The association of gallstone disease and diabetes mellitus

A meta-analysis

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ABSTRACT

الأهداف: دراسة العلاقة بين مرض السكري وأمراض الحصاة الصفراوية.

الطريقة: أجريت هذه الدراسة في مستشفى اكسينجايا، هونان، الصين وذلك في شهر سبتمبر 2013م. في البداية، قمنا ببحث الدراسات المناسبة في قاعدة البيانات المكتبة الطبية الوطنية في الولايات المتحدة الأمريكية وقاعدة بيانات كوكورين المركزية من البداية حتى سبتمبر 2013م. وبعد ذلك، استخدمنا، نموذج عشوائي لحساب وتقدير المخاطر المحتملة. اشتملت دراسة التحليل على 403001 حالة و411877 مجموعة شاهد و من 6 دراسات الحالات والشواهد، و 3 دراسة اترابية، و 13 دراسات مقطعية. وفي النهاية أجري التحليل الإحصائي طبقاً لنوع الدراسة.

النتائج: كانت نسبة اختطار السكري وأمراض الحصاة الصفراوية 1.75 (95% فترة الثقة 1.44–2.13) $p<0.00001$، 1.67 (95% فترة الثقة 1.24–2.5) $p<0.00001$، و 2.02 (95% فترة الثقة 1.59–2.85، $p<0.00001$). أن تحليل الحساسية المعتمد على إبعاد أي دراسة لم يغير من تجانس اختبار مربع أي، ونسبة الخطر. لاحظنا براهين تشير إلى تحيز في النشر.

الخاتمة: تشير الدراسة التحليلية إلى علاقة إيجابية قوية بين مرض السكري وخطورة الإصابة بأمراض الحصاة الصفراوية.

Objectives: To assess the association between diabetes mellitus and gallstone disease (GSD) by meta-analysis.

Methods: This study was carried out at Xiangya Hospital, Changsha, Hunan, China in September 2013. First, eligible studies were searched in PubMed and Cochrane Central databases from their inception to September 2013. Then, a random effect model was used to calculate the overall combined risk estimates. The meta-analysis included 403,001 cases and 411,877 controls from 6 case-control studies, 3 cohort studies, and 13 cross-sectional studies. Finally, statistical analyses were conducted according to the classification of study.

Results: Risk ratios for diabetes mellitus and GSD were 1.75 (95% confidence interval [CI]: 1.44-2.13, $p<0.00001$], 1.76 (95% CI: 1.24-2.5, $p<0.00001$), and 2.02 (95% CI: 1.59-2.58, $p<0.00001$). Sensitivity analysis based on the exclusion of any study did not change the heterogeneity I-square test, and risk ratios. Little evidence of publication bias was observed.

Conclusion: This meta-analysis suggested that there was a very strong positive association between diabetes mellitus and risk of GSD in the patients.

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Diabetes mellitus is a metabolic disease with high prevalence among the population. The prevalence of this disease is increasing according to lifestyle changes in the society. Gallstone is frequently found in diabetic patients, especially in women with type 2 diabetes mellitus.[1-5] The pathogenesis of gallstones is multifactorial. Cholesterol supersaturating, presence of crystal nucleation, and impaired gallbladder motility are the main promoting factors. Type 2 diabetics always tend to be obese and have hypercholesterolemia, and visceral neuropathy damaged in diabetics may lead to impaired gallbladder emptying.[6] Several studies found higher volumes of fasting gallbladder and residual gallbladder, and lower levels of plasma cholecystokinin

(CCK) protein, and CCK-A receptor mRNA expression in the diabetic groups than in controls,[7-10] suggesting that impaired gallbladder motility exists in diabetic patients. Numerous studies that looked into the prevalence of gallstone in a diabetic population showed an increased association. A cross-sectional study in the United States from 1976-1984 including 121,700 female had drawn a conclusion that a higher intake of carbohydrates, dietary glycemic load, and glycemic index increased the risk of cholecystectomy.[11] A population-based cohort study from 2000-2008, which included 60,734 diabetic patients, and 48,116 controls showed that the diabetic group exhibited significantly higher risk of GSD.[1] Another cross-sectional study in Iran between August 2005 and April 2007, which included 599 patients had a similar conclusion.[3] Several more studies had been carried out in Japan,[12] Italy,[13] Libya,[14] and Iraq,[15] and so forth. All these studies found a positive association between diabetes and risk of GSD. However, not all authors agree on it. Population-based studies on Puma Indians and Mexican Americans of the United States did not find any relation between the 2 diseases.[16,17] The contradiction may be caused by differences in the study design, sample size, survey method, and study population. Meta-analysis is a systematic method that obtains data from several independent studies to include bigger size of samples and integrates them for statistical analysis. The aim of this investigation was to perform a study to examine the association between diabetes mellitus and the risk of GSD by meta-analysis.

Methods.

This study was carried out at Xiangya Hospital, Changsha, Hunan, China in September 2013.

Search strategy. A computerized literature search was performed from PubMed electronic database and the Cochrane Central Register of Controlled Trials (Central) to identify all relevant studies. Search terms included "diabetes", "glucose", "blood sugar", and "gallstone". References of the retrieved articles were screened for relevant studies. The search strategy was performed literatively until no new relevant articles were found (until and including September 19, 2013).

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Selection criteria. Titles and abstracts of all relevant papers were browsed. Samples were chosen for the meta-analysis according to the following criteria from the papers: 1) the study had been designed as a case-control study or a cohort study; or 2) the study had been designed as a retrospective investigation and a cross-sectional study; 3) the exposure of interest was diabetes mellitus and GSD; 4) odds ratio (OR) or relative risk (RR), and the corresponding 95% confidence interval (CI) were mentioned; and 5) when multiple publications reported on the same or overlapping data, the recent article which based on the largest study population was selected.

Exclusion criteria. Reviews, editorials, commentaries, and conference abstracts were excluded from the study.

Quality assessment and data extraction. The Newcastle-Ottawa-Scale (NOS) was utilized in quality assessment of non-randomized observational studies including both case-control studies and cohort studies.[18,19] Two authors independently assessed the quality of each paper based on the NOS. A "star system" was originated from the NOS, and it was used for the present analysis to judge all included studies according to selection of study groups, comparability of groups, and the ascertainment of either the exposure for case-control studies, or the outcome for cohort studies. We assigned the number of stars to every paper with these standards. A study was conferred a maximum of one star for each numbered item according to the selection and exposure, or outcome categories. A 2 star was assigned for comparability at most. The total NOS star count ranged from 0 to 9. Decisions were reached by comparison, and consensus was reached by discussion. The quality of cross-sectional studies was assessed by the standards, which were set by the Agency for Healthcare Research and Quality (AHRQ).[20] This standard includes 11 items, with the answers of "yes", "no", and "unclear: 1) whether the source of data was clear and definite (surveys, literature review); 2) whether the selection and exclusion criteria of the case group and the control group have been listed; 3) whether the identification of patient's time phase had been offered; 4) whether the data of research objects were continuous, if they were not crowd-sourced; 5) whether the subjective factors of reviewers have covered other information of the research objects; 6) whether the assessment was designed to ensure quality have been described (such as the main outcome indicators test/re-test); 7) whether the reason to rule out analysis of any patient have been explained; 8) whether the measure of controlling confounding factors have been described; 9) whether how to deal with missing data in analyzing progress if possible have been explained; 10) whether the response rate of the patients

and the integrity of the data collection has summarized; and 11) whether the result of follow-up have been described, and the percentage of the expectations of patients with incomplete data was obtained. Data were extracted independently by 2 reviewers. A consensus was been reached by discussion. A third party took part when necessary. The following items were extracted from the articles: the first author, year of publication, study location, study period, duration of follow-up, source of control group (population-based, hospital based, or mixed), average age of the subjects, sample size (case and control group in case-control studies, and baseline population size in cohort studies), and statistical adjustments for confounding factors.

Statistical analysis. The RR was used as a common measure of the association between diabetes and risk of GSD. Standardized incidence ratios (SIR) and incidence density ratios (IDR) were directly considered as RRs. The pooled RRs were calculated. The heterogeneity assumption was assessed using Cochran's χ^2-based Q statistic test and I-square (I^2) test. Between-study heterogeneity was not considered to be significant when $p>0.10$ and $I^2<50\%$.[21] The pooled RR estimate of each study was calculated with a fixed effect model if no significant heterogeneity were found, otherwise, the random effects model was used.[22] Stratification analysis by study location, source of controls, and duration of follow-up was conducted to reduce the impact of heterogeneity, and achieve more accurate results. A sensitivity analysis was conducted using a quality assessment and a leave-one-out sensitivity procedure.

Visual inspection of the Begg's funnel plot with the purpose of assessing the potential publication bias. In addition, the Begg's rank correlation, and Egger's linear regression tests were performed (significance level at $p<0.10$). All statistical tests were carried out using RevMan software version 5.0. A $p<0.05$ for any test or model was deemed to be statistically significant except when specified.

Results.

Literature search. We obtained 483 potentially relevant citations from PubMed and Cochrane Central databases. However, most citations found through the initial search were excluded as they were reviews, editorials, or not relevant to our meta-analysis by checking title and abstracts. After a full-text review of 57 publications, 4 additional articles were found by reviewing reference lists. Among these 61 full-text articles, 40 were excluded as either they did not assess the association between diabetes and risk of GSD, or they did not provide sufficient outcomes. In the end, 21 studies that met the standards were included in our study (**Figure 1**).

Eligible studies. The characteristics of 6 case-control studies,[5,10,23-26] 3 cohort studies,[1,27,28] and 13 cross-sectional studies[2,4,8,9,30-38] are presented in **Tables 1-3.** There were 1,296 cases and 1,976 controls involved in the case-control studies that were separately conducted in Iraqi, Libya, New Zealand, Sweden, Finland, and Nigeria.[5,14,23-26] There were 383,895 cases and 421,461 controls involved in the cohort study, which were separately conducted in the United States, Germany, and Taiwan.[1,27,28] The total number of participants was 6250, including 1,058 cases in the 13 cross-sectional studies.[2,4,12,15,29-37] Five of the studies were conducted in Japan,[4,12,30,32,34] 3 in China,[31,33,35] and 2 in the United States;[2,37] the other 3 were conducted in Denmark,[29] Iran,[36] and Italy.[15] There were follow-up durations in the Japanese studies ranging from 1-8 years. The results of most studies were adjusted by age, gender, body mass index, smoking, educational achievement, alcohol intake, sport activity, and family history of GSD. One of case-control studies[24] was assigned as 6 stars after the assessment of risk bias using the NOS. The remaining studies received from 7-9 stars. The quality of cross-sectional studies was assessed by the standards, which was set by AHRQ.[20]

Quantitative synthesis. Analysis with case-control studies. The results (**Figure 2**) showed that the incidence of GSD was significantly associated with diabetes mellitus in the combined 6 case-control studies (OR = 1.75; 95% CI - 1.44-2.13; $p<0.00001$) under the random effects model (heterogeneity $I^2 = 37\%$).

Analysis with cohort studies. Based on the statistical analysis results of the 3 combined cohort studies in **Figure 3**, the incidence of GSD was also significantly associated with diabetes mellitus (RR = 1.76; 95% CI - 1.24-2.5; $p<0.00001$) under the random effects model (heterogeneity $I^2 = 99\%$).

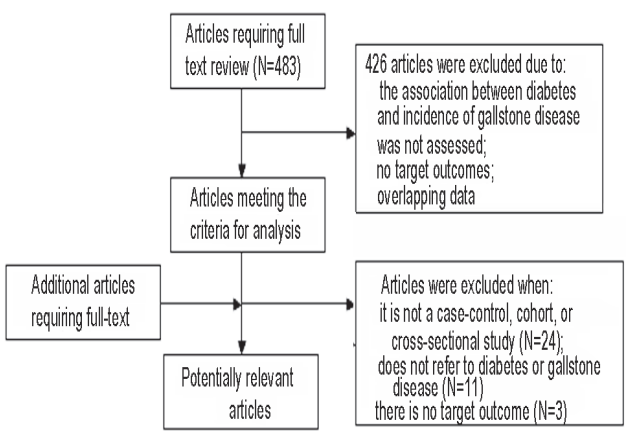

Figure 1 - Flowchart of the literature selection in this study.

Table 1 - Characteristics of case-control studies included in a meta-analysis in this study.

First author	Location	Duration	Age (years)		Source of control	Quality	N		Adjusted variables
			Case	Control			Case	Control	
Al-Bayati & Kodayer[5]	Iraq	April to December 2008	57±20	52±32	HB	9	100	100	Gender, age, BMI, family history of gallstone, duration of diabetes, HbA1c
Elmehdawi et al[14]	Libya	2007	52.5±11.7	49.5±19.9	HB	8	161	166	Gender, age, BMI, weight, duration of diabetes, history of gallstone and cholecystectomy
Chapman et al[23]	New Zealand	1992	30-75	30-75	HB	7	308	318	Gender, age, BMI, history of gallstone and cholecystectomy, pregnancy, lipid, alcohol use
Persson & Thulin[24]	Sweden	1985-1987	57.5±15	56.8±16	PB	6	360	359	Gender, age, BMI, weight, lipid
Niemi et al[25]	Finland	1998	40-60	40-60	PB	7	267	933	Gender, age, BMI, lipid, Apo E, OGTT, history of gallstone
Olokoba et al[26]	Nigeria	June 2003 to May 2004	52.9±10.7	49.0±12.5	HB	8	100	100	Age, BMI, WHR, gallbladder volume, history of gallstone

BMI - body mass index, HB - hospital based, PB - population-based, HbA1c - hemoglobin A1C, OGTT - oral glucose tolerance test, FPG - fasting plasma glucose, Apo E - apolipoprotein E, WHR - waist hip ratio

Table 2 - Characteristics of cohort studies included in a meta-analysis in this study.

First author	Location	Duration (years)	Age (years)		Source	Quality	N		Adjusted variables
			Case	Control			Case	Control	
Liu et al[1]	Taiwan, China	1997-2008	60.1±12.7	60.0±12.8	PB	9	48116	60734	Age, gender, occupation, income, history of gallstone
Weikert et al[27]	Germany	1994-2005	35-65	35-65	PB	8	849	24317	Age, gender, BMI, WC, sport activity, smoking, educational achievement, alcohol intake
Noel[28]	USA	1999-2005	All ages	All ages	PB	8	334930	336410	Age, gender, history of gallstone and cholecystectomy

BMI - body mass index, WC - waist circumference, USA - United States of America, PB - population-based

Analysis with cross-sectional studies. **Figure 4** showed the results of statistical analysis of combined samples from the 13 included cross-sectional studies. The incidence of GSD was also significantly associated with diabetes mellitus (OR = 2.02; 95% CI - 1.59-2.58; $p<0.00001$) under the random effects model (heterogeneity I^2 = 86%).

Sensitivity analysis. Sensitivity analyses were conducted by leaving out certain studies. The statistical analysis results showed that there were no evident alterations upon exclusion of any of the studies in all case-control studies, cohort studies, and cross-sectional studies (**Table 4**).

Publication bias. A funnel plot was used to check the existence of publication bias in the meta-analyses. The results (**Figure 5**) showed that the 2 sides of dash line were not symmetric, and some publication bias existed consequently.[38,39]

Discussion.

Despite an increasing number of studies, the association between GSD and diabetes mellitus remains controversial. Some autopsy and population-based studies have shown an association,[10,31-38] while others have not.[40,41] The discrepancy may be because of the differences in study design, sample size, survey method, statistical power, and study population. We designed a study with meta-analysis, a stronger statistical power, and a large number of samples, which were collected from PubMed and the Cochrane Central databases update until September 2013, to detect the prevalence of GSD in diabetics relative to controls. Our results demonstrated a higher incidence of GSD in patients with diabetes mellitus. There was a 24% increase at least, at risk of developing GSD in diabetics compared to the controls with normal blood glucose. Existing publication bias did not affect the meta-analysis results.

Table 3 - Characteristics of cross-sectional studies included in the meta-analysis in this study.

First author	Location	Duration (years)	Age (years)	Source	Total number of participants	N baseline	Cases	Adjusted variables
Ruhl & Everhart[2]	US	1988-1994	20-74	PB	5653	699	162	Age, race, BMI, WHR, smoking, lipid, alcohol use, physical activity, and number of live births
Kono et al[4]	Japan	1991-1992	49-55	PB	2188	480	40	Age, BMI, WHR, smoking, alcohol use, physical activity, OGTT
Jørgensen[29]	Denmark	1982-1984	30-60	PB	3418	67	9	Age, gender, BMI, physical activity, smoking, consumption of coffee, history of diabetes mellitus
Kono et al[30]	Japan	1978-1985	48-56	PB	1605	209	11	Age, BMI, lipid, FPG, OGTT, smoking, alcohol use
Sun et al[31]	China	Jan-Dec 2007	≥18	PB	3573	96	29	Age, gender, BMI, lipid, FPG, history of hypertension
Kono[32]	Japan	1986-1994	All ages	PB	2116	444	20	Age, gender, BMI, OGTT, smoking, alcohol use
Sasazuki et al[12-]	Japan	1986-1994	48-59	PB	6899	1457	152	Age, gender, BMI, OGTT, smoking, alcohol use, lipid, physical activity
Chen et al[33]	Taiwan, China	2003-2003	≥18	PB	3259	1317	82	Age, gender, BMI, FPG, lipid, family history of gallstone disease
Kono et al[34]	Japan	1986-1990	48-56	PB	2739	23	467	Age, gender, BMI, OGTT, smoking, alcohol use
Lu et al[35]	Taiwan, China	Jan-Feb 1989	≥30	PB	858	67	8	Age, gender, BMI, FPG, OGTT, history of DM
De Santis et al[15]	Italy	1981-1982	20-69	PB	2320	54	6	Age, gender, BMI, smoking, alcohol use, history of DM, physical activity, family history of gallstone disease
Toosi et al[36]	Iran	2005-2007	All ages	PB	599	11	4	Age, gender, BMI, history of DM
Haffner et al[37]	US	1984-1988	25-64	PB	2907	268	68	Age, gender, BMI, WHR, race, history of DM

BMI - body mass index, FPG - fasting plasma glucose, OGTT - oral glucose tolerance test, WHR - waist hip ratio, DM - diabetes mellitus, USA - United States of America, PB - population-based

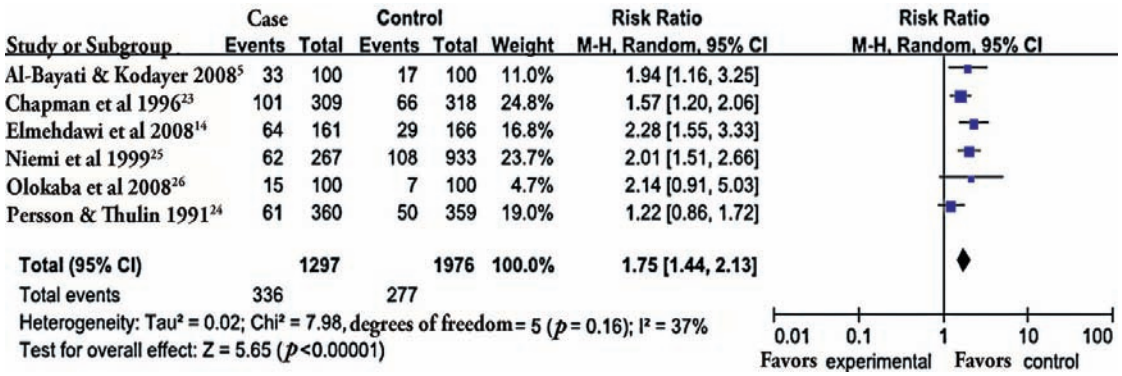

Figure 2 - Forest plot of 6 case-control studies examining the association between gallstone and diabetes in this study. M-H - Mantel-Haenszel method, CI - confidence interval, I^2 - I-square test.

Several plausible mechanisms may explain why a significant positive association of diabetes mellitus with gallstones was observed in the present analysis. The most important link between GSD and diabetes mellitus is obesity. Diabetics with obesity had more risk of GSD.[39] Diabetics with GSD had higher concentration of fasting insulin, lower concentrations of total- and low-density lipoprotein cholesterol, and lower concentration of high density lipoprotein cholesterol than diabetics without GSD.[42] A study compared the bile lipid composition and bile acid pool size in patients with juvenile diabetes, maturity-onset diabetes, and control subjects. It was found that the saturation index of bile was much higher, and the absolute values for biliary bile

acid concentration were significantly lower in maturity-onset diabetes. It suggested that maturity-onset diabetes had supersaturated bile.[43] Some other studies revealed that gallbladder volume in diabetics was significantly higher than in the control group. Gallbladder motility was significantly reduced in diabetics with autonomic neuropathy than in the diabetics without autonomic neuropathy. Autonomic neuropathy complicated with impairment of gallbladder motility causes cholestasis, and results in cholesterol gallstone crystal formation and gallstone growth.[44]

Our study showed that diabetes mellitus promoted the incidence of GSD. Conversely, some studies found that GSD also affected the incidence of diabetes mellitus.[28,45] Mechanism studies demonstrated that the CCK-A receptor gene plays an important role in that, diabetes mellitus promotes the incidence of GSD. It was demonstrated that the gene expression of CCK-A receptor in the smooth muscle of the gallbladder was significantly lower in patients with gallstone and diabetes mellitus than in those with a gallstone only.[46-48] These results were consistent with the decreased motility of gallbladder in the diabetics with GSD. Diabetic patients with abnormality of CCK-A receptor gene may have more chance to acquire GSD.

As we know, the pathogeneses of diabetes mellitus and GSD are complex and multiple. However, it has been widely accepted that 4Fs (female, fat, forty, fertilization) are main risk factors for gallstone, and the 4Fs are also risk factors in the incidence of diabetes mellitus. It suggests that there are some positive relationship between diabetes mellitus and GSD. The association between GSD and diabetes remains controversial. The results of our meta-analysis supported the viewpoint that diabetes mellitus increases the risk of GSD in the patients. Sensitivity analysis suggested that removing any study did not change the results of heterogeneity and RR.

Although the sensitivity analysis shows that this research result is stable and reliable, several limitations might be acknowledged in this meta-analysis. First of all, substantial heterogeneity was observed among the studies of diabetes mellitus and GSD risks. It was not surprising to notice the differences in characteristics of populations, ascertainment of diabetes, and adjustment

Table 4 - Sensitivity analysis of studies included in the meta-analysis in this study.

Studies removed	I^2 (%)	Odds ratio or relative risk (95% confidence interval)
Al-Bayati & Kodayer[5]	51	1.72 (1.37, 2.17)
Elmehdawi et al[14]	45	1.82 (1.42, 2.34)
Chapman et al[23]	33	1.65 (1.34, 2.02)
Persson & Thulin[24]	41	1.67 (1.32, 2.12)
Niemi et al[25]	51	1.73 (1.39, 2.14)
Olokoba et al[26]	0	1.85 (1.58, 2.18)
Liu et al[1]	100	1.55 (1.04, 2.31)
Weikert et al[27]	88	2.08 (1.71, 2.51)
Noel et al[28]	99	1.70 (0.94, 3.06)
Ruhl & Everhart[2]	88	2.12 (1.63, 2.76)
Kono et al[4]	87	2.14 (1.63, 2.80)
Jørgensen[29]	86	1.98 (1.52, 2.56)
Kono et al[30]	88	2.11 (1.62, 2.76)
Sun et al[31]	88	2.06 (1.58, 2.69)
Kono[32]	88	2.12 (1.62, 2.77)
Sasazuki et al[12]	88	2.13 (1.63, 2.78)
Chen et al[33]	87	2.14 (1.64, 2.80)
Kono et al[34]	88	2.07 (1.57, 2.75)
Lu et al[35]	87	2.03 (1.52, 2.72)
De Santis et al[15]	84	2.15 (1.65, 2.80)
Toosi et al[36]	85	1.92 (1.50, 2.46)
Haffner et al[37]	85	1.89 (1.50, 2.39)

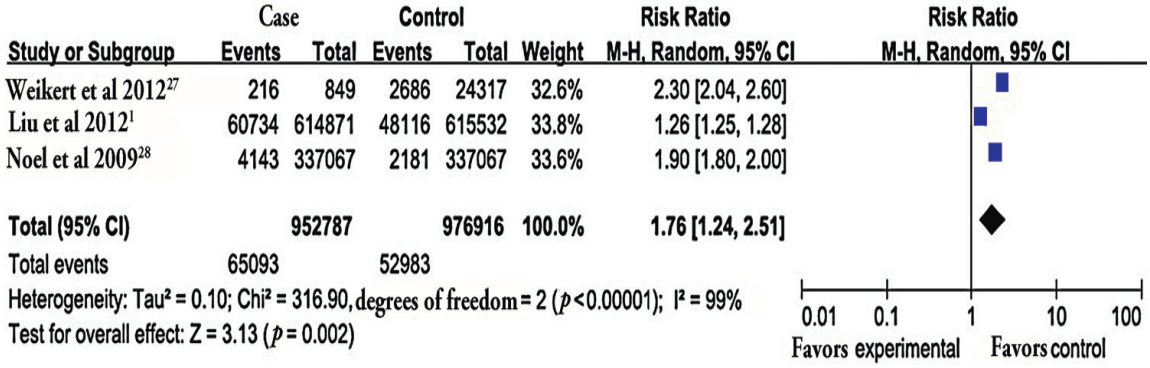

Figure 3 - Forest plot of 3 cohort studies examining the association between gallstone and diabetes included in this study. M-H - Mantel-Haenszel method, CI - confidence interval, I^2 I-square test.

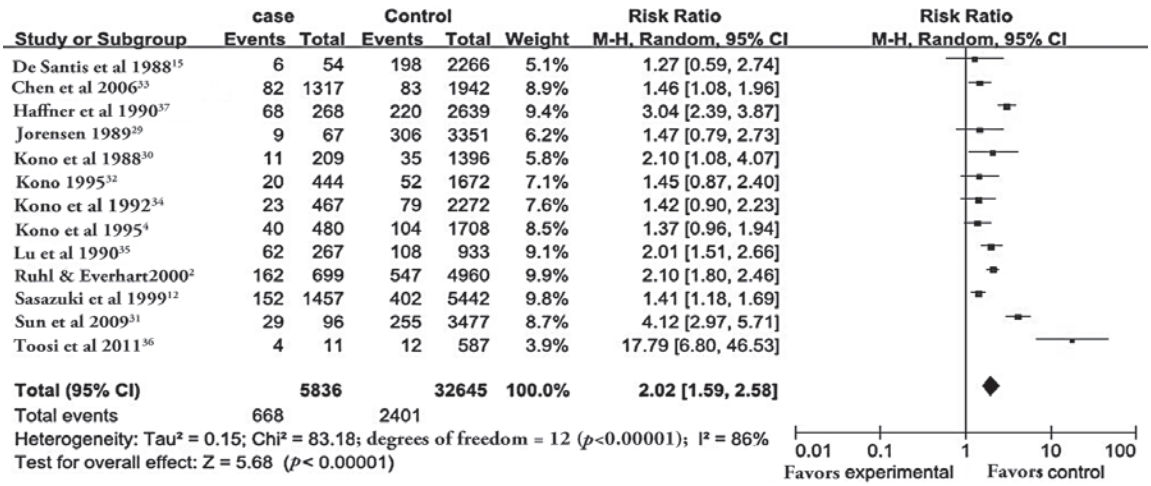

Figure 4 - Forest plot of 13 cross-sectional studies examining the association between gallstone and diabetes included in this study.

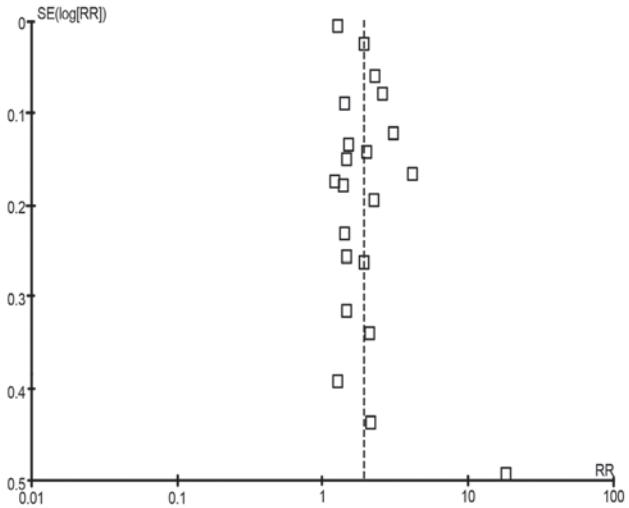

Figure 5 - Funnel plot of all studies included in the meta-analysis in this study.

for confounding factors. Secondly, despite that sensitivity analyses were performed, we were unable to detect the major source of heterogeneity. Noteworthy however, the merged results still turned out to be significant. In addition, there were some residual and unmeasured confounding factors, such as age, gender, and socioeconomic in the study. These factors may confound the interpretation of the diabetes mellitus-GSD association and potentially publication biases, which was a common phenomenon existing in the medical literatures. Finally, although little evidence of publication bias was observed, the conclusion will not be changed by it. In future research work, we can place the research direction on propose effective measures for diabetics to prevent gallstone formation and development.

In conclusion, this meta-analysis study suggested that there was a strong association between diabetes mellitus and the prevalence of GSD. Diabetes mellitus has been justified as a significant risk factor in gallstone formation for evidence-based medicine.

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