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Diabetes mellitus and the risk of gallbladder disease: A systematic review and meta-analysis of prospective studies

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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. For this reason we conducted a systematic review and meta-analysis of the available cohort studies.

Materials and methods: We searched the PubMed and Embase databases for studies of diabetes and gallbladder disease (defined as gallstones, cholecystectomy, or cholecystitis) 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 223,651 cases among 7,365,198 participants. The summary RR for diabetes patients was 1.56 (95% CI: 1.26–1.93, $I^2 = 99.4\%$, $p_{heterogeneity} < 0.0001$). 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.

1. Introduction

Gallbladder disease, including gallstones and cholecystitis, is a major cause of morbidity in the US and in the Europe. The prevalence of asymptomatic gallstones is 10–15% in European populations (Kratzer, Mason, & Kachele, 1999), while symptomatic gallstones are less frequent and affects 2% of the population (Friedman, Raviola, & Fireman, 1989). Of digestive diseases that require hospitalization gallstones are the most frequent and costly; the economic costs of hospital treatment of gallstones are over 6.5 billion US dollar per year (Shaffer, 2006). In the United Kingdom 49,000 cholecystectomies are conducted every year (Sanders & Kingsnorth, 2007), while in the US the number is >700,000 (Shaffer, 2006).

There is strong evidence that greater body fatness (Tsai, Leitzmann, Willett, & Giovannucci, 2004a; Tsai, Leitzmann, Willett, & Giovannucci, 2006a) and low physical activity (Leitzmann et al., 1998; Leitzmann et al., 1999) are associated with increased risk of gallstones. In addition, there is increasing evidence to suggest that components of the metabolic syndrome including insulin resistance, hyperinsulinemia, and elevated triglycerides may be associated with increased risk (Banim et al., 2011; Kim et al., 2011; Tsai, Leitzmann, Willett, & Giovannucci, 2008). Epidemiological studies on the risk of gallbladder disease among diabetes patients have been inconsistent. Some studies have found a positive association between diabetes and risk of gallbladder disease or gallstones (Campbell, Newton, Patel, Jacobs, & Gapstur, 2012; Chen, Hsu, Liu, & Tung, 2014; Etminan, Delaney, Bressler, & Brophy, 2011; Festi et al., 2008; Jamal, Yoon, Vega, Hashemzadeh, & Chang, 2009; Liu et al., 2012; Noel, Braun, Patterson, & Bloomgren, 2009; Strom et al., 1986), however, other studies found no association (Boland, Folsom, & Rosamond, 2002; Gonzalez-Perez & Garcia Rodriguez, 2007; Halldestam, Kullman, & Borch, 2009). In addition the size of the risk estimates has varied considerably, and this could potentially be due to confounding by other risk factors such as obesity and physical activity or other risk factors. As the prevalence of diabetes is projected to increase from 366 million people in 2011 to 552 million by 2030 it will be important to clarify whether there is an association between a diabetes diagnosis and gallbladder disease risk independent of body fatness and other confounding factors. For this reason we conducted a systematic review and meta-analysis of

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published cohort studies of gallbladder disease risk among diabetes patients with the aim of clarifying the direction and strength of the association and potential sources of heterogeneity that may explain the differing results between studies.

2. Materials and methods

2.1. Search strategy and inclusion criteria

We searched the PubMed, and Embase databases up to January 9th 2015 for eligible studies. As part of a larger project we used the following search terms in the PubMed search: (body mass index OR BMI OR overweight OR obesity OR anthropometry OR fatness OR body fatness OR abdominal fatness OR abdominal obesity OR waist circumference OR waist-to-hip ratio OR physical activity OR exercise OR sports OR walking OR biking OR running OR fitness OR exercise test OR inactivity OR diabetes OR smoking OR tobacco OR risk factor OR risk factors) AND (gallstones OR gallbladder disease OR cholelithiasis OR cholecystectomy OR cholecystitis). Similar search terms were used for the Embase search. We followed standard criteria for conducting and reporting meta-analyses (Stroup et al., 2000). In addition, we searched the reference lists of the identified publications for further studies.

2.2. Study selection

We included published retrospective and prospective cohort studies and nested case–control studies within cohorts that investigated the association between diabetes mellitus and the risk of gallbladder disease including gallstones, cholecystectomy or cholecystitis. Adjusted estimates of the relative risk had to be available with the 95% CIs in the publication. We identified ten cohort studies that could be included in the analysis (Boland et al., 2002; Campbell et al., 2012; Chen et al., 2014; Etminan et al., 2011; Festi et al., 2008; Gonzalez-Perez & Garcia Rodriguez, 2007; Jamal et al., 2009; Liu et al., 2012; Noel et al., 2009; Strom et al., 1986). Two of these studies were identified in a separate search on diabetes and cancer risk (Campbell et al., 2012; Jamal et al., 2009). A list of the excluded studies can be found in Supplementary Table 1.

2.3. Data extraction

The following data were extracted from each study: the first author's last name, publication year, country where the study was conducted, study period, sample size, number of cases and participants, subgroup, relative risks and 95% confidence intervals for diabetes versus no diabetes and variables adjusted for in the analysis.

2.4. Statistical methods

We calculated summary relative risks of gallbladder disease for patients with diabetes mellitus compared with patients without diabetes mellitus using the random-effects model by DerSimonian and Laird (DerSimonian & Laird, 1986) which takes into account both within and between study variation (heterogeneity). The average of the natural logarithm of the relative risks was estimated and the relative risk from each study was weighted by the inverse of its variance.

Heterogeneity between studies was evaluated using Q and I^2 statistics (Higgins & Thompson, 2002). I^2 is a measure of how much of the heterogeneity that is due to between study variation rather than chance. I^2-values of 25%, 50% and 75% indicates low, moderate and high heterogeneity respectively. We conducted main analyses (all studies combined) and stratified by study characteristics such as sample size, number of cases, geographic location, study quality and by adjustment for confounding factors to investigate potential sources of heterogeneity. Study quality was assessed using the Newcastle Ottawa scale which rates studies according to selection, comparability and outcome assessment with a score range from 0 to 9 (Wells et al., 2014).

Publication bias was assessed using Egger's test (Egger, Davey, Schneider, & Minder, 1997) and Begg–Mazumdar's test (Begg & Mazumdar, 1994) and by inspection of the funnel plot. The statistical analyses were conducted using the software package Stata, version 10.1 software (StataCorp, Texas, US).

3. Results

We identified 10 cohort studies (Boland et al., 2002; Campbell et al., 2012; Chen et al., 2014; Etminan et al., 2011; Festi et al., 2008; Gonzalez-Perez & Garcia Rodriguez, 2007; Jamal et al., 2009; Liu et al., 2012; Noel et al., 2009; Strom et al., 1986) that could be included in the analysis of diabetes mellitus and gallbladder disease risk including 223,651 cases among 7,365,198 participants (Fig. 1, Table 1). Six of the studies were from the USA, two were from Europe, and two were from Taiwan. The summary relative risk for patients with diabetes mellitus versus patients without diabetes was 1.56 (95% CIs: 1.26–1.93) with very high heterogeneity, $I^2 = 99.4\%$, $p_{heterogeneity} < 0.0001$ (Fig. 2). Exclusion of two outlying studies (Liu et al., 2012; Strom et al., 1986) reduced the heterogeneity slightly, $I^2 = 86.2\%$, $p_{heterogeneity} < 0.0001$, although it remained high, while the summary estimate was slightly strengthened, summary RR = 1.65 (95% CIs: 1.52–1.79). There was no evidence of publication bias neither with Egger's test, $p = 0.70$ nor with Begg's test, $p = 0.37$ or by inspection of the funnel plot (Supplementary Fig. 1). The summary RR ranged from 1.46 (95% CI: 1.18–1.81) when excluding the study by Strom et al. (1986) to 1.70 (95% CI: 1.51–1.92) when excluding the study by Liu et al. (2012) (Supplementary Table 2).

3.1. Subgroup and sensitivity analyses

There were positive associations in all subgroup analyses, defined by gender, duration of follow-up, outcome type, geographic location, number of cases, study quality and adjustment for confounding factors (including age, alcohol, smoking, body mass index [BMI], and physical activity), although not always statistically significant (Table 2). With meta-regression analyses there was no evidence that the results differed between these subgroups. Although heterogeneity in general was very high, there was no heterogeneity among the studies with longer duration of follow-up (Table 2).

4. Discussion

This meta-analysis of prospective studies suggests that a diagnosis of diabetes mellitus may increase the relative risk of gallbladder disease by 56%. Positive associations were observed both in men and women, but were more pronounced among American studies than in European and Asian studies, however, there were few studies from the latter geographic areas. The current study is consistent with other studies which have found that the metabolic syndrome (Mendez-Sanchez, Chavez-Tapia, et al., 2005), insulin resistance (Mendez-Sanchez, Bermejo-Martinez, et al., 2005), and overweight and obesity (Aune, Norat, & Vatten, 2015) are associated with increased gallbladder disease, as all these factors also are closely related to the risk of type 2 diabetes (Abdullah, Peeters, de Court, & Stoelwinder, 2010; Ford, Li, & Sattar, 2008). Interestingly the risk of gallstones was increased with increasing number of metabolic perturbations, suggesting that dyslipidemia, insulin resistance, and obesity might independently contribute to gallstone disease development (Mendez-Sanchez, Chavez-Tapia, et al., 2005). However, it is also possible that increasing number of metabolic disturbances simply reflects increasing general or abdominal adiposity as dyslipidemia and insulin resistance increases with increasing adiposity (Whitlock et al., 2009). Nevertheless, we found that the association between diabetes and gallbladder disease persisted among studies that adjusted for BMI, suggesting an independent effect of diabetes on gallbladder disease risk. While the relative risk associated with diabetes (RR =

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