REVIEW ARTICLE

Smoking habits and gallbladder disease: a systematic review and meta-analysis study

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Abstract

Background: It has been claimed that smoking is linked with an increased risk for gallbladder disease (GBD); however, related issues need further consolidation and clarification. The present systematic review and meta-analysis aimed to further investigate the potent correlation between GBD and smoking.

Methods: We conducted a comprehensive literature review to identify every study published from January 1989 to December 2019, reporting risk estimates regarding GBD and smoking. The random-effect, generic inverse variance method, according to description by DerSimonian and Laird, was used to compute pooled estimates. We used the Newcastle-Ottawa quality assessment scale to appraise the included studies' quality.

Results: Thirty published case-control, cross-sectional, and cohort studies including 4,623,435 individuals met the eligibility criteria and were considered for data synthesis. Compared to the non-smokers, ever smokers had 1.25 times higher odds of developing GBD [95 % confidence interval (CI): 1.09-1.44]; however, increased heterogeneity was observed (I^2 =96 %, 95 % CI: 62-100 %, p <0.001). Publication bias was non-significant (Eggers' regression p =0.072). The main sources of heterogeneity, as detected by meta-regression analyzing study characteristics, biases and confounders, were non-adjustment for family history (p =0.007) and alcohol (p =0.020), respectively. Subgroup analysis indicated a comparable risk for GBD as far as current, former and ever smokers are concerned (p =0.520). Quantitative analysis suggested a dose-effect for current smoking and GBD (p =0.010).

Conclusions: Non-smokers were demonstrated to be at a lower risk of presenting GBD when compared with ever smokers; all relevant risk estimates necessitate adjustment for family history and alcohol intake. HIPPOKRATIA 2020, 24(4): 147-156.

Keywords: Gallbladder diseases, cholelithiasis, Smoking, Review, Meta-Analysis

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Introduction

Gallbladder disease (GBD), constituting gallstones, cholecystitis, and other causes, is a major public health determinant with significant morbidity and mortality worldwide[1]. Its frequency ranges from <5 % in Chinese, Japanese, and Thai to >60 % in Indians[2]. Risk for GBD rises with age while it is increased in females and individuals with family history or genetics (non-modifiable factors); however, a series of modifiable factors as obesity, rapid weight loss, and sedentary lifestyle have been recognized[3-5].

Several studies investigated the possible relation of smoking and GBD, surprisingly with seemingly contradictory results. The related topic remained obscure as published results were based on studies that differ significantly concerning characteristics and methodology. A five-year-old meta-analysis, including ten published studies, suggested that there might be a positive correlation between smoking and GBD[6]. Since then, the effect of smoking in GBD is believed to be minor, if any[7]. A recently published study reports that lifetime smoking abstinence could contribute only a small portion of the multivariate and mutually adjusted partial population attributable risks for symptomatic cholelithiasis (1 % for women and 5 % for men)[8].

To investigate the potent underlying pathophysiology between smoking and GBD, a sonographic study exhibited that the maximal emptying time of the gallbladder was larger in smokers compared to non-smokers; however, the result was not statistically significant. Thus, the study proposed that chronic smoking delays gallbladder contraction and leads to a significant decrease in gallbladder emptying volume, though it does not influence gallbladder refilling. As a result, bile stasis, a cause of most gallbladder disorders, could be attributed to smoking adverse effects[9].

The present systematic review and meta-analysis aim to provide any additional evidence concerning the poten-

tial correlation between GBD and smoking by detecting all relevant studies and summarizing the results derived from them.

Materials and Methods

Literature search

We conducted a systematic review of the literature using the EMBASE, PubMed/Medline, and Cochrane Library databases and ClinicalTrials.gov from January 1989 to December 2019 to identify every study that reported risk estimates regarding GBD and smoking. We utilized Google Scholar as a secondary pool of published data; iterative search lasted until no additional publication could be traced. Lastly, we scavenged, wherever possible, unpublished dissertations and other unpublished work. The study protocol was submitted to the PROSPERO database on 24/7/2019 and revised on 28/10/2019 (ID: 144620).

Study selection

Study selection was independently performed by two authors (V.P. and D.F.) and included a search for the following terms: (cholelithiasis OR gallstones OR gallbladder disease OR cholecystitis OR cholecystectomy) AND (smoking OR tobacco); the third author (K.M.) closely observed the process and was responsible for dissolving any dispute. We did not use any software for the study retrieval process. Wherever possible, we traced every source of financial support. Eligible studies were considered to be all that i) were published in English; ii) were case-control, cross-sectional, or cohort ones; iii) reported a risk estimate in the form of an odds ratio (OR) or provided sufficient information for result conversion to OR format; iv) reported a measure of statistical significance; and v) were not duplicates.

Outcome measures

The study was carried out according to the PRISMA statement guidelines to pre-specify eligibility criteria based on the well-established PICO [P- for Populations/People/Patient/Problem: patients with GBD and controls, I- for Intervention(s): smoking, C- for Comparison: between ever smokers and never smokers (primary endpoint); between current smokers and never smokers; between ex-smokers and never smokers, O- for Outcome: cholelithiasis] worksheet and search strategy[10]. AMSTAR checklist was used to assess the quality of the present meta-analysis[11].

Data extraction

A pre-specified structured form for data collection by means of an Excel worksheet was used for data extraction from each study. In detail, title of the study, first author's name, publication year, country where the study was conducted, number of patients with cholelithiasis, number of healthy individuals, risk estimates in the form of an OR for current smokers, ex-smokers, and never smokers, adjustment for potent confounders (sex, age, alcohol intake, and family history) and quality assessment data. Two of the authors (V.P. and D.F.) independently performed data extraction, while K.M. closely observed the process and was responsible for cross-checking in case of any dispute.

Quality assessment of the studies

We used the Newcastle-Ottawa quality assessment scale (NOS) to estimate the quality of the included studies by means of three distinct grouping items, namely i) the selection item (referring to the identification and recruitment of participants), ii) the comparability item (referring to the comparability between the two groups), and iii) the exposure/outcome of interest item (referring to the ascertainment of either the exposure or the outcome of interest regarding case-control and cohort studies, respectively). We used a modified version of NOS[12] for cross-sectional studies. In detail, the selection item was given a maximum of either four stars (in case of cohort / case-control studies) or five stars (in case of cross-sectional studies), comparability item a maximum of two stars, and exposure/outcome of interest a maximum of three stars. The inter-rater agreement evaluation concerning the NOS assessment was performed using Kappa statistics.

Data synthesis

Data synthesis was performed using the Revman 5.3 software that is freely available from the Cochrane Collaboration[13]. As effect estimates, the natural logarithm of OR (LnOR) was used; wherever OR was not available, conversion from relative risk (RR) or hazard ratio (HR) was performed using the formulas $OR = RR \bullet (1-r)/(1 - RR \bullet r)$ and $RR = [1-e^{HR \bullet \ln(1-r)}]/r$.

Conventional meta-analytic techniques assume that all effect size estimates derived from different studies are independent; however, this assumption might be violated if several estimates based on the same individuals are available, as is the case here. A commonly used methodology is simply ignoring that some of the effect size estimates might not be independent and thus use the same meta-analytic approaches as usual. Generally, this strategy inflates type I error rates as far as the significance of the moderators is concerned[14]; nevertheless, it may not be too misleading if the number of studies reporting more than one effect size is relatively small. Additionally, it may lead to conservative estimation of the difference between average effects of different types, which may, in fact, be sufficient for rough inferences[15].

Statistical analysis

Given the OR and confidence intervals (CI) of each risk estimation, standard error (SE) was calculated; Furthermore, the random effects model was used to estimate overall OR and its CI; for that purpose, the Revman 5.3 software was preferred[13].

We performed analysis of publication bias through several approaches, including Eggers' regression, funnel plot accompanied by the relevant trim-and-fill analysis, Galbraith plot, normal quantile plot, standardized residu-

al histogram, Rosenthal failsafe-N test as well as Gleser and Olkin number of unpublished studies using Meta-Essentials software[16].

Heterogeneity was approached using Q test and I^2 statistic as derived from Meta-Essentials (Q test p-value <0.10 and/or I^2 >50 % was indicative of significant heterogeneity). CI of I^2 statistics was computed using either the formula $\pm 1.96 \bullet 0.50 \bullet \{[Ln(Q)-Ln(df)]/[(2Q)^{½}-(2 \bullet df-1)^{½}]$ for Q >df+1 or $\pm 1.96/\{[2 \bullet (df-1) \bullet \{1-\{1/[3 \bullet (df-1)^2]\}\}\}^{½}$ *for* $Q \leq df+1$, where df denotes degrees of freedom[17].

Heterogeneity was quantitatively approached through three separate meta-regressions focusing separately on the study characteristics, quality assessment, and potential confounders; subgroup analyses followed in all cases, independently of the result of the multivariate analysis.

Quantitative analysis regarding the potential effect of current smoking was based on pooled data expressed as OR for every increment of ten cigarettes/day up to 30. Spearman's r non-parametric correlation coefficients between medians of the above-mentioned increments and the relevant OR were computed. Regression was used to define the best fit curve that could approach the phenomenon.

The IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY, USA) was used for all statistical tests.

Results

Study characteristics

Our concise literature search revealed 920 publications of interest in EMBASE (377), PubMed/Medline (448), Cochrane Library (89), and ClinicalTrials.gov (4). Two additional publications were scavenged through Google Scholar search. No unpublished data of interest was traced. No personal contact was performed.

After the initial exclusion of 397 duplicates, we reviewed the remaining 523 publications based on the title and abstract; during this procedure, we excluded 460 as being ineligible. Moreover, 31 failed to fulfill the eligibility criteria based on the type of article, measured outcomes, and risk estimates. We included the remaining 32 publications in the qualitative synthesis; two were excluded from meta-analysis as they reported unadjusted risk estimates.

Finally, 30 studies (four case-control, 12 cross-sectional, and 14 cohort studies), including 4,623,435 individuals, were considered for quantitative data synthesis (Figure 1). Based on these studies, 91 risk estimates (63 direct and 28 pooled) regarding current, ex-, or ever versus never smokers and GBD were collected.

All characteristics regarding leading author, year of publication, study design, origin, endpoint, outcome measures, sex representation, number of patients and controls, adjustment for potent confounders, and OR regarding smokers, ex-smokers and ever smokers vs non-smokers are analytically presented in Table 1.

Quality assessment items are analyzed in Table 2.

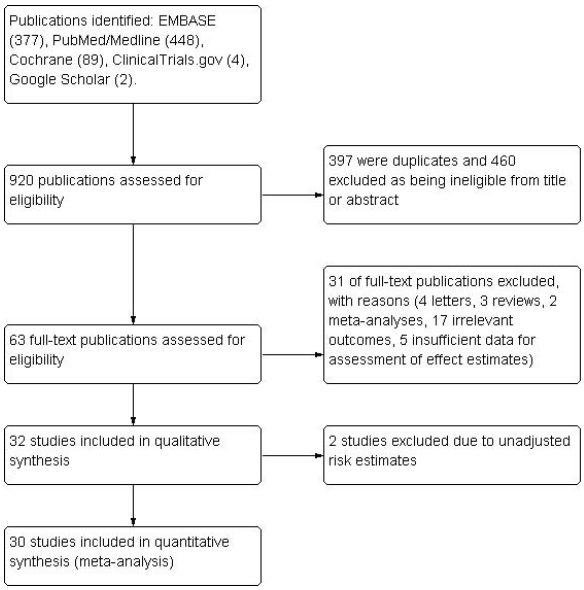

Figure 1: Flow chart of the systematic review of the literature from January 1989 to December 2019 for studies reporting risk estimates regarding gallbladder disease and smoking.

The inter-rater agreement between the two authors who accomplished the quality assessment process was high (kappa =0.74).

Publication bias

There was cumulative evidence for absence of significant publication bias. In detail, Eggers' regression was not significant (p =0.072), Rosenthal failsafe-N test failed to reject the *ad hoc* rule (Failsafe-N =70), and Gleser & Olkin number of unpublished studies yielded a null result. Moreover, no lack of symmetry was observed in the funnel plot, no imputed data points were produced in the relevant trim-and-fill analysis (Figure 2), and all studies were within the 95 % CI area of the Galbraith plot (Figure 3).

Primary outcome

Compared to the non-smokers, ever smokers had 1.25 times higher odds of developing cholelithiasis (95 % CI: 1.09-1.44); however, increased heterogeneity was observed (I^2 =96 %, 95 % CI: 62-100 %, p <0.001) (Figure 4).

Meta-regression analysis

The main sources of heterogeneity, as detected by meta-regression analyzing potent confounders, were family history (p =0.007) and alcohol (p =0.020) non-adjustment (Table 3). Interestingly, sex was not considered as a major determinant of heterogeneity (p =0.330). No statistically significant result was revealed from the meta-regression carried out regarding study characteristics and quality assessment.

Table 1: Eligible studies published from January 1989 to December 2019, reporting risk estimates regarding GBD and smoking: the 30 published case-control, cross-sectional, and cohort studies that were considered for data synthesis.

Study	Design	Region	Endpoint	Outcome measures	Sex	Case/Total	OR (Smokers vs non-smokers)	OR (Ex-smokers vs non-smokers)	OR (Ever smokers vs non-smokers)	Adjusted confounders
Jorgensen, 1989[18]	CS	Denmark	Cholelithiasis	Medical history, questionnaire, ultrasound	M/F	308/3417			M: 3.01 (2.07-3.95) F: 1.24 (0.89-1.59) M/F, pooled: 1.92 (0.81-4.59) †	Slimming treatment, physical exercise, coffee
Pastides, 1990[19]	CC	Greece	GBD	Medical history, questionnaire, ultrasound	M/F	100/271	0.5 (0.2-0.9)			Alcohol, eye color, dietary pattern
La Vecchia, 1991[20]	CC	Italy	Cholelithiasis	Hospital records, questionnaire	M/F	195/1317	1.114 (0.781-1.858)	1.472 (0.781-2.733)	1.19 (0.87-1.63) †	Sex, age, BMI, area of residence, coffee, alcohol, history of liver disease
McMichael, 1992[21]	CC	Australia	GBD	Hospital records, questionnaire	F	267/508	1.7 (0.9-3.2) 1-14 cig.: 1.10 (0.93-1.31)	1.4 (0.7-3.0)	1.57 (0.97-2.54) †	Parity, age, BMI, alcohol, sugar intake, oral contraceptive use
Stampfer, 1992[22]	PrC	USA	Cholelithiasis	Medical history, questionnaire, ultrasound	F	2610/90302	15-24 cig.: 1.03 (0.90-1.19) 25-34 cig.: 1.33 (1.09-1.61) 35+ cig.: 1.53 (1.21-1.94) Pooled: 1.21 (1.02-1.43) †	1.06 (0.96-1.17)		Parity, age, BMI, alcohol, weight change, calorie intake, PUFA intake, postmenopausal hormone use
Kato, 1992[23]	PrC	USA	Cholelithiasis	Medical history, questionnaire, ultrasound	M	471/7831	1.656 (1.000-2.120)			Age, BMI, alcohol, height, calorie intake, physical activity, serum glucose, triglycerides and uric acid levels, blood pressure
Murray, 1994[24]	PrC	UK	GBD	GP reports	F	1087/46377	1.196 (1.062-1.352)			Parity, age, social class
Grodstein, 1994[25]	CS	USA	Cholelithiasis	Medical history, questionnaire	F	425/96211	1.302 (1.000-1.705)			Parity, age, BMI, alcohol, weight change, oral contraceptive use, postmenopausal hormone use
Kono, 1995[26]	CS	Japan	Cholelithiasis	Medical history, questionnaire, ultrasound, laboratory tests	M	72/2228	0.9 (0.6-1.4)	0.9 (0.3-2.3)	0.9 (0.62-1.31) †	BMI, alcohol, hospital, rank, exercise, glucose tolerance
Misciagna, 1996[27]	PrC	Italy	Cholelithiasis	Medical history, questionnaire, ultrasound	M/F	226/2472	1.89 (1.18-3.03)			Sex, age, BMI
Kratzer, 1997[28]	CS	Germany	Cholelithiasis	Medical history, questionnaire, ultrasound	M/F	67/1116			1.381 (0.82-2.331)	Age
Martinez de Pancorbo, 1997[29]	CS	Spain	Cholelithiasis	Medical history, questionnaire, ultrasound, laboratory tests	M/F	67/894	1.492 (1.097-2.209)			Sex, age, BMI, alcohol, dyspeptic symptoms, hypolipidemic drugs, total cholesterol
Sahi, 1998[30]	PrC	USA	GBD	Personal contact with physician, questionnaire	M	685/16785	1-19 cig.: 1.457 (1.00-2.157) ≥20 cig.: 1.554 (1.031-2.365) Pooled: 1.50 (1.14-1.98) †	1.295 (0.886-1.919)	1.42 (1.14-1.77) †	Age
Okamoto, 2002[31]	CS	Japan	Cholelithiasis	Questionnaire, ultrasound, laboratory tests	M/F	483/9946	M, 1-19 cig.: 1.55 (0.66-3.67) M, ≥20 cig.: 1.36 (0.63-2.90) F: 1.36 (0.84-2.19) M/F, pooled: 1.39 (0.97-2.01) †	M: 0.95 (0.65-1.38) F: 0.68 (0.29-1.56) M/F, pooled: 0.90 (0.64-1.27) †	1.10 (0.86-1.41) †	Age, BMI, alcohol, % of body fat, HDL-C, LDL-C, fasting blood sugar, HbA1c
Völzke, 2005[32]	CS	Germany	Cholelithiasis	Medical history, questionnaire, ultrasound, laboratory tests	F	586/2150	0.76 (0.56-1.02)			Age, BMI, waist-to-hip ratio, parity, physical activity, cholesterol levels
Yamada, 2005[33]	PrC	Japan	Cholelithiasis	Medical history, questionnaire, ultrasound	M/F	1136/11982			1.214 (1.022-1.461)	Sex, age, alcohol, residence, radiation dose, duodenal and gastric ulcer, liver disease
Gonzalez-Peres, 2007[34]	PrC	Spain	GBD	GP reports, medical history of cholecystectomy	M/F	2353/12353	1.05 (0.94-1.19)	1.18 (0.99-1.41)	1.09 (0.98-1.21) †	Sex, age, BMI, alcohol, diabetes, heart failure, hyperlipidemia, hypertension, ischemic heart disease, stroke, osteoarthritis, rheumatoid arthritis
Abu-Eshy, 2007[35]	CS	Saudi Arabia	Cholelithiasis	Medical history, questionnaire, ultrasound	M/F	34/291	1.61 (0.29-8.95)			Sex, age, BMI, education, coffee, family history of gall stones, history of diabetes, hypertension, pancreatitis
Katsika, 2007[36]	PrC	Sweden	Cholelithiasis	Hospital records, questionnaire	M/F	1666/58402	0.99 (0.78-1.27)	1.15 (0.95-1.39)	1.08 (0.93-1.25) †	Sex, age, BMI, alcohol
Panpimanmas, 2009[37]	CC	Thailand	Cholelithiasis	Hospital records, medical history, questionnaire, ultrasound	M/F		1.8 (0.7-4.6)	2.4 (1.1-5.2)	2.14 (1.17-3.91) †	Sex, age
Halldestam, 2009[38]	PrC	Sweden	Cholelithiasis	Medical history, questionnaire, ultrasound, laboratory tests, death certificates	M/F	42/503			1.18 (0.43-3.25)	Sex, age, BMI, alcohol, family history of gall stones, occupation, diabetes mellitus, HDL-C, LDL-C, triglycerides and Lp(a) levels, NSAID use
Liu, 2009[39]	PrC	UK	GBD	Hospital records, questionnaire	F	23989/1290413	1-9 cig.] 1-9 cig.: 1.126 (1.06-1.196) 10-19 cig.: 1.255 (1.202-1.310) ≥20 cig.: 1.308 (1.238-1.382) Pooled: 1.23 (1.14-1.33) †	1.138 (1.106-1.171)	1.20 (1.12-1.29) †	Age, BMI, residence, socioeconomic status, alcohol
Walcher, 2010[40]	CS	Germany	Cholelithiasis	Medical history, questionnaire, ultrasound	M/F	170/1967	0.89 (0.57-1.38)	1.36 (0.88-2.11)	1.10 (0.72-1.68) †	Sex, age, BMI, education, coffee, alcohol, family history of gall stones
Etminan, 2011[41]	RetroC	USA	GBD	Medical history of cholecystectomy	F	27087/2721014			2.072 (2.002-2.154)	Age, obesity, diabetes, inflammatory bowel disease, pancreatitis, sickle cell anemia, statin use, fibrate use, oral contraceptives use
Palermo, 2013[42]	CS	Argentina	Cholelithiasis	Medical history, questionnaire, ultrasound	M	276/1336	2.83 (1.81-4.42)			Age, family history, pain, sedentary habits
Shabanzadeh, 2016[43]	PrC	Denmark	Cholelithiasis	Medical history, questionnaire, ultrasound, laboratory tests	M/F	256/2592			0.84 (0.63-1.12)	Sex, age, BMI, alcohol, coffee, type of diet, physical activity level, blood lipids, benign gallbladder findings, female sex hormones use
Figuierdo, 2017[3]	PrC	USA	GBD	Medical history, hospital records, questionnaire	M/F	13437/144409	M, 1-19 cig.: 1.1682 (1.04-1.31) M, 20+ cig.: 1.2320 (1.09-1.39) F, 1-19 cig.: 1.1646 (1.08-1.26) F, 20+cig.: 1.3562 (1.24-1.49) M/F, pooled: 1.23 (1.14-1.33) †	M, 1-19 cig.: 1.0944 (1.01-1.18) M, 20+ cig.: 1.1682 (1.07-1.28) F, 1-19 cig.: 1.1028 (1.04-1.17) F, 20+ cig.: 1.311 (1.18-1.46) M/F, pooled: 1.16 (1.08-1.24) †	1.19 (1.13-1.25) †	Age, BMI, alcohol, ethnicity, education, diabetes
Kang, 2018[44]	CS	China	GBD	Medical history, questionnaire, ultrasound, laboratory tests	M/F	1876/21435	1.15 (1.01-1.31)	1.37 (1.13-1.65)	1.24 (1.04-1.48) †	Sex, age, residence, dietary habits regarding fish and soya
Chang, 2019[45]	PrC	Taiwan	Cholelithiasis	Medical examination, questionnaire, laboratory tests	M/F	106/4839	M: 0.78 (0.4-1.54) F: 2.93 (0.68-12.35) M/F, pooled: 1.29 (0.36-4.54)			Sex, age, BMI, educational level, alcohol, sport habits, vegetarian diet, cholesterol levels, diabetes, kidney disease, lipid-lowering medications, menopause
Kim, 2019[46]	PrC	Korea	GBD	Questionnaire, ultrasound, laboratory tests	M/F	10673/69568	1.00 (0.90-1.11)			BMI, waist and thigh circumference, alcohol, Cholesterol, HDL, LDL

CC: Case-control, CS: Cross-sectional, RetroC: Retrospective cohort, PrC: Prospective cohort, GBD: gallbladder disease, M: males, F: females, cig: cigarettes per day, †: pooled odds ratio, BMI: body mass index, HDL: high-density lipoprotein, LDL: low-density lipoprotein, NSAID: nonsteroidal anti-inflammatory drug.

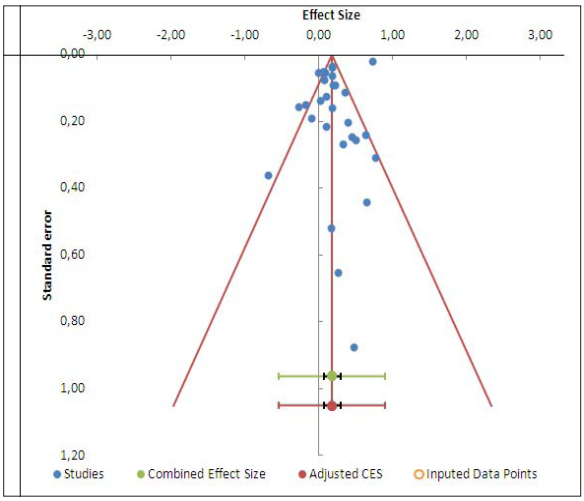

Figure 2: Funnel plot with trim-and-fill analysis indicating absence of significant publication bias as the plot is symmetrical and no imputed data points have been added.

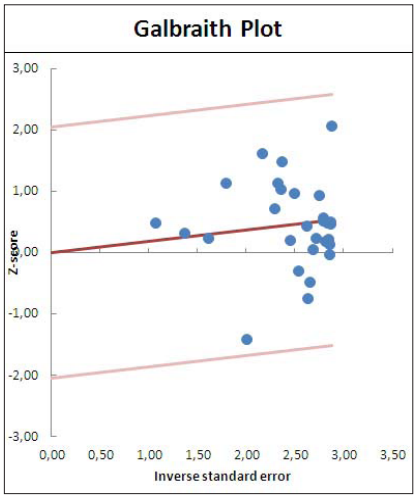

Figure 3: Galbraith plot depicting all studies within its 95 % confidence intervals area.

Table 2: Quality assessment based on selection (identification and recruitment of participants; maximum of 4☆ for cohort and case-control studies, and 5☆ for cross-sectional studies), the comparability between the two groups (maximum of 2☆), and the ascertainment of either the exposure (for case-control studies; maximum of 3☆) or the outcome of interest (for cohort and cross-sectional studies; maximum of 3☆).

Study	Design	NOS	Selection	Comparability	Exposure	Outcome
Jorgensen, 1989[18]	CS	6	☆☆	☆☆		☆☆
Paśtides, 1990[19]	CC	5	☆☆	☆	☆☆	
La Vecchia, 1991[20]	CC	7	☆☆☆	☆	☆☆☆	
McMichael, 1992[21]	CC	6	☆☆☆☆	☆	☆	
Stampfer, 1992[22]	PrC	8	☆☆☆	☆☆		☆☆☆
Kato, 1992[23]	PrC	9	☆☆☆☆	☆☆		☆☆☆
Murray, 1994[24]	PrC	8	☆☆☆☆	☆☆		☆☆
Grodśtein, 1994[25]	CS	5	☆☆	☆		☆☆
Kono, 1995[26]	CS	5	☆☆	☆		☆☆
Misciagna, 1996[27]	PrC	7	☆☆☆☆	☆		☆☆
Kratzer, 1997[28]	CS	6	☆☆	☆☆		☆☆
Martinez de Pancorbo, 1997[29]	CS	6	☆☆☆	☆		☆☆
Sahi, 1998[30]	PrC	7	☆☆☆	☆☆		☆☆
Okamoto, 2002[31]	CS	5	☆☆	☆		☆☆
Völzke, 2005[32]	CS	6	☆☆	☆		☆☆☆
Yamada, 2005[33]	PrC	8	☆☆☆☆	☆☆		☆☆
Gonzalez-Peres, 2007[34]	PrC	8	☆☆☆☆	☆		☆☆☆
Abu-Eshy, 2007[35]	CS	5	☆☆	☆		☆☆
Katsika, 2007[36]	PrC	5	☆☆☆	☆		☆
Panpimanmas, 2009[37]	CC	5	☆☆	☆	☆☆	
Halldeśtam, 2009[38]	PrC	8	☆☆☆☆	☆		☆☆☆
Liu, 2009[39]	PrC	9	☆☆☆☆	☆☆		☆☆☆
Walcher, 2010[40]	CS	5	☆☆	☆		☆☆
Etminan, 2011[41]	RetroC	5	☆☆	☆		☆☆
Palermo, 2013[42]	CS	3		☆		☆☆
Shabanzadeh, 2016[43]	PrC	7	☆☆☆☆	☆		☆☆
Figuierdo, 2017[3]	PrC	9	☆☆☆☆	☆☆		☆☆☆
Kang, 2018[44]	CS	7	☆☆☆	☆		☆☆☆
Chang, 2019[45]	PrC	8	☆☆☆☆	☆		☆☆☆
Kim, 2019[46]	CS	6	☆☆☆	☆		☆☆

CC: Case-control, CS: Cross-sectional, RetroC: Retrospective cohort, PrC: Prospective cohort, NOS: Newcastle-Ottawa quality assessment scale.

Subgroup analysis

Pooled OR between case-control, cross-sectional, and cohort studies and GBD was 1.23 (95 % CI: 0.77-1.97), 1.20 (95 % CI: 1.02-1.42), and 1.27 (95 % CI: 1.04-1.55), respectively (Figure 4). No sources of heterogeneity were identified regarding the basic issues of smoking habits and type of study by subgroup analysis (p =0.920).

Moreover, pooled OR between current, former, and ever versus never smokers and GBD was computed to be 1.19 (95 % CI: 1.10-1.28), 1.15 (95 % CI: 1.10-1.19), and 1.24 (95 % CI: 1.05-1.47), respectively (Figure 5). Subgroup analysis indicated comparable risk as far as current, former, and ever smokers are concerned (p =0.520).

Interestingly, a positive dose effect was observed

for smoking, at least current; Spearman's r =1.000 (p =0.010). The best-fit regression model was linear, as demonstrated after analysis of various alternatives. Linear regression analysis revealed a 0.011±0.002 increase in OR per cigarette per day (p =0.046). Analytical presentation of pooled ORs per ten cigarettes/day increments is available in Figure 6.

As far as quality assessment is concerned, studies with optimal comparability (two stars independently of the type of the study), when compared with studies with suboptimal comparability, were characterized by a more conservative positive correlation of smoking with GBD (p <0.001).

Lastly, potential confounders, as non-adjustment for age and alcohol intake (Q test P=0.05 and P=0.08, respectively), could lead to statistically significant heterogeneity and thus affect pooled effect estimates.

Sensitivity analysis

About one-third of increased heterogeneity was attributed to the study of Etminan (2011)[40]; excluding this study, I^2 falls from 96 % to 60 %. In that case, compared to the non-smokers, smokers still had 1.17 times higher odds of developing GBD (95 % CI: 1.10-1.25).

Discussion

Whether smoking is associated with GBD remained disputable for a long period of time. Interestingly, some early publications proposed a prophylactic effect of smoking over symptomatic cholelithiasis or even the whole spectrum of GBD[19,47,48]. Two meta-analyses based on few studies suggested a positive correlation of smoking with GBD; however, the limited number of studies included could be considered potent drawbacks[6,41].

The present meta-analysis, being the first to incorporate as many as 30 studies of different types, concludes that smoking is positively correlated with GBD and that this phenomenon is dose-dependent, at least as far as current smoking is concerned.

In particular, it is hereby clearly stated for the first time that there is a comparable risk between current, former, and ever smokers as indicated by subgroup analysis. Consequently, smokers, independently of being reported as current or ex-, could be considered in practice as a single group, as a comparable increase of risk for GBD was observed between relevant subgroups. Furthermore, our main result, namely the 25 % increased odds ratio of GBD among either current or former or ever smokers, although characterized by increased heterogeneity, is merely uniformly repeated in all analyzed subgroups. This finding considerably enhances the possibility that it indeed reflects a true statement.

Of interest, a clear-cut positive dose-dependent effect was observed for smoking, at least current, and GBD through quantitative analysis: every additional cigarette per day increases by 0.011±0.002 the OR for GBD. More complex methods as that proposed by Greenland and Longnecker[49] were avoided during that process as all risk

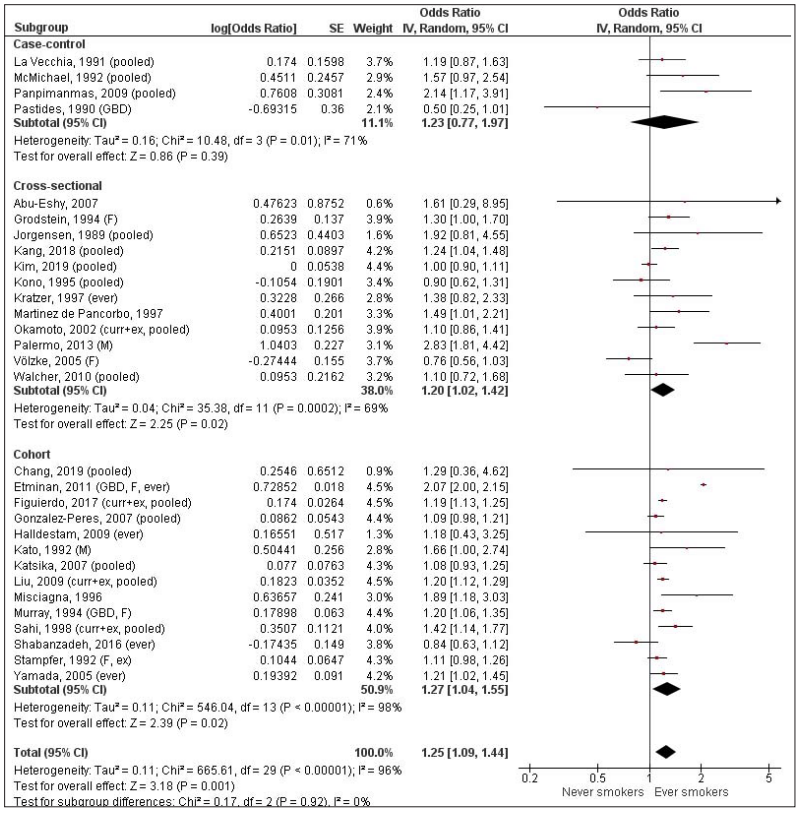

Figure 4: Subgroup analysis according to study type (never versus ever smokers).

Table 3: Meta-regression and subgroup analysis (never versus ever smokers, pooled data).

Parameter	Meta-regression		Subgroup analysis			
	Univariate analysis (Spearman's r, p)	Multivariate analysis (beta, 95 % CI, p)	OR	95 % CI	I^2, p value within subgroups	I^2, p value between subgroups
Study characteristics						
Studies including former smokers	0.036, 0.850					
Yes			1.17	1.11-1.22	23%, 0.18	0%, 0.34
No			1.35	1.01-1.80	96%, <0.001	
Publication year						
1999 and before	0.016, 0.935		1.26	1.12-1.41	43%, 0.05	
Between 2000 and 2009	-0.164, 0.387		1.12	1.03-1.23	46%, 0.06	31%, 0.24
2010 and later	0.152, 0.421		1.33	0.98-1.80	98%, <0.001	
Type of study						
Case-control	0.028, 0.882		1.23	0.77-1.97	71%, 0.01	
Cross-sectional	0.165, 0.383		1.20	1.02-1.42	69%, <0.001	0%, 0.92
Cohort	-0.181, 0.337		1.27	1.04-1.55	98%, <0.001	
Origin of study						
Europe	-0.166, 0.381		1.12	1.02-1.23	54%, 0.02	
Asia and Middle East	-0.026, 0.891		1.13	1.00-1.28	42%, 0.05	57%, 0.10
America and Australia	0.213, 0.258		1.54	1.17-2.03	98%, 0.002	
Endpoint: entire GBD spectrum	-0.076, 0.691					
Yes			1.23	0.98-1.54	98%, <0.001	0%, 0.97
No (cholelithiasis only)			1.22	1.09-1.38	58%, <0.001	
Sample size ≥10000	-0.114, 0.549					
Yes			1.24	1.02-1.50	98%, <0.001	0%, 0.87
No			1.27	1.05-1.53	66%, <0.001	
Sex						
Females	0.119, 0.532		1.26	0.94-1.70	98%, <0.001	
Males	-0.171, 0.368		1.54	1.01-2.33	80%, 0.002	11%, 0.33
Both	-0.040, 0.830		1.14	1.06-1.23	46%, 0.02	
Quality assessment						
Selection	-0.152, 0.423					
Optimal			1.18	1.12-1.25	32%, 0.14	0%, 0.56
Suboptimal			1.26	1.02-1.55	95%, <0.001	
Comparability	0.008, 0.965					
Optimal			1.20	1.15-1.24	0%, 0.56	99%, <0.001
Suboptimal			1.70	1.65-1.75	95%, <0.001	
Exposure (case-contrrol studies)	-0.258, 0.742					
Optimal			1.19	0.87-1.63	NA†	0%, 0.95
Suboptimal			1.22	0.56-2.65	80%, 0.006	
Outcome (cross-sectional and cohort studies)	-0.372, 0.061					
Optimal			1.15	1.08-1.23	47%, 0.07	32%, 0.22
Suboptimal			1.32	1.07-1.63	95%, <0.001	
Adjustment for potent confounders						
Adjustment for family history						
Yes	0.257, 0.017	0.454, [0.129-0.733], 0.007	1.61	1.05-2.49	58%, 0.05	33%, 0.22
No			1.21	1.05-1.44	96%, <0.001	
Adjustment for alcohol						
Yes	-0.311, 0.004	-0.383, [(-0.506)-(-0.047)], 0.020	1.15	1.09-1.21	25%, 0.16	68%, 0.08
No			1.47	1.13-1.93	96%, <0.001	
Adjustment for age						
Yes	0.258, 0.017		1.30	1.12-1.50	96%, <0.001	73%, 0.05
No			0.94	0.70-1.26	51%, 0.10	
Adjustment for BMI						
Yes	-0.378, <0.001		1.20	1.01-1.43	97%, <0.001	6%, 0.30
No			1.36	1.15-1.62	68%, 0.001	
Adjustment for sex						
Yes	0.022, 0.841		1.29	1.09-1.53	96%, <0.001	0%, 0.35
No			1.14	0.93-1.39	48%, 0.11	

CI: confidence interval, †NA: Not Applicable.

estimates used for pooling were adjusted for confounders. As we have observed that current and former smoking had comparable effects over GBD, it was reasonable to assume that the dose-dependent effect also referred to ex-smoking. Our results agree with those reported by Kato et al, who demonstrated a positive correlation between pack-years of cigarettes and GBD[23]; similar observations are reported by Figueiredo et al independently of current or former smoking status[3].

Furthermore, the study performs publication bias analysis as well as subgroup analyses and meta-regression regarding the potent effect of publication period, study type, region of origin, sample size, outcomes (either the whole spectrum of GBD or cholelithiasis only), quality assessment (either optimal or suboptimal in every NOS grouping item), and potent confounders on pooled OR. Interestingly, no publication bias was detected, which could be because there had been no clear-cut pre-defined or pre-judged size or even direction of difference in the whole literature. However, several potential sources of heterogeneity were proposed.

Among the three quality assessment items, subgroup analysis suggested that comparability might contribute to the increased heterogeneity; retaining only the group of studies with optimal comparability diminishes heterogeneity from 96 % to 0 %. Furthermore, subgroups regarding adjustment to age and alcohol intake exhibit statistically significant differences. Using meta-regression,

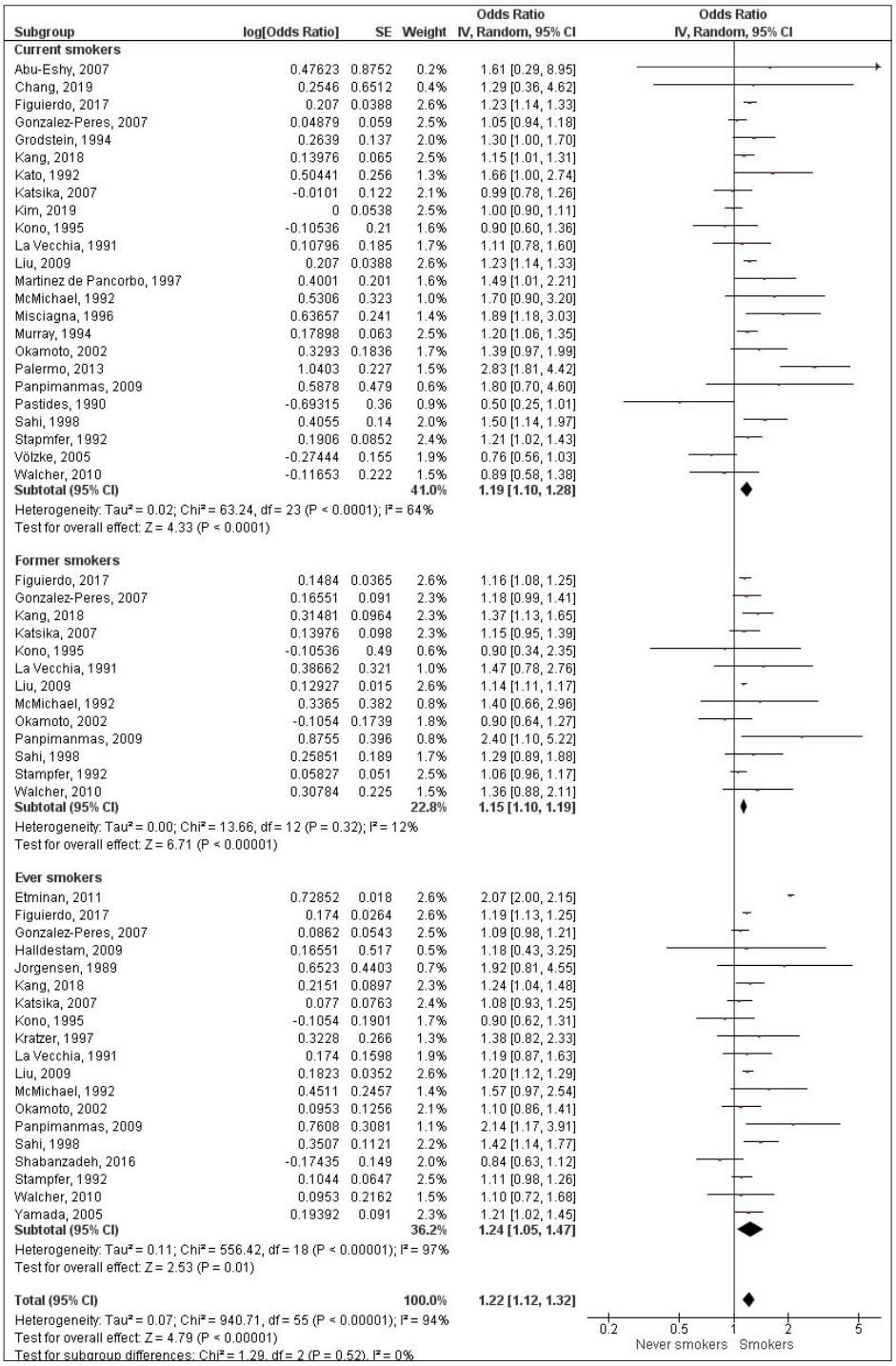

Figure 5: Subgroup analysis according to smoking habits.

lack of adjustment for family history and alcohol intake is shown to be independently correlated with LnOR. All our findings align with existing knowledge and current literature: age, family history, and alcohol are known determinants for GBD[50,51]. Understanding heterogeneity sources might enable more careful data interpretation and more precise study design in the future.

Sensitivity analysis carried out for each study separately indicated that the study of Etminan et al explained 37.5 % of total heterogeneity, while no other study contributed more than 1 % itself[40]. Thus, despite this study being the largest one included in the present meta-analysis by contributing 2,721,014 women (58.9 % of the total number of individuals), its influence on the results needs special care due to the major drawback of lack of adjustment to any confounder. Additionally, a positive though not decisively significant correlation of oral contraceptives with cholelithiasis was reported, thus explaining at least a portion of substantially increased OR for female smokers and GBD in the study of Etminan et al[51]. Based

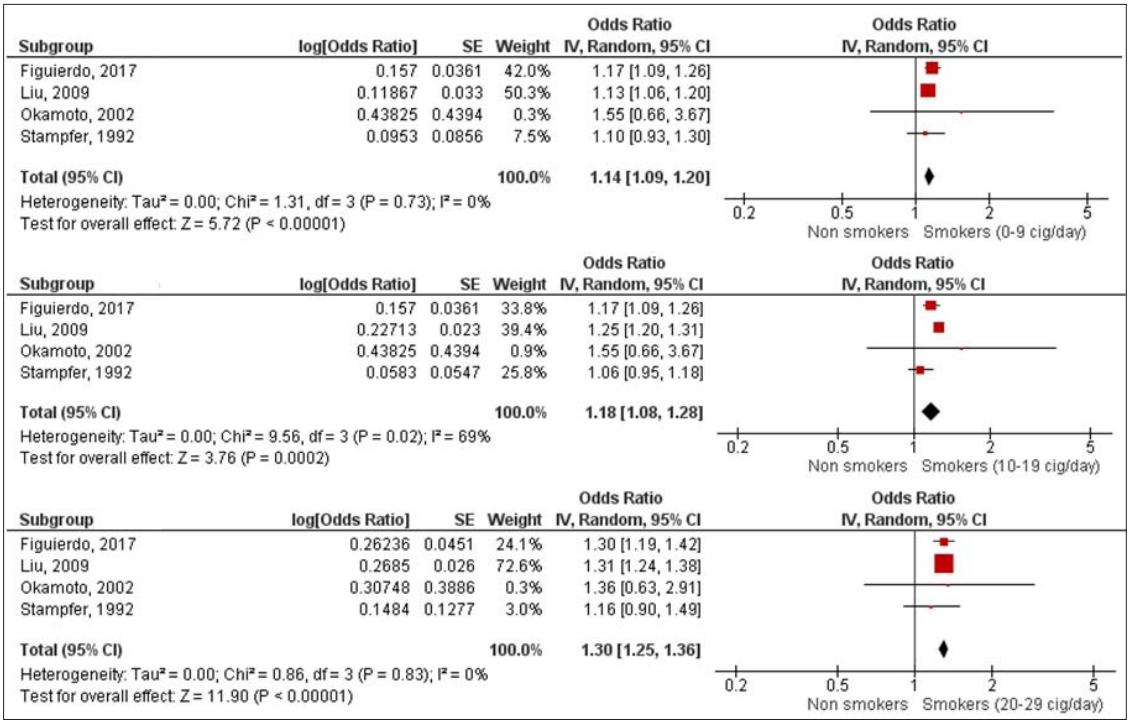

Figure 6: Quantitative (subgroup) analysis for different levels of smoking (from top to bottom: 0-9 cig/day, 10-19 cig/day, and 20-29 cig/day versus never smokers). Assuming that OR =1 for non-smokers, Spearman's r =1.000 (p <0.01).

on the above, the fact that the study of Etminan et al was included in the meta-analysis published by Aune et al might be disputable[6]. Nevertheless, the present study still included the vast study of Etminan et al, as all appropriate measures have been used to interpret heterogeneity, concluding to an overall OR that agrees with that reported by Aune at al.

Data combination from different kinds of studies, thus case-control, cross-sectional, and cohort ones might be considered the present study's major limitation. However, neither subgroup analysis nor meta-regression revealed any statistically significant difference regarding overall OR. Therefore, our approach might be considered non-misleading. A second limitation is that we failed to incorporate unpublished data; despite that neither positive nor negative prejudiced correlation between smoking and GBD had been prevailed in the literature, the observed absence of any publication bias would be further strengthened in case of implementation of unpublished sources.

In the present systematic review and meta-analysis, we argue that smoking, either current or former, has an apparent positive effect on gallbladder disease. We had also demonstrated that this effect is dose-dependent, at least for current smoking. Additionally, we concluded that family history and alcohol intake could represent potential confounders; therefore, all risk estimates regarding smoking and GBD have to be appropriately adjusted for proper study design and performance in the future.

Conflict of interest

All authors declared no conflict of interest.

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