MECHANISMS IN ENDOCRINOLOGY

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.

European Journal of
Endocrinology
(2016) **175**, R231–R245

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.

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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 cardiometabolic disease in future life (4, 5, 6, 7, 8, 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, 14, 15, 16). But it remains controversial since other studies have found no relationship between parity and risk of type 2 diabetes (17, 18, 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 on the 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 nonhuman 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 (P L and M X) independently screened all studies by title or abstract and then by full-text assessment. Any disagreements were solved by discussion with the senior reviewer (Z S).

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 9 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 (P L and L Z); any discrepancy between the two authors was solved by discussion with the senior reviewer (Z S).

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 independent reports.

First, 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 an 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 and 75% respectively (29). We conducted a meta-regression analysis and subgroup analyses to explore sources of heterogeneity. Subgroup analyses were performed according to the 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 (Statacorp). Two-sided *P*<0.05 was considered statistically significant.

Figure 1

Flow diagram of literature search and study selection.

Table 1 Characteristics of eligible studies included in this meta-analysis of parity and type 2 diabetes risk.

Reference	Design and study name	Country	Study period (follow-up years)	Age (years)	No. of participants/controls	No. of type 2 diabetes cases	Exposure assessment	Outcome ascertainment	Comparison categories and corresponding relative risk (95% CI)	Covariates in fully adjusted model	Scale
(14)	CSS Health Community Programs at Biomelab Research Center	Colombia	2004–2007	61.9 ± 10	1795	133	Medical history	Medical history	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)	Age, BMI, FHD, smoking history, breastfeeding, marital status and waist hip ratio	8
(13)	CSS The Tongji-Dongfeng Cohort Study	China	2008–2010	≥45	14 196	2,552	Questionnaire	Self-report of physician diagnosis, anti-diabetic treatment, FPG level	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)	Age, BMI, education, marital status, passive smoking status, smoking status, alcohol drinking status, FHD, physical activity, hypertension, menopause status, ever use of contraceptives, ever use of hormone replacement therapy and abortion	9
(15)	CS The Singapore Chinese Health Study (SCHS)	Singapore	1993–2004 (5.7)	45–74	25 021	1,294	Interview	Self-report of physician diagnosis, validated by hospital-based discharge summary databases and telephone-administered supplementary questionnaire	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)	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	9

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(35)	CS The European Prospective Investigation into Cancer and Nutrition (EPIC)	Germany	1994–2010 (10.7)	35–65	13 612	900	Questionnaire	Self-report confirmed by physicians, or validated by medical records	0, 1.0 (referent) 1–2, 1.11 (0.78–1.58); 3–4, 1.13 (0.75–1.71); ≥5, 1.88 (0.92–3.85) Per parity, 1.06 (0.98–1.14)	Age, BMI, total number of pregnancies/ pregnancy loss, history of hypertension, hyperlipidemia, smoking, alcohol consumption, waist to hip ratio, physical activity, and education	8
(39)	CSS The Dubbo study	Australia	1988–1989	≥60	1571	117	Questionnaire	Previous diagnosis, use of diabetes medications, FPG level	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)	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	8
(16)	CS	Denmark	1982–2006 (23.9)	27.3 ± 4.74	100 669	2,021	National Birth Register	Danish National Registry of Patients	<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) ≥33 years 1, 1.0 (referent); 2, 0.74 (0.63–0.87); 3, 0.87 (0.73–1.02); ≥4, 1.64 (1.38–1.94)	age, fetal weight (Z-score) and duration of gestation at index pregnancy	8
(17)	CS The Cardiovascular Health Study (CHS)	USA	1989–2007 (16.4)	≥65	2761	215	Interview	Use of diabetes medications, FPG level	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)	Age, race, marital status, income, education, height (in centimeters), alcohol, clinic and smoking	7
(Continued)											

Table 1 (Continued).

Reference	Design and study name	Country	Study period (follow-up years)	Age (years)	No. of participants/controls	No. of type 2 diabetes cases	Exposure assessment	Outcome ascertainment	Comparison categories and corresponding relative risk (95% CI)	Covariates in fully adjusted model	Scale
(40)	CSS The University of California San Diego Filipino Women's Health Study	USA	1995–1999	48–73	152	51	Questionnaire	OGTT, FPG level, diagnosis by physician, use of diabetes medications	1–2, 1.0 (referent); ≥6, 3.40 (1.13–10.2) Per parity, 1.27 (1.09–1.49)	Age, adiponectin concentration, visceral adipose tissue, FHD, hypertension, current estrogen use, and education	7
(36)	CS The Atherosclerosis Risk in Communities (ARIC) Study	USA	1986–1998	45–64	7024	754	Interview	Reported history of physician-diagnosed diabetes, use of diabetes medications, FPG level	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)	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	9
(18)	CSS The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) The Crossroads Undiagnosed Disease Study (CUDS)	Australia	1999–2003	≥25	6782		Questionnaire	OGTT, FPG level	0, 0.76 (0.51–1.14); 1–2, 0.67 (0.49–0.91); 3–4, 0.74 (0.55–0.99); ≥5, 1.0 (referent)	Age, obesity, socioeconomic status, and cluster	8

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(41)	CSS The Sandy Lake Health and Diabetes Project (SLHDP)	Canada	1993–1995	12–79	383	74	Interview	OGTT, FPG level	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)	Age, waist circumference, and oral contra- ceptive use	8
(37)	CSS	India	1965–1985	≥20	2779		Interview	OGTT, FPG level	Per parity, 0.94 (0.83–1.06)	Age, BMI	6
(38)	PCCS The San Luis Valley Diabetes Study	USA	1983–1988	20–74	583	196	Interview	OGTT, FPG level, medical record	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)	Age, BMI, ethnicity, county of residence, and subscapular skin-fold thickness	8
(19)	CS The Nurses’ Health Study	USA	1976–1988 (11.3)	30–55	113 606	2,310	Questionnaire	Supplemen- tary question- naire (classic symptoms, FPG level, random plasma glucose level, use of diabetes medications)	Per parity, 1.04 (0.98–1.11) 0, 1.0 (referent); 1, 1.14 (0.90–1.44); 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)	Age, BMI	7
(42)	CSS	Nauru	1987	40–80	202	99	Interview	OGTT, FPG level	Per parity, 0.97 (0.89–1.05)	Age, obesity and FHD	8
		Mauritius	1987	40–70	1333	267	Interview	OGTT, FPG level	Per parity, 0.99 (0.95–1.04)	Age, obesity and FHD	
		Kiribati	1981	40–81	562	56	Interview	OGTT, FPG level	Per parity, 1.09 (1.00–1.19)	Age, obesity and FHD	
		Fiji (Melane- sians)	1980	40–87	389	48	Interview	OGTT, FPG level	Per parity, 1.04 (0.95–1.13)	Age, obesity, and FHD	
(34)	CSS The Second National Health and Nutrition Examina- tion Survey (NHANES II)	Fiji (Indians) USA	1980 1976–1980	40–95 20–74	247 1874	57 180	Interview Interview	OGTT, FPG level OGTT, FPG level	Per parity, 1.07 (0.97–1.18) 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)	Age, obesity, and FHD Age, BMI, education, and income	9
									Per parity, 1.07 (0.98–1.17)		

(Continued)

Table 1 (Continued).

Reference	Design and study name	Country	Study period (follow-up years)	Age (years)	No. of participants/controls	No. of type 2 diabetes/cases	Exposure assessment	Outcome ascertainment	Comparison categories and corresponding relative risk (95% CI)	Covariates in fully adjusted model	Scale
(12)	CS Rancho Bernardo Heart and Chronic Disease Survey	USA	1984–1987(3)	41–92	1186	146	Interview	Self-report confirmed by OGTT	Per parity, 1.16 (1.04–1.29)	Age, obesity (BMI or waist-hip ratio), and FHD	7

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.

Results

Literature search

Figure 1 shows the flow diagram of the procedure used to identify the relevant studies. We identified 2481 articles from PubMed and 3343 articles from Embase before 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, 32, 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 three 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, one 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, 13, 14, 15, 16, 17, 18, 19, 34, 35, 36, 37, 38, 39, 40, 41, 42) were eligible for this meta-analysis including 7 cohort studies (12, 15, 16, 17, 19, 35, 36), 1 case-control study (38) and 9 cross-sectional studies (13, 14, 18, 34, 37, 39, 40, 41, 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 seven 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), one in South America (14), two in Europe (16, 35), three in Asia (13, 15, 37), two in Oceania (18, 39) and one 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 1186 to 113 606 and the number of type 2 diabetes cases varied from 146 to 2310. For cross-sectional studies, the number of

participants ranged from 152 to 14 196 (51–2552 people were considered as type 2 diabetes). Study-specific quality scores were summarized in [Supplementary Tables 1 and 2](#), see section on [supplementary data](#) given at the end of this article. 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 6–9 points, which suggested high quality of the studies included in the meta-analysis.

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.

Highest vs lowest number of parity

Fifteen reports from 14 studies ([13, 14, 15, 16, 17, 18, 19, 34, 35, 36, 38, 39, 40, 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 vs lowest categories of parity was 1.54 (95% CI: 1.29–1.83). There was moderate heterogeneity among the studies ($I^2=59.3\%$, $P=0.002$) ([Fig. 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 four 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 three articles ([31, 32, 33](#)) that were excluded previously and another five reports ([42](#)) that also provided raw data for the calculation of unadjusted RRs; the pooled RR was 1.78 (95% CI: 1.42–2.23).

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 2 Summary risk estimates of the association between parity number and risk of type 2 diabetes.

	Highest versus lowest						Dose-response analysis (per 1 parity)					
	Summary RR (95% CI)			Summary RR (95% CI)			Summary RR (95% CI)			Summary RR (95% CI)		
	No of reports	Q Statistic	I ² (%)	P _h ^a	P _h ^b	No of reports	No of reports	Q Statistic	I ² (%)	P _h ^a	P _h ^b	No of reports
Overall	15	1.54 (1.29–1.83)	34.39	59.3	0.002		21	156.47	87.2	<0.001		
Subgroup analyses												
Study design												
Prospective studies	7	1.44 (1.12–1.84)	21.41	72.0	0.002		8	96.75	92.8	<0.001	0.183	
Non prospective studies	8	1.72 (1.30–2.29)	12.25	42.9	0.092		13	57.50	79.1	<0.001		
Study location											0.496	
North America	7	1.46 (1.00–2.13)	20.63	70.9	0.002		8	26.66	73.7	<0.001		
Europe	3	1.69 (1.44–1.99)	1.44	0.0	0.487		3	8.73	77.1	0.013		
Asia	2	1.52 (1.29–1.80)	1.17	14.7	0.279		3	43.55	95.4	<0.001		
Oceania	2	1.31 (0.91–1.90)	0.01	0.0	0.940		5	4.21	4.9	0.379		
Publication year											0.075	
≥1995	12	1.62 (1.40–1.89)	18.04	39.0	0.081		11	41.35	75.8	<0.001		
<1995	3	1.00 (0.80–1.24)	1.96	0.0	0.375		10	32.65	72.4	<0.001		
Number of cases											0.719	
≥500	7	1.41 (1.19–1.68)	16.97	64.6	0.009		6	85.28	94.1	<0.001		
<500	8	1.91 (1.27–2.86)	13.71	49.0	0.057		15	61.16	77.1	<0.001		
Number of participants											0.690	
≥10 000	6	1.50 (1.20–1.88)	19.32	74.1	0.002		6	97.08	94.8	<0.001		
<10 000	9	1.61 (1.19–2.18)	14.82	46.0	0.063		15	46.94	70.2	<0.001		
Outcome ascertained by OGTT											0.257	
Yes	5	1.88 (1.20–2.92)	7.78	48.6	0.100		11	41.57	75.9	<0.001		
No	10	1.45 (1.20–1.75)	24.46	63.2	0.004		10	100.28	91.0	<0.001		
Adjustment for confounders or important risk factors ^c											0.134	
BMI												
Yes	10	1.39 (1.16–1.67)	16.93	46.8	0.050		16	79.13	81.0	<0.001		
No	5	1.91 (1.30–2.80)	11.14	64.1	0.025		5	29.04	86.2	<0.001		
FHD											0.597	
Yes	4	1.59 (1.17–2.16)	5.24	42.8	0.155		10	26.86	66.5	0.001		
No	11	1.52 (1.21–1.91)	29.14	65.7	0.001		11	125.77	92.0	<0.001		
Education											0.419	
Yes	7	1.49 (1.30–1.72)	6.45	7.0	0.375		7	11.33	47.1	0.079		
No	8	1.62 (1.17–2.24)	27.82	74.8	<0.001		14	127.49	89.8	<0.001		
Income											0.695	
Yes	4	1.31 (1.04–1.64)	1.74	0.0	0.627		3	2.74	26.9	0.255		
No	11	1.67 (1.33–2.08)	31.50	68.3	<0.001		18	153.74	88.9	<0.001		

^aP value for heterogeneity within each subgroup; ^bP value for heterogeneity between subgroups with meta-regression analysis; ^cFor all the included studies had age in the fully adjusted model, no subgroup analysis for whether adjusted age was conducted.

Dose-response meta-analysis

When assuming a linear relationship, there were 16 studies (12, 13, 14, 15, 16, 17, 19, 34, 35, 36, 37, 38, 39, 40, 41, 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 ($I^2=87.2\%$, $P<0.001$) (Fig. 2B). Eight studies (13, 14, 15, 16, 17, 19, 36, 39) with nine reports were included in the cubic spline model, and a nonlinear association between parity and risk of type 2 diabetes was found (Fig. 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 one child, 1.08 (95% CI: 1.00–1.16) for women with two children, 1.20 (95% CI: 1.12–1.30) for women with three children, 1.32 (95% CI: 1.22–1.42) for women with four children, 1.37 (95% CI: 1.27–1.48) for women with five children, 1.39 (95% CI: 1.26–1.52) for women with six children and 1.39 (95% CI: 1.23–1.57) for women with seven 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, 41, 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, 32, 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 the 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 with 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 was 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 vs lowest categories of parity and was 1.09 (95% CI: 1.02–1.16) per live birth (Fig. 2). Furthermore, when we removed nonprospective 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 four 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 four children, 1.18 (95% CI: 1.07–1.30) for women with five children, 1.22 (95% CI: 1.08–1.34) for women with six children and 1.26 (95% CI: 1.08–1.40) for women with seven 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, 14, 15, 16, 35, 36, 40). Charles *et al.* (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.

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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, 14, 15, 16, 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 with 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, 45).

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 one child (46), as do upward of 90% of women in most lower- and middle-income nations (6). This data suggested that women who did not have any children may suffer from infertility in addition to personal will. Besides, 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 two 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 nondiabetic 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 *et al.* (15) found parity was positively associated with HbA1c levels in women reporting no history of diabetes diagnosis; this result suggested

that even in nondiabetic 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, 57, 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 with 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 is warranted and more potential confounders should be taken into consideration in the study design.

This meta-analysis has several strengths. First, we included seven cohorts, one case-control and nine 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 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.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0321>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

This work was funded by the National Science and Technology Support Program (2012BAI02B02). The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Author contribution statement

P L 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. Z S helped formulate the study, provided advice on meta-analysis methodology and contributed to writing, reviewing or revising the manuscript. L Z helped extract quantitative data from the eligible papers and commented on drafts. M X and Y Z searched the databases and checked them according to the inclusion and exclusion criteria and commented on drafts. W B and Y R provided advice on meta-analysis methodology and contributed to writing, reviewing or revising the manuscript. W Y helped develop search strategies, supervised the study and revised the manuscript. L L 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.

Acknowledgments

The authors thank the investigators, staff and participants of all studies included in our meta-analysis for their contributions.

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Received 8 April 2016

Revised version received 11 June 2016

Accepted 21 June 2016