake of red meat, high saturated fat foods, and high cholesterol foods can increase the risk of gallbladder disease Alcohol consumption can reduce the risk of gallbladder disease |
| Diaz, <i>et al.</i> , 2018 | Case control | Case: 14 (3 male, 11 female) Control: 14 (3 male, 11 Female) | Case : subject with history of cholelithiasis Control : healthy subject without gastrointestinal disease | Case: mean 51.50 ±14.10 years old Control: mean 46.50 ±11.47 years old | Individual dietary intake according with types of food in Food Frequency Questionnaire(FFQ) which divided into 17 groups based on CESNID Classification | The colelithiasis patients (case population) had lesser consumption of non-alcoholic drinks, vegetables, and sauces, and more intake of potatoes |
| Park <i>et al.</i> , 2017 | Case control | case: cholesterol cholelithiasis: 40, pigment cholelithiasis: 59 control: 99 | Case : subject with cholelithiasis (differentiate based characteristic of stone : cholesterol cholelithiasis and pigment cholelithiasis) Control : healthy subject without gastrointestinal disease | Control: mean 49.49 ± 14.79 years old Case: mean Cholesterol: 45.98 ± 14.92 years old, pigmen: 52.00 ± 15.70 years old | Type of Individual dietary intake according with types of food in Food Frequency Questionnaire(FFQ) then it is classified into 25 groups and The frequency of food which is classified into 10 categories | Subjects with cholesterol cholelithiasis had higher intakes of fat, animal fat, meat, pork, and fried foods compared to other subjects. Meanwhile, subjects with pigments cholelithiasis had higher noodle and carbohydrate intakes compared to other subjects |

From all the journals that have been collected, there were some similarities in the results of the research. A diet rich in animal fats, meat, and fried foods is said to have a significant risk factor for cholelithiasis. In the study of Figueredo et al (2017), it is said that consumption of red meat >36.1 g/1000 kcal/day has a risk of 1.13 times the risk of cholelithiasis in men, and 1.23 times in women ($p < 0.0001$).⁴ As for cholesterol consumption, this study only found significance in women, where it was said that intake >128.7 mg/1000 kcal/day increased the risk by 1.2 times ($p < 0.0001$). In the same journal, it was also found that the intake of >10.8% calories from saturated fat increased the risk of cholelithiasis 1.14 times in men ($p = 0.0134$) and 1.2 times in women ($p = 0.0001$). Meanwhile, Park et al (2017) stated that a diet consisting of beef, pork, and fried food increases the risk of cholesterol stones by 1,737 ($p = 0.016$).⁵ Whereas in the study of Wirth et al (2018) which only used a male population, it was said that the intake of red meat and processed meat was one to half times less likely to reduce risk (HR (95% CI): 0.77 (0.66-0.89)).⁶ In his research, it was also mentioned that low intake of trans-fat and sodium also contributed to reduced risk (HR (95% CI): trans-fat: 0.71 (0.62–0.81), sodium: 0.71 (0.59–0.86)).

On the other hand, there were significant protective factors for a high intake pattern of fruit, nuts, fish, MUFA/SFA, n-3 FA/omega-3 fatty acids, and vegetables against cholelithiasis. From the results of the study by Figueredo et al (2017), it was found that dietary fiber >14.8 g/1000 kcal/day can reduce the risk by 0.89 times for both men and women ($p = 0.001$).⁴ Then, for the intake of vegetables (> 239.8 g/kcal/day), women have a protection factor of 0.8 times ($p = 0.0007$) and men 0.85 times ($p < 0.0001$). For foods containing carbohydrates, only found

the significance was only found in women, in which the intake of > 58.2% of calories from carbohydrates reduced the risk as much as 0.86 times ($p < 0.0001$). In a study by Wirth et al (2018), it was found that consumption of 6-8x portions of food, including healthy foods such as fruit, vegetables, nuts, whole-grain products, can reduce the risk of cholelithiasis (HR ((95% CI): nuts- nuts 0.68 (0.59–0.78), fruits: 0.77 (0.67–0.89), n-3 FA: 0.81 (0.71–0.92), fish: 0.83 (0.72–0.94), MUFA/SFA: 0.83 (0.73–0.95)).⁶

Supporting the risk factors and protective factors described above, cholelithiasis patients were found to have low levels of energy, macronutrients (carbohydrates, total fat, PUFA), and micronutrients (folate, calcium, magnesium, and vitamin C). Besides, there is also a low intake of several phenolic mixtures: Flavonoids (anthocyanins, flavanones, flavones, and flavonols), lignans, phenolic acids (hydroxybenzoic, hydroxycinnamic, and hydroxyphenyl acetic acids), and tyrosols.⁷

Apart from the above types of food, alcohol has several times been mentioned as having a significant protective role against cholelithiasis. In the study of Figueredo et al (2017), it was stated that daily alcohol intake significantly decreased the incidence of cholelithiasis ($p < 0.0001$) for both women and men.⁴ Meanwhile, the results of the study by Wirth et al (2020) said that moderate alcohol consumption (0.5-1.5 times/day) reduced the risk by up to 13% in women while in men moderate alcohol consumption (0.5-2 times/day) reduced the risk up to 7%.⁸ In the study of Park et al (2017), it was also stated that control subjects (without cholelithiasis) had a higher average alcohol intake than subjects with cholelithiasis ($p < 0.0004$).⁵

In the study of Wirth et al (2018), diet-quality score assessments with aMed, AHEI-2010,

and DASH in men had an inverse association with the incidence of symptomatic cholelithiasis.⁶ The higher scoring score indicates a healthier diet so that it has a lower risk value for symptomatic cholelithiasis. This study also confirmed the findings of others journals in which a diet with a total score of more than 2 quintiles according to the AHEI-2010 score calculation reduced the risk of developing cholelithiasis in women by 8% and in men by 11%.⁸ Coffee consumption has a significant influence to be a protective factor for cholelithiasis. In the study of Wirth *et al.* (2020), the habits of drinking coffee ≥ 2 cups/day in women can reduce the risk by 10%, while in men the results are higher, namely 18%.⁸

DISCUSSION

A diet rich in animal fats, meat, and fried foods is said to have a significant risk factor for cholelithiasis. Animal fats and fried foods contain saturated fat. The possibility to get a gallstone may be increased if foods with high saturated fat and refined sugar are consumed.⁹

A diet that can be a protective factor for cholelithiasis is a high intake of fruits, nuts, fish, MUFA/SFA, n-3 FA/omega-3 fatty acids, and vegetables. MUFAs may have a protective role in gallbladder disease (Misciagna *et al.*, 1999). n-3 FA/omega-3 fatty acids are associated with the PUFA ω -3 content of various types of fish. The mechanism of ω -3 PUFA prevents cholelithiasis is by increasing the cholesterol saturation index and nucleation time (Mendez *et al.*, 2001). By changing the cholesterol metabolism, biliary cholesterol saturation and biliary protein concentrations can be reduced.¹⁰ Fruits and vegetables that are rich in fiber are associated with a reduced risk of developing cholelithiasis. By

accelerating intestinal transit and reducing the formation of secondary bile acids such as deoxycholate,^{11,12} which have been associated with increased bile cholesterol saturation,^{13,14} fiber protects gallstone formation.^{13,14} Consuming nuts are also said to reduce the risk of cholelithiasis because nuts contain unsaturated fats which function as a protective factor against cholelithiasis. Consumption of nuts which often contain unsaturated fats greatly reduces the risk of cholelithiasis.¹⁵

Cholelithiasis is also associated with energy levels, macronutrients (carbohydrates, total fat, PUFA), and micronutrients which include vitamin C, calcium, folate, and magnesium. Moreover, there is also a low intake of anthocyanins, flavanones, flavones, flavonols (flavonoids group), lignans, hydroxybenzoic, hydroxycinnamic, and hydroxyphenyl acetic acids (phenolic acids group), and tyrosols, which classified as phenolic mixtures.⁷ A study showed the deficiency of vitamin C in guinea pigs causes supersaturation of bile cholesterol and the formation of cholesterol gallstones by reducing the activity of cholesterol 7-hydroxylase, which causes supersaturation of bile cholesterol and formation of cholesterol gallstones.¹⁶ A study by Gustafsson *et al.* 1997 showed that supplementation of ascorbic acid is associated with decreasing the incidence of gallbladder disease in women but not in men¹⁷. Calcium is hypothesized can prevent the occurrence of gallstone by reducing the deoxycholate and cholesterol content of bile by binding the secondary bile acids including deoxycholate in the lumen of the small intestine. An inverse association between gallbladder disease and dietary calcium has been stated by several studies.¹⁸⁻²⁰

Apart from the above foods, alcohol has several times been mentioned as having a

significant protective role against cholelithiasis. Alcohol decreases the cholesterol saturation of bile which results in a decrease in cholesterol stones. The protective effect of alcohol against gallstones is also explained by the increased conversion of cholesterol to bile acids and by changes in the type of bile acids that undergo enterohepatic circulation.²¹⁻²³ Increased serum concentrations of HDL cholesterol are associated with moderate alcohol consumption.^{24,25} Coffee consumption also has a significant influence to be a protective factor for cholelithiasis. Coffee can increase the enterohepatic circulation of bile acids so that it becomes a protective factor. The components of coffee stimulate the release of cholecystokinin, increase gallbladder movement, inhibit the absorption of gallbladder fluids, reduce crystallization of cholesterol in bile, and possibly also decrease intestinal activity.²⁶

The effect of diet on the incidence of cholelithiasis is related to gender. Diet as a risk factor for cholelithiasis has a greater effect on female gender than male. Female gender and diet are both risk factors for cholelithiasis. However, female gender is a prominent risk factor, as evidenced by several studies documenting that the risk of cholelithiasis incidence is greater in female than male at all ages.²⁷ This has been linked to sex hormones and, furthermore, parity as a risk factor for cholelithiasis. During pregnancy, biliary sludges, which are a mixture of cholesterol crystals, calcium bilirubin, and mucin, which are potential precursors for cholelithiasis, increase by 30% and cholelithiasis also begins to form by 1-3%. After delivery or during the puerperium, more than half of the biliary sludges and 30% of small gallstones (less than 10mm in diameter) vanish.²⁸ The disappearance of biliary sludges and small gallstones may be

caused by silent migration into the small intestine or by spontaneous dissolution.²⁹ In addition, estrogen is also thought to be one of the causes. This is evidenced by the moderate risk of cholelithiasis incidence in women who take low-dose oral contraceptives (less than 50 micrograms), in contrast to postmenopausal women who are undergoing estrogen replacement therapy whose risk of cholelithiasis is increased.²⁷

Meanwhile, diet as a protective factor for cholelithiasis has a greater effect on the male gender than the female. This statement is suitable with the result of a study conducted by Tseng *et al.*, (2000) which reports that an inverse association between traditional intake patterns, which primarily consists of beans and corn, with gallbladder disease was only found in the male.³⁰

Apart from the two types of diet that have been mentioned above, alcohol consumption can reduce the risk of cholelithiasis in both male and female, but it is stronger in female than male. This statement is in line with the results of a study by La Vecchia, Decarli, Ferraroni & Negri (1994) which states that the inverse association between alcohol consumption and the incidence of cholelithiasis is stronger in female than male, but indeed the association is seen in both genders and is consistent in every age and each level of body mass index.³¹ Moreover, the habits of regular coffee consumption can reduce the risk of cholelithiasis incidence more strongly in male than in female. However, this statement contradicts the results of a study conducted by Zhang *et al.* who explained that the significant inverse association between coffee consumption and the incidence of cholelithiasis was only found in female, which was observed in a cohort.³² The type of cholelithiasis that is influenced by dietary factors is cholesterol stone. Cholesterol stones are formed by the

deposition of cholesterol monohydrate crystals followed by the aggregation of bile salt and mucin. One of many risk factors causing cholesterol stone formation is a high-saturated-fat and low-fiber diet.³³ Several types of diet such as a low carbohydrate diet which is rich in vegetables and nuts can affect the composition of bile and gallbladder function which is related to the pathogenesis of cholesterol stone formation.³⁴ Meanwhile, pigment stones are not influenced by dietary factors but rather related to poor hygiene and environmental conditions.⁵ Unfortunately, studies that look at the correlation between diet and the incidence of pigment stones in humans are still rare.

CONCLUSION

Based on the results of this systematic review, it can be concluded that a diet rich in animal fats, meat, and fried foods increases the risk of cholelithiasis. Meanwhile, a diet high in vegetables, fruit, fish, MUFA/SFA, n-3 FA/omega-3 fatty acids, and nuts lowers the risk of cholelithiasis.

AUTHOR CONTRIBUTION STATEMENT

Pudji Lestari, Annora Zerlina Lysandra, Nabilah Azzah Putri Wairooy, Rania Tasya Ifadha, Adra Achirultan Ramainaldo S., Ivan Angelo Albright, Alifah Fajriyyatul Izzah, Viky Nafi'ah Rahma M. conceived and designed the research, collected the data, analyzed and interpreted the data, and wrote the paper.

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