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**Link Between Gallbladder Disease and diabetes patient**

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## **Abstract**

**Background:** Diabetes has been hypothesized to increase the risk of gallbladder disease based on the observation that obesity and insulin resistance are associated with gallbladder disease. Although several studies have investigated the association between a diabetes diagnosis and risk of gallbladder disease, the results have not been entirely consistent and to our knowledge no meta-analysis has been published on the subject. For this reason we conducted a systematic review and meta-analysis of the available cohort studies.

**Material and methods:** We searched the PubMed and Embase databases for studies of diabetes and gallbladder disease up to January 9th 2015. Prospective studies were included if they reported relative risk estimates and 95% confidence intervals of gallbladder disease associated with a diabetes diagnosis. Summary relative risks were estimated by use of a random effects model.

**Results:** We identified 10 prospective studies that could be included in the meta-analysis which included 323651 cases among 7365198 participants. The summary RR for diabetes patients was 1.56 (95% CI: 1.26-1.93, I<sup>2</sup>=99.4%, heterogeneity<0.0001). The results persisted when stratified by gender, and in most subgroup analyses and there was no heterogeneity among studies with more than 10 years duration of follow-up. There was no evidence of publication bias.

**Conclusions:** Our analysis provides further support for an increased risk of gallbladder disease among diabetes patients.

**Keywords:** Diabetes mellitus, gallbladder disease, gallstones, systematic review, meta-analysis.

## **Abstract**

Gallbladder disease (GBD) is related to several diabetes risk factors. The present study was to examine whether GBD was independently associated with type 2 diabetes in the China Kadoorie Biobank study. After excluding participants with prevalent diabetes and prior histories of cancer, heart disease, and stroke at baseline, 189,154 men and 272,059 women aged 30–79 years were eligible for analysis. The baseline prevalence of GBD was 5.7% of the included participants. During 4,138,687 person-years of follow-up (median, 9.1 years), a total of 4,735 men and 7,747 women were documented with incident type 2 diabetes. Compared with participants without GBD at baseline, the multivariate-adjusted hazard ratios (HRs) for diabetes for those with GBD were 1.09 (95% CI: 0.96–1.24; P = 0.206), 1.21 (95% CI: 1.13–1.30; P < 0.001), and 1.17 (95% CI: 1.10–1.25; P < 0.001) in men, women, and the whole cohort respectively. There was no statistically significant heterogeneity between men and women (P = 0.347 for interaction). The association between GBD and diabetes was strongest among participants who reported  $\geq 5$  years since the first diagnosis and were still on treatment at baseline (HR = 1.48; 95% CI: 1.16–1.88; P = 0.001). The present study highlights the importance of developing a novel prevention strategy to mitigate diabetes through improvement of gastrointestinal health.

## **Introduction**

Type 2 diabetes has become epidemic worldwide (1) . a rapid increase in diabetes incidence was observed in recent decades, with a prevalence of 11.6% in 2010<sup>2</sup>. Gallbladder disease (GBD) remains a common gastrointestinal disorder in both developed countries<sup>(3)</sup> and Asian populations such as Chinese<sup>4),(5)</sup> GBD is related to several cardiometabolic risk factors such as obesity, dyslipidemias (hypertriglyceridemia and low high-density lipoprotein cholesterol), unhealthy diet, and sedentary lifestyle<sup>( 3),(6)</sup>. Several prospective studies have supported that the presence of GBD was associated with increased risk of coronary heart disease, which could not be explained by traditional risk factors<sup>(7)</sup>. Whether there is a similar association between GBD and diabetes remains unclear.

## Results

During a median follow-up of 9.1 years (interquartile range: 1.92 years; total person-years: 4,138,687), there were 4,735 incident cases of diabetes in men and 7,747 in women. In age- and sex-adjusted (model 1) and multivariable-adjusted analyses in the whole cohort (model 2), the presence of GSD was associated with increased risk of incident diabetes (Table 2). The association was moderately attenuated after further adjustment for BMI and WC (model 3). Compared with participants without GSD at baseline, the adjusted hazard ratio (HR) for type 2 diabetes (model 3) was 1.17 (95% confidence interval [CI]: 1.10–1.25;  $P < 0.001$ ) for those with GSD in the whole cohort. There was no statistically significant heterogeneity between men (HR = 1.09; 95% CI: 0.96–1.24;  $P = 0.206$ ) and women (HR = 1.21; 95% CI: 1.13–1.30;  $P < 0.001$ ) in the aforementioned association ( $P = 0.347$  for interaction with sex). These associations were not materially changed with additional adjustment for weight change since 25 years of age; or additional adjustment for significant weight change during the past 12 months; or additional adjustment for histories of chronic hepatitis/cirrhosis and peptic ulcer; or excluding participants with diabetes occurring during the first two years of follow-up (data not shown).

	Person-years	Cases	Age- and sex-adjusted (model 1)	Multivariable-adjusted <sup>a</sup> (model 2)	Further adjustment for BMI and WC (model 3)
Total					
Without GSD	3,905,602	11,352	1.00	1.00	1.00
With GSD	233,084	1,130	1.33 (1.25–1.42)	1.32 (1.24–1.40)	1.17 (1.10–1.25)
Men					
Without GSD	1,615,585	4,484	1.00	1.00	1.00
With GSD	59,953	251	1.29 (1.13–1.46)	1.22 (1.08–1.39)	1.09 (0.96–1.24)
Women					
Without GSD	2,290,017	6,868	1.00	1.00	1.00
With GSD	173,131	879	1.33 (1.24–1.43)	1.33 (1.24–1.43)	1.21 (1.13–1.30)

## Discussion :-

In this large prospective study with close to ten years of follow-up, we observed that the presence of GBD was prospectively associated with increased risk of diabetes after adjustment for potential confounding from traditional risk factors of diabetes(8). Such association was strongest among participants who had a long history of GBd and were still on treatment at baseline. The association between GBD and diabetes was consistent in men and women, but the stronger association was observed in non-abdominal obese than in abdominal obese women(9)(10).

To our knowledge, only one study has prospectively examined the association of GBD with diabetes in a European population (EPIC-Potsdam study) with a mean follow-up of 7.0 years(11)It was consistent with our findings that persons with GBD had an increased risk of diabetes after adjustment for sex, age, WC, and lifestyle risk factors(12).

Several potential mechanisms may help explain the association between GBD and diabetes. Higher prevalence of Gallbladder stone has been reported in persons with obesity, hyperinsulinemia<sup>8</sup>, insulin resistance<sup>16</sup>, and metabolic syndrome(13). The coexistence of these risk factors for type 2 diabetes might be the reason that participants with GSD had an increased diabetes risk. In the current study, the adjustment for BMI and WC moderately attenuated the association between GBD and 1 diabetes, suggesting that obesity might only partly explain the higher risk of diabetes in patients with GBD. In addition, statistically significant associations remained after adjustment for risk factors such as hypertension and lifestyle factors, suggesting other mechanisms might also be involved. A similar change in the risk estimates with adjustment for potential confounders was also observed in the EPIC-Potsdam study . In addition, we explored whether the association between GSD and type 2 diabetes was confounded by long- and short-term weight change, which has been related to both diabetes<sup>1</sup> and gallstone formation<sup>3</sup>. Additional adjustment for weight change since 25 years of age or significant weight change in the past 12 months did not affect the association appreciably.

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