

Fruits and vegetables consumption and the risk of gallstone disease

A systematic review and meta-analysis

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Abstract

Background: The role of fruit and vegetables (FVs) consumption in decreasing gallstone disease risk remains contradictory. We performed a meta-analysis to analyze this potential correlation, followed by investigation of dose-response relationship of FVs consumption with gallstone disease.

Materials and methods: PubMed, Embase, as well as Web of Science were searched to determine all published researches about the connection of FVs consumption with gallstone disease before March 2018. Relative risks (RRs) or odds ratios (ORs) along with corresponding 95% confidence intervals (CIs) was pooled utilizing random effect models, aiming at examining the correlation of FVs consumption with gallstone disease risk.

Results: One cross-sectional study, our case-control studies as well as nine cohort studies were enrolled, covering approximately 33,983 patients with gallstone disease and 1,53,3752 participants. In a pooled analysis, vegetables consumption was significantly related to a decreased gallstone disease risk, (RR=0.83, 95% CI, 0.74–0.94, $I^2=91.1\%$), and for fruits consumption, RR was similar (RR=0.88, 95%CI, 0.83–0.92, $I^2=0.01\%$). This inverse correlation of FVs consumption with gallstone disease risk was solid in most subgroup analysis. The nonlinear dose-response correlation indicated that gallstone risk was reduced by 4% (RR=0.96, 95%CI, 0.93–0.98) and 3% (RR=0.97, 95%CI, 0.96–0.98) for every 200g per day increment in vegetables consumption ($P=.001$) and fruits consumption ($P=.001$), respectively.

Conclusion: This study suggests vegetables and fruits consumption is correlated with a significantly reduced risk of gallstone disease.

Abbreviations: CIs = confidence intervals, FVs = fruits and vegetables, NOS = Newcastle–Ottawa Scale, ORs = odds ratios, RRs = relative risks, VS = versus.

Keywords: diet, fruits, gallstone disease, meta-analysis, vegetables

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1. Introduction

Gallstone disease is among the most common and costly gastrointestinal disorders worldwide, resulting in over 7,00,000 cholecystectomies, annually accounting for \$6.5 billion cost in US alone.^[1] About 10%–20% of the national adults are estimated to be burdened with gallstones at present. Additionally, gallstone prevalence is generally considered to be increasing as a consequence of nutritional and lifestyle changes.^[2,3]

Therefore, the reduction of the incidence of gallstone disease could help to decrease the economic burden of gallstone disease on the healthcare system. Although genetic, environmental, metabolic, and related conditions have been proved to be associated with gallstone formation, factors like advanced age and gender are unalterable. However, diet can be a modifiable risk factor to prevent gallstone disease.^[3,4] As a result, identification of the relationship between vegetables and fruits consumption and gallstone disease may provide the opportunity to reduce occurrence of gallstone disease.

Evidence has been reported that dietary intervention plays a part in primarily preventing gallbladder stones in adults.^[5] Higher consumption of fruit and vegetables (FVs) is recommended as part of a healthy diet, which might be protective against gallstone disease.^[6,7] However, no unequivocal correlation of FVs consumption with the risk of developing gallstones has been identified. The protective role of FVs consumption on

decreasing gallstone risk has been reported in several studies,^[8–13] whereas other studies could not confirm an association.^[8,11,14–17] In addition, FVs consumption has been revealed to be negatively correlated with gallstone risk in other researches.^[14]

Evidence from nutritional epidemiology also suggests that FVs consumption is related to the decrease of gallstone diseases.^[15] In view of public health recommendations, it is necessary for us to explore the negative relation between FVs and gallstone disease. Strong evidence can help us to take more fruits and vegetables to reduce gallstone diseases.

The study was designed to perform a systematic review and meta-analysis by enrolling case-control and cohort studies, aiming at determining the correlation of FVs consumption with gallstone disease risk. It can provide a better understanding of the evidence for physicians, when they give diet prescription for subjects with a high risk of gallstones.

2. Methods/design

We followed the guideline of the PRISMA guidelines.^[16]

2.1. Data sources and search strategies

Three databases were thoroughly searched: Web of Science, EMBASE (host: OVID) from 1974 to June 2018 as well as Medline (host: OVID) from 1946 to April 2017. The following searching strategy was used ([gallbladder stone*] OR [gallbladder cholelith] OR [gallbladder lithiasis] OR [gallstone*] OR [gallstone*] OR [gall cholelith] OR [gall lithiasis] OR [cholelithiasis] OR [cholecystectomy]) and ([fruit*] OR [vegetabl*] OR [Diets, Vegetarian] OR [Vegetarian, Diets] OR [Vegetarian, Diet] OR [Diet, Vegetarian] OR [Vegetarianism] OR [Mediterranean diet] OR [diet] OR [dietary] OR [melon] OR [citrus] OR [tomato] OR [apple] OR [grapes] OR [kiwi fruit] OR [banana] OR [broccoli] OR [strawberries] OR [spinach] OR [lettuce] OR [carrots] OR [pumpkin] OR [blueberries] OR [cherries] OR [mango] OR [berries] OR [barberis] OR [pomegranate] OR [apricot] OR [watermelon]), restricting to researches in humans. Additionally, the reference lists of all included studies were reviewed, as well as those of several recent review articles that may fulfill our eligibility requirements in order to avoid missing relevant studies. If we needed to require additional information, we tried to contact the authors.

2.2. Study selection and inclusion criteria

Two authors (Zhang and Xiong) performed the research by following a standard procedure. Then, the studies were screened by title. If the studies could not be excluded by reading the title, then the abstract and full text were reviewed. The inclusion criteria were as follows: first, cohort study or case control design; second, investigating the relationship of FVs consumption with gallstone risk; third, providing multivariate adjusted effect estimates along with 95% CI or adequate information for calculation; and fourth, published before March 2018.

2.3. Data extraction

All information was independently collected by two authors (Zhang and Xiong) using a specified form, and disparities were

discussed with author Xu before the final analysis. The following items were collected from every study: year of publication, name of first author, number of cases, geographic region, participants' age and sex, measurement methods of FVs consumption, follow-up period, RR (95% CI) of the highest versus (vs) lowest FVs consumption, as well as adjusted covariates. In terms of dose-response analysis, we collected the number of participants (person-years) and cases as well as RR (95% CI) for every dose of FVs consumption, as well. The median value of FVs consumption for every category was assigned to each corresponding RR estimate in every study. We set the lower boundary to zero if the lowest category was opened; the mid-point of the category was set at 1.5 times the lower boundary, if the highest category was open-ended.^[17]

2.4. Statistical analyses

We assessed the relationships of FVs consumption with gallstone disease risk via OR/RR values along with corresponding 95% CIs. Although ORs and RRs were provided in case-control and cohort studies, respectively, we assumed OR and RR as the same because of the low incidence of gallstone disease. In consideration of between-study and within-study diversification, random-effects model was utilized for quantification of the correlation of FVs consumption and gallstone risk. According to this method, studies were considered as random samples from a population of studies.^[18] If the data of males and females were separately shown, each gender was taken as an independent factor.^[12] If studies reported information on vegetable protein consumption, it was defined as vegetable consumption in our analysis.^[8,19] Cochran's Q test was determined to evaluate the heterogeneity, which was assessed by I^2 statistics. The cut-off value of I^2 for high, medium, and low heterogeneity were determined as 75%, 50%, and 25%, respectively,^[20] where definite heterogeneity was assumed if $P < .1$. Subgroup analysis and meta-regression were done to explore the potential source of heterogeneity among studies. Subgroup analysis and meta-regression were both conducted in accordance with diverse variables, including sex, publication year (before 2010 vs 2010 and thereafter), study design (case-control vs cohort studies), number of cases (≥ 1000 vs < 1000), geographical region (Western vs Eastern), study quality (Newcastle–Ottawa Scale < 7 vs Newcastle–Ottawa Scale ≥ 7) and the endpoint of study.

2.5. Assessment of study quality

Newcastle–Ottawa Scale (NOS) was utilized to evaluate the enrolled researches. Study design selection, comparability, sample size, tools used in assessing FVs consumption and outcome ascertainment were evaluated on this scale, with a maximal score of 9. Additionally, studies with scores ≥ 7 were regarded as high quality. In terms of study design, the first item concerned the study design. cohort studies were considered to have a lower risk of bias. Hospital-based case-control studies was considered to have a higher risk of bias. When it comes to quantification of FVs consumption, studies confirming that the instrument used to measure FVs consumption was considered to have a lower risk of bias, whereas studies that did not provide this information were considered to have a higher risk of bias. About the confounding bias in the included studies, we considered age, education, race, employment, income, and marital status as confounders of the association between physical activity and

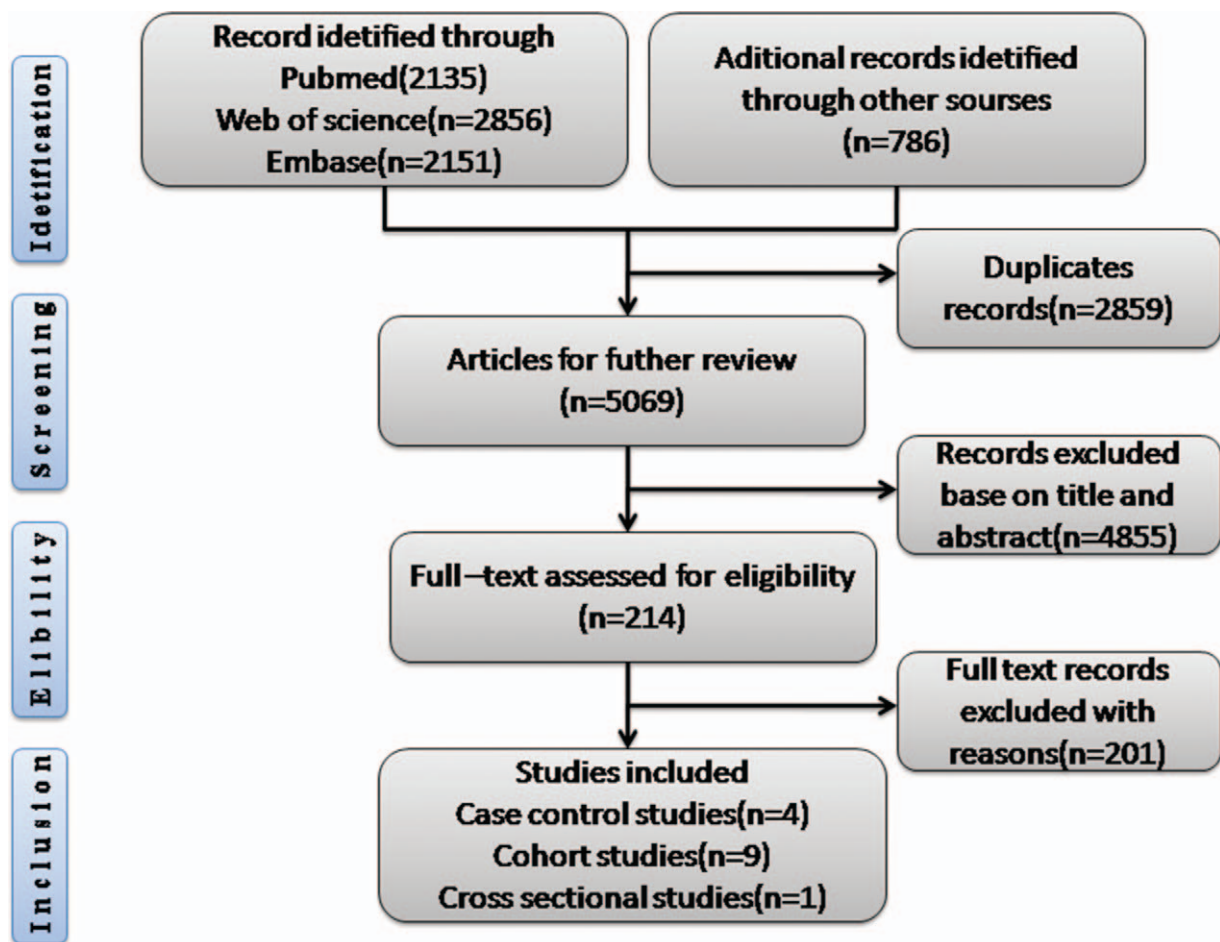


Figure 1. Flow diagram of study selection process.

gallstone disease. Studies that controlled for the more than half of confounding effects were considered to have a lower risk of bias than those that did not.

2.6. Sensitivity analysis

In the case of significant heterogeneity, a sensitivity analysis was conducted following the data extraction. Sensitivity was used to test the influence of one study to our whole results by sequentially omitting studies one by one.

2.7. Assessment of publication bias

Begg's funnel plot as well as Egger's linear regression test was conducted to assess publication bias.^[21,22] And funnel plots were also used to assess publication bias.

2.8. Dose-response analysis

Researches reporting about the dose of FVs were included. A two-stage random-effect dose-response meta-analysis was conducted to investigate the possible nonlinear relationship.^[23] Then, we extracted the number of participants (person-years) and cases as well as RR (95% CI) for every category of FVs consumption from

studies. To be specific, 80 g for fruits and 77 g for vegetables were considered as the mean serving.^[24] And if the separate person years for each dose was not provided in the studies, we calculated by using the data in the studies. Then a restricted cubic spline model with three knots at 75%, 50%, and 25% of the distribution of FVs consumption was estimated. A *P* value of nonlinearity was obtained by examining the speculation of the coefficient equality of the second and third spline. Stata version 12.0 was employed, and a *P* < .05 was considered as statistical significance throughout the study.

3. Results

3.1. Enrolled studies

The flow diagram of literature search was displayed in Figure 1. In total, 7142 articles were primarily retrieved from the above-described datasets and 786 records were searched from references, while 2319 duplicates were initially eliminated from the records. After screening the titles of 5609 studies, we carefully reviewed the abstracts of 214 studies, which identified 18 studies reaching the inclusion criteria, followed by reviewing in full-text. Three studies were excluded due to cross-sectional studies. Finally, 14 articles were enrolled in this meta-analysis.

The major features of the enrolled researches (all of observational properties) in this meta-analysis were shown in Table 1. Studies were conducted in these countries: five in the United States, and the others separately in Sweden, the United Kingdom, Iran, France, Germany, French, Canada, and India. Nine and four studies were of cohort design and case-control design, respectively. In assessing gallstone disease cases, nine studies reported gallstone diseases as the outcome, three studies reported cholecystectomy, and one study reported cholesterol gallstone. We enrolled 1,53,752 subjects in this meta-analysis, including 33,983 subjects with gallstone. The age of patients ranged from 40 to 92 years old, and the follow-up duration varied from 1 to 20 years. The NOS scores of enrolled researches varied from 6 to 9 years, with twelve and one of high-quality and low-quality studies (Stable 1, <http://links.lww.com/MD/D104>), respectively. In the majority of studies, risk estimates adjusted for age (8 researches), sex (4 researches), body mass index (6 researches), education level (5 researches), smoking (6 researches), and alcohol consumption (8 researches) physical activity (7 researches) were available; while in fewer studies, coffee consumption (2 studies) and hormone replacement therapy use (2 studies) were adjusted. (Table 1)

4. Quantitative synthesis

4.1. Vegetables consumption and risk of gallstone

In the pooled analysis of RR (CI) for the enrolled studies, vegetables consumption was significantly and inversely related to gallstone risk (RR=0.75, 95% CI, 0.61–0.88) (Fig. 2). Due to the high heterogeneity, Begg's funnel plot as well as Egger's linear regression analyses were conducted for estimation of the possible publication bias, which was limited [Begg's test, $P=1.000$ (Supplementary Fig. 1) and Egger's test, $P=.682$ (Supplementary Fig. 2, <http://links.lww.com/MD/D104>)]. In addition, none of individual study was revealed to harbor excessive pooled effect in sensitivity analysis (Supplementary Fig. 3, <http://links.lww.com/MD/D104>). There was evidence of publication bias in the vegetables study according to the visual inspection of the funnel plots (Supplementary Fig. 4, <http://links.lww.com/MD/D104>)

For dose-response analysis, six cohort studies with 35,558 patients burdened with gallstone disease were eligible to assess the dose-response correlation of vegetable consumption with gallstone disease risk. The restricted cubic splines model revealed that the rejection of a linear correlation of vegetable with gallstone (P for nonlinearity=.01). Hence, a nonlinear correlation with a nonlinear regression model was determined (P for linearity=.19). We demonstrated that the gallstone risk was reduced by 4% with each additional 200g per day (RR=0.96, 95% CI=0.93–0.98, $P=.001$) (Fig. 3).

4.2. Fruits Consumption and Risk of Gallstone

Reports from five cohort researches were accessible to calculate the effect estimates for fruits consumption.^[8,9,12,25,26] In the pooled analysis of the cohort studies, fruits consumption were inversely related to gallstone disease risk (RR=0.88 95% CI=0.83–0.92; $I^2=0.01\%$) (Fig. 3). Publication bias was insignificant in the meta-analysis (Begg's test, $P=1.0$ [Supplementary Fig. 5] and Egger's test, $P=.735$ [Supplementary Fig. 6, <http://links.lww.com/MD/D104>]). Sensitivity analysis indicated that study by Figueiredo et al^[12] was the primary source of the heterogeneity

(Supplementary Fig. 7, <http://links.lww.com/MD/D104>). And there was no indication of a potential publication bias among fruits study according to the visual inspection of the funnel plots (Supplementary Fig. 8, <http://links.lww.com/MD/D104>).

Four cohort studies with 18,335 subjects with gallstone disease were eligible to evaluate the dose-response correlation of fruits consumption with gallstone disease risk. The application of restricted cubic splines model revealed the rejection of the examination of a linear relationship of fruits with gallstone ($P=.01$). Hence, a nonlinear relationship with a linear regression model was determined ($P=.19$) by using fixed model (P for heterogeneity=.01). In addition, gallstone risk was found to be decreased by 3% with each additional 200g per day (RR=0.97, 95% CI = 0.96–0.98, $P=.001$) (Fig. 4)

4.3. Subgroup Analysis and Meta-Regression

For vegetables consumption, the negative association with gallstone disease risk was consistent in subgroup analysis by the sex, study quality (NOS <7, versus NOS ≥7) and the endpoint of study (Table 2). In the stratification analysis by study design, vegetable consumption was revealed to be correlated with a significantly decreased risk of gall bladder disease in case-control study (RR=0.39, 95% CI=0.24–0.62; $I^2=59.2\%$, $P=.058$) compared to that in cohort studies (RR=0.92, 95% CI=0.82–1.02; $I^2=80.2\%$, $P=.001$) (Table 1). By the subgroup of the endpoint of studies, vegetable consumption was related to significantly reduced gallstone disease risk (RR=0.79, 95%CI=0.68–0.92, $I^2=85.9\%$, $P=.001$) compared to that in cholecystectomy (RR=0.94, 95%CI=0.85–1.03; $I^2=0.01\%$, $P=.884$). Regarding geographical locations, vegetables consumption was significantly and inversely related to gallstone disease in Eastern countries (RR=0.35, 95%CI=0.17–0.73, $I^2=73\%$, $P=.025$), but not in Western countries (RR=0.89, 95%CI=0.81–0.99, $I^2=79.9\%$, $P=.001$). In subgroup analyses by year of publication, the studies after 2010 failed to show that vegetables consumption was inversely and significantly correlated with gallstone disease. For the number of cases, we got the results as the subgroup of study design. Meta-regression models demonstrated that study design ($P=.70$), sex ($P=.75$), study quality ($P=.85$), geographical regions ($P=.96$), publication year ($P=.46$), number of cases ($P=.16$), or endpoint ($P=.83$) was not significantly correlated with heterogeneity. (Fig. 5)

For fruits consumption, the inverse association with gallstone disease risk was consistent in subgroup analysis by sex (Table 3). In the subgroup of geographical locations, the above inverse correlation was only detected in Western countries (RR=0.88; 95% CI=0.83–0.92). On the contrary, the enrolled cohort study failed to demonstrate a positive correlation of fruits consumption with gallstone disease in Eastern countries (RR=0.77; 95% CI=0.29–1.25) (Table 3). For the number of studies <10, there was no need to perform meta regression.^[27]

5. Discussion

To our knowledge, it is the first meta-analysis to examine the correlation as well as dose-response of FVs consumption with gallstone disease risk. FVs consumption was detected to have an inverse correlation with gallstone risk, which was consistent in most subgroup analyses. Moreover, a linear dose-response correlation indicated that gallstone risk was reduced by 3% and 6% for every 200g per day increment in FVs consumption,

Table 1

Characteristics of the enrolled studies.

Study/publication	Sex	Age (years)	Country	No. case/number of participants	Follow	Sources of controls	Study design	Adjusted factors	Outcome	Adjusted OR/RR (95% CI)	Dose-response
Nordenfall 2018	Men and women	40–79	Sweden	2120/939715	1998–2011	Population	Cohort	Age, sex, education, smoking status, alcohol drinking, physical activity, use of aspirin, energy intake, coffee consumption	Cholecystectomy	V+F:0.95 (0.83–1.08)	Yes
Park 2017	Men and women	35–65	Korea	99/198	2014–2015	Hospital	Case-control	Age, sex, BMI, family history of gallstone disease, medical history, physical exercise, smoking, drinking, using of vitamins, minerals, n–3 fatty acids, ginseng, and plant extracts	Cholesterol gallstone Pigment gallstone	V:0.646 (0.38–1.09) F:0.771 (0.43–1.39) V:0.958 (0.63–1.47) F:1.104 (0.73–1.68)	NA
McConnell 2017	Men and women	25–63	UK	1182/49652	2003–2017	Population	Cohort	Stratified by sex, method of recruitment and region of residence and adjusted for smoking, alcohol intake, education level, Townsend deprivation index, long-term medical treatment for any condition and use of hormone replacement therapy	Symptomatic gallstone disease	V:1.22 (1.06–1.41)	NA
Figueredo 2017	Men and women	45.3–94.8	USA	13473/144409	1993–2012	Population	Cohort	Birth year, ethnicity, study area, duration of Medicare enrollment, smoking-pack years (never, past <20, past ≥20, current <20, current ≥20), alcohol intake (0, <24, 24–48, >48 ethanol g/day), body mass index (<25, 25–30, 30+ kg/m ²), diabetes (no/yes), calories, and education (≤high school, some college, > college graduate)	Gallbladder disease	M:V:0.85 (0.78–0.92) F:0.89 (0.83–0.96) W:V:0.93 (0.85–1.01) F:0.85 (0.80–0.91)	Yes
Barre 2017	Women	68–92	French	2778/64052	1993–2011	Population	Cohort	Age, educational level, body mass index, use of oral contraceptive, menopausal hormone therapy, smoking status, energy intake excluding alcohol, alcohol, physical activity, number of live births, diabetes, cholesterol-lowering drug	Cholecystectomy	F:0.75 (0.59–0.97) V:1.03 (0.58–1.82)	Yes
Lander 2016	Women	50 and 79	USA	3522/130, 859	1993–2016	Population	Cohort	Age, total energy, BMI, physical activity), NSES, race/ethnicity, oral contraceptive use, hormone therapy use, history of liver disease, statin use at baseline, thiazide use at baseline, alcohol use, clinical trial arms	Gallbladder disease	V P:0.87 (0.81–0.93)	Yes
Oskarsson 2015	Men and women	63–101	USA	2129/74773	1998–2011	Population	Cohort	Age, sex, education, smoking, alcohol intake, physical activity, aspirin use, coffee consumption, and energy intake	Cholecystectomy	V+F:0.92 (0.81–1.05)	NA
Lisa 2015	Women	20–30	USA	314/3070	–	Pregnant	Cohort	Age, prepregnancy body mass index, race, parity, cholesterol intake, total caloric intake, total fat intake, and total protein intake	Gallstone	V P:1.09 (0.60–1.96)	Yes
Walcher 2010	Women and men	18–65	Germany	171/2147	Retrospective	Population	Cohort	Alcohol consumption, caffeine consumption, nicotine consumption, vitamin C supplementation, physical activity, cholesterol level, serum HDL and LDL levels, diabetes mellitus, waist circumference, waist-to-hip ratio and chronic inflammatory bowel disease	Gallstone	V:1.14 (0.39–3.35)	NA
Tsai 2006	Women	30–55	USA	6608/77090	1984–2000	Population	Cohort	Age, BMI, hormone replacement therapy, current alcohol use, smoking coffee intake	Cholecystectomy	V+F:0.73 (0.61–0.88) V: 0.77 (0.62–0.97) F:0.88 (0.71–1.10) V:0.44 (0.28–0.69).	Yes
Bertola 2015	Women and men	NA	Argentina	51/120	NA	Hospital	Case-control	NA	Gallstone	V:0.14 (0.048–0.4)	NA
Jessri 2015	Women	40–65	Iran	101/305	NA	Hospital	Case-control	Education occupation, marital status, number of live births, physical activity, energy intake, calcium supplement intake, familial history of gallstone, and history of rapid weight loss	Gallstone	V:0.14 (0.048–0.4)	NA
Jayanthi1998	Women and men	NA	Indian	76/669	NA	Hospital	Case-control	NA	Gallstone	V:0.33 (0.19–0.57)	NA
Vecchia1998	Women and men	15–75	Italian	1359/46693	NA	Population	Cross-sectional	NA	Gallstone	V:0.92 (0.80, 1.07)	NA

F = female, F = fruits, M = male, NA = not available, No. = number, OR = odds ratio, RR = related ratio, UK = The United Kingdom, USA = The United States of America, V = vegetables, VP = vegetable protein.

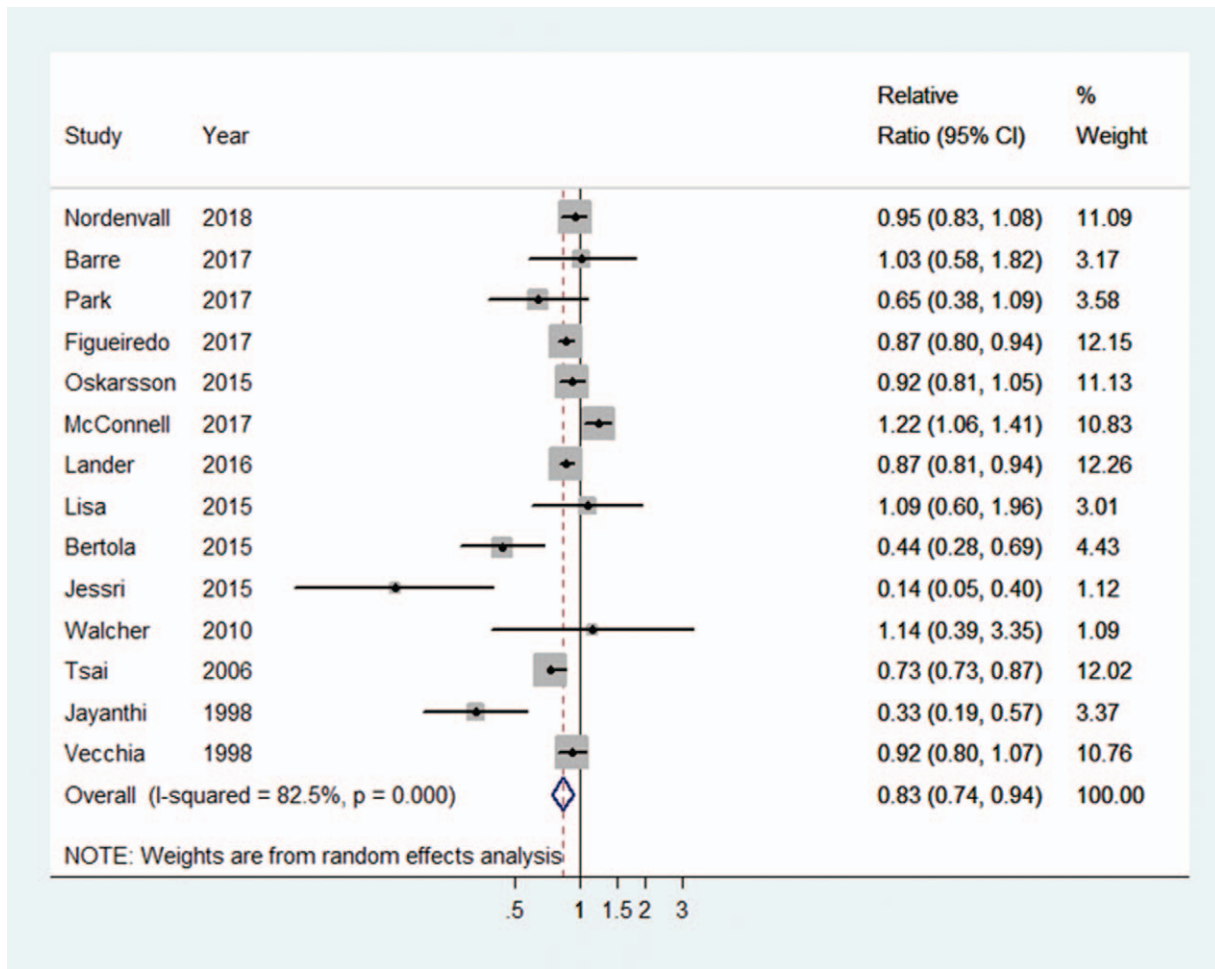


Figure 2. Forest plot of vegetables consumption with the risk of gallstone disease. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent 95% confidence intervals.

respectively. The clinicians can give this advice for those who have higher potential to develop gallstone disease to decrease the incidence. However, because our conclusion is all based on

observational studies, more experimental studies still need to do to prove it. A variety of chronic diseases have been studied with regard to FVs consumption, such as type 2 diabetes,^[28] depression,^[29] cardiovascular disease,^[30,31] and cancers.^[32,33] While eating more FVs has been showed to reduce the risk of all those disease, its association with gallstone disease still needs more studies.

5.1. Possible biological mechanisms

We can explain this inverse association from different aspects. On the one hand, higher FVs consumption increases dietary fiber, which shortens the intestinal transit.^[34] And dietary fiber has been inversely related to gallstone disease risk.^[35] Experimental researches indicated that dietary fiber might decrease both total and LDL cholesterol by increasing bile acid excretion and decreasing hepatic synthesis of cholesterol.^[36] In the contrast, higher FVs consumption possibly reduces fat intake.^[34] In the pathogenesis of gallstone disease, cholesterol supersaturation of the bile and cholesterol nucleation leading the dysmotility of gallbladder plays an important role.^[37] Because we cannot explain the beneficial effect of FVs from one point, it is reasonable to suggest that lots of studies are needed to explore it. Our

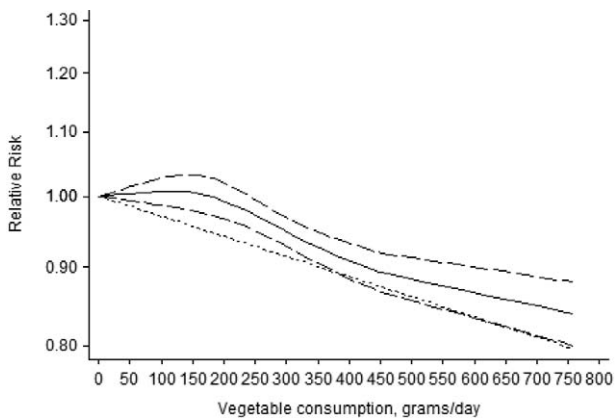


Figure 3. The dose-response analysis between vegetables consumption and the risk of gallstone disease. The solid line and long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.

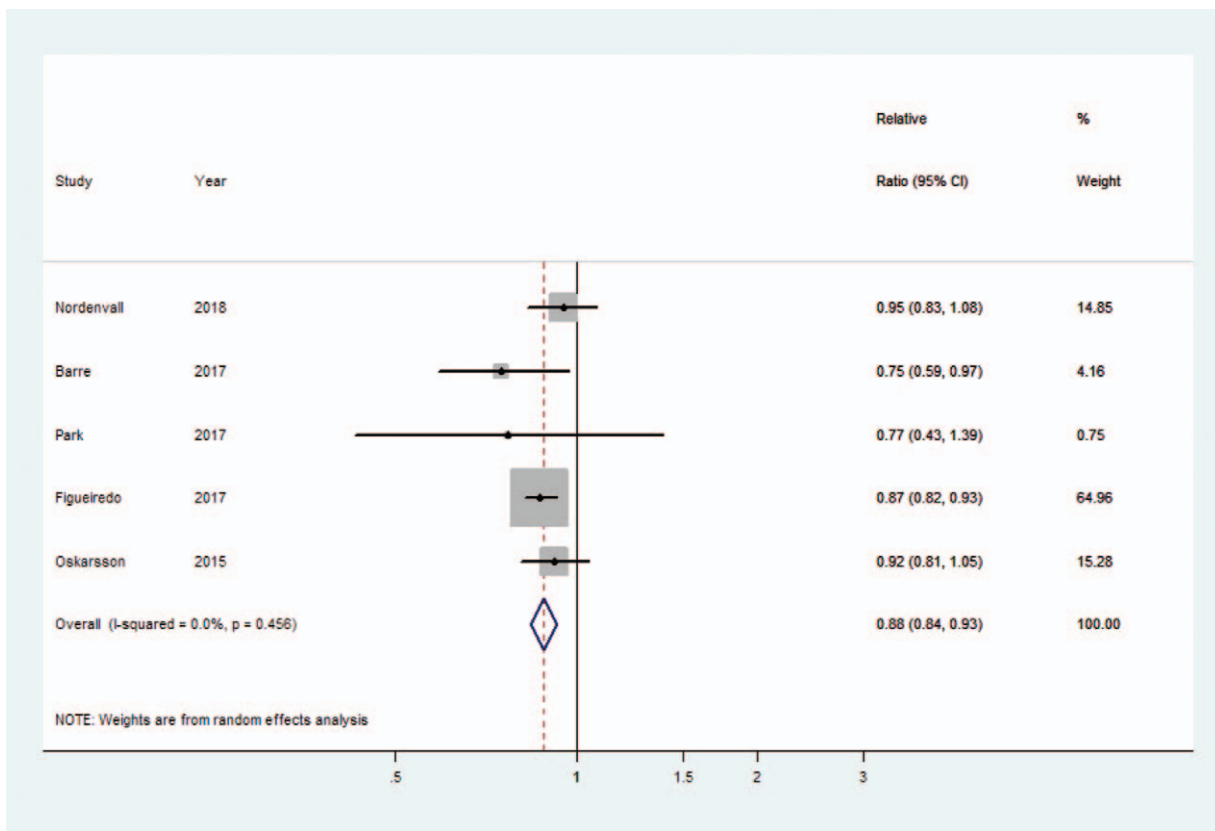


Figure 4. Forest plot of fruits consumption with the risk of gallstone disease. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent 95% confidence intervals.

Table 2
The main results of subgroup analysis of risk estimates between vegetables consumption and risk of gallstone disease.

Subgroup of vegetables consumptions	No. of study	RR (95%CI)	<i>Q</i> statistics	<i>I</i> ² value	<i>P</i> value
Sex					
Women	8	0.80 (0.68, 0.94)	54.3	85.3	.001
Mixed	6	0.83 (0.72, 0.96)	10.95	63.5	.027
Study design					
Cohort	9	0.92 (0.82, 1.02)	40.43	80.2	.001
Case control	4	0.39 (0.24, 0.62)	7.47	59.8	.058
Cross sectional	1	0.92 (0.80, 1.07)	-	-	-
Geographical locations					
West	11	0.89 (0.81, 0.99)	49.81	79.9	.001
East	3	0.35 (0.17, 0.73)	7.41	73	.025
Publication year					
After 2010	10	0.88 (0.77, 1.0)	43.30	79.2	.001
Before 2010	4	0.72 (0.55, 0.95)	16.81	82.2	.001
Number of cases					
≥1000	10	0.92 (0.83, 1.01)	40.86	78.0	.001
<1000	4	0.39 (0.24, 0.62)	7.47	59.8	.058
Endpoint of study					
Cholecystectomy	3	0.94 (0.85, 1.03)	0.25	0.01	.884
Gallstone disease	11	0.79 (0.68, 0.92)	70.88	85.9	.001
NOS scores					
NOS ≥7	12	0.86 (0.76, 0.97)	61.88	82.2	.001
NOS <7	2	0.57 (0.21, 1.56)	12.51	92	.001

CI=confidence interval, No.=number, RR=related risk.

meta-analysis also supports the present dietary guideline of elevated consumption of FVs as a healthy diet, and it is recommendable for people to decrease the risk of symptomatic gallstone disease requiring cholecystectomy.^[38,39]

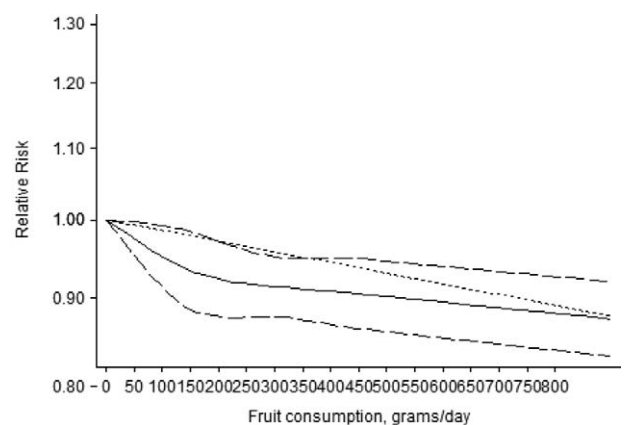


Figure 5. The dose-response analysis between fruits consumption and the risk of gallstone disease. The solid line and long dash line represent the estimated relative risk and its 95% confidence interval. Short dash line represents the linear relationship.

Table 3

The main results of subgroup analysis of risk estimates between fruits consumption and risk of gallstone disease.

Subgroup of fruits consumptions	No. of study	RR (95%CI)	<i>I</i> ² statistics	<i>P</i> value	<i>P</i> value
Sex					
Women	1	0.75 (0.58, 0.96)		–	–
Men	4	0.89 (0.84, 0.94)	1.92	0.01	.588
Geographical locations					
West	4	0.89 (0.83, 0.94)	3.44	12.8	.329
East	1	0.77 (0.43, 1.39)		–	–

CI=confidence interval, No.=number, RR=related risk.

5.2. Strengths and limitations of study

There are several advantages in the present study. To begin with, one of the major strengths is that it is the first study to examine the dose-response correlation of FVs consumption with gallstone disease. Secondly, it is a large-scale study (32,624 cases of gallstone patients and 14,87,059 participants), which makes it more convincing. From the perspective of clinical view, our findings indicate that we can decrease the incidence of gallstone disease by eating more FVs. Thirdly, most included studies were matched or adjusted for both age and BMI, which were considered to be major potential confounders that influence gallstone formation. In addition, the majority of enrolled studies in the meta-analysis were of high quality, which together to make the present outcomes more convincing.

Nevertheless, there are certain limitations. To begin with, because some subjects are likely to alter their dietary habits during follow-up, misclassification of FVs consumption should be taken into consideration. Secondly, there are many types of FVs, however, data concerning which type of fruits and vegetables were inaccessible, thereby affecting the virtual outcomes. As a result, we cannot conclude which type is better for preventing gallstone disease. Thirdly, we could clearly observe the heterogeneity among studies, which may make our results not so credible. Fourthly, results of meta-analysis for fruit consumption came from only five cohort studies. The enrolled case control studies harbored limited number of participants. The low number of studies can also be a source of heterogeneity. Finally, both case-control and cohort studies were enrolled, and the former one harbors recalled bias.

6. Conclusions

Collectively, our findings support the speculation that FVs consumption was able to decrease the risk of gallstone disease. The dose-response correlation indicated that gallstone risk was reduced by 3% and 4% for every 200g per day increment in FVs consumption.

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