ORIGINAL ARTICLE

Gut and Liver, Vol. 13, No. 1, January 2019, pp. 114-131

Alcohol Consumption Can Reduce the Risk of Gallstone Disease: A Systematic Review with a Dose-Response Meta-Analysis of Case-Control and Cohort Studies

Byung Hyo Cha[1], Myoung-jin Jang[2], and Sang Hyub Lee[3]

[1]Department of Gastroenterology, Division of Medicine, Sheikh Khalifa Specialty Hospital, Ras Al Khaimah, UAE, [2]Medical Research Collaborating Center, and [3]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Background/Aims: Gallstone disease (GSD) is a common gastrointestinal disorder. Clinical epidemiological studies revealed that alcohol consumption has a preventive effect on the development of GSD. This study aimed to evaluate the relative risks of drinking for GSD development and investigate the dose-response relationships. **Methods:** A systematic search of the MEDLINE, EMBASE, and Cochrane Library databases for studies published up to 2018 was performed. All studies that satisfied the following eligibility criteria were included: patients with GSD with or without cholecystitis; and cohort or case-control studies investigating the association between alcohol consumption and GSD development. **Results:** Sixteen case-control studies including 24,401 gallstone cases and 76,185 controls, and eight cohort studies with 14,693 GSD cases among 2,432,471 person-years were enrolled. Alcohol consumption presented a decreased overall risk of GSD (pooled relative ratio [RR], 0.84; 95% confidence interval [CI], 0.79 to 0.89; p=0.02). Subgroup analyses according to drinking levels indicated a gradual risk reduction for GSD compared to nondrinkers (light: RR, 0.96; 95% CI, 0.94 to 0.99; p=0.75; moderate: RR, 0.80; 95% CI, 0.75 to 0.85; p=0.27; high: RR, 0.66; 95% CI, 0.56 to 0.79; p<0.01). A nonlinear risk reduction was observed in a dose-response meta-analysis of all the studies (n=14, p<0.01 for nonlinearity). **Conclusions:** In this systematic review with meta-analysis, alcohol consumption could decrease the risk of GSD, and the dose-response analysis revealed a dose-dependent linear risk reduction and a weakened linear trend between alcohol consumption levels less than and greater than 28 g/day. **(Gut Liver 2019;13:114-131)**

Key Words: Gallstone disease; Alcohol drinking; Dose-response relationship; Meta-analysis; Review

INTRODUCTION

Gallstone disease (GSD) is a common gastrointestinal disease with a spectrum of clinical presentations from asymptomatic silent gallstones to severe acute cholecystitis. The prevalence is reported to be 10%–15% in adults with risk factors including old age, female gender, obesity, metabolic syndrome, and chronic liver disease.[1] Gallstones with or without cholecystitis are one of the most common reasons for hospital admission, and treatment by laparoscopic cholecystectomy has become more popular in recent years. The burden of GSD has increased in recent years, with direct and indirect costs of the disease estimated to be more than $6.2 billion in the United States.[2,3]

Notwithstanding that alcohol consumption is a known risk factor for many chronic diseases and malignancies,[4-6] there have been many clinical epidemiological studies regarding the negative correlation between alcohol consumption and GSD risk. Thereafter, two meta-analyses revealed that alcohol consumption has a preventive effect on the development of GSD,[7,8] and Wang *et al*.[8] presented a linear relationship with a 12% risk reduction with each 10 g/day increment of alcohol (relative ratio [RR], 0.88; 95% confidence interval [CI], 0.84 to 0.92) in a dose-response meta-analysis. This systematic review was carried out to define the optimal level of alcohol consumption to maximize the protective effect on GSD.

Correspondence to: Byung Hyo Cha
Department of Gastroenterology, Division of Medicine, Sheikh Khalifa Specialty Hospital, Truck Road, Ras Al Khaimah 6365, UAE
Tel: +971-56-385-3131, Fax: +971-7-244-4437, E-mail: doctorhyo@gmail.com
Received on June 16, 2018. Revised on August 31, 2018. Accepted on September 3, 2018.
pISSN 1976-2283 eISSN 2005-1212 https://doi.org/10.5009/gnl18278
Byung Hyo Cha and Myoung-jin Jang contributed equally to this work as first authors.

MATERIALS AND METHODS

Two authors (B.H.C. and M.J.J.) performed a comprehensive systematic search for published studies that aimed to evaluate the relationship between alcohol consumption and GSD risk.

1. Search methods to identify studies

A comprehensive, systematic search was conducted for published articles from database inception to March 01, 2018 using MEDLINE, EMBASE, and Cochrane Controlled Trials Register. We confined our search to only English publications. The MEDLINE search strategy was adapted for use in the other databases searched (Appendix 1). The reference lists of retrieved articles were also examined for additional, eligible studies.

2. Selection criteria

Studies were included if they met the following criteria: (1) cohort or case-control studies published as original articles (abstracts, letters, reviews, and meta analyses were excluded); (2) studies reporting the relative risks (odds ratio [OR], RR, or hazard ratio [HR]) between alcohol consumption and GSD or sufficient data to calculate them. Case-control studies were excluded if drinking categories were based on alcohol consumption at the time of interview.[9] When studies with overlapping populations were identified, the most appropriate study for this comparison was selected in terms of bias. When additional information was required, we contacted the corresponding authors of the study.

3. Data extraction

Data extraction was completed by two authors (B.H.C. and M.J.J.) independently from all included studies with a predefined information sheet, in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[10] Any discrepancies in extracted data were resolved through consensus or discussion with a third author (S.H.L.). The following information was taken from each article: publication year, country, study design, sample size, age, gender, endpoint definition (cholelithiasis, GSD, cholecystitis, or cholecystectomy from calculous cholecystitis), the number of cases and controls or number of events and subjects at risk/person-years, risk ratio estimates with 95% CIs, and covariates adjusted in the statistical analysis. The adjusted RRs were extracted and when they were not available, and unadjusted RRs and 95% CIs were extracted or calculated.

4. Quality assessment

The overall study quality was assessed independently by two authors (B.H.C. and M.J.J.) using the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies.[11] The NOS consists of three domains: selection (four items, one star each), comparability (one item, up to two stars), and outcome (three items, one star each). Nine stars on the NOS reflects the highest quality. Studies with a NOS score of 7 to 9 and less than 7 were considered to have a low and high risk of bias, respectively. Any disagreements between the reviewers were resolved through discussion (Appendix 2).

5. Statistical analysis

The association between alcohol consumption and the risk of GSD was examined on the basis of the pooled relative risks and their 95% CIs. For the pooling analysis, alcohol consumption was converted into grams of ethanol per day using the standard drink size provided by the study or the conversion factors (0.8 g/mL, 28.35 g/oz, 14 g/drink, and 7.9 g/unit). The drinking level for each RR was assigned as the median or mean amount (in grams) of alcohol intake in each exposure category. When the median or mean intake per category was not reported, the midpoint of the upper and lower boundaries in each category was given. For the open-ended upper boundary, a value of 1.2 times the lower boundary was assigned to the category.[12] For the open-ended lower boundary, the lower boundary was assumed to be zero. Nondrinking was considered as the reference category. There are several published guidelines defining moderate, heavy and binge drinking levels according to standard drinking definition: 1–2 drinks/day (7–14 g/day), more than 2 drinks/day (>14 g/day), and 4–5 drinks/day (28–35 g/day).[13-15] Based on those criteria, we classified consumption into light, moderate and high drinking as follows: <7, 7–14, and >14 g/day for women and <14, 14–28 and >28 g/day for men, respectively. For the studies in which the lowest category included both nondrinking and light drinking, the lowest category was used as the reference category. If there was more than one RR for each drinking category defined for this study, the study-specific risk estimates were combined with the Hamling *et al*.[16] if the numbers of cases and person-years or numbers for each nondrinking and drinking group were available or calculable; otherwise, the data were pooled with inverse variance weighting. For study-specific RR for overall drinking compared to nondrinking, the RR was estimated by pooling all RRs for the drinking categories defined in each study using the same method as described above. For the study reporting RR per drinking unit, RR for overall drinking was estimated by the RR at the mean or median drinking unit in the study, as the power of RR by the mean or median value. When raw data were available, all necessary RRs were obtained from analysis of the raw data. For the association of alcohol consumption and risk of GSD, pooled RRs among studies and their 95% CIs and p-values were calculated using the random-effects model. Statistical heterogeneity between the studies was assessed with Cochran Q-test and I^2 statistics. I^2 values of 25%, 50% and 75% have been suggested to be indicators of low, moderate, and high heterogeneity, respectively.[17] Subgroup analysis was performed on study design and participant sex. Heterogeneity between subgroups was assessed using Cochran Q-test. Funnel plots and Egger tests for asymmetry

were applied to assess the possibility of publication bias among the studies. To examine the dose-response association between alcohol consumption and GSD risk, 2-stage, random-effects, dose-response meta-analyses were performed.[18,19] First, a study-specific restricted cubic spline model with four knots at the fixed 5th, 35th, 65th, and 90th percentiles of alcohol consumption levels was estimated using generalized least square regression accounting for the correlation between estimates within each study. Second, study-specific estimates were pooled using the restricted maximum likelihood method in a random-effects meta-analysis. A p-value for nonlinearity was calculated by testing the null hypothesis that the regression coefficients of the spline transformations are all equal to zero. The predicted RR of alcohol intake was estimated based on the linear or restricted cubic splines. Statistical analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX, USA) or R version 3.4.1 (The R Foundation for Statistical Computing, Vienna, Austria). Two-sided p-values <0.05 were considered to be statistically significant.

RESULTS

1. Description of studies

In total, 190 articles were identified as relevant by an initial search strategy, and 47 duplicated cases were removed (Fig. 1). One hundred and twenty-six articles were excluded during screening for eligibility due to unmatched enrollment criteria. Finally, 17 articles that met the inclusion criteria were selected. The article of Thijs *et al*.[20] had four case-control studies (studies A, B1, B2, and B3). Among the four studies, study A was not included for this meta-analysis because its cases or controls overlapped those of the other two studies (studies B1 and B3), and the study design was more susceptible to protopathic bias than the other studies were. Of these, three articles (Scragg *et al*.,[21] Rhodes and Venables,[22] Banim *et al*.[23]) reported the effects of drinking by gender, in one study by Cha *et al*.,[24] the effects by gender were calculated from raw data, and one article[25] reported the sex-adjusted effects in both sex groups and the effects for females only. Lastly, a total of 24 studies (16 case-control studies and 8 cohort studies) were included in this meta-analysis study.

The summary of baseline characteristics is described in Table 1.[20-36] In total, 24,401 patients with gallstones and 76,185 controls were estimated from 16 case-control studies, and 14,693 cases of GSD developed among 2,432,471 person-years in eight cohort studies. Among the 24 enrolled studies, six reported their estimates in female-only groups, another four in male-only groups, and the other 14 studies reported data on both sex groups. The majority of selected studies were performed in the USA and Europe, while four were in Asia, and one was in Australia. Each study provided adjusted risk measurements regarding different confounding factors.

2. Quality of the included studies

The NOS scores of the 24 included studies ranged from 6 to 9 stars (Appendixes 2 and 3). Eight of the 24 studies had a NOS score of 9, seven studies had a score of 8, where scores of 8 were given to seven studies because two studies used self-report for ascertainment of exposure (zero stars in assessment of exposure), and five studies controlled for important factors (only one star in comparability domain). Three studies were scored as 7, with no stars in items of representativeness of study population,

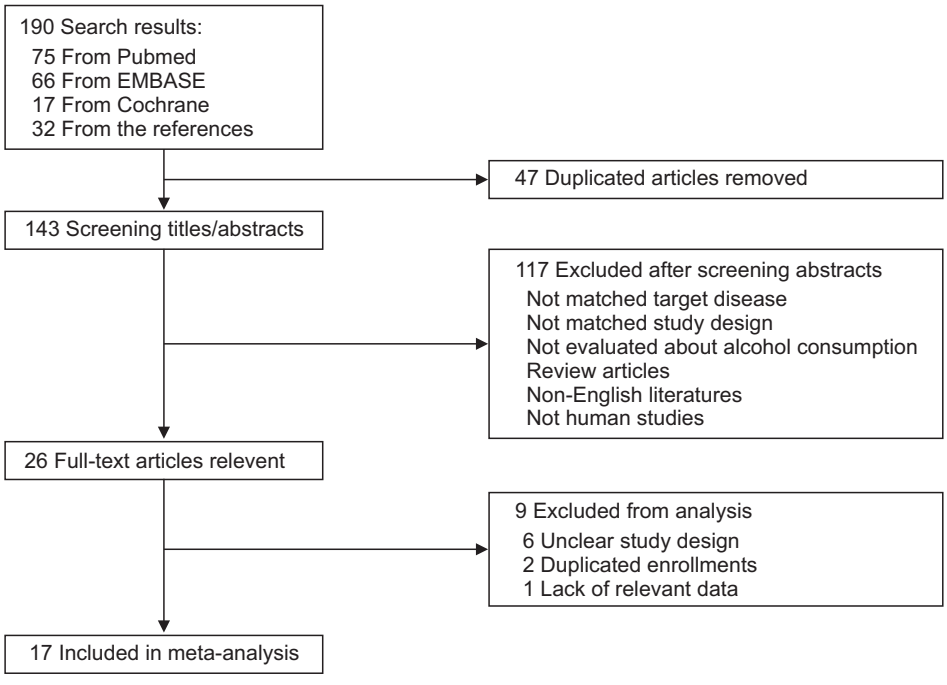

Fig. 1. Flowchart of Study Selection for Inclusion in Meta-analysis.

Table 1. Baseline Characteristics of Studies Included in the Meta-Analysis (n=24)

Study	Design	Region	Outcome measures	Sex, age (yr)	Case/total	Alcohol (unit)	Alcohol category (g/day)	Alcohol category (L/M/H)	RR (95% CI)	Adjusted confounders	NOS
La Vecchia *et al.* (1991)[26]	CC	Italy	Cholelithiasis or cholecystitis undergone, Cholecystectomy, Interview	Both, 21–74	195/1,317	0 (drinks/day)	0	Ref	1	Age, sex, area of residence, smoking, coffee, history of liver disease, BMI	9
						1–3	28	M	0.8 (0.6–1.3)		
						>3	67.2	H	0.5 (0.3–0.8)		
Kato *et al.* (1992)[27]	Cohort	Hawaiian Japanese	Cholelithiasis and/or cholecystitis, Interview	Male, ≥45	461/7,716	Nondrinker (oz/mo)	0	Ref	1	Age	8
						<4.7	2.2	L	1.0 (0.8–1.3)		
						4.7–24.6	13.8	M	1.0 (0.7–1.2)		
						≥24.7	28	H	0.8 (0.6–1.0)		
Grodstein *et al.* (1994)[28]	Cohort	US	Symptomatic gallstones, Self-administrated questionnaire	Female (nurse), 25–42	425/96,211	0 (g/day)	0	Ref	1	Age, oral contraceptive use, postmenopausal hormone use, BMI, weight change, parity, cigarette smoking	6
						0.1–4.9	2.5	L	0.8 (0.7–1.0)		
						5–14.9	10	M	0.8 (0.6–1.0)		
						≥15	18	H	0.7 (0.4–1.4)		
Leitzmann *et al.* (1999)[29]	Cohort (Health professionals)	US	Gallstone diseases, Self-administrated FFQ	Male, 40–75	1,081/46,006	0 (g/day)	0	Ref	1	Age, BMI, weight change, physical activity, history of diabetes mellitus, pack-years of smoking, coffee consumption, intake of cholesterol-lowering drugs, thiazide diuretics, NSAIDs, energy-adjusted dietary, energy-adjusted carbohydrates	7
						0.1–1.4	0.8	L	0.97 (0.76–1.22)		
						1.5–4.9	3.2	L	0.95 (0.79–1.14)		
						5.0–14.9	10	L	0.83 (0.69–0.99)		

Table 1. Continued

Study	Design	Region	Outcome measures	Sex, age (yr)	Case/total	Alcohol (unit)	Alcohol category (g/day)	Alcohol category (L/M/H)	RR (95% CI)	Adjusted confounders	NOS
						15.0–29.9	22.5	M	0.75 (0.60–0.93)		
						30+	36	H	0.64 (0.50–0.81)		
Leitzmann *et al.* (2003)[30]	Cohort (nurse)	US	Cholecystectomy, Self-administrated FFQ	Female, 30–55	7,831/80,898	0 (g/day)	0	Ref	1	Time period, age, BMI, weight change, oral contraceptive use, hormone replacement therapy, physical activity, history of diabetes mellitus, pack-years of smoking, use of thiazide diuretics, energy-adjusted fiber intake, energy-adjusted carbohydrate intake, energy-adjusted polyunsaturated fat intake, coffee intake	7
						0.1–4.9	2.5	L	0.95 (0.89–1.00)		
						5.0–14.9	10	M	0.86 (0.80–0.93)		
						15.0–29.9	22.5	H	0.8 (0.72–0.89)		
						30.0–49.9	40	H	0.67 (0.57–0.78)		
						≥50	60	H	0.62 (0.49–0.79)		
Banim *et al.* (2011)[23]	Cohort	UK	Symptomatic gallstone disease, Self-administrated questionnaire	Female, 40–74	201/1,3075	0 (g/day)	0	Ref	1	Age, hormone replacement therapy, parity	7
						0.11–7.9	4	L	1.01 (0.70–1.46)		
						7.9–15.8	11.9	M	0.72 (0.42–1.24)		
						15.8–23.7	19.8	H	0.99 (0.48–2.05)		
						23.7	28.4	H	1.10 (0.39–3.11)		
Banim *et al.* (2011)[23]	Cohort	UK	Symptomatic gallstone disease, Self-administrated questionnaire	Male, 40–74	95/11,188	0 (g/day)	0	Ref	1	Age, physical activity, BMI	8
						0.11–7.9	4	L	1.10 (0.58–2.14)		
						7.9–15.8	11.9	L	1.20 (0.58–2.46)		
						15.8–23.7	19.8	M	0.58 (0.21–1.58)		
						23.7	28.4	H	0.46 (0.17–1.25)		

Table 1. Continued

Study	Design	Region	Outcome measures	Sex, age (yr)	Case/total	Alcohol (unit)	Alcohol category (g/day)	Alcohol category (L/M/H)	RR (95% CI)	Adjusted confounders	NOS
Bodmer *et al.* (2011)[31]	CC (matched)	UK	Cholecystectomy, Not reported on alcohol survey	Both, ≥20	22,574/95,050	0 (units/wk)	0	Ref	1	Age, sex, BMI, general practice, years of history in the database, and calendar time by matching, smoking, a history of ischemic heart disease, congestive heart failure, and hypertension, use of statins, use of oral contraceptives (females only)	8
						1–7	4.5	L	0.98 (0.95–1.02)		
						8–14	12.4	M	0.80 (0.75–0.85)		
						15–29	24.8	M	0.68 (0.62–0.74)		
						30+	40.6	H	0.53 (0.46–0.62)		
Misciagna *et al.* (1999)[32]	CC (matched)	Italy	Gallstone, Self-administrated FFQ	Both, 0–69	100/390	0 (g/day)	0	Ref	1	Age, sex, BMI, energy, energy, protein, saturated fat, monounsaturated fat, polyunsaturated fat, cholesterol, glycogen, refined sugar, fiber from cellulose, fiber from noncellulose, calcium	9
						0.1–15.6	7.9	L	0.83 (0.39–1.78)		
						15.6–38.5	27.1	M	0.74 (0.32–1.67)		
						≥38.5	46.2	H	0.42 (0.14–1.28)		
Cha *et al.* (2017)[24]	CC	Korea	Symptomatic GBS, Interview	Female, 16–92	73/143	0 (g/day)	0 (median)	Ref	1	Age, hypertension, diabetes mellitus, BMI	9
						7–14	8.1	M	0.38 (0.06–2.35)		
						≥14	32.3	H	0.11 (0.02–0.53)		
Cha *et al.* (2017)[24]	CC	Korea	Symptomatic GBS, Interview	Male, 16–88	97/193	0	0	Ref	1	Age, hypertension, diabetes mellitus, vascular occlusive disease, obesity	9
						7–28	16.1	M	0.30 (0.1–0.85)		
						≥28	64.6	H	0.29 (0.11–0.78)		
Thijs *et al.* (1991)[20] Study B1	CC	Nether-land	Acute gallstone, Disease, Interview	Both	151/602	0 (drinks/day)	0	Ref	1	Age, sex, coffee use, smoking, pregnancies, duration of oral contraceptive use, duration of perimenopausal sex hormone use, diabetes mellitus, BMI, skipping breakfast, sedentary life style, sporting activities, slimming courses, age at menarche, number of years postmenopausal, cholesterol-lowering drug use, long-term daily analgesic use, parents with gallstones, brothers with gallstones, sisters with gallstones, interviewer	9

Table 1. Continued

Study	Design	Region	Outcome measures	Sex, age (yr)	Case/total	Alcohol (unit)	Alcohol category (g/day)	Alcohol category (L/M/H)	RR (95% CI)	Adjusted confounders	NOS
						<1	7	L	1.1 (0.5–2.28)		
						1–2	21	M	0.7 (0.32–1.6)		
						3–7	70	H	1.5 (0.63–3.4)		
Thijs *et al.* (1991)[20] Study B2	CC	Netherland	General hospital, Population, Interview	Both	63/852	0 (drinks/day)	0		1	Age, sex, coffee use, smoking, pregnancies, duration of oral contraceptive use, duration of perimenopausal sex hormone use, diabetes mellitus, BMI	9
						<1	7	L	0.9 (0.42–2.01)		
						1–2	21	M	1 (0.45–2.07)		
						3–7	70	H	1 (0.36–2.6)		
Thijs *et al.* (1991)[20] Study B3	CC	Netherland	Radiologic screening, Interview	Both	77/352	0 (drinks/day)	0	Ref	1	Age, sex, coffee use, smoking, pregnancies, duration of oral contraceptive use, duration of perimenopausal sex hormone use, diabetes mellitus, BMI	9
						<1	7	L	0.9 (0.38–2)		
						1–2	21	M	0.6 (0.29–1.39)		
						3–7	70	H	1.5 (0.43–5.39)		
Katsika *et al.* (2007)[33]	Cohort (twin)	Sweden	Symptomatic GBS, Self-administrated questionnaire	Both	1,666/58,402	0 (g/day)		Ref	1	Sex, BMI, alcohol, smoking and smoke-free tobacco	7
						0.1–60 (F), 0.1–80 (M)	(L, M, H)	-	0.93 (0.83–1.04)		
						>60 (F), >80 (M)	(H)	-	0.57 (0.49–0.67)		
Shabanzadeh *et al.* (2017)[34]	Cohort	Denmark	Gallstones or cholecystectomy, Self-administrated questionnaire	Both, 30–60	256/2,848	Unit/wk	-	-	0.94 (0.89–1.00)*	Age, sex, and BMI	8
Scragg *et al.* (1984)[21]	CC (matched)	Australia	FFQ interview	Female, <70	176/352	Drinking			0.51 (0.34–0.78)†	Sex, age, residential area, sugar in drinks and sweets, total fat, interaction between fat and age, cholesterol	9

Table 1. Continued

Study	Design	Region	Outcome measures	Sex, age (yr)	Case/total	Alcohol (unit)	Alcohol category (g/day)	Alcohol category (L/M/H)	RR (95% CI)	Adjusted confounders	NOS
				Male, <70	57/114				0.24 (0.08–0.73)†	Sex, age, residential area, sugar in drinks and sweets, energy, interaction between energy and age	9
Halldestam *et al.* (2009)[35]	Cohort	Sweden	Self-administrated questionnaire	Both, 35–85	42/503	≥1/wk			0.29 (0.09–0.98)	Age, sex, follow-up interval, BMI, heredity of gallstone, skilled current or previous occupation, smoking, NSAID intake, diabetes mellitus, HDL, LDL, TG, lipoprotein A	8
Panpimanmas and Manmee (2009)[25]	CC	Thailand	Self-administrated questionnaire	Both	207/407	Nondrinkers			1	Age, sex, BMI, smoking history, fat content in dietary meat, diabetes mellitus	8
						<5 yr			1.0 (0.5–2.2)		
						5–10 yr			1.2 (0.6–2.4)		
						>10 yr			0.8 (0.4–1.9)		
Panpimanmas and Manmee (2009)[25]	CC	Thailand	Self-administrated questionnaire	Female	132/274	Nondrinkers			1	Age, BMI, fat content in dietary meat, diabetes mellitus, no of children, duration of contraceptive use	8
						<5 yr			1.1 (0.4–3.1)		
						5–10 yr			1.9 (0.6–5.7)		
						>10 yr			1.0 (0.4–2.6)		
Rhodes and Venables (1991)[22]	CC	UK	Cholecystectomy, Self-administrated questionnaire	Female, 25–92 (mean=59)	178/356	Regular drinking (mean=6 units /wk)			0.72 (0.47–1.1)	Age and sex (matched)	8
Rhodes and Venables (1991)[22]	CC	UK	Cholecystectomy, Self-administrated questionnaire	Male, 33–85 (mean=64)	69/138	Regular drinking (mean=23 units/wk)			0.29 (0.07–0.91)	Age and sex (matched)	8
Kato *et al.* (1990)[36]	CC	Japan	Self-administrated questionnaire	Both, ≥30	86/202	Daily drinking			1.97 (0.8–4.82)	Age, sex and residence	7

L, light; M, moderate; H, high; RR, relative risk; CI, confidence interval; NOS, Newcastle-Ottawa Scale; CC, case-control; BMI, body mass index; FFQ, food frequency questionnaire; NSAIDs, nonsteroidal anti-inflammatory drugs; GBS, gallbladder stone; M, male; F, female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride.
*OR for median drinking=0.99^{6}(0.98^{6}, 1.00^{6}) calculated with OR=0.99 (0.98, 1.00) for 1 unit/week and median drinking of 6 units/week; †OR for mean drinking calculated with one-unit OR estimates reported and mean drinking of 4 g and 11g for females and males, respectively.

ascertainment of outcome or exposure, since their study populations were health professionals, nurses or twins; two studies used self-report for ascertainment of outcome, and the other had no description of ascertainment of exposure. One study was rated as 6 stars since it used self-report for ascertainment of exposure and outcome in nurses.

3. Categorical meta-analysis

1) Overall drinking compared to nondrinking

The pooled RR of GSD for alcohol drinking compared to nondrinking was 0.84 (95% CI, 0.79 to 0.89; I^2=61%) based on 23 studies; only one of these studies included sex-adjusted effects for both sex groups (Fig. 2).[25] The subgroup analyses by study design showed that there was a significant difference between study designs (p=0.02). The pooled analysis from case-control studies showed a greater decreased effect of drinking than that found in cohort studies. The pooled RR from studies with a cohort design was 0.89 (95% CI, 0.84 to 0.89) with low heterogeneity between studies (I^2=28%), and the pooled RR from studies with a case-control design was 0.74 (95% CI, 0.63 to 0.86) with

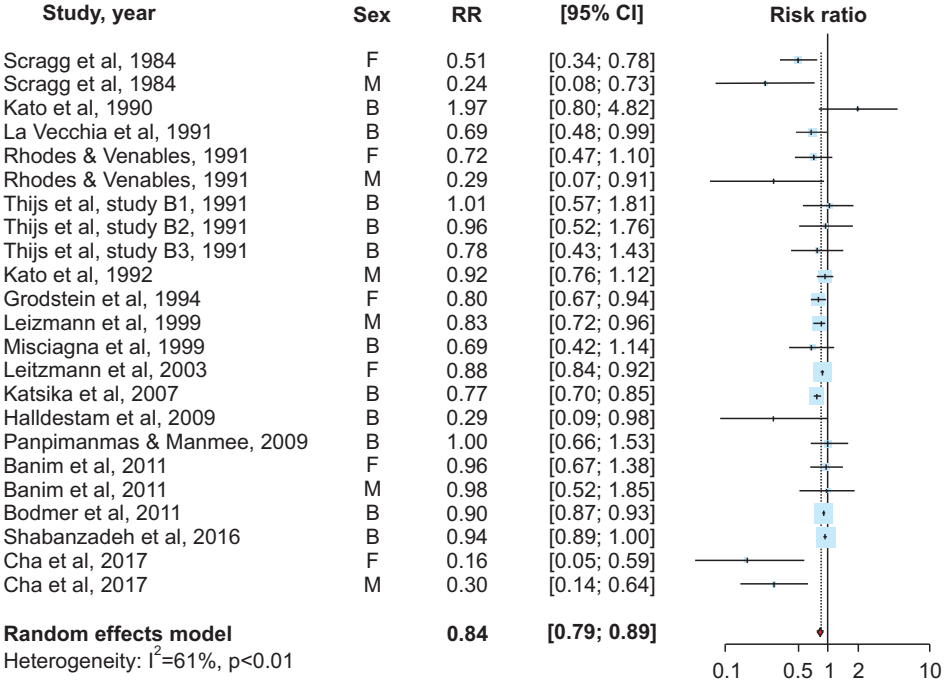

Fig. 2. Relative risks (RRs) of overall alcohol consumption for gallstone disease development (n=23).
CI, confidence interval; F, female; M, male, B, both.

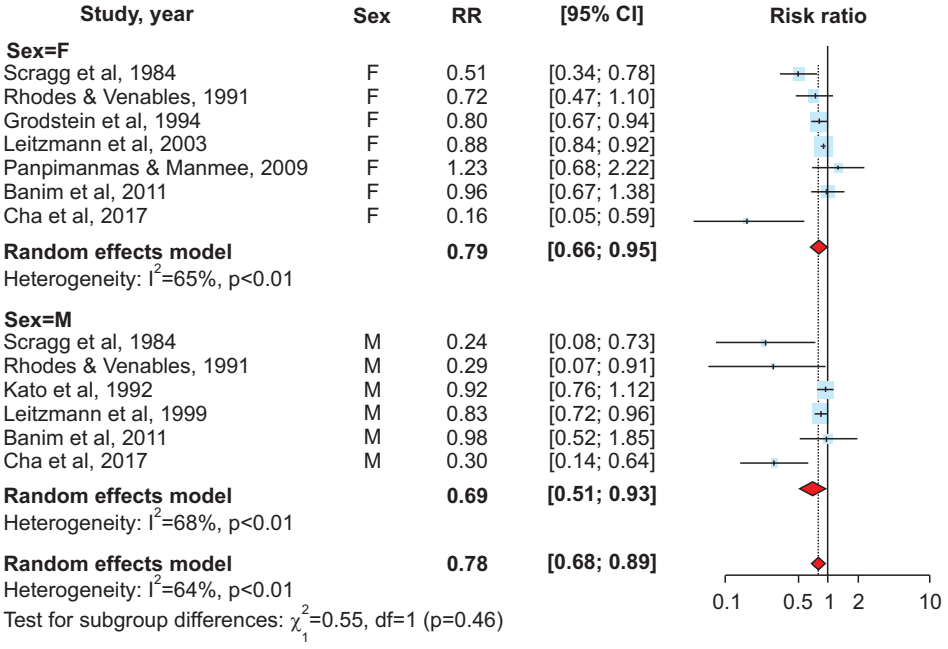

Fig. 3. Relative risks (RRs) of alcohol consumption for gallstone disease development among females and males (n=21).
CI, confidence interval; F, female; M, male.

large heterogeneity (I^2=70%). The pooled RRs by sex were 0.79 (95% CI, 0.66 to 0.95; I^2=65%) for females and 0.69 (95% CI, 0.51 to 0.93; I^2=68%) for males, with no significant difference between sex (p=0.46) (Fig. 3).

2) Drinking categories compared to nondrinking

Pooled analysis revealed that every alcohol consumption category was significantly associated with a decreased risk of GSD, with greater decreased risk in the higher alcohol consumption groups (Fig. 4). The pooled RRs for the light, moderate and high alcohol consumption groups compared to those in the nondrinking groups were 0.96 (95% CI, 0.94 to 0.99; I^2=0%), 0.80 (95% CI, 0.75 to 0.85; I^2=17%) and 0.66 (95% CI, 0.56 to 0.79; I^2=61%), respectively. The high alcohol consumption groups showed the greatest decreased risk of GSD with significantly large heterogeneity between studies. In the subgroup analysis by study design, the pooled effects of moderate and high alcohol consumption in case-control studies were larger than those in cohort studies (Fig. 5).

4. Dose-response meta-analysis

The dose-response meta-analysis of 14 studies suggested a nonlinear relationship between alcohol consumption and risk of GSD from 14 studies (p=0.002 for nonlinearity) (Fig. 6). The risk of GSD decreased with increasing alcohol consumption up to approximately 30 g/day, and the decrease in risk plateaued above 30 g/day. The RRs (95% CIs) of GSD compared to nondrinking groups were 0.92 (0.89 to 0.95), 0.82 (0.79 to 0.85), 0.67

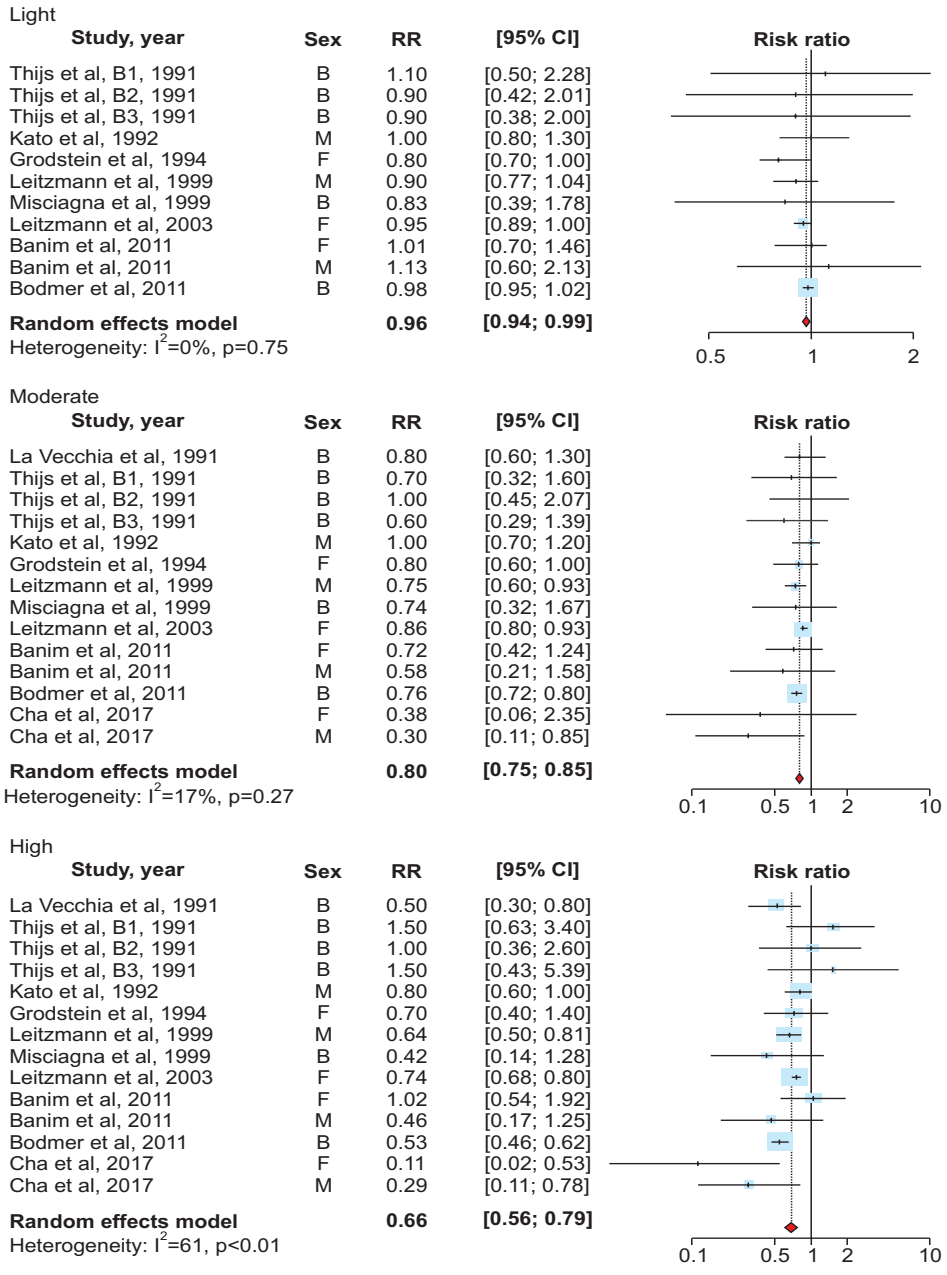

Fig. 4. Relative risks (RRs) of alcohol consumption for gallstone disease development based on alcohol drinking categories (light, moderate, and high). Drinking level for each category: light, F<7 and M<14 g/day; moderate, F 7–17 and M 14–18 g/day; high, F>14 and M>28 g/day. CI, confidence interval; F, female; M, male, B, both.

(0.64 to 0.71), and 0.62 (0.58 to 0.66), and 0.61 (0.52 to 0.71) for 7, 14, 28, 40, and 60 g/day of alcohol consumption, respectively. However, the dose-response results by study design showed that the nonlinear relationship between alcohol consumption and the risk of GSD was statistically significant in case-control studies but not in cohort studies (p=0.001 and p=0.184 for nonlinearity in case-control and cohort studies, respectively).

5. Publication bias

Funnel plots and Egger's tests for overall drinking suggested significant asymmetry (Egger test p=0.009) (Fig. 7). However, no significant asymmetries were found by alcohol consumption categories (Egger tests p=0.383, p=0.523, and p=0.602 for low-, moderate-, and high-consumption categories, respectively).

DISCUSSION

To estimate the association of alcohol consumption and GSD risk, we performed this meta-analysis of 16 case-control and eight cohort studies and found a significant dose-dependent, risk-reduction effect of drinking alcohol as a result (RR, 0.84; 95% CI, 0.79 to 0.89).

There were two published meta-analyses regarding the correlation between alcohol consumption and gallstone development risk.[7,8] One meta-analysis found no significant correlation between alcohol consumption and incidental gallstone risks.[7] Another meta-analysis showed a statistically significant, inverse relationship between the highest and lowest consumption categories (RR, 0.62; 95% CI, 0.49 to 0.78), whose pooled risk reduc-

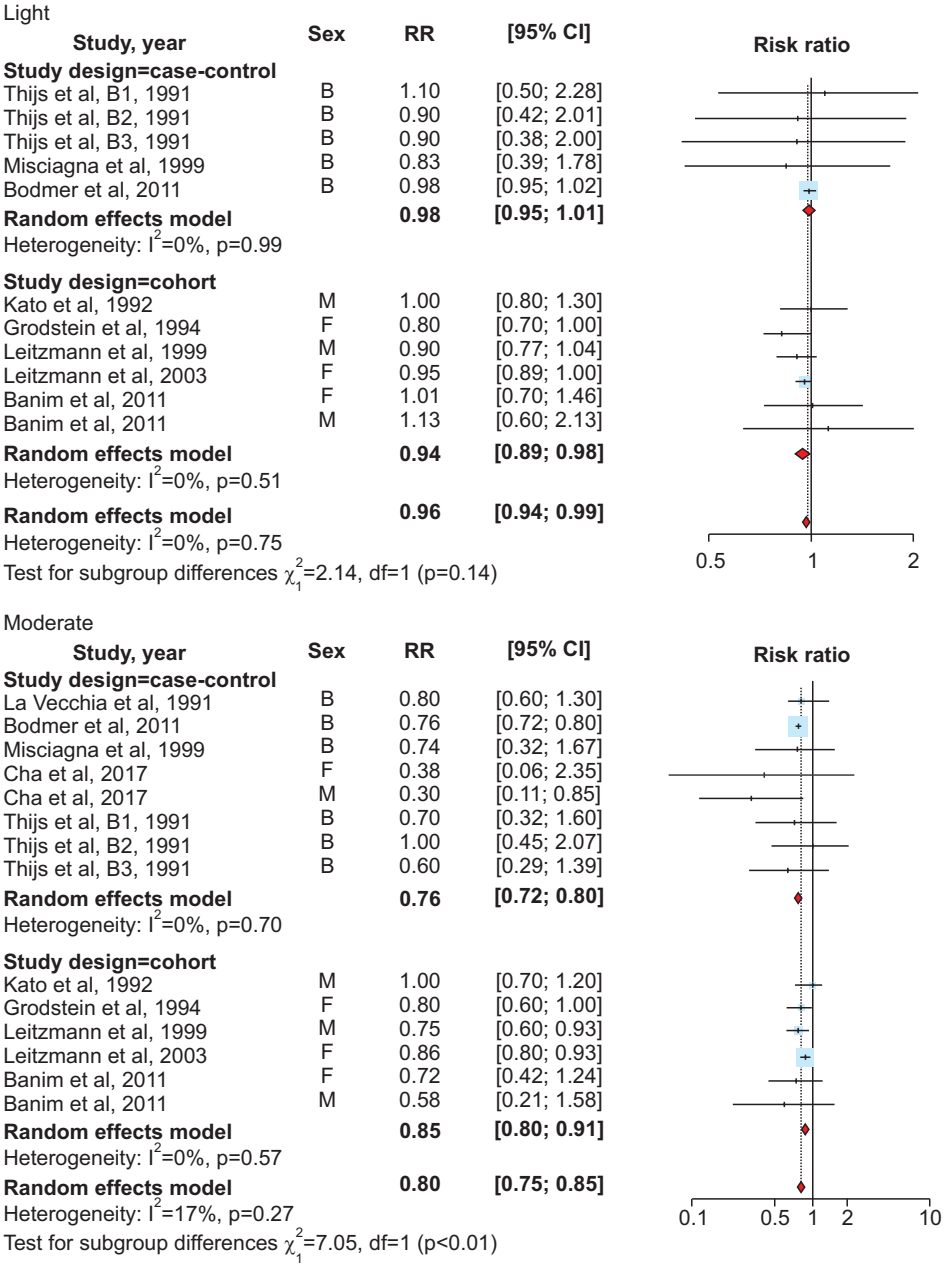

Fig. 5. Relative risks (RRs) of alcohol consumption for gallstone disease development based on alcohol drinking categories (light, moderate, and high) among case-control and cohort studies. Drinking level for each category: light, F<7 and M<14 g/day; moderate, F 7–17 and M 14–18 g/day; high, F>14 and M>28 g/day.
CI, confidence interval; F, female; M, male, B, both.

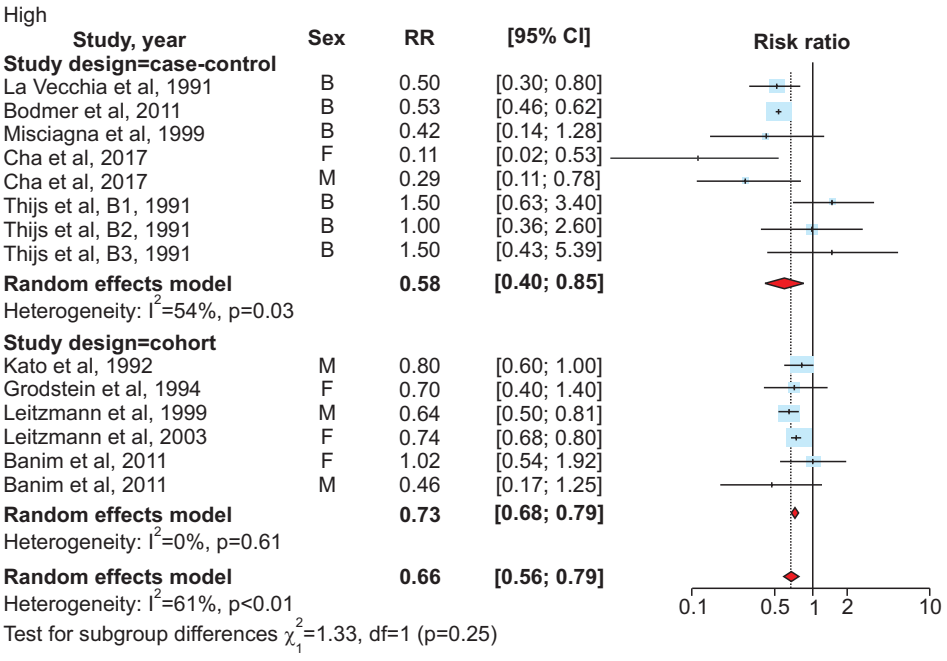

Fig. 5. Continued..

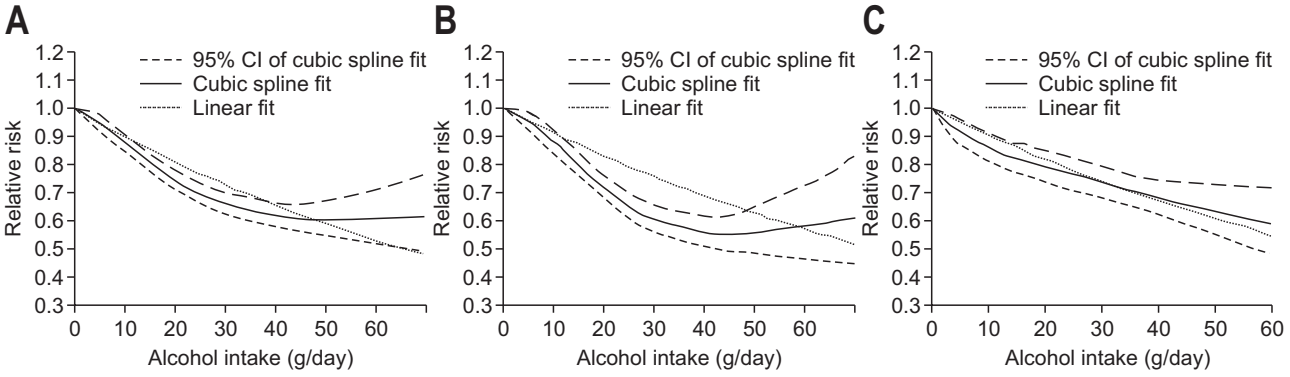

Fig. 6. Dose-response relationship between alcohol consumption and gallstone disease risk. (A) All included studies (n=14), p for nonlinearity <0.001. (B) Case-control study (n=8), p for nonlinearity=0.001. (C) Cohort study (n=6), p for nonlinearity=0.1839.

tion was larger than that of the overall drinking data relative to nondrinking or to the lowest category in this meta-analysis.[8]

Mechanisms underlying the protective effect of alcohol against gallstone formation have been explained in several ways: (1) decreased cholesterol saturation;[37-39] (2) increased high-density lipoprotein by reduction of cholesteryl ester transfer protein;[40-43] and (3) increased gallbladder motility.[44-46]

To discover the optimum level of alcohol drinking, we extracted quantitative alcohol consumption amounts with individual risk estimates in each category or continuous variables from each study and then sorted those data into new three categories: light, moderate, and high consumption. From the results, we obtained each different pooled RR according to the increment of alcohol consumption: 0.96 (0.94 to 0.99) in the light group; 0.80 (0.75 to 0.85) in the moderate group; 0.66 (0.56 to 0.79) in the high group. Furthermore, we carried out a dose-response meta-analysis for overall consumption and each subgroup of study design and sex. The RRs for GSD showed a weak trend between 28 and 40 g/day with a plateau occurring above 40 g/day, with RRs of 0.62 (0.58 to 0.66) and 0.61 (0.52 to 0.71) at 40 and 60 g/day, respectively. The dose-response relationship in case-control studies showed the same tendency as the overall group did, whereas a steady linear decline in RR for GSD was demonstrated in cohort studies, in which only two of the six studies had a drinking level of over 30 g/day.

Contrast to the former meta-analysis, we summarized the risk estimations measured by daily alcohol consumption according to standardized categories, which was comparable to different alcohol types based on the recommended statistical methods.[12,16,17] Secondarily, we discovered a trend of linear decline in GSD risk according to an increase in alcohol consumption and a weakened linear trend between 28 and 40 g/day compared to

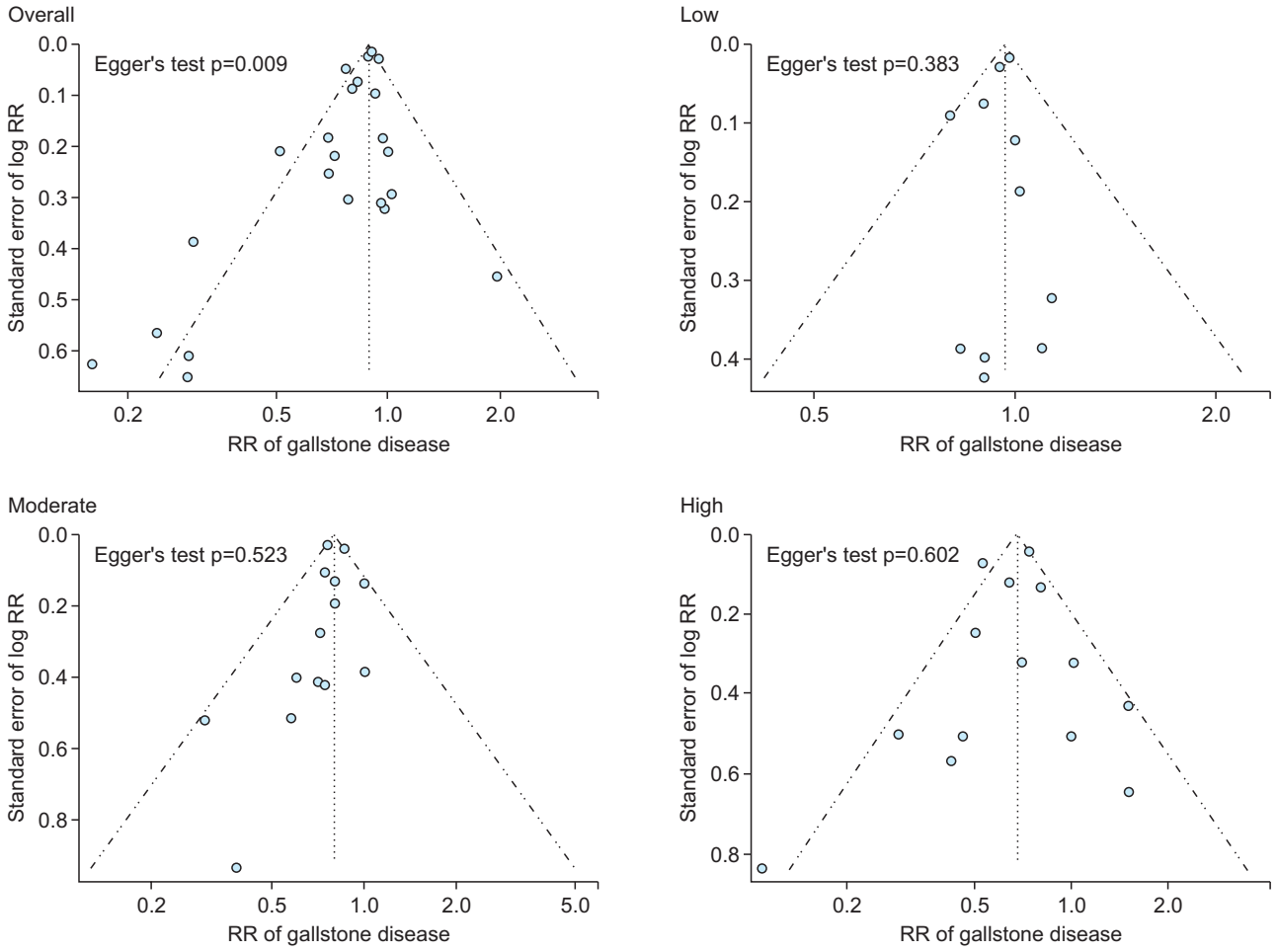

Fig. 7. Funnel plots of all included studies and different alcohol consumption levels.
RR, relative risk.

that of under 28 g/day in the overall and case-control studies but not in the cohort studies. The previous meta-analysis included one Asian study, which was completed in Thailand. We enrolled three more articles published in Asia (2 Chinese and 1 Korean), but two of them were cross-sectional studies; therefore, we included one more case-control study from Asia.[24]

There were limitations in our study. Although we achieved a nonlinear trend shown in the dose-response analysis among the overall studies and case-control studies, the same trend was not found among the cohort studies, which have the highest level of evidence. We attempted to enroll more studies published in various countries, for example, Asia, Africa, and South America; however, the majority of studies included for the dose-response meta-analysis were performed in North America and Europe due to newly published Asian studies having lower levels of evidence. Meanwhile, it was quite difficult to compare the quantitative alcohol effects in various beverage types and among the diverse individuals who are drinking in different ways, for example, in frequency and amount. Therefore, more important studies from varied regions and more comparable standardization methods are warranted to generalize the conclusions from our study.

In addition to the above limitations, clinicians need to be cautious in recommending drinking for the purpose of GSD prevention because excessive drinking, defined as binge drinking, and chronic heavy alcohol consumption results in multiple psychiatric and clinical illnesses, including mortality from a variety of chronic diseases.[47-50]

In conclusion, we confirmed that alcohol drinking decreases the risk of GSD development based on our meta-analysis of case-control and cohort studies. There was a linear risk reduction and weakened linear trend between consumption levels below and above 28 g/day in the dose-response analysis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

Authors contributions: Two authors (B.H.C. and M.J.J.) per-

formed a comprehensive systematic search for published studies which aimed to evaluate the relationship between alcohol consumption and gallstone disease risk. Data extraction was completed by two authors (B.H.C. and M.J.J.) independently from all included studies with a predefined information sheet, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses.[44] Any discrepancies in extracted data were solved through consensus or discussion with a third author (S.H.L.). The overall study quality was assessed independently by two authors (B.H.C. and M.J.J.) using the Newcastle–Ottawa Scale (NOS).

REFERENCES

1. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver 2012;6:172-187.
2. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. Gastroenterology 2009;136:376-386.
3. Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? Curr Gastroenterol Rep 2005;7:132-140.
4. Andreotti G, Liu E, Gao YT, et al. Medical history and the risk of biliary tract cancers in Shanghai, China: implications for a role of inflammation. Cancer Causes Control 2011;22:1289-1296.
5. Ahrens W, Timmer A, Vyberg M, et al. Risk factors for extrahepatic biliary tract carcinoma in men: medical conditions and lifestyle: results from a European multicentre case-control study. Eur J Gastroenterol Hepatol 2007;19:623-630.
6. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015;112:580-593.
7. Shabanzadeh DM, Novovic S. Alcohol, smoking and benign hepato-biliary disease. Best Pract Res Clin Gastroenterol 2017;31:519-527.
8. Wang J, Duan X, Li B, Jiang X. Alcohol consumption and risk of gallstone disease: a meta-analysis. Eur J Gastroenterol Hepatol 2017;29:e19-e28.
9. Park Y, Kim D, Lee JS, et al. Association between diet and gallstones of cholesterol and pigment among patients with cholecystectomy: a case-control study in Korea. J Health Popul Nutr 2017;36:39.
10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-341.
11. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa: Ottawa Hospital Research Institute [cited March 2017]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
12. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology 1993;4:218-228.
13. Kloner RA, Rezkalla SH. To drink or not to drink? That is the question. Circulation 2007;116:1306-1317.
14. Kerr WC, Greenfield TK, Tujague J, Brown SE. A drink is a drink? Variation in the amount of alcohol contained in beer, wine and spirits drinks in a US methodological sample. Alcohol Clin Exp Res 2005;29:2015-2021.
15. National Institute on Alcohol Abuse and Alcoholism. The physicians' guide to helping patients with alcohol problems. Washington, DC: Government Printing Office, 1995.
16. Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008;27:954-970.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560.
18. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol 2012;175:66-73.
19. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata J 2006;6:40-57.
20. Thijs C, Knipschild P, Leffers P. Does alcohol protect against the formation of gallstones? A demonstration of protopathic bias. J Clin Epidemiol 1991;44:941-946.
21. Scragg RK, McMichael AJ, Baghurst PA. Diet, alcohol, and relative weight in gall stone disease: a case-control study. Br Med J (Clin Res Ed) 1984;288:1113-1119.
22. Rhodes M, Venables CW. Symptomatic gallstones: a disease of non-smokers? Digestion 1991;49:221-226.
23. Banim PJ, Luben RN, Bulluck H, et al. The aetiology of symptomatic gallstones quantification of the effects of obesity, alcohol and serum lipids on risk. Epidemiological and biomarker data from a UK prospective cohort study (EPIC-Norfolk). Eur J Gastroenterol Hepatol 2011;23:733-740.
24. Cha BH, Lee BS, Lee SH, Kang SJ, Park MJ. A study of alcohol consumption and obesity as main risk factor for symptomatic gallbladder stone: a case-control study. Asian Pac J Cancer Prev 2017;18:715-719.
25. Panpimanmas S, Manmee C. Risk factors for gallstone disease in a Thai population. J Epidemiol 2009;19:116-121.
26. La Vecchia C, Negri E, D'Avanzo B, Franceschi S, Boyle P. Risk factors for gallstone disease requiring surgery. Int J Epidemiol 1991;20:209-215.
27. Kato I, Nomura A, Stemmermann GN, Chyou PH. Prospective study of clinical gallbladder disease and its association with obesity, physical activity, and other factors. Dig Dis Sci 1992;37:784-790.
28. Grodstein F, Colditz GA, Hunter DJ, Manson JE, Willett WC, Stampfer MJ. A prospective study of symptomatic gallstones in women: relation with oral contraceptives and other risk factors. Obstet Gynecol 1994;84:207-214.

29. Leitzmann MF, Giovannucci EL, Stampfer MJ, et al. Prospective study of alcohol consumption patterns in relation to symptomatic gallstone disease in men. Alcohol Clin Exp Res 1999;23:835-841.
30. Leitzmann MF, Tsai CJ, Stampfer MJ, et al. Alcohol consumption in relation to risk of cholecystectomy in women. Am J Clin Nutr 2003;78:339-347.
31. Bodmer M, Brauchli YB, Jick SS, Meier CR. Diabetes mellitus and the risk of cholecystectomy. Dig Liver Dis 2011;43:742-747.
32. Misciagna G, Centonze S, Leoci C, et al. Diet, physical activity, and gallstones: a population-based, case-control study in southern Italy. Am J Clin Nutr 1999;69:120-126.
33. Katsika D, Tuvblad C, Einarsson C, Lichtenstein P, Marschall HU. Body mass index, alcohol, tobacco and symptomatic gallstone disease: a Swedish twin study. J Intern Med 2007;262:581-587.
34. Shabanzadeh DM, Holmboe SA, Sørensen LT, Linneberg A, Andersson AM, Jørgensen T. Are incident gallstones associated to sex-dependent changes with age? A cohort study. Andrology 2017;5:931-938.
35. Halldestam I, Kullman E, Borch K. Incidence of and potential risk factors for gallstone disease in a general population sample. Br J Surg 2009;96:1315-1322.
36. Kato I, Kato K, Akai S, Tominaga S. A case-control study of gallstones: a major risk factor for biliary tract cancer. Jpn J Cancer Res 1990;81:578-583.
37. Thornton J, Symes C, Heaton K. Moderate alcohol intake reduces bile cholesterol saturation and raises HDL cholesterol. Lancet 1983;2:819-822.
38. Schwesinger WH, Kurtin WE, Johnson R. Alcohol protects against cholesterol gallstone formation. Ann Surg 1988;207:641-647.
39. Kurtin WE, Schwesinger WH, Stewart RM. Effect of dietary ethanol on gallbladder absorption and cholesterol gallstone formation in the prairie dog. Am J Surg 1991;161:470-474.
40. Langer RD, Criqui MH, Reed DM. Lipoproteins and blood pressure as biological pathways for effect of moderate alcohol consumption on coronary heart disease. Circulation 1992;85:910-915.
41. Hagiage M, Marti C, Rigaud D, et al. Effect of a moderate alcohol intake on the lipoproteins of normotriglyceridemic obese subjects compared with normoponderal controls. Metabolism 1992;41:856-861.
42. Gaziano JM, Buring JE, Breslow JL, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. N Engl J Med 1993;329:1829-1834.
43. Mukamal KJ, Jensen MK, Grønbaek M, et al. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. Circulation 2005;112:1406-1413.
44. Probert CS, Emmett PM, Heaton KW. Some determinants of whole-gut transit time: a population-based study. QJM 1995;88:311-315.
45. Robles EA, Mezey E, Halsted CH, Schuster MM. Effect of ethanol on motility of the small intestine. Johns Hopkins Med J 1974;135:17-24.
46. Tsai TJ, Chan HH, Lai KH, et al. Gallbladder function predicts subsequent biliary complications in patients with common bile duct stones after endoscopic treatment? BMC Gastroenterol 2018;18:32.
47. Harwood H. Updating estimates of the economic costs of alcohol abuse in the United States: estimates, update methods, and data. NIH Publication no. 00-1583, Rockville: National Institute on Alcohol Abuse and Alcoholism, 2000.
48. Stahre M, Roeber J, Kanny D, Brewer RD, Zhang X. Contribution of excessive alcohol consumption to deaths and years of potential life lost in the United States. Prev Chronic Dis 2014;11:E109.
49. Edelman EJ, Fiellin DA. In the Clinic. Alcohol Use. Ann Intern Med 2016;164:ITC1- ITC16.
50. Moss HB, Chen CM, Yi HY. Prospective follow-up of empirically derived Alcohol Dependence subtypes in wave 2 of the National Epidemiologic Survey on Alcohol And Related Conditions (NESARC): recovery status, alcohol use disorders and diagnostic criteria, alcohol consumption behavior, health status, and treatment seeking. Alcohol Clin Exp Res 2010;34:1073-1083.