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Lactation and progression to type 2 diabetes in patients with gestational diabetes mellitus: A systematic review and meta-analysis of cohort studies

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ABSTRACT

Aims/Introduction: To explore the association between lactation and type 2 diabetes incidence in women with prior gestational diabetes.

Materials and Methods: We searched PubMed, Embase and the Cochrane Library for cohort studies published through 12 June 2017 that evaluated the effect of lactation on the development of type 2 diabetes in women with prior gestational diabetes. A random effects model was used to estimate relative risks (RRs) with 95% confidence intervals (CIs).

Results: A total of 13 cohort studies were included in the meta-analysis. The pooled result suggested that compared with no lactation, lactation was significantly associated with a lower risk of type 2 diabetes (RR 0.66, 95% CI 0.48–0.90, I^2 = 72.8%, P < 0.001). This relationship was prominent in a study carried out in the USA (RR 0.66, 95% CI 0.43–0.99), regardless of study design (prospective design RR 0.56, 95% CI 0.41–0.76; retrospective design RR 0.63, 95% CI 0.40–0.99), smaller sample size (RR 0.52, 95% CI 0.30–0.92, P = 0.024) and follow-up duration >1 years (RR 0.75, 95% CI 0.56–1.00), and the study used adjusted data (RR 0.69, 95% CI 0.50–0.94). Finally, by pooling data from three studies, we failed to show that compared with no lactation, long-term lactation (>1 to 3 months postpartum) was associated with the type 2 diabetes risk (RR 0.69, 95% CI 0.41–1.17).

Conclusions: The present meta-analysis showed that lactation was associated with a lower risk of type 2 diabetes in women with prior gestational diabetes. Furthermore, no significant relationship between long-term lactation and type 2 diabetes risk was detected. The impact of long-term lactation and the risk of type 2 diabetes should be verified in further large-scale studies.

INTRODUCTION

Gestational diabetes mellitus (GDM) is the most common pregnancy-related complication[1]. GDM is diabetes that is first diagnosed in the second or third trimester of pregnancy that is not clearly either pre-existing type 1 or type 2 diabetes[2]. GDM occurs annually in 3–5% of all pregnant women in the USA[3]. GDM is associated with substantial rates of adverse maternal outcomes. These outcomes include increases in pre-eclampsia, gestational hypertension and cesarean section in the mother, as well as increases in macrosomia, birth injury, respiratory distress syndrome and hyperbilirubinemia in the infant[4–6].

Soon after delivery, glucose hemostasis returns to non-pregnancy levels. However, women affected by GDM remain at high risk of developing type 2 diabetes mellitus in the future[7]. A meta-analysis of 20 cohort studies found that GDM significantly predisposed women to the development of type 2 diabetes mellitus[3]. There was an almost linear increase in the cumulative incidence of type 2 diabetes mellitus during the first 10 years post-delivery[8]. Several risk factors contribute to the development of type 2 diabetes mellitus in patients with prior GDM, including body mass index, family history of diabetes,

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non-white ethnicity, advanced maternal age, multiparity, hypertension and preterm delivery[7,9].

It has been suggested that breast-feeding might have protective effects against the development of type 2 diabetes mellitus[10]. The importance of breast-feeding has long been recognized for mothers and their children, irrespective of their geographical location or economic status[11]. Breast-feeding has various health benefits[12]–it might protect children from infectious diseases and type 2 diabetes mellitus, and positively impact their intelligence. In mothers, lactation is associated with a reduced risk of obesity and breast cancer[11,13].

However, mothers with GDM are less likely to partly or exclusively breast-feed[14]. Lactation for mothers with GDM is often delayed as a result of pregnancy-related complications and increased neonatal morbidity[14]. Even if mothers with GDM do initiate breast-feeding, lactation typically lasts a shorter duration than in women without GDM[15]. It remains unclear whether lactation in mothers with GDM could affect the progression of future type 2 diabetes mellitus risk. Current evidence suggests conflicting results. Several studies have advocated breast-feeding[10,16], whereas others have failed to show the positive role of lactation[17,18]. Furthermore, the duration and intensity of lactation varied among previous studies. Therefore, we carried out the present systematic review and meta-analysis to investigate the association between lactation and development of type 2 diabetes mellitus in women with prior GDM.

METHODS

All analyses were based on previous published studies, therefore, ethical approval and patient consent were not required.

Data sources, search strategy and study selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines when carrying out this meta-analysis[19]. We carried out a systematic literature search of studies published in the English language that investigated the association between lactation and type 2 diabetes mellitus in GDM patients. The literature was searched in the PubMed, Embase and the Cochrane Library databases from inception to 12 June 2017. We used the following keywords and medical terms: ('lactation' OR 'breastfeeding' OR 'breast-feeding') AND ('gestational' OR 'maternal' OR 'pregnant' OR 'pregnancy') AND ('glucose intolerance' OR 'type 2 diabetes mellitus' OR 'hyperglycemia'). We also manually searched the bibliographies of key articles in this field and those cited by critical reviews.

Two authors (Lijun Feng and Qunli Xu) independently screened the titles and abstracts of the search results, and selected studies of relevant topics. Any disagreement was resolved by discussion with a third author (Hongying Pan). We included studies that fulfilled the following criteria: (i) prospective or retrospective cohort studies on women with prior GDM; (ii) exploration of the association between lactation and the outcomes of type 2 diabetes mellitus; and (iii) studies in which participants developed type 2 diabetes mellitus at least 6 weeks after delivery; in these cases, type 2 diabetes mellitus diagnosis was established based on the results of an oral glucose tolerance test or fasting plasma glucose concentration.

Data extraction and quality assessment

Two authors independently reviewed eligible studies and extracted the following information for a standardized electronic data form: author, publication year, country, study design, sample size, mean or median age, incidence of type 2 diabetes mellitus, diagnostic criteria of GDM and type 2 diabetes mellitus, studied population, lactation duration, comparison groups, stratified subgroups, comparisons, and follow-up duration. The quality of included studies was appraised using the Newcastle–Ottawa Scale (NOS) for cohort studies[20]. This scale included three items: (i) selection of study group; (ii) comparability of study groups; and (iii) ascertainment of the outcome of interest. A star rating of 0–9 was allocated to each study based on these aspects. We assigned scores of 0–3, 4–6 and 7–9 for low-, moderate- and high-quality of studies, respectively. The data extraction and quality assessment were carried out independently by two authors. Information was examined and adjudicated independently by an additional author referring to the original studies.

Statistical analysis

We examined the relationship between lactation and risk of type 2 diabetes mellitus on the basis of the effect estimate and its 95% confidence interval (CI) published in each study. Relative risks (RRs) were expressed with its 95% CIs and were either extracted directly or calculated indirectly[21,22]. Heterogeneity between studies was investigated by using the Q statistic, and we considered P-values <0.10 as indicative of significant heterogeneity[23,24]. Meta-regression analysis was carried out to determine whether study-level covariates potentially accounted for the heterogeneity. The influence of individual studies was also investigated using the leave-one-out cross-validation method to test the robustness of the primary outcomes[25]. Subgroup analyses were carried out based on the following variables: study setting (USA or non-USA), study size (<500 participants or ≥500 participants), study design (prospective or retrospective), follow-up duration (<1 years vs ≥1 year), adjusted (adjusted RR vs non-adjusted RR) and calculated (calculated RR vs extracted RR). Publication bias was evaluated using a funnel plot. We also used the Egger[26] and Begg's[27] tests to examine funnel plot asymmetry. Statistical significance was based on a P-value <0.05 in all analyses. Statistical analyses were carried out using STATA software (version 10.0; Stata Corporation, College Station, TX, USA) and R software (version 3.3.3; Lucent Technologies, Murray Hill, NJ, USA).

RESULTS

The search strategy yielded 648 records, including 360 studies from PubMed, 260 from Embase and 28 from the Cochrane Library database. After excluding 124 duplicates, 524 studies

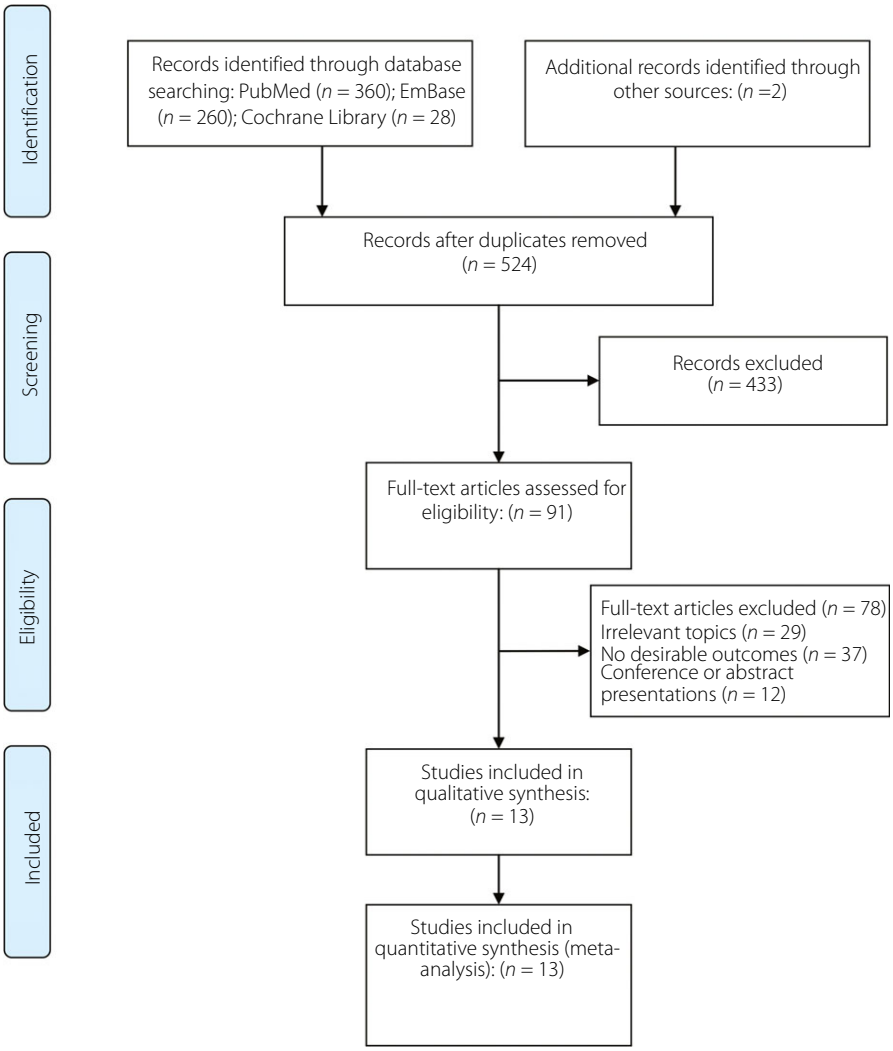

Figure 1 | Flow diagram showing the study selection process. [Colour figure can be viewed at wileyonlinelibrary.com]

were assessed for eligibility. Furthermore, an additional two records were identified, but the data from these abstracts were not used for analysis[28,29]. We further excluded irrelevant studies and those without sufficient data; 13 studies were included in the meta-analysis[10,16,17,30–39]. A flow diagram of the study selection process is shown in Figure 1. The characteristics of the included studies are summarized in Table 1. Six studies were prospective cohort studies, and seven were retrospective cohort studies. Six studies were carried out in the USA, and the rest in Ireland, Korea, Germany, Belgium and Australia. Sample sizes ranged from 91 to 116,671 participants. The average maternal age of women with GDM was approximately 30 years in most studies. The diagnostic criteria for GDM included National Diabetes Data Group, American Diabetes Association, World Health Organization, third GDM workshop conference, Carpenter–Coustan Criteria and countrywide criteria. Type 2 diabetes mellitus was diagnosed according to the American Diabetes Association, National Diabetes Data Group, World Health Organization or countrywide guidelines[3]. The duration of lactation was only considered in four studies. The follow-up period varied from approximately 3 months to >10 years. The average score was 6.7, and the score for each study was ≥5, suggesting that all the studies were of moderate or high quality (Table S1).

Effect of lactation versus no lactation on the development of type 2 diabetes mellitus

Nine studies showed a correlation between lactation and type 2 diabetes mellitus development. Capula *et al.*[35] showed crude data for RR, whereas other studies reported four-layer table data to calculate RR. The study authored by Stuebe *et al.*[16] included five subgroups of participants with different lactation duration. Gunderson *et al.*[36] presented three subgroups of participants with different lactation intensities. The data from these subgroups were pooled using the fixed-effects model in each study. Ziegler *et al.*[10] focused on breast-feeding for >3 months

Table 1 | Characteristics of included studies

Author (year)	Region	Design	No. patients	Age (years)	T2DM occurrence	GDM criteria	T2DM or IGT criteria	Population showing data	Lactation duration	Subgroups	Comparison	Follow-up duration
Kjos *et al.* (1993)[30]	USA	Prospective cohort	809	31	Event rate: 7%	NDDG	NDDG	GDM	4–12 weeks	Insulin therapy	BF vs no BF	3 months
Kjos *et al.* (1998)[17]	USA	Retrospective cohort	904	30	Event rate: 19%	NDDG	NDDG	GDM women using non-hormonal contraception	NA	None	BF vs no BF	7.5 years
Buchanan *et al.* (1998)[31]	USA	Prospective cohort	91	30	Event rate: 15%	Third GDM workshop conference	WHO	T2DM not within 6 months postpartum	NA	None	BF vs no BF	11–26 months
Stuebe *et al.* (2005)[16]	USA	Retrospective cohort	116,671	35	IR: 6.24 per 1000 person-years	Questionnaire	NDDG	GDM	NA	BF duration	BF vs no BF	12 years
Nelson *et al.* (2008)[32]	USA	Retrospective cohort	572	32	Event rate: 14%	Medical record	ADA	GDM followed at 1 year	NA	None	BF vs no BF	1 year
Kim *et al.* (2011)[33]	Korea	Prospective cohort	381	34	Event rate: 5.2%	Carpenter–Coustan	ADA	GDM	≈2 months	None	BF vs no BF	6–12 weeks
O'Reilly *et al.* (2011)[34]	Ireland	Retrospective cohort	564	33	Event rate: 3%	WHO or IADPSG	ADA	GDM	NA	Europeans	BF vs no BF	3 months
Ziegler *et al.* (2012)[10]	Germany	Prospective cohort	304	Median: 31	CR: 63.6% (95% CI 55.8–71.4)	Germany Diabetes Association	ADA	IAA (–) GDM (89.5%)	IAA (–) Median: 9 weeks	GDM treatment, BMI	BF >3 months vs. BF ≤3 months or no BF	19 years
Capula *et al.* (2014)[35]	Italian	Retrospective cohort	454	Median: 35	Event rate: 4%	Carpenter–Coustan or IADPSG	ADA	GDM	NA	None	BF vs no BF	6–12 weeks
Gunderson *et al.* (2015)[36]	USA	Prospective cohort	1035	Mean: 33	IR: 5.64 (95% CI 4.60–6.68) per 1000 person-months	ADA	ADA	GDM	80% >2 months	BF duration, BF intensity	BF > 2 months vs BF ≤2 months; BF vs no BF	Median: 1.8 years
Moon *et al.* (2015)[37]	Korea	Prospective cohort	418	32	Event rate: 12.7%	Third GDM workshop conference	ADA	GDM	NA	None	BF vs no BF	Median: 4 years
Chamberlain *et al.* (2016)[38]	Australia	Retrospective cohort	483	NA	CR: 18.3% (12.6–26.3%) for indigenous; CR: 6.4% (3.4–11.7%) for non-indigenous	Australian Diabetes (pregnancy guidelines)	Australian guidelines	GDM	NA	Indigenous Australians	Fully BF vs partial BF vs no BF	7 years
Benhalima (2016)[39]	Belgium	Retrospective cohort	191	32	Event rate: 5.9%	WHO	ADA	GDM	NA	None	BF vs no BF	12 weeks

ADA, American Diabetes Association; BMI, body mass index; BF, breast-feeding; CR, cumulative risk; GDM, gestational diabetes mellitus; IAA, islet autoantibody; IADPSG, International Association of Diabetic Pregnancy Study Group; ICA, islet cell antibody; IGT, impaired glucose tolerance; IR, incidence rate; NDDG, National Diabetes Data Group; NA, not available; T2DM, type 2 diabetes mellitus; USA, the United States of America; WHO, World Health Organization.

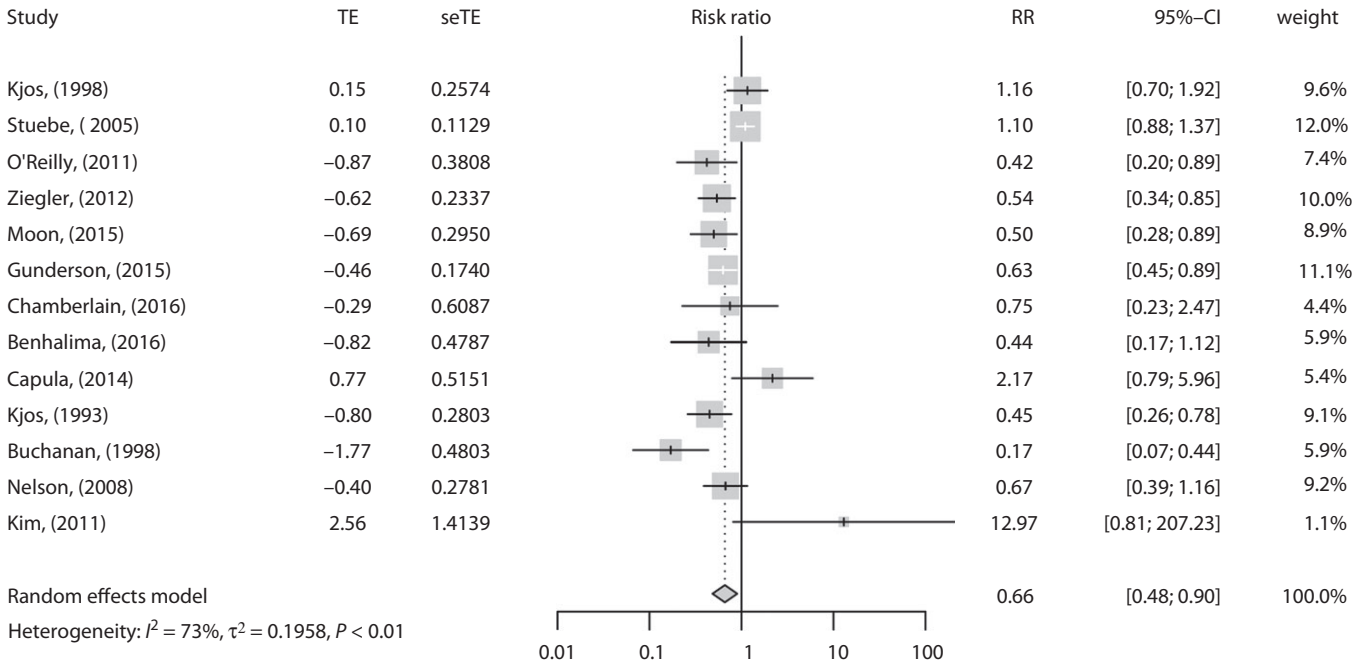

Figure 2 | Forest plot of studies showing the relative risk (RR) for the association between lactation and type 2 diabetes mellitus risk. CI, confidence interval; seTE, standard error of the log risk ratio; TE, transformation of relative risk.

and compared it with insufficient breast-feeding (no lactation or breastfeeding for ≤3 months). Chamberlain *et al.*[38] compared the effects of exclusive lactation with no lactation. The pooled data showed that compared with no lactation, lactation was associated with a lower risk of type 2 diabetes mellitus in women with prior GDM (RR 0.66, 95% CI 0.48–0.90; Figure 2). A large amount of heterogeneity was revealed (I^2 = 72.8%, P < 0.001). In sensitivity analysis, the overall effect was a non-significant change with mutual exclusion of the studies (Figure 3). The heterogeneity could be decreased by omitting Stuebe *et al.*[16] in the new analysis (RR 0.61, 95% CI 0.45–0.83, I^2 = 60.2%; Figure 3).

To investigate the effects of various study characteristics on the pooled RR, subgroup analysis and meta-regression were carried out by subgroups. In subgroup analyses, the overall effect was non-significant for studies that were not carried out in the USA (P = 0.085), had a sample size >500 (P = 0.122), had a follow-up duration <1 year (P = 0.154), data were not adjusted (P = 0.416) or regardless of calculated RR (Table 2). No statistical significances were identified in the overall effects for various subgroups by univariate and multivariate meta-regression analyses. Detailed data are shown in Table 2. The funnel plot was symmetrical (Figure 4). No publication bias was shown by the Egger's test (P = 0.320) or the Begg's test (P = 1.000).

Effect of long-term lactation versus no lactation on the outcome of type 2 diabetes mellitus

Just three studies specifically investigated the impacts of lactation duration[10,16,36]. Stuebe *et al.*[16] compared lactation lasting 3 months with formula feeding. Gunderson *et al.*[36] compared lactation lasting 3 months with breast-feeding lasting <3 months. Ziegler *et al.*[10] compared lactation lasting 3 months with breast-feeding lasting <3 months or formula feeding. The pooled data showed that compared with no lactation, long-term lactation (>1–3 months postpartum) was not associated with the risk of type 2 diabetes mellitus (RR 0.69, 95% CI 0.41–1.17, I^2 = 84.4%, P < 0.050). However, when excluding the study by Stuebe *et al.*, the pooled result became significant (RR 0.53, 95% CI 0.40–0.72, I^2 = 0, P = 0.950).

DISCUSSION

In the present meta-analysis, a significant correlation between lactation and the reduction of type 2 diabetes mellitus risk was detected (RR 0.66, P = 0.008), this association was stable in sensitivity analysis. The exclusion of 13 studies, one-by-one, unanimously, resulted in an overall marginally significant result. By pooling six prospective studies, the impact of lactation was markedly significant (RR 0.56; 95% CI 0.41–0.76). Furthermore, the impact of lactation remained significant for multiple subgroups. No publication bias was detected in our analyses. We failed to identify a significant protective role of long-term lactation on type 2 diabetes mellitus risk (OR 0.69, P = 0.170). However, the result was limited, as just three studies were included.

The mechanism underlying the preventive role of lactation against type 2 diabetes mellitus remains unclear. Lactation has high energy demands, which might lead to alterations in the metabolic process, including changes in glucose metabolism,

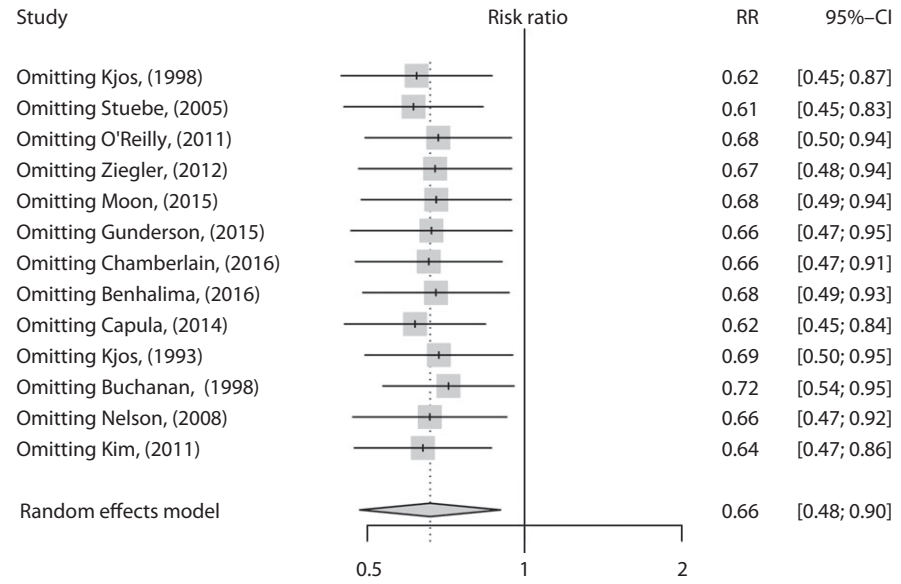

Figure 3 | The finding of sensitivity analysis. CI, confidence interval; RR, relative risk.

Table 2 | Subgroup analysis and meta-regression for studies showing the association between lactation and type 2 diabetes mellitus risk in women with prior gestational diabetes mellitus

Subgroups	*n*	RR (95% CI)	*P*-value	I^2 (*P*-value)	*P* for subgroup	Meta-regression	
						Univariate	Multivariate
Total	13	0.66 (0.48–0.90)	0.008	72.8% (<0.001)			
Region					0.971	0.930	0.828
USA	6	0.66 (0.43–0.99)	0.047	81.3% (<0.001)			
Non-USA	7	0.66 (0.42–1.06)	0.085	53.7% (0.04)			
Design					0.389	0.579	0.144
Prospective	5	0.56 (0.41-0.76)	<0.001	35.2% (0.187)			
Retrospective	8	0.63 (0.40-0.99)	0.044	73.6% (<0.001)			
Sample size					0.279	0.327	0.408
<500	6	0.52 (0.30–0.92)	0.024	58.1% (0.036)			
≥500	7	0.75 (0.53–1.08)	0.122	76.2% (<0.001)			
Follow up					0.546	0.392	0.197
<1 year	6	0.59 (0.28–1.22)	0.154	73.5% (0.002)			
≥1 year	7	0.75 (0.56–1.00)	0.050	65.5% (0.008)			
Adjusted					0.949	0.895	0.155
Yes	8	0.69 (0.50–0.94)	0.018	67.7% (0.003)			
No	5	0.71 (0.31–1.63)	0.416	79.0% (0.001)			
Calculate RR					0.413	0.321	0.196
Yes	4	051 (0.22–1.16)	0.108	74.1% (0.009)			
No	9	0.74 (0.54–1.01)	0.057	68.3% (0.001)			

CI, confidence interval; GDM, gestational diabetes mellitus; RR, relative risk; T2DM, type 2 diabetes mellitus.

increased lipolysis and increased energy expenditure[40]. A series of experimental studies showed that lactation might increase insulin sensitivity and lower insulin levels[41,42]. A previous study carried out in a rat model showed a 12-fold increase in insulin uptake by the mammary glands of lactating rats, as well as a significant decrease in the half-life of insulin in the plasma[43]. Lactating women have physiologically elevated prolactin, which is positively correlated with lower mean fasting glucose and insulin levels 8 weeks after delivery[44]. Current research evidence calls for exclusive breast-feeding during the first 6 months of an infant's life[11]. Lactation has multiple benefits, including protective effects against gynecological cancers in mothers, and

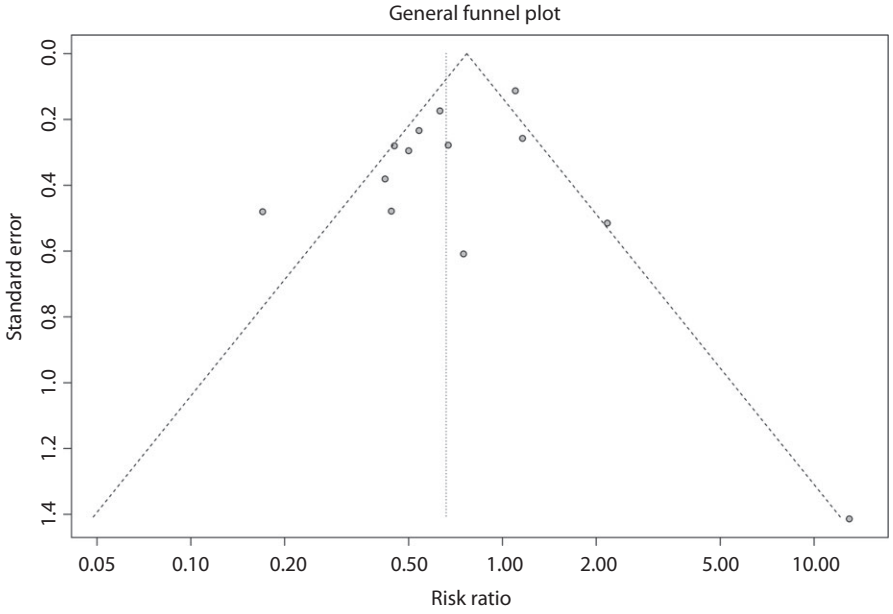

Figure 4 | Funnel plot of included studies.

infection and obesity in children[11]. As for diabetic outcomes, aside from our finding that lactation prevents subsequent type 2 diabetes mellitus in women with prior GDM, breast-feeding might also help reduce the risk of future type 2 diabetes mellitus in children[45]. Breastfeeding is a convenient and low-cost method of improving postpartum health. However, many studies that analyzed the risk factors for progression of GDM to type 2 diabetes mellitus overlooked the mother's lactation status[46–49]. Mothers with prior GDM were less likely to breast-feed their children than mothers without diabetes[14]. Lactation might be more difficult to initiate for these mothers because of neonatal morbidity and concerns regarding fluctuating blood glucose concentrations[50]. Notably, several studies have proven that racial, educational and socioeconomic status were important predictors of lactation initiation among women with GDM[51,52].

Several relevant systematic reviews or meta-analyses exploring the association between breast-feeding and risk of type 2 diabetes mellitus in mothers have already been published. Taylor *et al.*[53] systematically reviewed the evidence about the association between breast-feeding and maternal type 2 diabetes mellitus, published before 2005. No data analysis was carried out. Rayanagoudar *et al.*[9] recently summarized and analyzed the risk factors for type 2 diabetes mellitus progression in women with GDM. They analyzed data from four studies and showed no association between lactation and type 2 diabetes mellitus risk. The role of lactation was only briefly mentioned among various other factors and was not explored in depth. The authors also acknowledged that their result might be imprecise, owing to the small number of studies and individuals[9]. Very recently, a meta-analysis by Tanase-Nakao *et al.*[54] was published. A total of 14 reports of nine research groups were included in the qualitative synthesis–the authors concluded that lactation lasting >4–12 weeks postpartum is associated with a reduction in the risk of type 2 diabetes mellitus compared with shorter lactation. Exclusive lactation lasting >6–9 weeks postpartum was also associated with a lower risk of type 2 diabetes mellitus compared with exclusive formula feeding. Breast-feeding practices were reported to be influenced by multiple factors, such as obesity[55]. In comparison, the present meta-analysis was primarily focused on exploring the association between lactation and type 2 diabetes mellitus, and included the most comprehensive relevant studies. Adjusted data were analyzed, with heterogeneity evaluated using subgroup, sensitivity and meta-regression analyses.

The study had several limitations. The risk of bias assessment was carried out using the NOS. However, according to the recommendations from the study by Lo *et al.*[56], we contacted the authors for information not published in the studies when applying the NOS in systematic reviews. However, only one of the authors responded, consequently, NOS assessment could not be carried out. The present findings are limited by the small number of included studies and the presence of significant heterogeneity. Several studies were retrospective case series, which might cause recall or selection bias. Furthermore, several studies did not discriminate total lactation from mixed lactation–formula feeding, which might weaken the association between lactation and diabetes risk. Although a significant association was shown when analyzing adjusted data, it is possible that residual confounding by factors not included in the adjusted model still occurred. Many studies did not show the important confounders for overall analysis, these potential

confounders include medication and lifestyle factors that might accompany breast-feeding, such as insulin therapy during pregnancy, contraception prescription after delivery, dietary habits and physical activity. The results of stratified analyses based on these factors were not provided, which restricted us from carrying out more detailed analysis to explore the source of heterogeneity. The discrepancy between crude and adjusted data reflected the crucial role of confounding factors. Notably, the diagnostic criteria varied among different regions. However, most criteria used the oral glucose tolerance test as the main screening test. The follow-up duration varied between included studies, and several studies only followed patients for a few months. The duration of lactation also varied greatly between included studies. No sufficient data were available to show the dose–response curve between lactation duration and type 2 diabetes mellitus risk.

In conclusion, based on the present systematic review and meta-analysis, lactation might protect against the future risk of type 2 diabetes mellitus in women with prior GDM. Future studies are warranted to explain the mechanism behind the association between lactation and maternal glucose metabolism. More prospective cohort studies are also required to determine the causality.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Newcastle–Ottawa scale for quality assessment of included studies.