Association between gallstone and cardio-cerebrovascular disease: Systematic review and meta-analysis

SHOU-FENG ZHAO[1], AI-MIN WANG[2], XIN-JUAN YU[1], LI-LI WANG[1], XIAO-NA XU[1] and GUANG-JUN SHI[3]

[1]Central Laboratories; [2]Medical Examination Center; [3]Department of Hepatobiliary Surgery, Qingdao Municipal Hospital, Qingdao, Shandong 266000, P.R. China

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Abstract. Increasing evidence connects gallstone disease (GD) to cardio-cerebrovascular disease (CVD). The aim of the present systematic review and meta-analysis was to determine whether and to what extent an association between GD and CVD existed. PubMed, EMBASE and the Cochrane Library were systemically searched up to March 3rd, 2018. A total of 10 studies (1,272,177 participants; 13,833 records; 5 prospective cohorts and 5 retrospective cohorts) were included. It was demonstrated that GD was associated with an increased risk of incidence [hazard ratio=1.24, 95% (CI) confidence interval: 1.17-1.31] and prevalence (unadjusted odds ratio=1.23, 95% CI: 1.21-1.25) of CVD. In conclusion, the presence of GD was associated with an increased risk of CVD incidence and prevalence. The association may be influenced by age and sex. These findings suggest that individuals identified with cardio-cerebrovascular disease should be evaluated for GD.

Introduction

Gallstone disease (GD) is the most common disease of the biliary system and the majority of cases are asymptomatic (1). The prevalence of GD has grown with the increasing occurrence of unhealthy lifestyles and the obesity epidemic (2). Patients with gallstones are characterized by distorted bile acid secretion, which is associated with an increased risk of cardiovascular disease (CVD). Several genetic, metabolic and environmental factors for GD and CVD development have been identified. Environmental CVD risk factors include a sedentary lifestyle, a high-fat diet and cigarette smoking, which in turn have all been associated with GD (3,4). Certain lipid metabolizing genes have been identified as susceptibility genes for GD and CVD in genome-wide association studies or meta-analyses (5,6). Recently, numerous cohort studies have reported an association between GD and CVD (7-9), while others have revealed no association (7). Therefore, a meta-analysis was performed in the present study to better explore the possible associations between CVD and GD.

Correspondence to: Professor Guang-Jun Shi, Department of Hepatobiliary Surgery, Qingdao Municipal Hospital, DongHai Middle Road (18 ZhuHai Road), ShiNan, Qingdao, Shandong 266000, P.R. China
E-mail: sgjzp@hotmail.com

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Materials and methods

Data search. Published studies indexed in EMBASE (http://www.embase.com/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and the Cochrane Library (http://www.thecochranelibrary.com/) were systematically searched from their dates of inception to March 3rd, 2018. Search terms included 'carotid' OR 'artery disease' OR 'carotid atherosclerosis' OR 'carotid plaques' OR 'carotid intimal thickness' OR 'carotid artery' OR 'atherosclerosis' OR 'cardiovascular disease' OR 'cerebrovascular disease' AND 'gallstone diseases' OR 'cholelithiasis' OR 'cholecystolithiasis' OR 'stone' OR 'cholecystectomy'. References in the included studies were examined to identify additional studies that were not captured by the initial literature search strategy.

Study selection. Studies were selected for the meta-analysis based on the following criteria: i) Only cohort studies were included for observational studies; ii) CVD, including coronary heart disease, stroke, coronary artery calcification, aortic atherosclerosis, peripheral artery disease, arterial stiffness and cerebral vascular accident; iii) hazard ratios (HRs), odds ratios (ORs) and 95% confidence intervals (CIs) were either extracted directly from the selected articles or calculated according to the provided data in the studies; and iv) letters, review articles, comments, case reports and systematic reviews were excluded. No language exclusions were applied.

Data extraction and quality assessment. Two authors (SZ and GS) independently extracted data from the selected studies. Disagreements were resolved by discussion; if this process did not solve a disagreement, a third author (AW) was consulted. The extracted information included authors, publication year, study design, age, sex, with or without CVD in GD group and control, years of follow-up, outcomes, ORs, HRs, confounder adjustment and CIs. The methodological quality of the selected studies was evaluated with the Newcastle-Ottawa Scale (10).

The scale contained nine points: Comparability (two stars), estimation of outcomes or exposures (three stars) and selection (four stars). Studies that received more than six stars were judged as high quality.

Statistical analysis and subgroup analysis. STATA version 12.0 (STATA Corp LP, College Station, TX, USA) was used in the present meta-analysis. The combined unadjusted OR and HR were calculated using the random-effects model (11). When information was reported for more than one subpopulation (for example, subjects with HRs and unadjusted ORs, subjects from different geographical areas or subjects with different sexes) in one study, each subpopulation was treated as a separate comparison in the meta-analysis. To assess across-study heterogeneity, the inconsistency index (I^2) was calculated with the significance level set at P<0.01. A high, moderate and low degree of heterogeneity was assessed using $I^2 \geq 75$, $I^2 \geq 50$ and $I^2 \geq 25\%$, respectively. A fixed-effect model for the various studies without heterogeneity was performed. By contrast, the random-effects model was used in the meta-analysis and subgroups to analyze the source of heterogeneity and potential factors. Subgroup analysis was stratified by area, sex, age, years of follow-up, study design and sample size. Between trial heterogeneity was assessed using the χ^2 test. The effect of each study on the overall estimates was assessed with sensitivity analysis. Direct observation of funnel plots was performed to assess the presence of publication bias and confirmed with an Egger's test (12).

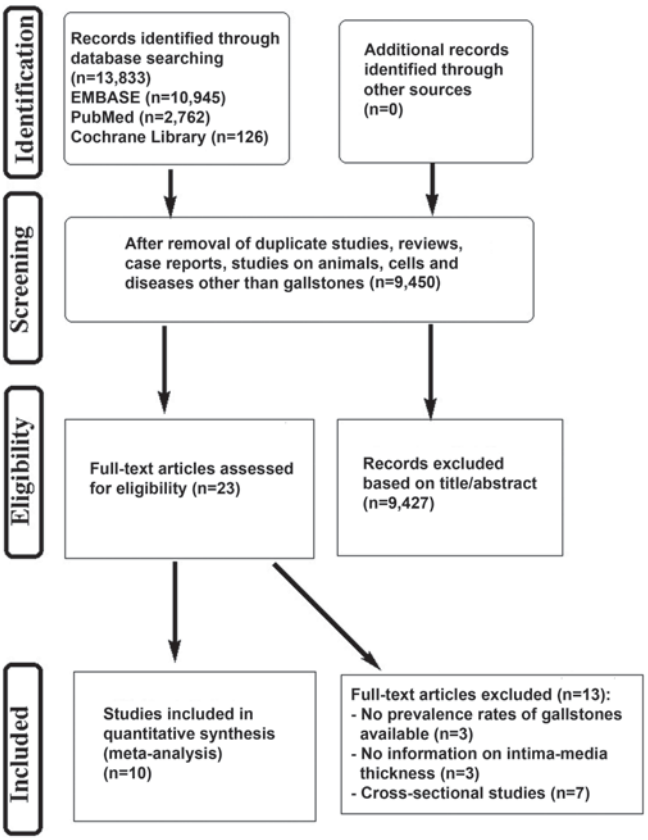

Figure 1. Preferred reporting items for meta-analyses. Flow diagram illustrates the study selection process.

Results

Study characteristics. The flowchart of the included studies was presented in Fig. 1. Overall, 13,833 records were identified through the EMBASE, PubMed and Cochrane Library search. According to the predefined inclusion and exclusion criteria, 10 studies, including retrospective cohort studies (n=7) and prospective cohort studies (n=3) published between 1985 and 2017 were included in the meta-analysis.

In terms of the location, five studies were from Asia (9,13-16) and five studies were from Western countries (2,8,17-19). Of the 10 studies included in the meta-analysis, seven reported HRs (2,8,9,13,14,16,17) and eight reported original data, from which unadjusted ORs were calculated (2,8,9,13-17). Among these studies, there were five prospective cohort studies (2,9,15,17,18) and five retrospective cohort studies (8,13,14,16,19). Cardiovascular diseases and cerebrovascular diseases were studied in nine and two included articles, respectively. For end-point incidence of these studies, two included mortality as an end-point (2,18) and eight studies used morbidity (8,9,13-17,19). The characteristics of the selected studies were summarized in Table I.

Main analysis and publication bias. The meta-analysis suggested a significantly increased risk of incidence (HR=1.24, 95% CI: 1.17-1.31; Fig. 2) and prevalence (unadjusted OR=1.23, 95% CI: 1.21-1.25; Fig. 3) of CVD with GD, but with substantial heterogeneity [P<0.001, I^2=80.2% (HR); P<0.001, I^2=95.8% (unadjusted OR); Figs. 2 and 3]. Publication bias of the HR was analyzed using the funnel plot, and the results revealed no symmetric distribution of the included studies on both sides of the funnel plot, suggesting a possibility of publication bias (Fig. 4). No publication bias of HR was identified by Egger's test (Pr>|z|=0.679). However, because the number of included studies for unadjusted OR was <10, the publication bias for it was not assessed. Collectively, it was not certain that the included studies had no publication bias, but there was no evidence to doubt the validity of the results.

Subgroup analysis. To investigate the influencing factors of heterogeneity, the data were initially stratified by HR and unadjusted OR, then group 1 was further stratified by mean age (HR≥45, unadjusted OR≤60), sex (female), geographical region, follow-up (<10 years), prospective cohort study and sample size (patients with gallstones>10,000). Group 2 was stratified by mean age (HR>45, unadjusted OR>60), sex (male), geographical region, years of follow-up (≥10 years), retrospective cohort study and sample size (patients with gallstone>10,000; Table II). The two groups with GD had a risk of CVD; although the risk in group 1 was greater than that of group 2, indicating that the association between GD and CVD was stronger in the younger population or female individuals. The heterogeneity of the HR was significantly reduced in the stratified analysis by years of follow-up and prospective cohorts, indicating that years of follow-up and study design factors may be potential sources of heterogeneity.

Discussion

In the present meta-analysis, it was demonstrated that compared with controls, GD was associated with a 1.24-fold

Table I. Characteristics of the included studies summarized in the meta-analysis.

Author, year	Group	Sex/age (years)	Gallstone patients and control with/without cardio-cerebrovascular diseases	OR/HR (95% CI)	Followed-up (years)	Study design	Region	Outcome	Confounder adjusted	Quality assessment (newcastle-ottawa scale)	(Refs.)
Wang *et al*, 2017	Whole cohort	51.7	A:192, B:215, T1:407, C:1851, D:3953, T2:5804	OR:1.9 (1.55,2.33)	3	Prospective cohort	Taiwan	AS	33	7	(15)
Zheng *et al*, 2016	Independent cohort 1	Female/48.6	T1:8796, T2:103724	HR:1.15 (1.1,1.21)	30	Retrospective cohort	USA	CHD	5,9,11,12,13,19,20, 22,24,25,27,28	8	(8)
	Independent cohort 2	Female/36.4	T1:5227, T2:107692	HR:1.33 (1.17,1.51)	22		USA	CHD	5,9,11,12,13,19,20, 22,24,25,27,28	8	(8)
	Independent cohort 3	Male/60.1	T1:1449, T2:42254	HR:1.11 (1.04,1.2)	24		USA	CHD	5,9,11,12,13,19,20, 22,24,25,27,28	8	(8)
Lv *et al*, 2015	Whole cohort	30-79	A:1942, B:26403, T1:28345, C:23017, D:436011, T2:459028	HR:1.23 (1.17,1.28)	7.2	Prospective cohort	China	IHD	1,2,7,12,14,15,16,17, 19,21,22,24,29,31,32	8	(9)
	Sex subgroup 1	Male/30-79	T1:7374, T2:191918	HR:1.11 (1.02,1.22)			China	IHD	1,2,7,12,14,15,16,17, 19,21,22,24,29,31,32	8	(9)
	Sex subgroup 2	Female/30-79	T1:21029, T2:267052	HR:1.27 (1.2,1.34)			China	IHD	1,2,7,12,14,15,16,17, 19,21,22,24,29,31,32	8	(9)
Wei *et al*, 2014	Whole cohort	NA	A:12234, B:123278, T1:135512, C:20680, D:250344, T2:271024	HR:1.29 (1.26,1.32)	8	Retrospective cohort Retrospective cohort	Taiwan	Stroke	1,11,17,19	7	(16)
	Disease subgroup 1	NA	A:10500, B:125012, T1:135512, C:17748, D:253276, T2:271024	HR:1.33 (1.25,1.41)			Taiwan	HS	1,11,17,19	7	(16)
	Disease subgroup 2	NA	A:1734, B:133778, T1:135512, C:2932, D:268092, T2:271024	HR:1.28 (1.25,1.31)			Taiwan	IS	1,11,17,19	7	(16)
	Sex subgroup 1	Male	T1:66792, T2:133584	HR:1.39 (1.28,1.51)			Taiwan	Stroke	1,17,18,19	7	(16)
	Sex subgroup 2	Female	T1:68720, T2:137440	HR:1.25 (1.14,1.37)			Taiwan	Stroke	1,17,18,19	7	(16)
	Age subgroup 1	<45	T1:30655, T2:61310	HR:2.41 (1.93,3.01)			Taiwan	Stroke	1,17,18,19	7	(16)
	Age subgroup 2	45-64	T1:50510, T2:101020	HR:1.46 (1.31,1.62)			Taiwan	Stroke	1,17,18,19	7	(16)
	Age subgroup 3	≥65	T1:54347, T2:108694	HR:1.12 (1.04,1.21)			Taiwan	Stroke	1,17,18,19	7	(16)
Lee *et al*, 2013	Whole cohort	60.9	A:126, B:252, T1:378	HR:2.11 (1.14,3.9)	3.9	Retrospective cohort	Korea	CAD	33	7	(13)
Wirth *et al*, 2013	Whole cohort	54.1	A:134, B:4696, T1:4828, C:785, D:40873, T2:41658	HR:1.09 (0.8,1.5)	8.2	Prospective cohort	German	CVD	1,2,7,14,19,24,26,	8 29,30,32	(17)
Olaiya *et al*, 2013	Whole cohort	NA	A:935, B:6046, T1:6981, C:2758, D:25166, T2:27924	HR:1.32 (1.22,1.43)	6	Retrospective cohort Retrospective cohort	Taiwan	CVD	1,4,17	7	(14)

Table I. Continued.

Author, year	Group	Sex/age (years)	Gallstone patients and control with/without cardio-cerebrovascular diseases	OR/HR (95% CI)	Followed-up (years)	Study design	Region	Outcome	Confounder adjusted	Quality assessment (newcastle-ottawa scale)	(Refs.)
	Disease subgroup 1	NA	NA	HR:1.15 (1.01,1.32)			Taiwan	Stroke	1,4,17	7	(14)
	Disease subgroup 2	NA	NA	HR:1.42 (1.28,1.58)			Taiwan	CHD	1,4,17	7	(14)
	Sex subgroup 1	Male	A:425, B:2632, T1:3057, C:1265, D:10963, T2:12228	HR:1.29 (1.15,1.44)			Taiwan	CVD	1,2,6,8,9,12,19,23	7	(14)
	Sex subgroup 2	Female	A:510, B:3414, T1:3924, C:1493, D:14203, T2:15696	HR:1.35 (1.22,1.5)			Taiwan	CVD	1,2,6,8,9,12,19,23	7	(14)
	Age subgroup 1	18-40	A:88, B:2057, T1:2145, C:228, D:8352, T2:8580	HR:1.42 (1.09,1.84)			Taiwan	CVD	1,2,6,8,9,11,17,19,23	7	(14)
	Age subgroup 2	41-60	A:464, B:2923, T1:3387, C:1273, D:12278, T2:13551	HR:1.35 (1.21,1.51)			Taiwan	CVD	1,2,6,8,9,11,17,19,23	7	(14)
	Age subgroup 3	>60	A:383, B:1066, T1:1449, C:1257, D:4536, T2:5793	HR:1.24 (1.1,1.39)			Taiwan	CVD	1,2,6,8,9,11,17,19,23	7	(14)
Ruhl and Everhart, 2011	Whole cohort	69.5	A:247, B:1771, T1:2018, C:639, D:11571, T2:12210	HR:1.5 (1.3,1.8)	18	Prospective cohort	USA	CVD	1	9	(2)
Khan *et al*, 2009	Whole cohort	78	A:889, B:1321, T1:2210, C:874, D:1336, T2:2210	OR:0.97 (0.86,1.90)	10	Prospective cohort	South East England	CHD	1,17	7	(18)
Bortnichak *et al*, 1985	Whole cohort	28-62	A:111, B:391, T1:502, C:649, D:3557, T2:4206	OR:1.56 (1.24,1.95)	26	Retrospective cohort	USA	CHD	33	7	(19)
	Sex subgroup 1	Female/28-62	A:44, B:278, T1:322, C:189, D:1989, T2:2178	OR:1.67 (1.17,2.37)			USA	CHD	33	7	(19)
	Sex subgroup 2	Male/28-62	A:67, B:113, T1:180, C:460, D:1568,T2:2028	OR:2.02 (1.47,2.78)			USA	CHD	33	7	(19)

A, gallstone with cardio-cerebrovascular diseases; B, gallstone without cardio-cerebrovascular diseases; T1, gallstone; C, control with cardio-cerebrovascular diseases; D, control without cardio-cerebrovascular diseases; T2, control; CVD, cardiovascular disease; CAD, coronary artery disease; CHD, coronary heart disease; HS, hemorrhagic stroke; IHD, ischemic heart disease; IS, ischemic stroke; NA, not applicable; 1, age; 2, alcohol consumption; 3, alcoholism; 4, all the co-morbid variables as covariates; 5, Alternative Health; 6, anemia; 7, body mass index; 8, chronic liver disease; 9, chronic obstructive pulmonary disease; 10, daily cholesterol intake; 11, daily energy intake; 12, diabetes mellitus; 13, Eating Index Score; 14, education; 15, family history of heart attack; 16, fresh fruits; 17, sex; 18, history of hypertension, diabetes, coronary heart disease, atrial fibrillation and hyperlipidemia; 19, hypertension; 20, hypercholesterolemia; 21, intake of red meat; 22, marital status; 23, peripheral vascular disease; 24, physical activity; 25, post-menopausal hormone replacement; 26, prevalent hypertension and hyperlipidemia; 27, race; 28, regular aspirin use; 29, smoking; 30, study center; 31, vegetables; 32, waist circumference; 33, unadjusted.

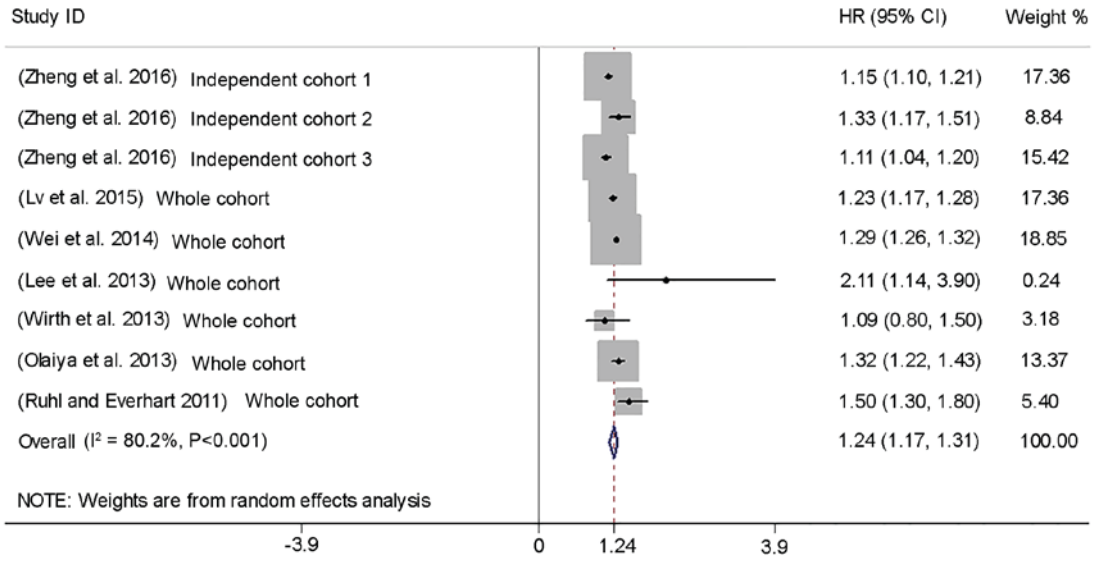

Figure 2. Forest plot of the included studies, comparing risk of cardio-cerebrovascular disease in patients with and without gallstone disease. A diamond data marker represents the overall HRs and the 95% CI for the outcome of interest. HR, hazard ratio; CI, confidence interval.

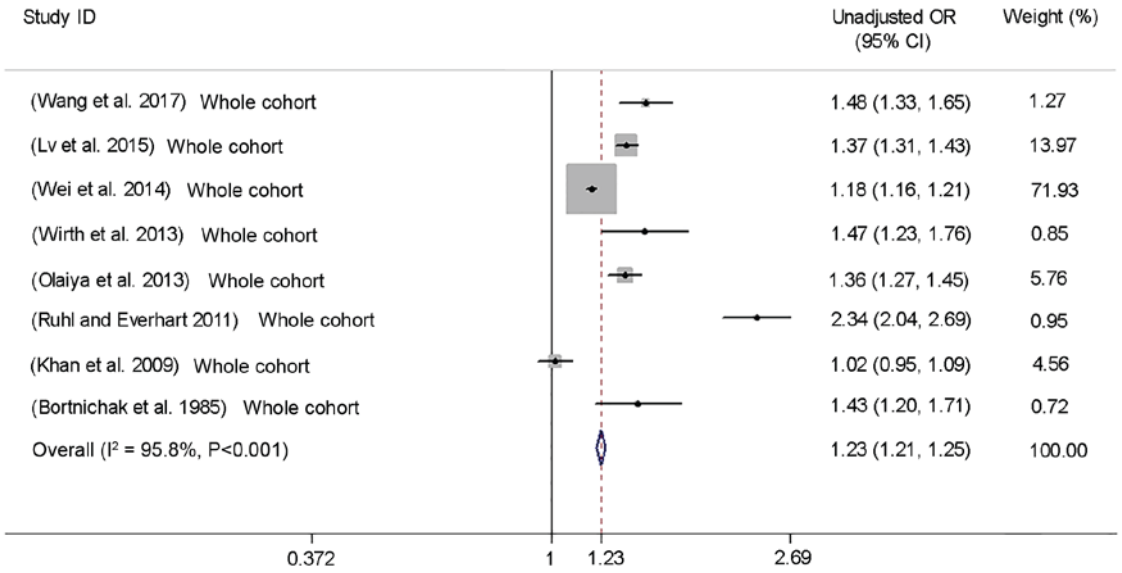

Figure 3. Forest plot of the included studies, comparing risk of cardiovascular disease in patients with and without gallstone disease. A diamond data marker represents the overall unadjusted ORs and 95% CI for the outcome of interest. OR, odds ratio; CI, confidence interval.

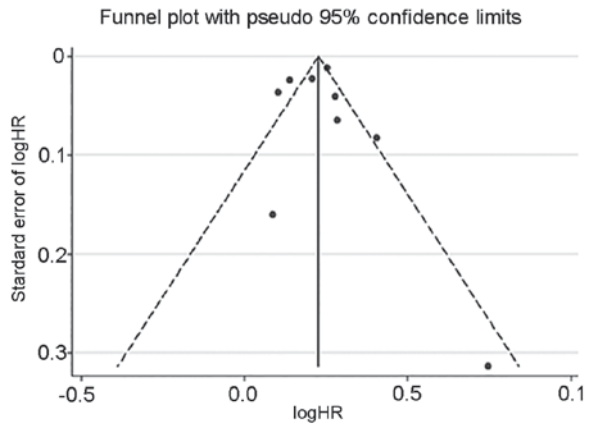

Figure 4. Funnel plot of the hazard ratios reported in the included studies. A funnel plot was constructed to check for the existence of publication bias. HR, hazard ratio.

increase in prevalence and a 1.23-fold increase in incidence for CVD, including cardiovascular disease, coronary artery disease and stroke. Previous studies have reached conflicting conclusions about the association between GD and CVD. Several reports have indicated that GD is associated with CVD (8,9), but others have concluded otherwise (7). The conflicting findings may be due to differences in the mean age, sex, geographical region, sample size, study design, follow-up and outcome. In the present study, subgroup analysis by mean participant age revealed that young participants had higher CVD risks, suggesting that more attention should be paid to the prevention of CVD in younger patients with GD. It is generally acknowledged that the prevalence of GD in younger individuals is lower than that in older individuals (20). Therefore, GD may have a greater impact on CVD risk in populations with a lower prevalence. The

Table II. Stratified analyses of the risk of cardiovascular disease among patients with gallstones.

A, Group 1

Subgroup	HR/unadjusted OR	RR (95% CI)	Reports	I^2 (%)	$P_{(heterogeneity)}$	Weight %
Mean age						
<45	HR: 1.65	(1.14, 2.40)	3	90.5	<0.001	29.85
≤60	Unadjusted OR: 1.47	(1.38, 1.58)	4	0	0.979	39.23
Sex						
Female	HR: 1.25	(1.18, 1.34)	5	70.5	0.009	56.13
Geographical region						
Asia	HR: 1.27	(1.21, 1.32)	5	55.5	0.061	53.89
Western	Unadjusted OR: 1.29	(1.22, 1.37)	4	97.4	<0.001	7.08
Follow-up (year)						
<10	HR: 1.26	(1.21, 1.32)	6	49.8	0.076	56.30
<10	Unadjusted OR: 1.27	(1.19, 1.34)	3	98.2	<0.001	6.23
Study design						
Prospective cohort study	HR: 1.29	(1.10, 1.50)	3	66.7	0.050	24.48
Prospective cohort study	Unadjusted OR: 1.35	(1.30, 1.39)	5	96.7	<0.001	21.59
Sample size (gallstone)						
>10,000	Unadjusted OR: 1.24	(1.21, 1.26)	5	96.8	<0.001	93.45

B, Group 2

Subgroup	HR/unadjusted OR	RR (95% CI)	Reports	I^2 (%)	$P_{(heterogeneity)}$	Weight %
Mean age						
≥45	HR: 1.20	(1.11, 1.30)	5	81.4	<0.001	70.15
>60	Unadjusted OR: 1.24	(1.17, 1.30)	3	98.2	<0.001	60.77
Sex						
Male	HR: 1.22	(1.08, 1.37)	4	85.8	<0.001	43.87
Geographical region						
Western	HR: 1.22	(1.11, 1.34)	5	74.4	0.004	46.11
Asia	Unadjusted OR: 1.23	(1.20, 1.25)	4	94.3	<0.001	92.92
Follow-up (year)						
≥10	HR: 1.23	(1.11, 1.36)	4	80.5	0.001	43.70
≥10	Unadjusted OR: 1.23	(1.21, 1.25)	5	92.9	<0.001	93.77
Study design						
Retrospective cohort study	HR: 1.23	(1.15, 1.31)	7	83.5	<0.001	75.52
Retrospective cohort study	Unadjusted OR: 1.20	(1.17, 1.22)	3	88.5	<0.001	78.41
Sample size (gallstone)						
≤10,000	Unadjusted OR: 1.15	(1.09, 1.22)	3	94.6	<0.001	6.55

HR, hazard ratio; OR, odds ratio; CI, confidence interval; RR, relative risk.

effect of GD on CVD was stronger in females in the current meta-analysis, which was consistent with the conclusion of a previous meta-analysis (21). Female patients with GD may have more CVD risks, such a pregnancy or oral contraceptive use (22). Furthermore, in postmenopausal women, a decrease in high-density lipoprotein (HDL) levels contributes to the development of GD (23). Recently, Fan *et al* (21) also conducted a meta-analysis on GD and CVD. A notable difference between their study and the present study was that they pooled OR to calculate the risk of CVD (21), whereas the current analysis included HR and unadjusted OR, which were pooled separately to calculate the risk of CVD. A previous meta-analysis also separated pooled HR and OR, but did not perform subgroup analysis (24).

Various pathogenic mechanisms have been suggested as possible explanations for GD and CVD. Cholesterol accumulation is a major component in atherosclerotic CVD and GD (15,25). These disorders share common risk factors, including age, sex and obesity, as well as lipid and glucose metabolism disorders, which are also key components of metabolic syndrome (MS) (26,27). MS is strongly associated with coronary artery disease, and gallstones may be considered a biliary feature of this syndrome (28,29). It was assumed that patients with GD had a higher risk of having the comorbidities

of hypertension, diabetes, coronary arterial disease, atrial fibrillation and hyperlipidemia, all of which have been proved to be conventional risk factors for stroke (16). However, Olaiya *et al* (14) revealed that GD and diabetes or GD and hyperlipidemia also interacted to increase the stroke risk. Diabetes and hyperlipidemia present the same risks in GD and stroke. Therefore, diabetes or hyperlipidemia with GD may have synergistic effects that can promote strokes. Considering this, checking for GD in patients with diabetes or hyperlipidemia maybe a new strategy for stroke prevention (16).

Aberrant inflammation is involved in the development of GD and CVD (30,31). Several inflammatory factors, including von Willebrand factor, lectin-like oxidized low-density-lipoprotein receptor-1, soluble urokinase plasminogen activator receptor, regulated upon activation, normal T-cell expressed and secreted, as well as microparticles, have been proposed as reducing the expression levels of these factors may improve CVD (32). The inflammatory process in GD may promote atherosclerosis or vasculopathy in the cerebral vasculature, thereby increasing the risk of CVD. Associated liver diseases, including non-alcoholic fatty liver disease and pyogenic liver abscesses, have been determined to increase the risk of subsequent CVD via a similar mechanism. Inflammation may also be a vascular risk factor in GD (31).

Dysbiosis is an alteration in the composition of the gut microbiota, and has been associated with several diseases, including CVD and GD (33,34). Specifically, dysbiosis has been implicated in CVD, with various aspects of cardiometabolic syndrome: Obesity, hypertension, chronic kidney disease and diabetes (35). A mechanistic link between gut microbiota formation of trimethylamine-N-oxide (TMAO) and CVD has been repeatedly demonstrated. TMAO has been implicated in atherosclerosis, platelet aggregation, diabetes and hypertension (36). Gut and biliary tract dysbiosis disequilibrates the enterohepatic circulation, leading to gallstone formation (37,38). Various mechanisms have been consequently speculated, including *Helicobacter* spp. in the gallstone nuclei, systemic immune response alteration and modulation of enterohepatic cycling of conjugated bile acids (39). Infection with *Helicobacter pylori* is positively associated with high low-density lipoprotein cholesterol (LDL-C), low HDL-C and CVD (40). Patients that are *Helicobacter* seropositive with the TT genotype of the polymorphic gene adiponectin receptor 2 rs1044471 constitute a risk group of cardiovascular event formation (41). In light of these findings, therapies targeting the gut microbiota present novel opportunities for CVD and GD treatment.

Genetic studies have highlighted several single nucleotide polymorphisms that may characterize patients with a high risk for GD and CVD. Several genes in the cholesterol metabolism pathway serve an important role in lipid biosynthesis, metabolism and transport. Variants of these genes may significantly influence plasma total cholesterol and LDL-C levels, and in turn affect the pathogenesis of GD and CVD. For example, the ATP-binding cassette G8 (ABCG8) gene is expressed exclusively in the liver and intestine, and forms heterodimers to regulate the efflux of sterols into the intestinal lumen and controls the hepatic secretion of sterols into the bile. The ABCG8 D19H variant is associated with plasma total cholesterol and LDL-C levels (42,43), and confers risk for CVD and GD. Previous research has revealed that the presence of the e4 allele of apolipoprotein E gene is a risk factor for CVD and GD, and is associated with significantly higher levels of LDL-C, TC and non-HDL-C (44,45).

Notably, this meta-analysis has several limitations. First, heterogeneity was revealed through the pooled analysis among studies. The present meta-analysis is unlikely to fully account for heterogeneity, even with the explanation of certain clues from the subgroup analysis. Therefore, the results of the meta-analysis must be interpreted with caution. Because of the potential heterogeneity in age, sex, follow-up, geographical region and study design, it was assumed that the estimated true effect would vary between study designs, in addition to the years of follow-up. Heterogeneity was accounted for by using combined results of the eligible studies with the random-effect model. Although the random-effect approach provides some heterogeneity allowance beyond sampling error or a limited influence, it does not necessarily rule out the heterogeneity effect. Second, although Egger's test suggested no publication bias for the HR; the inverted funnel plots of the HR were not symmetrical. The source of publication bias may originate from the nonrandomized studies, including prospective cohort and retrospective cohorts. Finally, unpublished data/studies that may have met the inclusion criteria were not included. In addition, potential biases may have been produced in the present meta-analysis.

In conclusion, the present study demonstrated that the presence of GD was associated with an increased risk of CVD incidence and prevalence. Further studies are required with more randomized controlled trials to elucidate the molecular mechanisms underlying the association between these two diseases, and whether preventive therapies would prevent the progression of CVD in patients with GD.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

SFZ performed the literature review, designed the study, was a major contributor in writing the manuscript and performed statistical analysis. GJS performed the literature review and designed the study. SFZ and GJS independently extracted the data from the selected studies. If there was a disagreement in the interpretation of the results, AMW was consulted. XJY was involved in writing the manuscript. LLW designed the workflow for the current meta-analysis. XNX was involved in writing the manuscript and revised the tables. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors have declared that no competing interests.

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