Parity and risk of type 2 diabetes: a systematic review and
dose-response meta-analysis

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Abstract

Objective: Epidemiologic studies regarding the association between parity and risk of type 2 diabetes have yielded inconsistent results. Therefore, we performed a systematic review and dose-response meta-analysis to determine the relation between parity and type 2 diabetes risk.

Methods: We searched PubMed and Embase for published epidemiologic studies that assessed the relation between parity and risk of type 2 diabetes up to 31 March 2016. A dose-response random-effects model was used to combine study-specific relative risks (RRs) and 95% confidence intervals (CIs). Potential sources of heterogeneity were explored by meta-regression and subgroup analyses.

Results: Seven cohort studies, 1 case-control study, and 9 cross-sectional studies including 296,923 participants were eligible for inclusion. The combined RR for the highest versus lowest category of parity indicated a 54% increment in type 2 diabetes risk (95% CI 29%-83%). In the cubic spline model, a nonlinear association was found between parity and risk of type 2 diabetes ($P = 0.02$ for nonlinearity). Compared with nulliparous women, the estimated RR (95% CI) of type 2 diabetes for women with one to seven children was 1.01 (0.96-1.07), 1.08 (1.00-1.16), 1.20 (1.12-1.30), 1.32 (1.22-1.42), 1.37 (1.27-1.48), 1.39 (1.26-1.52) and 1.39 (1.23-1.57), respectively.

Conclusions: Higher parity is significantly associated with an increased risk of type 2 diabetes. Further studies are warranted to fully adjust for the potential confounders and explore the causality between parity and type 2 diabetes risk.
Introduction

The prevalence of diabetes mellitus has increased substantially in recent decades in both developed and developing countries (1). According to data of the International Diabetes Federation, the number of people living with diabetes is 415 million in 2015 (a number previously forecast for 2030), and will escalate to 642 million by 2040 (2). Diabetes is also a major risk factor for cardiovascular disease which is still the leading cause of death and imposes a significant public health as well as financial burden on society (3). Thus, the primary prevention of diabetes is clearly imperative.

Pregnancy is an essential stage of life for most women. In this stage, women are prone to alter their composition of diet, increase energy intake, reduce the duration and intensity of physical activity, these changes of lifestyle may impact on women’s health including insulin resistance, fat accumulation, redistribution, dyslipidemia, and inflammation, especially on the risk of diabetes and other cardio-metabolic disease in future life (4-9). Among the different reproductive factors that have been investigated, parity (the number of live births in a woman’s lifetime) is less prone to recall bias and misclassification (10). Until now, many studies have focused on the role of parity in the development of type 2 diabetes, suggesting that parity might be independently associated with glucose tolerance (11, 12), impaired fasting glucose (11, 13), and type 2 diabetes (13-16). But it remains controversial since other studies have found no relationship between parity and risk of type 2 diabetes (17-19). Therefore, we conducted a systematic review and dose-response meta-analysis of current available epidemiologic studies to quantify the association between parity and risk of type 2
diabetes.

**Methods**

**Search strategy**

We conducted a systematic literature search of PubMed (Medline) and Embase databases from inception to March 2016 for studies investigating the association between parity and diabetes mellitus. PubMed search terms were (parity OR reproductive history OR live birth OR gravidity) AND ("Diabetes Mellitus"[Mesh] OR "diabetes"[All Fields]). Similar search terms were used for Embase. In addition, we also scrutinized reference from relevant original papers to identify further pertinent studies. No language restrictions were imposed. We followed the standard guidelines for conducting meta-analysis of observational studies and reporting the results (20).

**Study selection**

Published studies were included in this meta-analysis if they met the following criteria: the exposure of interest was parity; the outcome was type 2 diabetes; and the study reported adjusted relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs) with 95% confidence intervals (CIs) for at least three quantitative categories of parity number or provided risk estimates per live birth in original. We excluded non-human studies, reviews, commentaries, editorials, letters, meeting abstracts, case reports, and studies that did not include parity as the exposure and type 2 diabetes as the outcome.
We also excluded studies in which the association of parity with impaired glucose
tolerance/impaired fasting glucose, but not the association of parity with type 2
diabetes, was examined. If a study provided raw data which may contribute to the
calculation of unadjusted risk estimates but was not able to derive the adjusted risk
estimates, we excluded it due to the lack of controlling for potential effects from
confounding factors such as age or body mass index (BMI) on the risk estimates. Two
investigators (PL and MX) independently screened all studies by title or abstract and
then by full-text assessment. Any disagreements were solved by discussion with the
senior reviewer (ZS).

Data extraction and quality assessment

For each eligible study, the following data were extracted: authors, year of publication,
study design, study name, country of origin, study period and years of follow-up (for
cohort study), participants’ age, number of participants and cases, exposure and
outcome assessment, covariates adjusted in the multivariable models, parity number
categories, the corresponding risk estimates (with their 95% CIs) and number of cases
along with participants or person-years for all categories of parity number. If multiple
estimates of the association were available, we abstracted the estimate that adjusted
for most potentially confounding variables. If the appropriate data were not readily
available, we requested the data from the study’s original authors.

For cohort and case-control studies, quality assessments were performed according
to the Newcastle-Ottawa Quality Assessment Scale (21). This scale awards a
maximum of nine points to each cohort study: 4 for selection of participants and measurement of exposure, 2 for comparability of cohorts on the basis of the design or analysis, and 3 for assessment of outcomes and adequacy of follow-up. Similar items were performed for case-control studies. We assigned scores of 0-3, 4-6, and 7-9 for low, moderate, and high quality of studies, respectively.

Assessment involving 11 items recommended by the Agency for Healthcare Research and Quality was used for cross-sectional studies (22). The quality of the studies was evaluated according to the established questions which awards a maximum of 11 points. For each item, 1 point was awarded if the answer was “yes” while 0 point if the answer was “no”, “unable to determine” or “not applicable”.

Data extraction and quality assessment were conducted independently by two investigators (PL and LZ), any discrepancy between the two authors was solved by discussion with the senior reviewer (ZS).

**Statistical analysis**

In this meta-analysis, we used the RRs and 95% CIs as the effect size for all included studies. Since the incidence of diabetes is adequately low in human, the ORs and HRs were considered equivalent to RRs, thereby we used RRs representing all of these measures for simplicity. For studies that did not use the category of lowest parity number as referent, we used the valid count method proposed by Hamling et al (23) to recalculate the relative risks. Moreover, as for study that reported results separately according to different age groups, races or geographic regions, we treated it as
Firstly, we evaluated the summary RR and 95% CIs for the highest versus the lowest categories of parity number. Given that significant heterogeneity was evident in this analysis, the risk estimates were pooled using the random-effects model (DerSimonian and Laird method) (24).

Then, we explored the possible linear or nonlinear relationship between parity number and risk of type 2 diabetes using a random-effects dose-response meta-analysis according to the method proposed by Greenland and Longnecker (25) and Orsini et al (26). Nearly half of the reports have investigated the linear relation between parity and type 2 diabetes, and provided RR per live birth in original. Thus, we explored the possible linear relationship at first. For reports that did not explore the linear relationship, we computed a RR with 95% CIs for an increased number of parity according to the existing data. The distribution of cases and person-years/number of participants, and the RRs with 95% CIs for at least three quantitative exposure categories were extracted according to the method. For each study, the median or mean level of exposure category was assigned to the corresponding RR. If the median or mean exposure level was not reported in the study, we assigned the midpoint of upper and lower boundaries in each category as the value of exposure. When the highest category was open ended, we assumed that the lower boundary plus 25% increment was the median level. To further examine the shape of the association, we evaluated a potential curve linear association between parity number and risk of diabetes, using restricted cubic splines with four knots at
percentiles 5%, 35%, 65% and 95% of the distribution (27). According to the method, the spline function is constrained to be linear in the tails, and $P$ value for curve linearity or nonlinearity was calculated by testing the null hypothesis that the regression coefficient of the second and third spline was equal to zero (28).

The heterogeneity among studies was estimated by using the Cochran’s Q test and $I^2$ statistic (29). Heterogeneity was considered statistically significant at $P < 0.10$. Low, moderate, and high degree corresponded to $I^2$ statistic of 25%, 50%, 75%, respectively (29). We conducted a meta-regression analysis and subgroup analyses to explore sources of heterogeneity. Subgroup analyses were performed according to study design, geographic location, year of publication, number of cases and participants, and methods of outcome ascertainment. We also stratified the meta-analysis by whether adjustment for potential confounders, such as age, BMI, family history of diabetes mellitus, education and income, was performed. To test the robustness of the associations, we performed sensitivity analyses by omitting one study at a time and estimating a pooled RR for the rest of the studies to evaluate whether the results were markedly influenced by a single one. The Begg and Egger tests were applied to assess the possible publication bias (30). All the data analyses were performed with Stata version 12.0 (Stata Corp). Two-sided $P < 0.05$ was considered statistically significant.

**Results**

**Literature search**
Figure 1 shows the flow diagram of the procedure used to identify the relevant studies. We identified 2,481 articles from PubMed and 3,343 articles from Embase prior to 31 March 2016. After exclusion of duplicates and studies that did not meet the predefined selection criteria, 33 potentially relevant articles were initially selected for this meta-analysis. After evaluating the full texts, 17 articles were excluded. Eight articles were further excluded owing to insufficient data; although 3 (31-33) of them provided original data, we could not calculate adjusted RRs with 95% CIs accordingly. Six articles were excluded because the outcome of interest was gestational diabetes mellitus. Other 3 articles in which fewer than three categories of parity number were provided were excluded for no contribution to the estimation of dose-response analysis. Moreover, 1 publication (34) was included by scanning reference from relevant papers. In one paper, the researchers indicated that they conducted a cross-sectional study initially, and followed up the remainders after excluding patients of diabetes for years (17), so we just included the results of the prospective study to avoid bringing the same subjects. Finally, 17 articles (12-19, 34-42) were eligible for this meta-analysis including 7 cohort studies (12, 15-17, 19, 35, 36), 1 case-control study (38), and 9 cross-sectional studies (13, 14, 18, 34, 37, 39-42). For studies conducted by Naver et al (16) and Collins et al (42), the estimates were reported by different age groups or geographic regions, we treated them as 7 separate reports. Therefore, our meta-analysis included 17 articles with 22 independent reports.

**Study characteristics**
Characteristics of the 17 eligible studies are shown in Table 1. Our included studies, which comprised 296,923 participants, were published between 1989 and 2015. Eight studies were conducted in the North America (12, 17, 19, 34, 36, 38, 40, 41), 1 in South America (14), 2 in Europe (16, 35), 3 in Asia (13, 15, 37), 2 in Oceania (18, 39), and 1 study in both Oceania and Africa (42). The average of follow-up duration of cohort studies was 11.4 years. The sample size of the included cohort studies ranged from 1,186 to 113,606 and the number of type 2 diabetes cases varied from 146 to 2,310. For cross-sectional studies, the number of participants ranged from 152 to 14,196 (51 to 2,552 people were considered as type 2 diabetes). Study-specific quality scores were summarized in Supplementary Table 1-2. The quality score ranged from 7 to 9 with a median score of 8 for all cohort and case control studies. Meanwhile, all the cross-sectional studies scored 6 to 9 points, which suggested high quality of the studies included in the meta-analysis.

**Highest versus lowest number of parity**

Fifteen reports from 14 studies (13-19, 34-36, 38-41) described the association between parity number and type 2 diabetes risk. Eleven reports considered nulliparous as the lowest category of parity while 3 reports (13, 16) treated one live birth as the lowest. One report (40) considered one or two live births as the lowest category of parity number. The pooled RR of type 2 diabetes risk for the highest versus lowest categories of parity was 1.54 (95% CI 1.29-1.83). There was moderate heterogeneity among the studies ($I^2 = 59.3\%, P = 0.002$) (Figure 2A).
In a sensitivity analysis, exclusion of one study at a time from the pooled estimate had little impact on the overall effect size. To confirm the robustness of the results, we conducted additional sensitivity analyses. We excluded 4 reports (13, 16, 40) that did not refer to nulliparous as the lowest category of parity number. The pooled RR was 1.47 (95% CI 1.15-1.89), with no substantial change. In addition, we performed a sensitivity analysis by including the 3 articles (31-33) that were excluded previously and another 5 reports (42) that also provided raw data for the calculation of unadjusted RR{s}, the pooled RR was 1.78 (95% CI 1.42-2.23).

Dose-response meta-analysis

When assuming a linear relationship, there were 16 studies (12-17, 19, 34-42) with 21 reports available for the dose-response analysis. The combined RR for type 2 diabetes was 1.06 (95% CI 1.02-1.09) per live birth, with evidence of high heterogeneity ($I^2 = 87.2\%$, $P < 0.001$) (Figure 2B). Eight studies (13-17, 19, 36, 39) with 9 reports were included in the cubic spline model, and a nonlinear association between parity and risk of type 2 diabetes was found (Figure 3, $P = 0.02$ for nonlinearity). Compared with nulliparous women, the estimated RR of type 2 diabetes was 1.01 (95% CI 0.96-1.07) for women with 1 child, 1.08 (95% CI 1.00-1.16) for women with 2 children, 1.20 (95% CI 1.12-1.30) for women with 3 children, 1.32 (95% CI 1.22-1.42) for women with 4 children, 1.37 (95% CI 1.27-1.48) for women with 5 children, 1.39 (95% CI 1.26-1.52) for women with 6 children, and 1.39 (95% CI 1.23-1.57) for women with 7 children.
In a sensitivity analysis, exclusion of one study at a time from the pooled estimate had little impact on the overall effect size. We also examined studies that presented RR of type 2 diabetes per live birth in original papers in linear dose-response analysis (12, 34, 35, 37, 38, 40-42), the pooled RR was attenuated to 1.04 (95% CI 0.99-1.08). Additionally, the summary RR of type 2 diabetes was 1.06 (95% CI 1.03-1.10) per live birth after including studies (31-33, 42) for which crude estimates could be derived, and the shape of the nonlinear association between parity and type 2 diabetes was similar to previous one. Overall, the sensitivity analyses did not lead to any significant changes on the association between parity and type 2 diabetes risk.

Subgroup analyses

Subgroup analyses were carried out to examine the sources of heterogeneity. The associations of parity number with risk of type 2 diabetes were similar in subgroup analyses (Table 2).

In the analysis of highest versus lowest categories of parity and type 2 diabetes risk, no significant heterogeneity between subgroups was found. The between-study heterogeneity was largely reduced when the analysis was stratified according to study location and publication year. Comparing to the high heterogeneity we observed among studies that did not adjust for education and income, the summary results of the studies that adjusted for aforementioned confounders had evident lower heterogeneity. This result may be attributable to the hypothesis that lower socioeconomic status might lead to both higher parity and risk of diabetes. Almost all
strata showed positive associations, although not all of them showed statistical significance. Similar patterns were also observed in the dose-response analyses. It is worth mentioning that the association between parity number and risk of type 2 diabetes were familiar when stratified by study design. When considered prospective studies, the pooled RR of type 2 diabetes risk was 1.44 (95% CI 1.12-1.84) for the highest versus lowest categories of parity and was 1.09 (95% CI 1.02-1.16) per live birth (Figure 2). Furthermore, when we removed non-prospective studies (13, 14, 39) out of the cubic spline model, there was still a J-shaped association between parity and risk of type 2 diabetes, and women with at least 4 children had significantly higher risk of type 2 diabetes. More specifically, compared with nulliparous women, the estimated RR of type 2 diabetes was 1.12 (95% CI 1.02-1.23) for women with 4 children, 1.18 (95% CI 1.07-1.30) for women with 5 children, 1.22 (95% CI 1.08-1.34) for women with 6 children, and 1.26 (95% CI 1.08-1.40) for women with 7 children.

Assessment of publication bias

There was no evidence of substantial publication bias for all meta-analyses according to the Begg and Egger tests ($P >0.05$ for both tests).

Discussion

To the best of our knowledge, this is the first meta-analysis exploring the association between parity and type 2 diabetes risk. Our results indicated that parity was positively associated with type 2 diabetes. Specifically, a nonlinear association
between parity and type 2 diabetes risk was observed in the cubic spline model. Higher parity (at least 3 live births) was found to be associated with significantly increased risk of type 2 diabetes. Our results were consistent with the previous epidemiologic studies (13-16, 35, 36, 40). Charles and colleagues (37) found that parity was associated with a significantly reduced risk of diabetes after adjustment for age and BMI. However, the individuals in that study were known to suffer from high rates of diabetes and the age ranged widely, which might lead to the particularity of the results.

In order to examine the shape of the possible association between parity and type 2 diabetes, a dose-response analysis was deemed essential. In our linear dose-response analysis, the risk of type 2 diabetes was increased by 6% for each birth. In the cubic spline model, a nonlinear association was observed: higher parity (at least 3 live births) was associated with a significantly elevated risk of type 2 diabetes. It is noteworthy that the reports we included in the analysis of linear or nonlinear relation were different, because only a few studies (13-17, 19, 36, 39) had sufficient data for nonlinear dose-response analysis apart from providing the RR of linear relation between parity and risk of type 2 diabetes. Thus, linear and nonlinear relations were both tested to quantify the association in this study. Aside from type 2 diabetes, prospective studies in populations have found an increased risk of metabolic syndrome in multiparous women compared to nulliparous (43, 44). Accumulating evidence also suggests that parity is associated with a higher risk of all-cause mortality in later life, especially with cardiovascular and cerebrovascular mortality (8,
Several potential mechanisms might contribute to the J-shaped association between parity and type 2 diabetes risk. Generally, more than 80% of women in high-income countries bear at least 1 child (46), as do upwards of 90% of women in most lower- and middle-income nations (6). This data suggested that women who didn’t have any children may suffer from infertility in addition to personal will. Beside, according to previous studies, several causes of infertility were associated with a higher diabetes risk such as polycystic ovary syndrome (47), ovulation disorders and tubal factor (48). This could partly explain the platform stage of the J-shaped relationship between parity and diabetes. The increase in type 2 diabetes risk with increasing parity after 2 children may be the results of accumulative physiological and lifestyle changes. First, a pronounced state of insulin resistance in peripheral tissues is induced in pregnancy period, gestational hormones might promote insulin resistance and pancreatic β cell proliferation (49). The β cell mass expands in response to the progressive insulin resistance to maintain maternal euglycemia during pregnancy and postpartum period (50). In susceptible non-diabetic women, insulin resistance may be severe enough to exhaust β cells and induce to the occurrence of gestational diabetes mellitus or even a permanent derangement of insulin secretion in later life (51). Mueller and colleagues (15) found parity was positively associated with HbA1c levels in women reporting no history of diabetes diagnosis, this result suggested that even in non-diabetic women multiparity may alter long-term glucose homeostasis due to repeated exposure to the hormone alterations. Second, pregnancy has been found to be accompanied by a
systemic inflammatory state as demonstrated by modest elevations in pro- and anti-inflammatory cytokines such as IFN-γ and TNF-α (7) which play important roles in the occurrence of insulin resistance and type 2 diabetes (52). Third, there is an increase in placental oxidative stress levels during pregnancy, even in a healthy placenta. A high placental mitochondrial activity could trigger an increase in reactive oxygen species production (53) which may serve as an important trigger of insulin resistance and type 2 diabetes (54). Pancreatic β cell may be more vulnerable to oxidative stress through pregnancy-induced increment in reactive oxygen species production and other physiologic changes (55). Moreover, pregnancy complications are considered to be associated with a greater risk of diabetes (56-58) and the recurrence of pregnancy complications in subsequent pregnancies may exert a cumulative burden on diabetes proceeding. Finally, pregnancy also impacts women’s dietary habits and physical activity. Lack of exercise and a high-calorie diet during pregnancy may induce excess gestational weight gain and postpartum obesity which could have impact on a woman’s health in future (59). Mamun et al (60) found that mothers who gained excess weight during pregnancy were 1.47 times more likely to experience diabetes compared to the mothers who gained adequate weight.

Therefore, the cumulative effect of these adaptations and risks may contribute to the above-noted J-shaped association between parity and type 2 diabetes risk. Nevertheless, it is still unclear whether normal pregnancies with increasing parity exert a cumulative burden on diabetes proceeding, whether advanced maternal age or other potential factors of multiparous women exert more diabetes risk or whether
women at high diabetes risk have more children. Thus, more insight into the
association between parity and maternal risk of type 2 diabetes are warranted and
more potential confounders should be taken into consideration in study design.

This meta-analysis has several strengths. First, we included 7 cohorts, 1
case-control and 9 cross-sectional studies with large sample size which provided
sufficient statistical power to detect potential association. The average score is 8 for
cohort and case-control studies and 7.9 for cross-sectional studies, which ensured the
high quality of the included studies. Second, we investigated a dose-response relation
between parity number and risk of type 2 diabetes, allowing us to examine the shape
of this possible association. Linear and nonlinear relations were both tested to
quantify the association. Third, in each of the included studies, we used the risk
estimates from the multivariable models adjusting for most established risk factors in
order to better control the confounders. In addition, subgroup analyses were also
conducted to explore whether some factors could explain the results.

Several limitations of our study should also be acknowledged. First, as a
meta-analysis of observational epidemiologic studies, the limitations inherent to
combining estimate risk from studies with heterogeneous study designs could not be
avoided. Cohort studies are less susceptible to recall bias than case-control and
cross-sectional studies due to the prospective design. Considering that parity is less
prone to recall bias and misclassification than other reproductive factors, and
subgroup analyses that included prospective studies only did not show any significant
difference, this matter may not substantially influence the results. Second, even
though we made an attempt to control confounding factors by using the adjusted estimates from multivariate models from contributing studies, we could not perform additional adjustments for residual or unmeasured confounders. The exclusion of papers that did not report adjusted estimates may slightly underestimate the association, but the sensitivity analyses and assessment of publication bias reassured that our results were unlikely to be appreciably affected by such exclusion. Finally, significant heterogeneity was present in the analyses, and sources of heterogeneity were not completely clear, which might be partly due to different study locations or the difference in confounder adjustment in the included studies.

Conclusions

Findings from this systematic review and dose-response meta-analysis suggested that higher parity was associated with an increased risk of type 2 diabetes. Further studies are warranted to fully adjust for the potential confounders and explore the causality between parity and type 2 diabetes risk.

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the study and had final responsibility for the decision to submit for publication.

Author contribution statement: PL formulated the study, searched the databases and checked them according to the inclusion and exclusion criteria, extracted and analyzed the data, and drafted and revised the manuscript. ZS helped formulate the study, provided advice on meta-analysis methodology, and contributed to writing, reviewing, or revising the manuscript. LZ helped extract quantitative data from the eligible papers and commented on drafts. MX and YZ searched the databases and checked them according to the inclusion and exclusion criteria, and commented on drafts. WB and YR provided advice on meta-analysis methodology, and contributed to writing, reviewing, or revising the manuscript. WY helped develop search strategies, supervised the study and revised the manuscript. LL formulated the study, supervised the study and had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors have read and approved the final version.

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Figure legends

Figure 1 Flow diagram of literature search and study selection.

Figure 2 Forest plots of the associations between parity and risk of type 2 diabetes. A) Forest plot of parity number (highest versus lowest) and type 2 diabetes risk; B) Forest plot of linear dose-response relation between parity (per live birth) and type 2 diabetes.

Figure 3 Dose-response analyses relating parity to type 2 diabetes risk. There was a nonlinear association between parity and risk of type 2 diabetes ($P = 0.02$ for nonlinearity). Parity number was modeled with restricted cubic splines by a random-effects dose-response model. Nulliparous was used as the reference to estimate all relative risks. Dotted lines represent the 95% CIs for the fitted trend.
<table>
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<th>First author</th>
<th>Publication year</th>
<th>Design and Study name</th>
<th>Country</th>
<th>Study period (follow-up years)</th>
<th>Age (years)</th>
<th>No. of participants/controls</th>
<th>No. of type 2 diabetes/cases</th>
<th>Exposure assessment</th>
<th>Outcome ascertainment</th>
<th>Comparison categories and corresponding relative risk (95% CI)</th>
<th>Covariates in fully adjusted model</th>
<th>Scale</th>
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<td>Cure 2015 (14)</td>
<td>CSS Health Community Programs at Biomelab Research Center</td>
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<td>61.9 ± 10</td>
<td>1,795</td>
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<td>medical history</td>
<td>0, 1.0 (referent); 1-2, 5.0 (1.1-22.9); 3-5, 4.1 (0.9-17.9); ≥6, 5.3 (1.2-23.5)</td>
<td>age, BMI, FHD, smoking history, breastfeeding, marital status, and waist hip ratio</td>
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<td>Tian 2014 (13)</td>
<td>CSS The Tongji-Dongfeng Cohort Study</td>
<td>China</td>
<td>2008-2010</td>
<td>≥45</td>
<td>14,196</td>
<td>2,552</td>
<td>questionnaire</td>
<td>self-report of physician diagnosis, anti-diabetic treatment, FPG level</td>
<td>1, 1.0 (referent); 2, 1.35 (1.20-1.52); 3, 1.59 (1.39-1.82); ≥4, 1.44 (1.21-1.71)</td>
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<td>Mueller 2013 (15)</td>
<td>CS The Singapore Chinese Health Study (SCHS)</td>
<td>Singapore</td>
<td>1993-2004 (5.7)</td>
<td>45-74</td>
<td>25,021</td>
<td>1,294</td>
<td>interview</td>
<td>self-report of physician diagnosis, validated by hospital-based discharge summary databases and telephone-administered supplementary questionnaire</td>
<td>0, 1.0 (referent); 1-2, 1.31 (0.98-1.76); 3-4, 1.62 (1.22-2.16); ≥5, 1.74 (1.29-2.33)</td>
<td>age, baseline BMI, interview year, dialect, education, age at menarche, menopausal status, hormone therapy, oral contraceptive use, smoking status, alcohol use, physical activity, dietary pattern, and total energy intake</td>
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<td>Kharazmi 2012 (35)</td>
<td>CS The European Prospective Investigation into Cancer and Nutrition (EPIC)</td>
<td>Germany</td>
<td>1994-2010 (10.7)</td>
<td>35-65</td>
<td>13,612</td>
<td>900</td>
<td>questionnaire</td>
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<td>N</td>
<td>Method</td>
<td>Measurements</td>
<td>OR (95% CI)</td>
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<td>Simons 2012 (39) CSS</td>
<td>CS</td>
<td>Australia</td>
<td>1988-1989</td>
<td>≥60</td>
<td>1,571</td>
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<td>previous diagnosis, use of diabetes medications, FPG level</td>
<td>0, 1.0 (referent); 1, 0.37 (0.10-1.34); 2, 1.32 (0.53-3.32); 3, 1.10 (0.44-2.76); 4, 1.31 (0.52-3.32); 5, 1.53 (0.58-4.09); ≥6, 1.27 (0.50-3.21)</td>
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<td>1982-2006</td>
<td>27.3 ± 4.74</td>
<td>100,669</td>
<td>National Birth Register</td>
<td>Danish National Registry of Patients</td>
<td>&lt;33 years 1, 1.0 (referent); 2, 1.61 (1.11-2.34); 3, 2.78 (1.82-4.25); ≥4, 2.46 (1.27-4.78)</td>
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<td>1989-2007</td>
<td>≥65</td>
<td>2,761</td>
<td>interview</td>
<td>use of diabetes medications, FPG level</td>
<td>0, 1.0 (referent); 1-2, 0.96 (0.63-1.47); 3-4, 0.86 (0.54-1.35); ≥5, 0.95 (0.54-1.67).</td>
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<td>Araneta 2010 (40) CSS</td>
<td>CSS</td>
<td>USA</td>
<td>1995-1999</td>
<td>48-73</td>
<td>152</td>
<td>questionnaire</td>
<td>OGTT, FPG level, diagnosis by physician, use of diabetes medications</td>
<td>1-2, 1.0 (referent); ≥6, 3.40 (1.13-10.2) per parity, 1.27 (1.09-1.49)</td>
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<td>Nicholson 2006 (36) CS</td>
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<td>USA</td>
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<td>45-64</td>
<td>7,024</td>
<td>interview</td>
<td>reported history of physician-diagnosed diabetes, use of diabetes medications, FPG level</td>
<td>never pregnant, 0.80 (0.54-1.18); 0, 1.31 (0.77-2.23); 1-2, 1.0 (referent); 3-4, 1.11 (0.92-1.34); ≥5, 1.27 (1.02-1.57).</td>
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8 age, BMI, cigarette smoking, any alcohol intake, serum lipids and lipoproteins, hypertension, peak expiratory flow, prior coronary heart disease or stroke, atrial fibrillation, depression score, physical activities of daily living, and self-rated health

9 age, BMI, center, race, income, education, smoking, FHD, caloric intake, physical activity score, menopause status, ever use of birth control pills, ever use of hormone replacement therapy, waist circumference, fibrinogen levels, and leukocyte count
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Database/Study</th>
<th>Country</th>
<th>Age Range</th>
<th>Participants</th>
<th>Method</th>
<th>Test</th>
<th>Odds Ratio (95% CI)</th>
<th>Associated Factors</th>
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<td>Simmons 2006 (18)</td>
<td>CSS: The Australian Diabetes, Obesity and Lifestyle Study (AusDiab)</td>
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<td>1999-2003</td>
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<td>6,782</td>
<td>Questionnaire</td>
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<td>Hanley 2002 (41)</td>
<td>CSS: The Sandy Lake Health and Diabetes Project (SLHDP)</td>
<td>Canada</td>
<td>1993-1995</td>
<td>12-79</td>
<td>383</td>
<td>Interview</td>
<td>OGTT, FPG level</td>
<td>0, 1.0 (referent); 1-2, 1.19 (0.61-2.32); 3-4, 1.23 (0.65-2.30); ≥5, 2.95 (1.74-5.01)</td>
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<tr>
<td>Charles 1994 (37)</td>
<td>CSS</td>
<td>India</td>
<td>1965-1985</td>
<td>≥20</td>
<td>2,779</td>
<td>Interview</td>
<td>OGTT, FPG level</td>
<td>0, 1.0 (referent); 1-2, 0.94 (0.83-1.06)</td>
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<tr>
<td>Alderman 1993 (38)</td>
<td>PCCS: The San Luis Valley Diabetes Study</td>
<td>USA</td>
<td>1983-1988</td>
<td>20-74</td>
<td>583</td>
<td>Interview</td>
<td>OGTT, FPG level, medical record</td>
<td>0, 1.0 (referent); 1-3, 0.58 (0.28-1.23); 4-6, 0.64 (0.30-1.37); 7-9, 0.79 (0.34-1.82); 10-12, 1.58 (0.54-4.61); ≥13, 0.95 (0.23-3.83)</td>
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<td>Manson 1992 (19)</td>
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<td>USA</td>
<td>1976-1988 (11.3)</td>
<td>30-55</td>
<td>113,606</td>
<td>Questionnaire</td>
<td>Supplementary questionnaire (classic symptoms, FPG level, random plasma glucose level, use of diabetes medications)</td>
<td>0, 1.0 (referent); 1, 1.14 (0.99-1.44); 2, 0.88 (0.72-1.08); 3, 0.87 (0.71-1.06); 4, 0.91 (0.74-1.12); 5, 0.90 (0.72-1.13); ≥6, 0.95 (0.75-1.19)</td>
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<td>Collins 1991 (42)</td>
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<td>Nauru</td>
<td>1987</td>
<td>40-80</td>
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<td>Interview</td>
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<td>562</td>
<td>56</td>
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<td>1.09 (1.00-1.19)</td>
<td>Age, obesity, and FHD per parity, 1.09 (1.00-1.19)</td>
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<td>Study</td>
<td>Year</td>
<td>Age Range</td>
<td>Cases</td>
<td>Controls</td>
<td>Study Type</td>
<td>Test</td>
<td>FPG Level</td>
<td>Per Parity OR (95% CI)</td>
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<td>Fiji (Melanesians)</td>
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<td>389</td>
<td>48</td>
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<td>OGTT, FPG level</td>
<td>1.04 (0.95-1.13)</td>
<td>Age, obesity, and FHD</td>
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<td>Fiji (Indians)</td>
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<td>57</td>
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<td>OGTT, FPG level</td>
<td>1.07 (0.97-1.18)</td>
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<td>Boyko 1990 (34)</td>
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<td>0, 1.0 (referent); 1, 0.76 (0.34-1.72); 2, 0.55 (0.26-1.16); 3, 1.47 (0.74-2.93); 4, 1.14 (0.51-2.55); 5, 0.54 (0.18-1.60); ≥6, 1.66 (0.79-3.52)</td>
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<td>Kritz-Silverstein 1989 (12)</td>
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<td>41-92</td>
<td>Interview</td>
<td>Self-report confirmed by OGTT</td>
<td>1.16 (1.04-1.29)</td>
<td>Age, obesity (BMI or waist-hip ratio), and FHD</td>
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</table>

BMI, body mass index; CI, confidence interval; CS, cohort study; CSS, cross-sectional study; FHD, family history of diabetes mellitus; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PCCS, population-based case-control study.
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<td><strong>Subgroup analyses</strong></td>
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<td>Study design</td>
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<td>Study location</td>
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<td>North America</td>
<td>7</td>
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<td>≥1995</td>
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Outcome ascertained by OGTT

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<td>24.46</td>
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<td>10</td>
<td>1.08 (1.03-1.13)</td>
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Adjustment for confounders or important risk factors

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<tr>
<td>Yes</td>
<td>10</td>
<td>1.39 (1.16-1.67)</td>
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<td>46.8</td>
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FHD

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Education

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Income

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OGTT, oral glucose tolerance test; BMI, body mass index; FHD, family history of diabetes mellitus.

a P value for heterogeneity within each subgroup.
b P value for heterogeneity between subgroups with meta-regression analysis.
For all the included studies had age in the fully adjusted model, no subgroup analysis for whether adjusted age was conducted.
Figure 1 Flow diagram of literature search and study selection.

209x296mm (300 x 300 DPI)
Figure 2 Forest plots of the associations between parity and risk of type 2 diabetes. A) Forest plot of parity number (highest versus lowest) and type 2 diabetes risk; B) Forest plot of linear dose-response relation between parity (per live birth) and type 2 diabetes.

285x350mm (300 x 300 DPI)
Figure 3 Dose-response analyses relating parity to type 2 diabetes risk. There was a nonlinear association between parity and risk of type 2 diabetes ($P = 0.02$ for nonlinearity). Parity number was modeled with restricted cubic splines by a random-effects dose-response model. Nulliparous was used as the reference to estimate all relative risks. Dotted lines represent the 95% CIs for the fitted trend.