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Higher parity is associated with increased risk of Type 2 diabetes mellitus in women: A linear dose–response meta-analysis of cohort studies

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ABSTRACT

Aim: The goal of this study is to investigate the association between higher parity and the risk of occurrence of type 2 diabetes mellitus (T2DM) in women and to quantify the potential dose–response relation.
Methods: We searched MEDLINE, and EMBASE electronic databases for related cohort studies up to March 10th, 2016. Summary rate ratios (RRs) and 95% confidence intervals (CIs) for T2DM with at least 3 categories of exposure were eligible. A random-effects dose–response analysis procedure was used to study the relations between them.
Results: After screening a total of 13,647 published studies, only 7 cohort studies (9,394 incident cases and 286,840 female participants) were found to be eligible for this meta-analysis. In the category analysis, the pooled RR for the highest number of parity vs. the lowest one was 1.42 (95% CI: 1.17–1.72, $I^2 = 71.5\%$, $P_{heterogeneity} = 0.002$, *Power* = 0.99). In the dose–response analysis, a noticeable linear dose–risk relation was found between parity and T2DM ($P_{for\ nonlinearity\ test} = 0.942$). For every live birth increase in parity, the combined RR was 1.06 (95% CI: 1.02–1.09, $I^2 = 84.3\%$, $P_{heterogeneity} = 0.003$, *Power* = 0.99). Subgroup and sensitivity analyses yielded similar results. No publication bias was found in the results.
Conclusion: This meta-analysis suggests that higher parity and the risk of T2DM show a linear relationship in women.

1. Introduction

Diabetes is a major cause of mortality and morbidity worldwide (Krug, 2016). According to the International Diabetes Federation, in 2015, almost 9% of the adult population have diabetes, with approximately 5 million deaths every year. Additionally, for every US$9 of global health-care expenditure, US$1 is spent on diabetes and its complications (Chan, Gregg, Sargent, & Horton, 2016; Peter & Lipska, 2016). Low- and middle-income countries always have a higher prevalence of diabetes compared to high-income countries (Kharroubi & Darwish, 2015). Notably, type 2 diabetes (T2DM) accounts for about 90% of diabetic cases (Chan et al., 2016).

The well-established risk factors for T2DM include genetic predisposition, obesity, unhealthy lifestyle and diseases of the pancreas (Chen, Magliano, & Zimmet, 2012). However, it is still controversial whether parity is an independent risk factor for the development of T2DM. Pregnancy does induce a state of insulin resistance which may progress to gestational diabetes mellitus (Kampmann et al., 2015). Levels of various hormones, such as placental lactogen, progesterone, cortisol, and tumor necrosis factor, change significantly during pregnancy, which may alter the glucose metabolism, utilization, and insulin production (Neckell & Munteanu, 2009; Ovesen, Jensen, Damm, Rasmussen, & Kesmodel, 2015). During abnormal metabolism, there is an increased demand for insulin in the target tissues and adaptation of the β–cell mass to insulin resistance (Yang et al., 2016). Additionally, an increase in insulin secretion occurs to meet the normal metabolism needs for longer periods (Alejandro, Gregg, Blandino-Rosano, Cras-Meneur, & Bernal-Mizrachi, 2015; Halban et al., 2014), which leads to extra burden on β-cell function and altered insulin secretion (Poulakos et al., 2015). However, whether these metabolic and physiological changes of pregnancy could increase the risk of diabetes mellitus in the later life of the woman is not yet proven.

Many large observational studies have evaluated the association between parity and T2DM. Most studies have suggested that greater parity, particularly (>5), may increase the risk for T2DM (Halban et al.,

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2014). However, other studies have found a weak or no association between parity and occurrence of T2DM (Kharazmi, Lukanova, Teucher, Gross, & Kaaks, 2012; Naver et al., 2011; Tian et al., 2014; Tobias et al., 2015b). These variable and inconsistent results need further exploration. Thus, we aimed to rigorously evaluate the association between parity and incidence of T2DM and potential dose–response relationship.

2. Materials and methods

This review was designed following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). Also, the protocol of this study was registered in the international prospective trial registration platform (http://www.crd.york.ac.uk/prospero), with a registration number CRD42016037263.

2.1. Publication search

We performed a literature search in PubMed and EMBASE databases from inception till March 10th, 2016 (Table S1). Cohort studies fulfilling certain inclusion criteria were considered for this review. The Medical subject headings (MeSH) and free text terms were used for database search, including ("parity" or "live birth" or "pregnancy" or "reproductive factor" or "reproductive" or "reproduction") AND ("diabetes" or "diabetes mellitus"). This search was supplemented by reviewing the reference sections of relevant articles, recent reviews, and meta-analyses. Our literature search was not restricted to certain language or any other parameters.

2.2. Eligibility criteria

Clinical studies with the following criteria were included in this analysis:

1. A cohort or case–cohort or nested case–control design,
2. Inclusion of subjects with parity ≥3 exposure categories; parity was defined as the number of live births, and
3. Analyses including reported rate ratios (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs) for incidence of T2DM and number of parity, but excluding Type 1 DM and gestational diabetes.

Reviews, abstract, editorials, letters and non-human studies were excluded.

2.3. Data collection and analysis

Two authors independently analyzed the records and applied the eligibility criteria for inclusion of the studies. In case of any disagreement, a language adviser was consulted. Then, two authors independently extracted data using the specific data extraction form. The following data were summarized into standardized electronic forms: first author's name, publication year, study design, T2DM ascertainment, participants gender, age range, geographic location, total sample and case size, person-years, length of follow-up, number of parity, adjusted effect sizes with 95% CIs, and well-adjusted covariates. Effect estimates controlling most confounders were preferred to use. If reference value was not from the lowest category, then the data was converted into a standard form according to the Hamling method (Hamling, Lee, Weitkunat, & Ambuhl, 2008). Cohen's Kappa test was used for the statistical measurement of inter-rater agreement for quality assessment (Landis & Koch, 1977). Any disagreement was resolved through discussion and consultation with the other review authors (Landis & Koch, 1977).

2.4. Quality assessment

The quality of studies was assessed according to the Newcastle–Ottawa Scale (NOS) (Wells et al., 2011). The NOS contains 9 items, categorized into 3 sections: selection (4 items), comparability (2 items), and exposure (3 items). One point is given for each criterion fulfilled by the study. A high–quality study was defined as having a NOS score ≥7, and a low-quality study had NOS score <7. Two reviewers independently assessed the quality of articles. Disagreements were resolved by a third reviewer (Table S2). More information is available at (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

2.5. Statistical analysis

In this categorical meta-analysis, we summarized the RRs for the highest versus lowest category (reference =0 or 1) of parity on T2DM. The highest exposure category of parity number was defined as 5 (Fowler-Brown et al., 2010). Whereas, in dose–response meta-analysis, we carried out the method described by Greenland and Longnecker (1992) and Orsini (2013), which fitted correlation with the log RR estimates across number of parity. Briefly, a restricted cubic spline with three knots at three percentiles (10, 50 and 90th) of the different parity levels was modeled (Orsini, Li, Wolk, Khudyakov, & Spiegelman, 2012). Moreover, the regression coefficients and the variance/covariance matrix within each study were combined into a multivariate random-effects meta-analysis. A chi-square test for nonlinear trend was used for testing the null hypothesis that the coefficient of the second regression coefficient equals zero (Orsini, Bellocco, & Greenland, 2005). When nonlinear trend was not detected, linear analysis was performed using the method mentioned earlier (Greenland & Longnecker, 1992). This analysis needs data on the RRs and 95% CIs, number of cases, person-years, and number of parity for each group. We assigned the reported median or mean number of parity of each category as the category number of parity to each of the included studies. When the highest category was open-ended, its category number of parity was calculated with the same amplitude of the adjacent one (Guo et al., 2015; Zhu et al., 2015). For a study offering 2 group data (Naver et al., 2011), we pooled them via fixed-effects models, then random-effects models were applied for all other data analysis (Jackson, White, & Thompson, 2010).

We conducted subgroup analysis on adjusted covariates, such as age, race, parity, smoking, alcohol drinking, body mass index (BMI), education level, hormone therapy, and history of diabetes (Higgins & Green, 2011). As these variables are from previous studies, there exists a possibility of confounding factors (Chan et al., 2009; Misra, 2015). We reported that our subgroup analysis follows the Guidelines for Interpreting Subgroup Analysis (Sun, Ioannidis, Agoritsas, Alba, & Guyatt, 2014). Meta-regression was conducted considering the discrepancy and interaction effect among subgroups (Altman & Bland, 2003). Sensitivity analysis was used to test whether the results were robust via omitting one study at a time or excluding studies with certain traits (Liu et al., 2016; Zhou, Luo, Li, Li, & Zhou, 2015).

Publication bias was evaluated by the funnel plot, and Egger's test (Egger, Davey Smith, Schneider, & Minder, 1997), and if bias was detected, the "trim and fill method" was fitted to judge the missing studies whether to have an impact on overall results (Duval & Tweedie, 2000). The statistical power of results was also assessed to judge whether the rationality and the credibility of the results of the subgroup are due to the limited number of studies (Cafri, Kromrey, & Brannick, 2009; Hedges & Pigott, 2001).

For all statistical analyses we used Stata/SE12.0 software (Stata Corp LP, TX, USA). Two–sided tests with $\alpha = 0.05$ was considered to be of significant level.