Cholecystectomy and risk of cardiovascular disease, all-cause and cause-specific mortality: a systematic review and updated meta-analysis

Yang Song[1], Haishu Wang[2] and Yaowen Xu[2]

[1] Yantai Nurses School of Shandong, Yantai, China
[2] Department of Cardiology, Qingdao Municipal Hospital, Qingdao, Shandong Province, China

ABSTRACT

Objective: Questions remain about the association among cholecystectomy, cardiovascular disease, all-cause and cause-specific mortality. We performed a systematic review and meta-analysis to clarify these associations.

Methods: PubMed, Web of Science, Embase, and Cochrane Library databases were searched up to February 2024. Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated using a DerSimonian–Laird random effects model.

Results: We screened 16,595 articles and included 14 studies. No significant association was found between cholecystectomy and cardiovascular disease (CVD), with RR being 1.03 (95% CI [0.77–1.37], $p = 0.848$, $I^2 = 99.6\%$), even in results with high heterogenous studies excluded (RR 1.20, 95% CI [0.97–1.49], $p = 0.095$, $I^2 = 77.7\%$). Same result was proved in its subtype, coronary heart disease (RR 1.06, 95% CI [0.84–1.33], $p = 0.633$, $I^2 = 96.6\%$). Cholecystectomy increased CVD risk compared with healthy controls without gallstones (RR 1.19, 95% CI [1.05–1.35], $p = 0.007$, $I^2 = 83.3\%$) and lowered CVD risk compared with gallstone carriers (RR 0.62, 95% CI [0.57–0.67], $p < 0.001$, $I^2 = 82.1\%$). As for mortality, increase in the risk for all-cause (RR 1.17, 95% CI [1.03–1.34], $p = 0.020$, $I^2 = 51.6\%$) and cardiovascular (RR 1.24, 95% CI [1.06–1.47], $p = 0.009$, $I^2 = 20.7\%$) mortality, but not for cancer mortality (RR 1.18, 95% CI [0.95–1.47], $p = 0.131$, $I^2 = 0.0\%$), were observed after cholecystectomy.

Conclusion: Cholecystectomy may not be associated with the overall development of CVD, as well as CHD. Cholecystectomized patients showed increased CVD risk compared with healthy controls without gallstones, but decreased CVD risk compared with gallstone patients. Increased risk for all-cause and cardiovascular, but not cancer mortality was observed following cholecystectomy.

Subjects Cardiology, Epidemiology, Evidence Based Medicine, Internal Medicine
Keywords Cholecystectomy, Cardiovascular disease, Mortality, Systemic review, Meta-analysis

INTRODUCTION

Gallstones represent a major health problem in general populations worldwide (*Stinton & Shaffer, 2012*). During follow-up period, approximately less than one fourth developed symptomatic gallstones which needed hospitalization, leaving most of gallstones

Submitted 24 May 2024
Accepted 4 September 2024
Published 30 September 2024

Corresponding author
Yaowen Xu,
xu18661937081@126.com

Academic editor
Yoshinori Marunaka

Additional Information and Declarations can be found on page 12

DOI **10.7717/peerj.18174**

remaining clinically silent (*Shabanzadeh, 2023*; *Shabanzadeh, Sorensen & Jorgensen, 2016*). Cholecystectomy is presently an appropriate and frequently-used treatment for symptomatic gallstones, as well as other gallbladder diseases. However, several persistent symptoms and clinical conditions have been reported following cholecystectomy (*Lamberts et al., 2013*), including pain (*Wennmacker et al., 2018*), carcinoma (*Kharazmi et al., 2023*; *Mu et al., 2023*; *Wang, Xie & Lin, 2019*), liver diseases (*Konyn et al., 2023*; *Luo et al., 2023*), *etc*.

It has been demonstrated that gallstones share similar risk factors with cardiovascular disease (CVD), including age, hypertension, obesity, diabetes, hyperlipidemia, fatty liver disease, *etc* (*Ata et al., 2011*; *Tsai et al., 2004*). Those similar risk factors could be explained by cholesterol, the main component of gallstones (*Di Ciaula, Wang & Portincasa, 2018*) and atherosclerotic plaque in CVD (*Momiyama et al., 2014*), as well as shared genetic architecture between the two diseases (*Zhang et al., 2023*). Previous meta-analyses have demonstrated that a remarkable increase in the risk of CVD among patients with gallstone disease (GSD) (*Fairfield, Wigmore & Harrison, 2019*; *Fan, Chen & Dai, 2017*; *Upala, Sanguankeo & Jaruvongvanich, 2017*). However, only one meta-analysis reported the association between cholecystectomy and CVD (*Fairfield, Wigmore & Harrison, 2019*), with only three studies included. The results indicated that cholecystectomy exerted an increased risk of CVD compared with controls without gallstones, but neutral effect compared with gallstone subjects without cholecystectomy (*Fairfield, Wigmore & Harrison, 2019*). No meta-analysis has focused on all-cause and cause-specific mortality following cholecystectomy. These unsolved issues raised more population-based cohort studies on this issue (*Chen, Lin & Kao, 2021*; *Kim et al., 2021*; *Park et al., 2022*; *Wei et al., 2019*) recently. A more comprehensive meta-analysis was needed considering with the publication of more population-based new research. Thus, we conducted a systematic review and meta-analysis of the current evidence to investigate these associations.

MATERIALS AND METHODS

Search strategy

This work was registered with ID number CRD42024499426 on PROSPERO. We did not publish the protocol online or elsewhere. The article was prepared in compliance with the newest PRISMA statement. We searched case-control and cohort studies aiming to investigate the association among cholecystectomy, CVD, all-cause and cause-specific mortality up to February 2024 in the following databases, PubMed, Web of Science, Embase, and Cochrane Library databases. Only articles written in English were searched and the key words were displayed as follows: ("cholecystectomy" OR "cholecystectomies") AND ("cerebrovascular disease" OR "cardiovascular disease" OR "carotid atherosclerosis" OR "angina" OR "ischaemic heart disease" OR "myocardial infarction" OR "coronary artery disease" OR "stroke" OR "mortality" OR "all-cause mortality").

Selection criteria

Studies meeting the following criteria were included: (a) population-based research with calculable data; (b) the intervention strategy was cholecystectomy; and (c) the outcome

contained at least one of the following outcomes: CVD, all-cause, cardiovascular and cancer mortality. The identification of CVD was in accordance with previous studies, which included coronary heart disease (CHD) and stroke, defined as International Classification of Diseases 10th version (ICD-10) codes of I20-I25 and I60-I69 (*Moon et al., 2023*). Studies with one of the following items were excluded: (a) reviews, letters, case reports/series; (b) guidelines, protocols, and replies; (c) no original data or incalculable data; (d) follow-up time less than 90 days or deaths due to acute complications; and (e) studies limited to specific populations, such as people with diabetes, hemodialysis, *etc*.

The titles, abstracts and full texts of the selected literature were reviewed by two authors (Yang Song and Haishu Wang) leaving discrepancies confirmed by Dr.Yaowen Xu. Relevant articles which met the inclusion criteria were added during the reviewing process.

Data extraction and quality assessment

The data extraction process was conducted by two researchers (Yang Song and Yaowen Xu). The final confirmation of data extraction results was verified by Dr. Yaowen Xu. The detailed characteristics of the included studies were recorded, including the author and publication year, number of participants and follow-up time, method of cholecystectomy identification, type of outcome, number of cases for outcome, and adjustment. The Newcastle–Ottawa Scale (NOS) (*Wells et al., 2013*) was utilized to assess the study quality. Studies with a score of 7 to 9 were considered as high quality, studies with a score of 4 to 6 of moderate quality, and studies with a score of 0 to 3 of low quality.

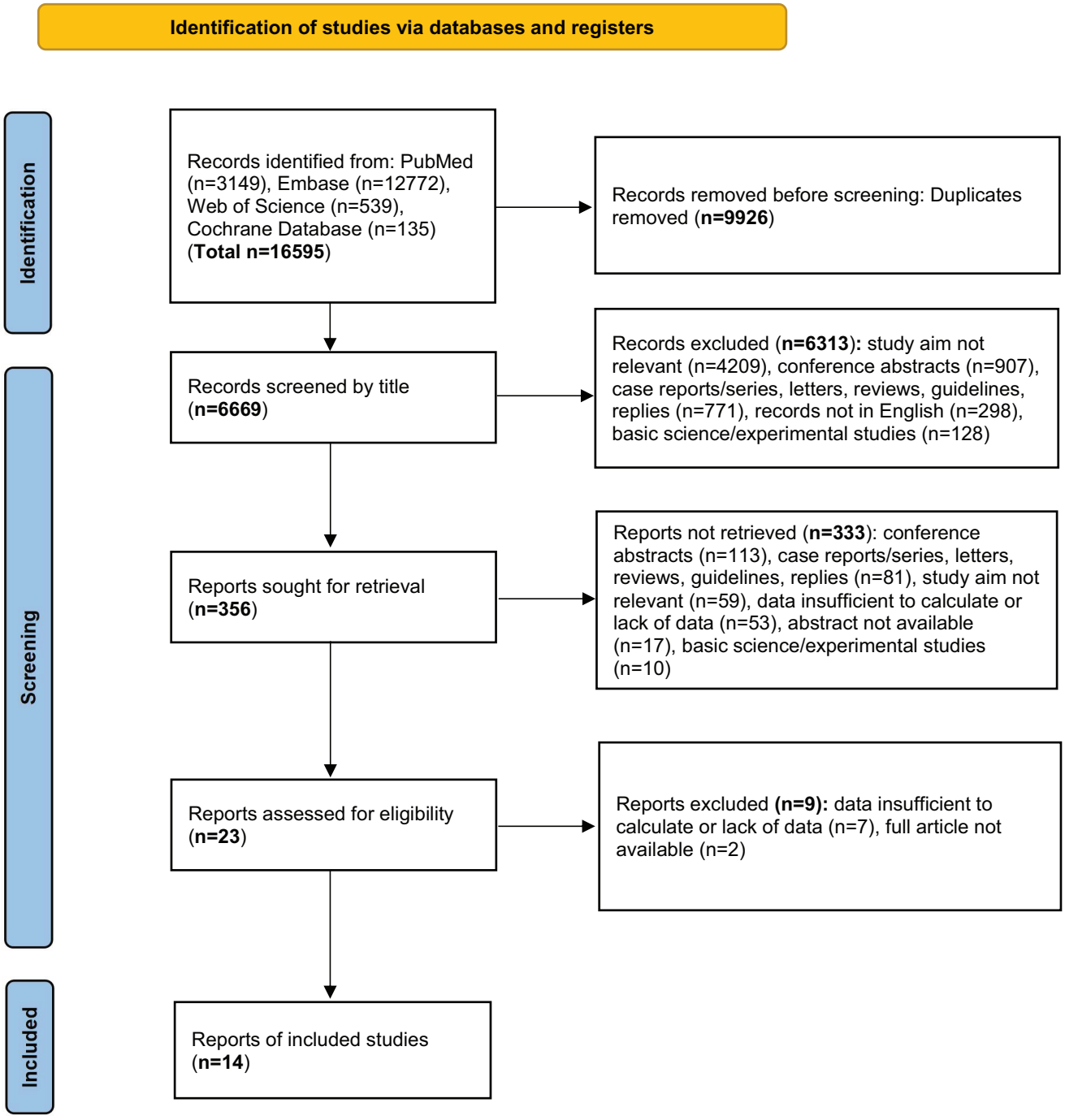
The certainty of the evidence was rated using the online GRADEpro software (https://www.gradepro.org/) (*Atkins et al., 2004*) by Dr. Yang Song and Yaowen Xu. Five aspects, including study limitations, consistency of effect, imprecision, indirectness, and publication bias (*Guyatt et al., 2008*) were evaluated in the GRADE system. The certainty of evidence in each dimension was categorized as high, moderate, low, or very low quality.

All data analyses were conducted using STATA 17.0 (College Station, TX, USA: StataCorp LLC). Pooled relative risk (RR) and 95% CI was calculated from RR, hazard ratio (HR), *etc*, using the DerSimonian–Laird method and p value for the pooled analysis was provided. Heterogeneity was assessed using the I^2 statistic (*Greenland, 1987*). I^2 value > 50% was identified as significant heterogeneity. Publication bias was identified by a funnel plot and Egger's test (*Harbord, Egger & Sterne, 2006*). A sensitivity analysis was also conducted performed to find the possible source of heterogeneity. The significance level was $\alpha = 0.05$.

RESULTS

Study selection and characteristics

Figure 1 showed the literature selection process. Totally the initial search yielded 16,595 articles, of which 9,926 repetitive articles were removed. After further review for title, articles were excluded due to the following reasons: study aim not relevant (n = 4,209), conference abstracts (n = 907), case reports/series, letters, reviews, guidelines, replies (n = 771), records not in English (n = 298), basic science/experimental studies (n = 128). After further revision for abstracts and full articles, a total of 14 articles were finally



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Figure 1 Flow diagram of literature search. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. Full-size DOI: 10.7717/peerj.18174/fig-1

Table 1 Characteristics of the studies included in the systematic review and meta-analysis.

Authors, Year	Study characteristics	Identification of CS	Type of outcome	No. of cases for outcome	Adjustment
Bortnichak et al. (1985)	Cohort study: 5,209 subjects at baseline (367 patients with CS) Follow up period: 26 years	Medical records	CVD (CHD)	706	Sex, diabetes, left ventricular hypertrophy, serum cholesterol, age, length of follow-up, systolic blood pressure, Framingham Relative Weight, cigarette smoking
Strom et al. (1986)	Case-control study: Women (550 MI cases and 1,658 controls), Men (1,511 MI cases and 3,837 controls)	Questionnaires	CVD (MI)	2,061	Age and geography
Andersen et al. (1995)	Cohort study: 11,123 CS patients at baseline Follow up period: 6 years	Medical records	All-cause mortality	869	Age differences
Rosenmuller et al. (2007)	Cohort study: 44,084 CS patients at baseline Follow up end: the date of death or the end of follow-up (December 31st 2004), whichever occurred first	Medical records	All-cause mortality	275	None
Ruhl & Everhart (2011)	Cohort study: 14,228 participants (12,210 non-GSD subjects and 2018 GSD subjects, including CS) Follow up period: 18 years	Medical records	All-cause, cardiovascular, and cancer mortality	2017 (all-cause) 737 (cardiovascular) 550 (cancer)	Age, sex, race/ethnicity, education, BMI, waist-to-hip ratio, glucose status, total serum cholesterol, high-density lipoprotein cholesterol, smoking, drinking, caffeine, physical activity, C-reactive protein
Wirth et al. (2015)	Cohort study: 46,468 participants free of CVD and diabetes at baseline Follow up period: 8 years	Questionnaires	CVD (stroke or MI)	919	Sex, age, study center, educational achievement, physical activity, smoking habits, alcohol intake, BMI, waist circumference, hypertension and hyperlipidemia
Shabanzadeh et al. (2017) **(mortality)**	Cohort study: 5,928 participants at baseline (gallstones at ultrasound: n = 402; CS: n = 189; no gallstones: n = 5,337) Follow up period: 24.7 years	Medical records	All-cause, cardiovascular, and cancer mortality	2,428 (all-cause) 652 (cardiovascular) 750 (cancer)	Age, sex, BMI, social group I–V, smoking, alcohol consumption, diabetes, SBP > 140 mmHg, DBP > 90 mmHg, non-HDL, HDL
Shabanzadeh et al. (2017) **(CVD)**	Cohort study: 5,496 participants at baseline (gallstones at ultrasound: n = 346; CS: n = 158; no gallstones: n = 4,992) Follow up period: 32 years	Abdominal ultrasound	CVD (CHD, cerebrovascular disease, and peripheral artery disease)	1,892	Age, sex, cohort number, BMI, SBP > 140 mmHg, DBP > 90 mmHg, non-HDL, HDL, smoking, alcohol consumption, diet, physical activity level, social group
Wei et al. (2019)	Cohort study: 155,356 CS and 155,356 control subjects in the study cohort Follow up end: until diagnosis of stroke of the end of 2013	Medical records	CVD (stroke)	19,098	Age, sex, and major comorbidities

(Continued)

Table 1 (continued)

Authors, Year	Study characteristics	Identification of CS	Type of outcome	No. of cases for outcome	Adjustment
Chen, Lin & Kao (2021)	Cohort study: 122,421 CS and 122,421 control subjects in the cohort Follow up period: until the diagnosis of AMI or the end of 2011	Medical records	CVD (AMI)	4,093	Age, sex, occupation, urbanization level, comorbidity of atrial fibrillation, hypertension, hyperlipidemia, diabetes, stroke, heart failure, and COPD
Kim et al. (2021)	Cohort study: 146,928 CS subjects and 268,502 control subjects at baseline Follow up period: 2.56 years (median)	Medical records	CVD (MI and heart failure)	8,924	Age, sex, income, place of residence, diabetes, hypertension, dyslipidemia, smoking, drinking, regular exercise, BMI
Park et al. (2022)	Cohort study: 491,267 gallstone patients (179,321 with CS) and controls (n = 4,912,670) Follow up period: 15 years	Medical records	CVD (MI and cerebral infarction)	15,691	Visit frequency as an outpatient
Su et al. (2022)	Cohort study: 13,975 ACS patients at baseline (12,265 without GSD and 1,710 with GSD, of which 511 had CS) Follow up period: 2.96 years (mean)	Medical records	All-cause and cardiovascular mortality	1,015 (all-cause) 540 (cardiovascular)	Age, sex, BMI, smoking habits, alcohol intake, classification of ACS, PCI therapy, previous myocardial infarction, hypertension, diabetes, and hyperlipidemia
Konyn et al. (2023)	Cohort study: 11,153 individuals were included (9,521 without GSD and 1,632 with GSD, of which 717 had CS) Follow up period: 23 years	Abdominal ultrasound	All-cause, cardiovascular, and cancer mortality	Not mentioned	Seasonality

Note:
Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CS, cholecystectomy; CVD, cardiovascular disease; CHD, coronary heart disease; DBP, diastolic blood pressure; GSD, gallstone disease; HDL, high-density lipoprotein; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

included in the meta-analysis (*Andersen et al., 1995*; *Bortnichak et al., 1985*; *Chen, Lin & Kao, 2021*; *Kim et al., 2021*; *Konyn et al., 2023*; *Park et al., 2022*; *Rosenmuller et al., 2007*; *Ruhl & Everhart, 2011*; *Shabanzadeh et al., 2017*; *Shabanzadeh, Sorensen & Jorgensen, 2017*; *Strom et al., 1986*; *Su et al., 2022*; *Wei et al., 2019*; *Wirth et al., 2015*).

Table 1 shows the number of studies, cases, participants and other main characteristics of included studies. Five studies were from Europe, four were from the USA, and five were from Asia. Eight studies reported outcome of CVD and six studies reported mortality, including all-cause, cardiovascular and cancer mortality. Cases from most studies derived from medical records in hospitals or data from health care programs. NOS scoring analysis were indicated in Table S1. The mean NOS score was 6.64.

Cholecystectomy and CVD

The pooled effect on the development of CVD in patients with cholecystectomy was 1.03 (95% CI [0.77–1.37], p = 0.848, I^2 = 99.6%, Fig. 2), with heterogeneity between studies. We did not detect significant publication bias through funnel plot and Egger's tests (Fig. 3). Sensitivity analysis indicated that four studies may be the main source of heterogeneity

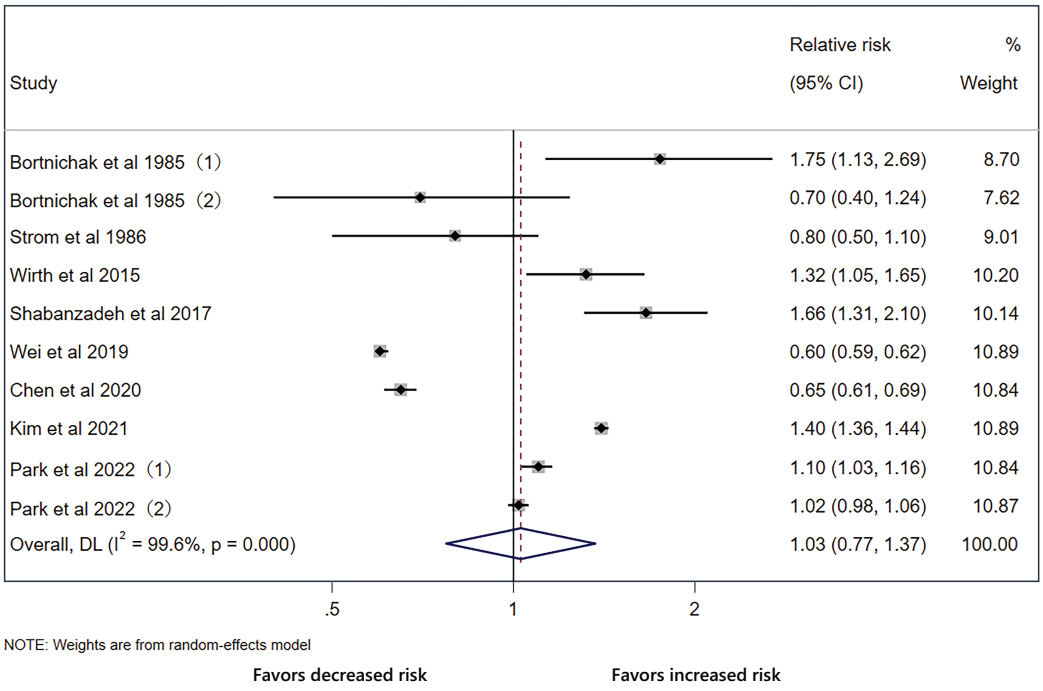


Figure 2 Pooled analysis of the effect of cholecystectomy on cardiovascular disease. Forest plot for cholecystectomy and risk of cardiovascular disease with all studies.
Full-size DOI: 10.7717/peerj.18174/fig-2

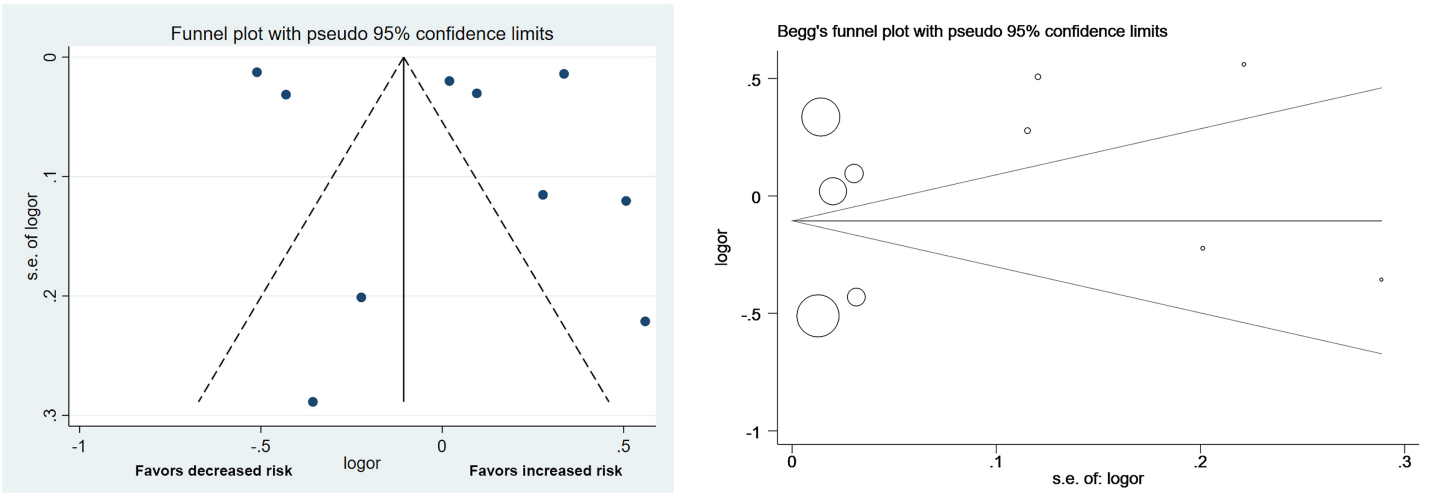


Figure 3 Funnel plot of the analysis. Publication bias of the included studies. (A) Funnel plot for publication bias. (B) Egger's test results.
Full-size DOI: 10.7717/peerj.18174/fig-3

(*Chen, Lin & Kao, 2021*; *Kim et al., 2021*; *Park et al., 2022*; *Wei et al., 2019*) (Fig. 4). After removal of the four studies, cholecystectomy still showed no association with CVD (RR 1.20, 95% CI [0.97–1.49], p = 0.095, I^2 = 77.7%, Fig. 5).

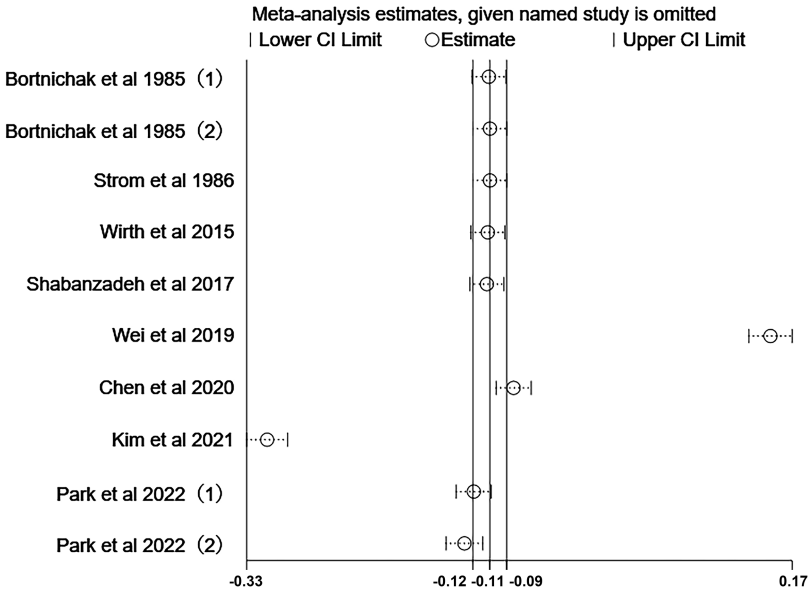


Figure 4 Sensitivity analysis. Sensitivity analysis of all included studies for cholecystectomy and cardiovascular disease. Full-size DOI: 10.7717/peerj.18174/fig-4

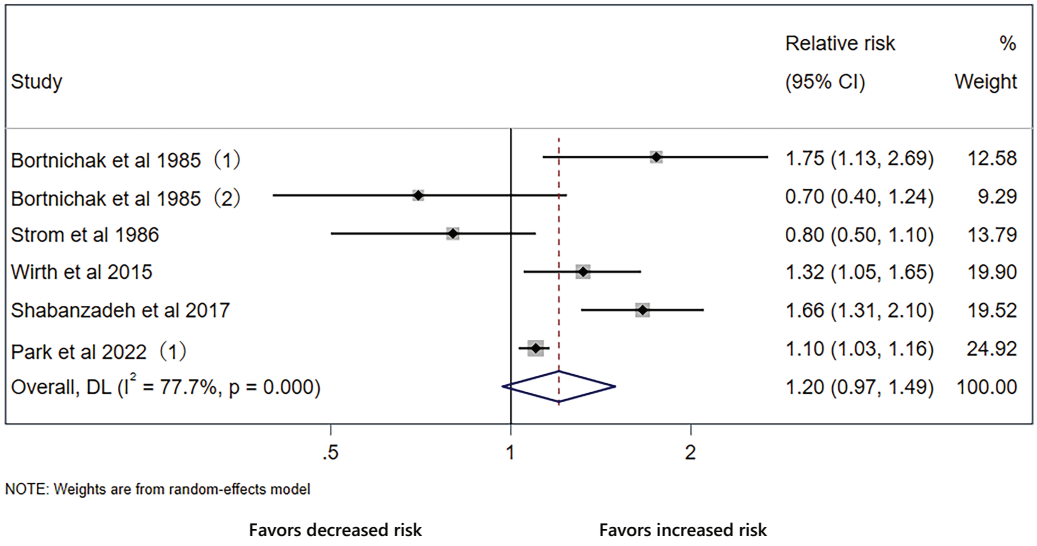


Figure 5 Analysis with stable results still shows no association between cholecystectomy and cardiovascular disease. Forest plot of relative risk between cholecystectomy and cardiovascular disease with stable results. Full-size DOI: 10.7717/peerj.18174/fig-5

The outcomes of the original analysis include CHD and stroke, which may be a possible explanation of heterogeneity. In the initial analysis, only two studies reported outcome of stroke and they were the major sources of heterogeneity. We conducted subgroup analysis of CHD. There was still no significant association between cholecystectomy and CHD (RR 1.06, 95% CI [0.84–1.33], $p = 0.633$, $I^2 = 96.6\%$, Fig. 6A). As for the type of control group, cholecystectomy increased CVD risk compared with healthy controls without gallstones (RR 1.19, 95% CI [1.05–1.35], $p = 0.007$, $I^2 = 83.3\%$, Fig. 6B) and lowered CVD risk

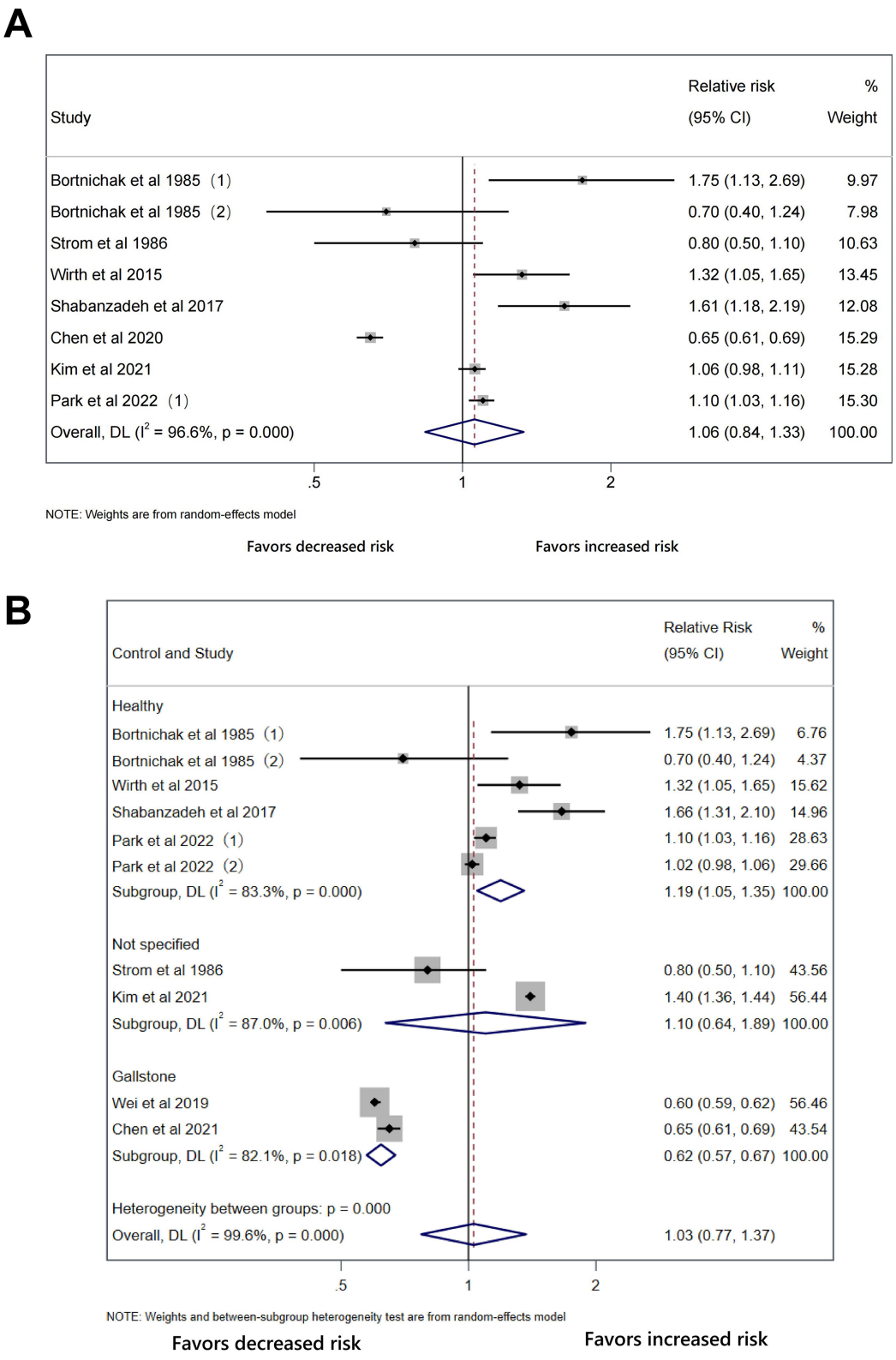


Figure 6 No association between cholecystectomy and coronary heart disease. Forest plot of relative risk between cholecystectomy and CVD in subgroup analysis. (A) Cholecystectomy in coronary heart disease. (B) Stratified by type of control group. Full-size DOI: 10.7717/peerj.18174/fig-6

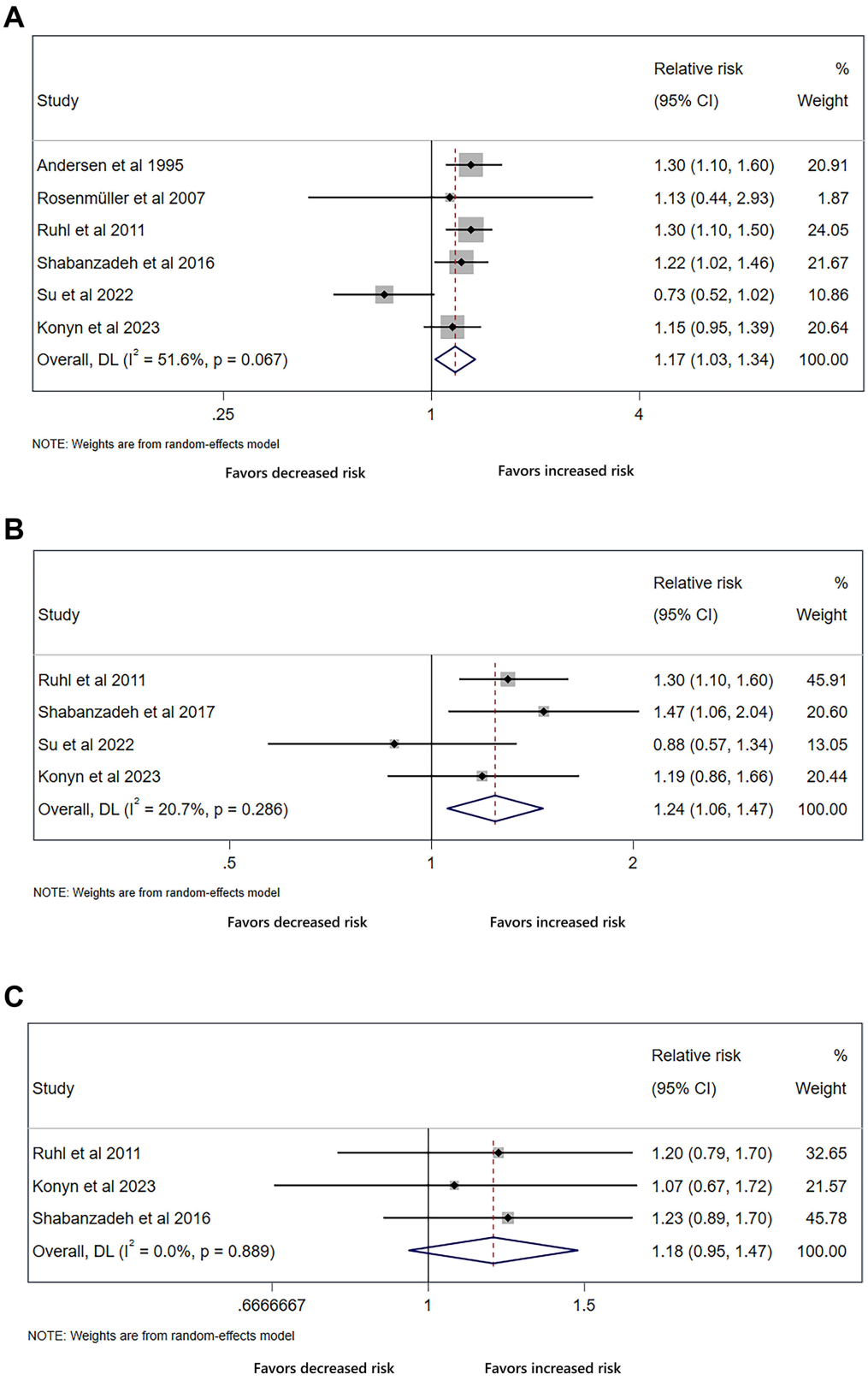


Figure 7 Cholecystectomy shows increased risk for all-cause and cardiovascular mortality. Forest plot of relative risk between cholecystectomy and mortality. (A) All-cause mortality. (B) Cardiovascular mortality. (C) Cancer mortality. Full-size DOI: 10.7717/peerj.18174/fig-7

compared with gallstone carriers (RR 0.62, 95% CI [0.57–0.67], $p < 0.001$, $I^2 = 82.1\%$, Fig. 6B).

Cholecystectomy, all-cause, cardiovascular and cancer mortality

The analysis of all-cause mortality included six studies, with four studies for cardiovascular mortality and three studies for cancer mortality. The results showed that cholecystectomy conferred an increased risk of all-cause mortality (RR 1.17, 95% CI [1.03–1.34], $p = 0.020$, $I^2 = 51.6\%$, Fig. 7A), and cardiovascular mortality (RR 1.24, 95% CI [1.06–1.47], $p = 0.009$, $I^2 = 20.7\%$, Fig. 7B). However, we did not detect significant difference in cancer mortality (RR 1.18, 95% CI [0.95–1.47], $p = 0.131$, $I^2 = 0.0\%$, Fig. 7C).

DISCUSSION

In our study, cholecystectomy was not associated with the overall development of CVD, as well as CHD. In subgroup analysis, cholecystectomy increased CVD risk compared with non-gallstone controls but lowered risk compared with gallstone patients. Besides, increase in risk were observed for all-cause and cardiovascular mortality, but not for cancer mortality. These results raised concern for surveillance strategies following cholecystectomy.

Several studies have reported significant association between GSD, especially cholesterol stone and CVD (*Upala, Sanguankeo & Jaruvongvanich, 2017*; *Zhang et al., 2023*; *Zheng et al., 2016*). One of the potential mechanisms is the established common risk factors between the two diseases, including hypertension, diabetes, insulin resistance, obesity, hyperlipidemia, *etc* (*Misciagna et al., 2000*; *Targher & Byrne, 2015*; *Tsai et al., 2004*; *Volzke et al., 2005*; *Wang, Cohen & Carey, 2009*), which is still significant even after adjustment of common risk factors. Besides, similar alterations in microbiota and microbiota-derived metabolites are also observed in the two diseases, with decreased abundance of *Faecalibacterium* (*van den Munckhof et al., 2018*; *Wu et al., 2013*) and increased concentration of trimethylamine-N-oxide (TMAO) (*Amrein et al., 2020*; *Chen et al., 2019*; *Zhu et al., 2021*). It seems that the above mechanisms focus more on gallstone, especially cholesterol stone itself, rather than cholecystectomy. Our study also demonstrated that cholecystectomy showed no association with the overall development of CVD, as well as CHD, based on current evidence. Partially in accordance with our results, a recent study demonstrated that the association between GSD and CVD might be identifies as sharing a similar biological mechanism, but not a direct causal effect (*Zhang et al., 2023*), characterized by multiple pleiotropic loci identified in cross-phenotype association study and shared gene-tissue pairs detected by transcriptome-wide association study (*Zhang et al., 2023*).

One of the interesting findings was that cholecystectomy increased CVD risk compared with healthy controls without gallstones, while lowered CVD risk compared with gallstone carriers. Besides, the reasons for cholecystectomy of the included studies in "cholecystectomy *vs* healthy controls" group were all due to gallstones. With the established conclusions that GSD imposed an increased risk on CVD (*Fairfield, Wigmore & Harrison, 2019*; *Upala, Sanguankeo & Jaruvongvanich, 2017*), it was logically anticipated that cholecystectomy in patients with gallstone could partially neutralize the detrimental

effects of the cardiovascular system caused by gallstone itself. However, it could still increase CVD risk significantly. With limited included studies in our meta-analysis, more population-based studies are still needed to verify these conclusions.

Our study also proved that cholecystectomy increased all-cause and cardiovascular mortality with little heterogeneity, but not cancer mortality. Currently, the underlying mechanisms are still uncertain. It is postulated that GSD shares similar features with the mechanisms of cardiovascular and other common causes of death (*Ruhl & Everhart, 2011*), including gallbladder hypomotility (*Portincasa, Moschetta & Palasciano, 2006*), insulin resistance (*Cortes, Barrera & Nervi, 2020*; *Jornayvaz, Samuel & Shulman, 2010*) and dysregulation of lipid metabolism in the liver (*Targher, Day & Bonora, 2010*). The above mechanisms, except for gallbladder hypomotility, are also verified in cholecystectomy (*Cortes et al., 2017*; *Latenstein et al., 2020*; *Shi et al., 2020*). One study pointed out that all-cause mortality for gallstones and cholecystectomy was nearly the same, but was higher compared with non-GSD controls (*Ruhl & Everhart, 2011*). However, the studies to investigate the association between gallstone and mortality is insufficient. Whether the increased all-cause and cardiovascular mortality for cholecystectomy is due to gallstone formation or other independent mechanisms still needs further investigation.

Our study has several limitations. Although most of the included studies were adjusted for major confounders such as age, sex, diabetes, hypertension, there were likely to be residual or unmeasured confounding factors. In addition, the high heterogeneity in this study arouse the need for more studies to confirm these associations. Although we conducted analysis to reduce heterogeneity according to sensitivity or subgroup analysis, the heterogeneity was still significant in some results. The heterogeneity may be ascribed to subtype of CVD, reasons for cholecystectomy, ethics, genetic differences and environmental and lifestyle-related factors, *etc*. Besides, the certainty of the evidence was low according to the assessment of limitations, indirectness, and imprecision.

CONCLUSIONS

Currently, there is no enough solid evidence on the association between cholecystectomy and CVD, including CHD. It should be noted that cholecystectomy may increase CVD risk compared with non-gallstone controls but lower risk compared with gallstone patients. Besides, we demonstrate an increased risk of all-cause and cardiovascular mortality following cholecystectomy. The current findings provide evidence for surveillance strategies for cholecystectomy. More population-based studies are needed for to confirm these associations.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

The authors received no funding for this work.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Yang Song conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Haishu Wang performed the experiments, prepared figures and/or tables, and approved the final draft.
- Yaowen Xu conceived and designed the experiments, performed the experiments, analyzed the data, authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

The raw measurements are available in the Supplemental File.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.18174#supplemental-information.

REFERENCES

Amrein ML, Lopez-Ayala P, Walter J, Widmer V, Mueller C. 2020. Coronary heart disease and TMAO concentrations. *Journal of the American College of Cardiology* **75(24)**:3102 DOI 10.1016/j.jacc.2020.03.079.

Andersen TF, Bronnum-Hansen H, Jorgensen T, Roepstorff C, Loft A, Madsen M. 1995. Survival until 6 years after cholecystectomy: female population of Denmark, 1977–1983. *World Journal of Surgery* **19(4)**:609–615 DOI 10.1007/BF00294734.

Ata N, Kucukazman M, Yavuz B, Bulus H, Dal K, Ertugrul DT, Yalcin AA, Polat M, Varol N, Akin KO, Karabag A, Nazligul Y. 2011. The metabolic syndrome is associated with complicated gallstone disease. *Canadian Journal of Gastroenterology* **25(5)**:274–276 DOI 10.1155/2011/356761.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connel D, Oxman AD, Phillips B, Schunemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S, Group GW. 2004. Grading quality of evidence and strength of recommendations. *BMJ* **328**:1490 DOI 10.1136/bmj.328.7454.1490.

Bortnichak EA, Freeman DH Jr., Ostfeld AM, Castelli WP, Kannel WB, Feinleib M, McNamara PM. 1985. The association between cholesterol cholelithiasis and coronary heart disease in Framingham. *American Journal of Epidemiology* **121(1)**:19–30 DOI 10.1093/oxfordjournals.aje.a113978.

Chen CH, Lin CL, Kao CH. 2021. The effect of cholecystectomy on the risk of acute myocardial infarction in patients with gallbladder stones. *Postgraduate Medicine* **133(2)**:209–216 DOI 10.1080/00325481.2020.1846964.

Chen Y, Weng Z, Liu Q, Shao W, Guo W, Chen C, Jiao L, Wang Q, Lu Q, Sun H, Gu A, Hu H, Jiang Z. 2019. FMO3 and its metabolite TMAO contribute to the formation of gallstones. *Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease* **1865(10)**:2576–2585 DOI 10.1016/j.bbadis.2019.06.016.

Cortes VA, Barrera F, Nervi F. 2020. Pathophysiological connections between gallstone disease, insulin resistance, and obesity. *Obesity Reviews* **21(4)**:e12983 DOI 10.1111/obr.12983.

Cortes V, Quezada N, Uribe S, Arrese M, Nervi F. 2017. Effect of cholecystectomy on hepatic fat accumulation and insulin resistance in non-obese Hispanic patients: a pilot study. *Lipids in Health and Disease* **16**:129 DOI 10.1186/s12944-017-0525-3.

Di Ciaula A, Wang DQ, Portincasa P. 2018. An update on the pathogenesis of cholesterol gallstone disease. *Current Opinion in Gastroenterology* **34(2)**:71–80 DOI 10.1097/MOG.0000000000000423.

Fairfield CJ, Wigmore SJ, Harrison EM. 2019. Gallstone disease and the risk of cardiovascular disease. *Scientific Reports* **9**:5830 DOI 10.1038/s41598-019-42327-2.

Fan LL, Chen BH, Dai ZJ. 2017. The relation between gallstone disease and cardiovascular disease. *Scientific Reports* **7**:15104 DOI 10.1038/s41598-017-15430-5.

Greenland S. 1987. Quantitative methods in the review of epidemiologic literature. *Epidemiologic Reviews* **9**:1–30 DOI 10.1093/oxfordjournals.epirev.a036298.

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. 2008. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336(7650)**:924–926 DOI 10.1136/bmj.39489.470347.AD.

Harbord RM, Egger M, Sterne JA. 2006. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* **25(20)**:3443–3457 DOI 10.1002/sim.2380.

Jornayvaz FR, Samuel VT, Shulman GI. 2010. The role of muscle insulin resistance in the pathogenesis of atherogenic dyslipidemia and nonalcoholic fatty liver disease associated with the metabolic syndrome. *Annual Review of Nutrition* **30**:273–290 DOI 10.1146/annurev.nutr.012809.104726.

Kharazmi E, Scherer D, Boekstegers F, Liang Q, Sundquist K, Sundquist J, Fallah M, Lorenzo Bermejo J. 2023. Gallstones, cholecystectomy, and kidney cancer: observational and mendelian randomization results based on large cohorts. *Gastroenterology* **165**:218–227 e218 DOI 10.1053/j.gastro.2023.03.227.

Kim YJ, Park YS, Shin CM, Han K, Park SH, Yoon H, Kim N, Lee DH. 2021. Risk of heart disease after cholecystectomy: a nationwide population-based cohort study in South Korea. *Journal of Clinical Medicine* **10(15)**:3253 DOI 10.3390/jcm10153253.

Konyn P, Alshuwaykh O, Dennis BB, Cholankeril G, Ahmed A, Kim D. 2023. Gallstone disease and its association with nonalcoholic fatty liver disease, all-cause and cause-specific mortality. *Clinical Gastroenterology and Hepatology* **21(4)**:940–948 e942 DOI 10.1016/j.cgh.2022.04.043.

Lamberts MP, Lugtenberg M, Rovers MM, Roukema AJ, Drenth JP, Westert GP, van Laarhoven CJ. 2013. Persistent and de novo symptoms after cholecystectomy: a systematic review of cholecystectomy effectiveness. *Surgical Endoscopy* **27(3)**:709–718 DOI 10.1007/s00464-012-2516-9.

Latenstein CSS, Alferink LJM, Darwish Murad S, Drenth JPH, van Laarhoven C, de Reuver PR. 2020. The association between cholecystectomy, metabolic syndrome, and nonalcoholic fatty liver disease: a population-based study. *Clinical and Translational Gastroenterology* **11(4)**:e00170 DOI 10.14309/ctg.0000000000000170.

Luo D, Chen XP, Dai Y, Kuang F, Kang MJ, Li B, Su S. 2023. Cholecystectomy and risk of liver disease: a systematic review and meta-analysis of 27 million individuals. *International Journal of Surgery* **109(5)**:1420–1429 DOI 10.1097/JS9.0000000000000332.

Misciagna G, Guerra V, Di Leo A, Correale M, Trevisan M. 2000. Insulin and gall stones: a population case control study in southern Italy. *Gut* **47**:144–147 DOI 10.1136/gut.47.1.144.

Momiyama Y, Adachi H, Fairweather D, Ishizaka N, Saita E. 2014. Inflammation, atherosclerosis and coronary artery disease. *Clinical Medicine Insights: Cardiology* **8(3)**:67–70 DOI 10.4137/CMC.S39423.

Moon JH, Jeong S, Jang H, Koo BK, Kim W. 2023. Metabolic dysfunction-associated steatotic liver disease increases the risk of incident cardiovascular disease: a nationwide cohort study. *EClinicalMedicine* **65**:102292 DOI 10.1016/j.eclinm.2023.102292.

Mu L, Li W, Ren W, Hu D, Song Y. 2023. The association between cholecystectomy and the risk of colorectal cancer: an updated systematic review and meta-analysis of cohort studies. *Translational Cancer Research* **12(6)**:1452–1465 DOI 10.21037/tcr-22-2049.

Park SM, Kim HJ, Kang TU, Swan H, Ahn HS. 2022. Cholecystectomy reduces the risk of myocardial and cerebral infarction in patients with gallstone-related infection. *Scientific Reports* **12**:16749 DOI 10.1038/s41598-022-20700-y.

Portincasa P, Moschetta A, Palasciano G. 2006. Cholesterol gallstone disease. *Lancet* **368(9531)**:230–239 DOI 10.1016/S0140-6736(06)69044-2.

Rosenmuller M, Haapamaki MM, Nordin P, Stenlund H, Nilsson E. 2007. Cholecystectomy in Sweden 2000–2003: a nationwide study on procedures, patient characteristics, and mortality. *BMC Gastroenterol* **7**:35 DOI 10.1186/1471-230X-7-35.

Ruhl CE, Everhart JE. 2011. Gallstone disease is associated with increased mortality in the United States. *Gastroenterology* **140(2)**:508–516 DOI 10.1053/j.gastro.2010.10.060.

Shabanzadeh DM. 2023. The symptomatic outcomes of cholecystectomy for gallstones. *Journal of Clinical Medicine* **12(5)**:1897 DOI 10.3390/jcm12051897.

Shabanzadeh DM, Skaaby T, Sorensen LT, Jorgensen T. 2017. Screen-detected gallstone disease and cardiovascular disease. *European Journal of Epidemiology* **32(6)**:501–510 DOI 10.1007/s10654-017-0263-x.

Shabanzadeh DM, Sorensen LT, Jorgensen T. 2016. A prediction rule for risk stratification of incidentally discovered gallstones: results from a large cohort study. *Gastroenterology* **150**:156–167 e151 DOI 10.1053/j.gastro.2015.09.002.

Shabanzadeh DM, Sorensen LT, Jorgensen T. 2017. Gallstone disease and mortality: a cohort study. *International Journal of Public Health* **62(3)**:353–360 DOI 10.1007/s00038-016-0916-7.

Shi Y, Sun M, Wang Z, Hsu HT, Shen M, Yang T, Fu Q. 2020. Cholecystectomy is an independent factor of enhanced insulin release and impaired insulin sensitivity. *Diabetes Research and Clinical Practice* **162**:108080 DOI 10.1016/j.diabres.2020.108080.

Stinton LM, Shaffer EA. 2012. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut and Liver* **6(2)**:172–187 DOI 10.5009/gnl.2012.6.2.172.

Strom BL, Schinnar R, Crown V, Soloway R, Stolley PD, Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. 1986. Does gallbladder removal protect against subsequent myocardial infarction? *American Journal of Epidemiology* **124(3)**:420–427 DOI 10.1093/oxfordjournals.aje.a114412.

Su W, Zhu JG, Li WP, Chen H, Li HW. 2022. Gallstone disease and the risk of cardiac mortality in patients with acute coronary syndrome. *Frontiers in Cardiovascular Medicine* **9**:1033959 DOI 10.3389/fcvm.2022.1033959.

Targher G, Byrne CD. 2015. Gallstone disease and increased risk of ischemic heart disease: causal association or epiphenomenon? *Arteriosclerosis, Thrombosis, and Vascular Biology* **35(10)**:2073–2075 DOI 10.1161/ATVBAHA.115.306339.

Targher G, Day CP, Bonora E. 2010. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *New England Journal of Medicine* **363(14)**:1341–1350 DOI 10.1056/NEJMra0912063.

Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL. 2004. Prospective study of abdominal adiposity and gallstone disease in US men. *The American Journal of Clinical Nutrition* **80**:38–44 DOI 10.1093/ajcn/80.1.38.

Upala S, Sanguankeo A, Jaruvongvanich V. 2017. Gallstone disease and the risk of cardiovascular disease: a systematic review and meta-analysis of observational studies. *Scandinavian Journal of Surgery* **106**:21–27 DOI 10.1177/1457496916650998.

van den Munckhof ICL, Kurilshikov A, Ter Horst R, Riksen NP, Joosten LAB, Zhernakova A, Fu J, Keating ST, Netea MG, de Graaf J, Rutten JHW. 2018. Role of gut microbiota in chronic low-grade inflammation as potential driver for atherosclerotic cardiovascular disease: a systematic review of human studies. *Obesity Reviews* **19(12)**:1719–1734 DOI 10.1111/obr.12750.

Volzke H, Baumeister SE, Alte D, Hoffmann W, Schwahn C, Simon P, John U, Lerch MM. 2005. Independent risk factors for gallstone formation in a region with high cholelithiasis prevalence. *Digestion* **71(2)**:97–105 DOI 10.1159/000084525.

Wang DQ, Cohen DE, Carey MC. 2009. Biliary lipids and cholesterol gallstone disease. *Journal of Lipid Research* **50**:S406–S411 DOI 10.1194/jlr.R800075-JLR200.

Wang Y, Xie LF, Lin J. 2019. Gallstones and cholecystectomy in relation to risk of liver cancer. *European Journal of Cancer Prevention* **28(2)**:61–67 DOI 10.1097/CEJ.0000000000000421.

Wei CY, Chuang SH, Lin CL, Kung WM, Tai HC, Tsai KW, Kao CH, Chen CH, Yeh YH, Hsu CY. 2019. Reduced risk of stroke following cholecystectomy: a nationwide population-based study. *Journal of Gastroenterology and Hepatology* **34(11)**:1992–1998 DOI 10.1111/jgh.14678.

Wells GSB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. 2013. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp*.

Wennmacker SZ, Dijkgraaf MGW, Westert GP, Drenth JPH, van Laarhoven C, de Reuver PR. 2018. Persistent abdominal pain after laparoscopic cholecystectomy is associated with increased healthcare consumption and sick leave. *Surgery* **163(4)**:661–666 DOI 10.1016/j.surg.2017.09.004.

Wirth J, di Giuseppe R, Wientzek A, Katzke VA, Kloss M, Kaaks R, Boeing H, Weikert C. 2015. Presence of gallstones and the risk of cardiovascular diseases: the EPIC-Germany cohort study. *European Journal of Preventive Cardiology* **22(3)**:326–334 DOI 10.1177/2047487313512218.

Wu T, Zhang Z, Liu B, Hou D, Liang Y, Zhang J, Shi P. 2013. Gut microbiota dysbiosis and bacterial community assembly associated with cholesterol gallstones in large-scale study. *BMC Genomics* **14**:669 DOI 10.1186/1471-2164-14-669.

Zhang L, Zhang W, He L, Cui H, Wang Y, Wu X, Zhao X, Yan P, Yang C, Xiao C, Tang M, Chen L, Xiao C, Zou Y, Liu Y, Yang Y, Zhang L, Yao Y, Li J, Liu Z, Yang C, Jiang X, Zhang B. 2023. Impact of gallstone disease on the risk of stroke and coronary artery disease: evidence from prospective observational studies and genetic analyses. *BMC Medicine* **21**:353 DOI 10.1186/s12916-023-03072-6.

Zheng Y, Xu M, Li Y, Hruby A, Rimm EB, Hu FB, Wirth J, Albert CM, Rexrode KM, Manson JE, Qi L. 2016. Gallstones and risk of coronary heart disease: prospective analysis of 270,000 men and women from 3 US cohorts and meta-analysis. *Arteriosclerosis, Thrombosis, and Vascular Biology* **36(9)**:1997–2003 DOI 10.1161/ATVBAHA.116.307507.

Zhu W, Romano KA, Li L, Buffa JA, Sangwan N, Prakash P, Tittle AN, Li XS, Fu X, Androjna C, DiDonato AJ, Brinson K, Trapp BD, Fischbach MA, Rey FE, Hajjar AM, DiDonato JA, Hazen SL. 2021. Gut microbes impact stroke severity via the trimethylamine N-oxide pathway. *Cell Host & Microbe* **29(7)**:1199–1208 e1195
DOI 10.1016/j.chom.2021.05.002.