

REVIEW ARTICLE

Metabolic effects of breastfeed in women with prior gestational diabetes mellitus: A systematic review and meta-analysis

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Summary

This study was undertaken to provide comprehensive analyses of current research developments in the field of breastfeed (BF) and metabolic-related outcomes among women with prior gestational diabetes mellitus (GDM). Database PubMed, Embase, BIOSIS Previews, Web of Science, and Cochrane Library were searched through December 3, 2017. Odds ratio (OR) and weighted mean difference (WMD) with 95% confidence interval (CI) were pooled by random-effects model using Stata version 12.0. Twenty-three observational studies were included in quantitative synthesis. Reduced possibility of progression to type 2 diabetes mellitus (T2DM; OR = 0.79; 95% CI, 0.68-0.92) and pre-DM (OR = 0.66; 95% CI, 0.51-0.86) were found among women with longer BF of any intensity after GDM pregnancy. The positive effect of longer BF on progression to T2DM gradually became prominent with the extension of follow-up period. Compared with women with shorter BF, those with longer BF manifested more favourable metabolic parameters, including significant lower body mass index, fasting glucose, triglyceride, and higher insulin sensitivity index. The findings support that BF may play an important role in protection against the development of T2DM-related outcomes in midlife of women with prior GDM. However, further studies are needed to reveal the etiological mechanism.

KEYWORDS

breastfeed, diabetes mellitus, gestational diabetes mellitus, meta-analysis

1 | INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with first onset during pregnancy.¹ It occurs in 9.8% to 25.5% of pregnancies, and the prevalence tends to increase annually.² Although hyperglycaemia usually normalizes soon after delivery, women with prior GDM have an increased risk for postpartum abnormalities in insulin secretion/action.³ Up to half of these women progress to develop type 2 diabetes mellitus (T2DM) in their later life, with

the highest occurrence rate in the first 5 years post partum.⁴ Accordingly, women with prior GDM are recognized to be at high risk of developing T2DM at younger ages and are a major target population for preventive measures.

In light of the immediate nutritional and immunological benefits, as well as the long-term favourable metabolic effects, breastfeed (BF) is recommended for women as a modifiable postpartum behaviour.⁵⁻⁷ The American Academy of Paediatrics recommends exclusive BF for about 6 months, followed by continued BF with complementary foods

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for 1 year or longer.⁸ However, only few GDM guidelines recommend BF for maternal health with minimal evidence.⁹⁻¹¹ Potential beneficial effects of BF in women with previous GDM have been discussed in several reviews,^{7,12-14} which are limited to the brief summary and presentation, and quantitative analyses are incomplete and insufficient.¹⁴ Thus, we think it is necessary to embark this systematic review and meta-analysis with comprehensive analyses of current research developments in the field of BF and metabolic-related outcomes.

2 | METHODS

This systematic review adheres to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.¹⁵ The MOOSE checklist for our study is shown in Table S1.

2.1 | Data sources and searches

Literature search was performed using databases PubMed, Web of Science, Cochrane Library, Embase, and BIOSIS Previews, available through December 3, 2017, without any restrictions. To include more potential literature, only terms for BF and GDM were designed in the overall search strategy, and the strategies in all the databases were similar. Details of the literature search in PubMed is shown as follow: (((("Breast Feeding"[Mesh]) OR "Lactation"[Mesh])) AND ((((((gestational diabetes) OR GDM) OR gestational diabetic) OR diabetic pregnancy)) OR "Diabetes, Gestational"[Mesh])). There was no language restriction. Bibliographies of selected original studies, reviews, and conference proceedings were screened for additional studies. Corresponding authors were selected to contact for incomplete data.

2.2 | Study selection

Observational studies (cohort and cross-sectional studies) were included if they (a) evaluated and defined exposure to BF in women with prior GDM, with effective comparison groups, (b) reported the incidence or status of T2DM, glucose intolerance, impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or other metabolic outcomes, or results of metabolic parameters, and (c) reported odds ratio (OR) /relative risk (RR) /hazard ratio (HR) with corresponding 95% confidence interval (CI) for binary variable, and reported sample size, mean, standard deviation for continuous variable, or provided sufficient data for their estimations. All the citations were merged in Endnote X7 to facilitate management. After eliminating duplicate literatures, two reviewers independently applied the inclusion criteria to all retrieved articles with titles, abstracts, and full texts, in an unblinded standardized manner.

2.3 | Data extraction and quality assessment

Data on characteristics of study (first author, publication year, location, study design), population (study population, testing for GDM, major exclusion criteria), exposure (BF measure, comparison group, follow-up), and outcome (sample size, mean, standard deviation, risk estimate, 95% CI, diagnostic criteria, adjusted factors, conclusion) were extracted

onto a piloted structured form independently by two reviewers. When there were multiple publications from the same study or population, the most comprehensive report would be given a priority, while the others might be included in subgroup analyses as supplementary. Results with longer follow-up period was given precedence in the overall analysis, if there were multiple follow up nodes in the same study. Discrepancies were resolved through consensus in consultation with a third reviewer, referring back to the original articles.

Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) was used to assess the quality of included studies.¹⁶ In this scale, studies were evaluated across six domains: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting. Low, high, or unclear risk of bias were evaluated separately for each domain.

2.4 | Data synthesis and analysis

For dichotomous risk factors, comparisons were conducted between women with longer and shorter BF (relative BF length in each included study, BF was measured at discharge or 4-14 weeks post partum) of any intensity after GDM pregnancy, and meta-analysis was performed using DerSimonian-Laird random-effects model to estimate pooled ORs and 95% CIs incorporating within- and between-study heterogeneity. For continuous metabolic parameters, all the units had been harmonized by data conversion prior to analysis, weighted mean difference (WMD) with 95% CIs were pooled using random-effects models to assess the differences between women with longer and shorter BF (measured at 4 weeks to 12 months post partum) of any intensity after GDM pregnancy. Adjusted estimate was preferred in the analysis process. Heterogeneity was quantified by estimated I^2 statistic, with values larger than 50% indicating substantial heterogeneity.

Subgroup analyses were stratified by study design, length of follow-up (1-6 months, 1-5 years, >5 years), and intensity of BF (fully, mixed, none). Multiple sensitivity analyses were performed to assess the robustness of the findings, which were based on (a) limiting the distinction point of BF measure to 4 to 14 weeks, (b) use of leave-one-out method to evaluate whether any single study dominated the findings, (c) use of an Inverse Variance fixed-effects model when I^2 lower than 50%, and (d) use of standardized mean difference (SMD) for the analyses of continuous metabolic parameters to increase the generalizability.¹⁷ All these statistical meta-analyses were two-sided, with the level of statistical significance setting at $P < 0.05$. Publication bias was assessed using Begg test and Egger test for analyses enrolling more than 10 studies, with $P \leq 0.1$ suggesting publication bias.^{18,19} All the statistical analyses were performed using Stata version 12.0 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Study identification

Study selection is shown in Figure 1. From a total of 1862 citations identified through the search strategy, 1081 abstracts and 209

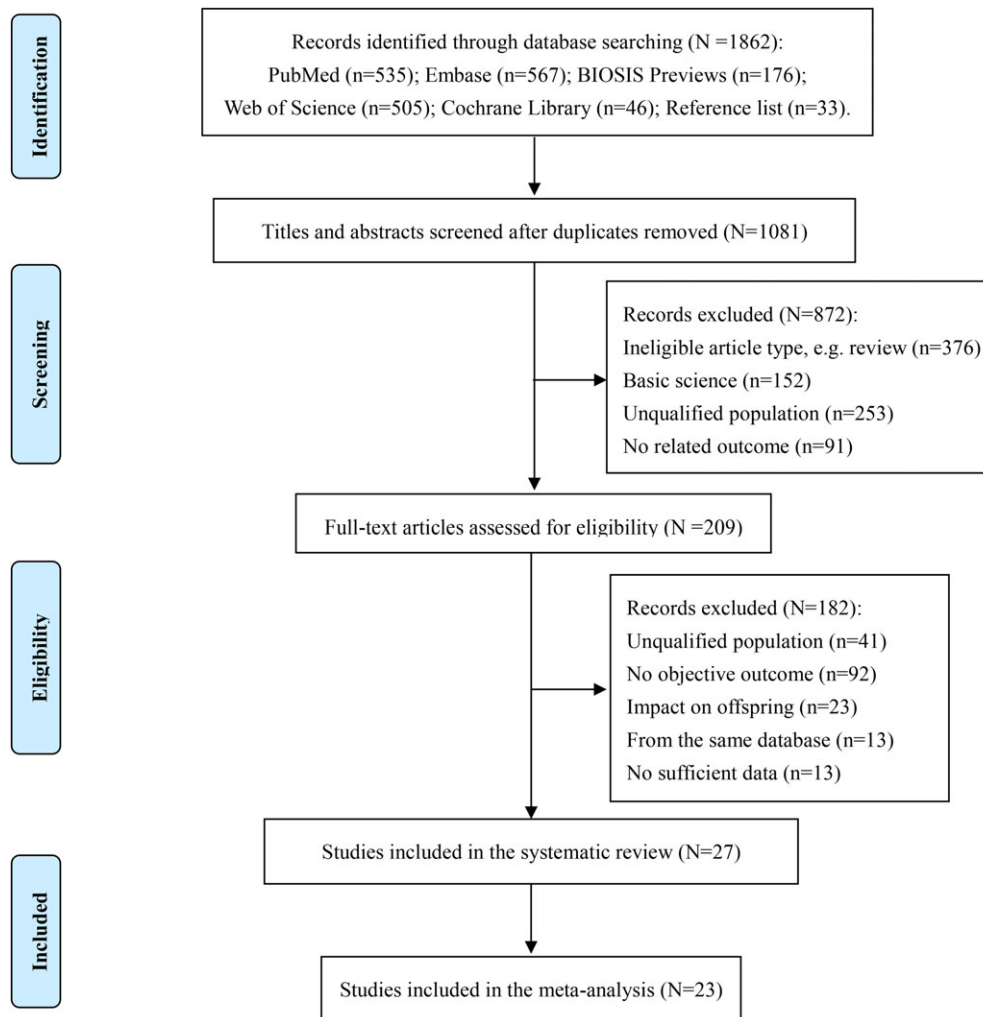


FIGURE 1 PRISMA flow diagram of study selection

resulting full-text studies were reviewed to determine their eligibility. Finally, 27 studies²⁰⁻⁴⁶ were included in this systematic review, 23 of which, involving more than 11 000 women with prior GDM, were further included in the meta-analysis. The remaining four studies were not included for the following reasons: effect size was unavailable,²² individual definition of BF (BF during the 2-hour 75 g oral glucose tolerance test at 6-9 weeks),³⁶ reported outcome was interesting but individual, which was not enough to be merged.^{38,42}

3.2 | Characteristics and quality of included studies

Characteristics of included studies are shown in Table 1. All the included women had a history of GDM, while the diagnostic criteria were various, involving the International Association of Diabetes and Pregnancy Study Group criteria,^{20,21,27,31} the American Diabetes Association criteria,^{28,41} the World Health Organization criteria,²⁵ Carpenter-Coustan criteria,^{26,29-31,33,37} the National Diabetes Data Group criteria,^{43,45} and some local criteria.^{24,35,44,46} Two kinds of BF measure (status, intensity) were used to describe and group the exposure in each study, with different distinction points, ranged from BF

initiation to 12 months. The duration of follow-up varied from 6 weeks to 24 years post partum, which was divided into three periods (1-6 months, 1-5 years, >5 years) during the subgroup analyses. A total of 21 studies^{20,21,23-29,31-33,35,37,39-41,43-46} evaluated the risk of developing T2DM or pre-DM (IGT and/or IFG), and 10^{20,21,26-30,34,41,45} reported the results of detailed metabolic parameters, including body mass index (BMI), fasting glucose, 2-hour post load glucose, fasting insulin, homeostasis model of assessment of insulin resistance (HOMA-IR), insulin sensitivity index (ISI), triglyceride, and cholesterol in women with prior GDM.

Quality assessments using RoBANS are summarized in Table S2. A total of 12 studies^{23,26,27,30-32,34,35,37,43-45} with diabetes-free at baseline had a low risk of selection bias caused by selection of participants. Meanwhile, seven studies^{20,23-25,35,40,43} had a low risk of confounding bias caused by confounding variables, due to the adequate adjustment for covariates. Performance bias indicating measurement of BF were judged to be "high" in 10 studies^{25,31,33-35,37,39,40,44,46} with self-administered questionnaire or without definition, and "unclear" for seven studies.^{21,28,29,32,41,43,45} Since the selected outcomes could not be influenced by the blinding of assessment, all the studies had a low risk of detection bias. Majority of studies had

TABLE 1 Characteristics of studies included in the systematic review and meta-analysis

First Author, Year, Country, Reference	Design; Study Name	Study Population and Testing for GDM	Major Exclusion Criteria	BF Measure and Comparison Group	Follow-up Time Point (Postpartum)	Outcomes Studied (Diagnostic Criteria)	Adjusted Factors	Conclusions
Yasui 2017, Japan ²⁰	Cross-sectional study	88 women with GDM history (Japanese criteria or IADPSG criteria) from Jan 2009 to Dec 2011.	Without any postpartum OGTT during the first year post partum.	Status (at 6-8 wk post partum) - 70 BF (BF > 80% of volume) - 18 no BF Status (at 12-14 mo post partum) - 35 BF - 42 no BF	6-8 wk; 12-14 mo.	Abnormal glucose tolerance (WHO criteria), BMI, fast plasma glucose, fasting insulin, HOMA-IR, disposition index.	Age, pre-pregnancy BMI, family history of T2DM, 2-h plasma glucose at diagnostic OGTT during pregnancy, diagnostic criteria, weight gain during pregnancy and weight change during post partum.	High-intensity BF for at least 6 mo had a significant effect in reducing insulin resistance and the risk of abnormal glucose tolerance during the first year post partum (all $P < 0.05$).
Corrado 2017, Italy ²¹	Cohort study	155 women diagnosed with GDM (IADPSG criteria) from Jan to Dec 2015.	Without postpartum OGTT.	Status (at 12-16 wk post partum) - 81 BF - 16 no BF	12-16 wk	OGTT, HOMA-IR, cholesterol, triglycerides, IFG/IGT (ADA criteria).	Fast glycaemia, HOMA-IR, total cholesterol and triglycerides.	HOMA-IR shows a significant association with BF (OR = 0.370; 95% CI, 0.170-0.805; $P < 0.01$) after the adjustment for confounders.
▽ Much 2016, Germany ²²	Cohort study; PINGUIN and POGO	197 women with a documented diagnosis of GDM (2000 ADA criteria from 2008 to 2013) during their most recent pregnancy.	Preexisting T2DM or diabetic glucose tolerance, positive islet-autoantibody, had not yet terminated BF at enrolment.	Status (at 3 mo post partum) - 135 BF - 62 no BF	0.7 (0.4-0.7) y; 6.0 (4.1-8.5) y.	ISI, HOMA-IR.	BMI at the postpartum study visit, age, time since delivery and educational level.	BF for >3 mo was significantly associated with a higher total lysophosphatidylcholine/phosphatidylcholine ratio at 30 and 120 min during an OGTT within 3.6 y post partum, with lower leucine and lower total BCAA concentrations at 30 min within 0.7 y post partum, but not associated with ISI or HOMA-IR.
Martens 2016, Canada ²³	Cohort study	4104 women living in Manitoba who had a live birth from Apr 1987 to Mar 2011, with a diagnosis of GDM.	A diagnosis of pre-pregnancy T2DM, GDM or incident T2DM within the first 20 wk of gestation.	Status (BF initiation before hospital discharge) - BF initiation - no BF initiation	24 y	T2DM (ICD 10th revision, Canada codes before Apr 1, 2004; ICD 9th revision after Apr 1, 2004)	Age at birth of child, parity, income quintile, year of delivery.	BF initiation had an inverse association with postpartum T2DM among first nations and non-mothers with or without GDM (all $P < 0.05$).
Chamberlain 2016, Australia ²⁴	Cohort study	289 women coded as having GDM	No postpartum screening tests	Intensity (at discharge)	8 y	T2DM (modified in consultation with	BMI, primary antenatal care	An increased rate of T2DM progression (Continues)

TABLE 1 (Continued)

First Author, Year, Country, Reference	Design; Study Name	Study Population and Testing for GDM	Major Exclusion Criteria	BF Measure and Comparison Group	Follow-up Time Point (Postpartum)	Outcomes Studied (Diagnostic Criteria)	Adjusted Factors	Conclusions
Benhalima 2016, Belgium ²⁵	Cross-sectional study	191 women with a recent history of GDM (2013 WHO criteria), from Mar 2014 to Feb 2016.	NR	Status (at 14 wk post partum) - 105 BF - 30 no BF	14.0 (13.0-15.0) wk	Pre-diabetes, IFG, IGT (ADA criteria).	Age, BMI, ethnicity.	BF was not an independent predictor for glucose intolerance (OR = 0.44; 95% CI, 0.17-1.11) in the multivariable regression analysis.
Gunderson 2015, USA ²⁶	Cohort study; SWIFT	1035 women diagnosed with GDM by Carpenter-Coustan criteria from Sep 2008 to Dec 2011.	Preexisting T2DM, T2DM at 6-9 wk post partum, delivered <35 wk gestation, mixed or inconsistent feeding within 4-6 wk post partum.	Intensity (at 6-9 wk post partum) - 205 exclusive BF - 387 mostly BF (≤ 6 ounces of formula/24 hr) - 214 mostly formula, mixed or inconsistent (> 7 ounces/24 hr) - 153 exclusive formula	6-9 wk; 1.8 (0.2-2.6) y	T2DM (ADA criteria), BMI, waist circumference, weight change post-delivery, HOMA-IR, OGTT, glucose tolerance, depression.	Age, race/ethnicity, education, pre-pregnancy BMI, GDM treatment, maternal and perinatal risk factors, newborn outcomes, postpartum lifestyle behaviours and so on.	The BF intensity and duration associated with T2DM incidence in a graded manner (all $P < 0.05$).
Dijigow 2015, Brasil ²⁷	Cohort study	272 women with single-child pregnancy, and a recent history of GDM by IADPSG criteria.	Patients with bariatric surgery prior gestation, with insufficient data, with glucose intolerance prior to gestation.	Status (at 40 days post partum) - 114 BF - 18 no BF	40 days	Weight, overweight or obese (BMI), OGTT, glucose tolerance (ADA).	None	BF was significantly associated with a decreased risk of developing glucose intolerance (OR = 0.27; 95% CI, 0.09-0.8).
Saucedo 2014, Mexico ²⁸	Cohort study	43 women with a history of GDM by 2000 ADA criteria, from Jul 2007 to May 2009.	Women with arterial hypertension, renal disease, liver disease, thyroid disorders or other endocrine or chronic diseases.	Status (at 6 wk post partum) - 21 BF - 22 no BF	6 mo	Glucose, cholesterol, triglyceride, insulin, HOMA-IR, IGT or glucose tolerance, T2DM (ADA).	None	The longer duration of BF was associated with lower levels of leptin and better metabolic profile in the early postpartum period.
Mattei 2014, Italy ²⁹	Cohort study	81 women with a history of GDM by Carpenter-Coustan criteria,	Positive antidiabetic acid decarboxylase	Status (at 4 wk post partum) - 62 BF - 19 no BF	3 y (32.2 ± 20.2 mo)	BMI, waist circumference, glucose, OGTT, insulin; HOMA-IR, ISI, cholesterol,	None	BF does not improve the glucose tolerance of women with prior GDM 3 y after

(Continues)

TABLE 1 (Continued)

First Author, Year, Country, Reference	Design; Study Name	Study Population and Testing for GDM	Major Exclusion Criteria	BF Measure and Comparison Group	Follow-up Time Point (Postpartum)	Outcomes Studied (Diagnostic Criteria)	Adjusted Factors	Conclusions
Gunderson 2014, USA ³⁰	Cohort study; SWIFT	1035 women diagnosed with GDM by Carpenter-Coustan criteria from Sep 2008 to Dec 2011.	Preexisting T2DM, T2DM at 6-9 wk post partum, drop out at baseline, without stored plasma specimens.	Intensity (at 6-9 wk post partum) - 437 exclusive BF - 183 mostly BF (≤ 6 ounces of formula/24 hr) - 128 inconsistent or mixed (>6 to ≤17 ounces/24 h) - 259 exclusive or mostly formula (>17 ounces/24 hr)	6-9 wk	BMI, waist circumference, weight loss from delivery, OGTT, insulin, HOMA-IR, IS _{0,120} , glucose tolerance, HDL, LDL, total cholesterol, triglycerides, leptin, adiponectin.	Race/ethnicity, education, WIC, time post partum (wk), pre-pregnancy BMI, and minutes BF during fasting period.	Higher BF intensity was associated with more favourable biomarkers for T2DM, except for lower plasma adiponectin, after GDM delivery.
Capula 2014, Italy ³¹	Cross-sectional study	454 women with a history of GDM by Carpenter-Coustan criteria from Jan 2004 to Apr 2010, by IADPSG criteria from May 2010 to 2012.	Preexisting T2DM, untreated endocrinopathies, use of medications and pregnancy at the time of postpartum OGTT.	Status (at 6-12 wk post partum) - 212 BF - 242 no BF	6-12 wk	Pre-diabetes, T2DM (ADA criteria)	None	The proportion of BF was not significant different between the normal glucose tolerance, pre-diabetes and T2DM groups (all $P > 0.05$).
Bentley-Lewis 2014, USA ³²	Cross-sectional study	39 women with prior GDM (physician-confirmed) within the previous 3 years.	Preexisting T2DM, Pregnant, lactating.	Status (at 3 mo post partum) - 29 BF - 9 no BF	12-30 wk	Pre-diabetes (IFG and IGT, based on ADA criteria)	None	Longer BF was not associated with a reduced risk of pre-diabetes, but a prior history of BF was associated with the greatest number of metabolite changes (all $P < 0.05$).
Benhalima 2014, Belgium ³³	Cross-sectional study	231 women with a recent history of GDM by Carpenter-Coustan criteria from Jan 2010 to Dec 2013.	Diagnosis of T2DM early after the delivery, without OGTT post partum.	Status (at 8-13 wk post partum) - 128 BF - 41 no BF	8-13 wk	IFG, IGT, glucose intolerance/ diabetes (ADA criteria)	None	The proportion of BF was not significant different between the normal glucose tolerance, IFG, IGT and glucose intolerance/ diabetes groups (all $P > 0.05$).
Chouinard-Castonguay 2013, Canada ³⁴	Cohort study	215 women with a history of GDM	Pregnant or exclusively BF	Status (at 10 mo post partum)	4 (±1.9) y	BMI, fasting glucose, 2-h OGTT glucose,	Age, current energy intake, current	Longer duration of BF is associated

(Continues)

TABLE 1 (Continued)

First Author, Year, Country, Reference	Design: Study Name	Study Population and Testing for GDM	Major Exclusion Criteria	BF Measure and Comparison Group	Follow-up Time Point (Postpartum)	Outcomes Studied (Diagnostic Criteria)	Adjusted Factors	Conclusions
Ziegler 2012, Germany ³⁵	Cohort study	304 women with a history of GDM (criteria of the German diabetes association) from 1989 to 1999.	Islet autoantibody-positive women.	Status (at 3 mo post partum) - 100 BF - 81 no BF	15 y	T2DM (ADA criteria)	Insulin treatment during pregnancy, BMI > 30 at early pregnancy, maternal age, smoking during pregnancy, parity status, recruitment year.	BF for > 3 mo had the lowest postpartum T2DM risk (15 y) vs. no or ≤ 3 mo of BF ($P < 0.001$) and a longer DM-free duration (18.2 y). full BF duration was inversely associated with T2DM incidence ($P = 0.001$).
▽ Gunderson 2012, USA ³⁶	Cohort study; SWIFT	835 women diagnosed with GDM by Carpenter–Coustan criteria from Sep 2008 to Dec 2011.	Preexisting T2DM, T2DM at 6–9 wk post partum, drop out at baseline.	Status (during the 2-hr 75 g OGTT at 6–9 wk) - 205 BF - 630 no BF	6–9 wk	BMI, glucose tolerance categories, glucose, insulin, IS _{0,120} , homeostatic model.	Race, parity, age, number of abnormal results 3-h prenatal OGTT (GDM severity), amount of formula (oz/24 h), and fasting period (hours).	BF an infant during the 2-h 75 g OGTT may modestly lower plasma 2-hr glucose (5% lower on average), as well as insulin concentrations in response to ingestion of glucose.
Kim 2011, Korea ³⁷	Cross-sectional study	573 women with a history of GDM by Carpenter–Coustan criteria from Jun 2006 to Mar 2009	Positive glutamic acid decarboxylase antibodies.	Intensity - 190 fully BF - 148 mixed BF - 43 no BF	6–12 wk	Pre-diabetes, T2DM (ADA criteria).	BMI, family history of DM, HOMA-B, insulin dosage, and postpartum factors (BMI, HbA _{1c} , HOMA-B, plasma triacylglycerol, energy intake).	Postpartum BF ($r = -0.016$, $P = 0.25$) and days of BF ($P = 0.92$) did not affect glycaemic homeostasis.
▽ Gunderson 2010, USA ³⁸	Cohort study; CARDIA	84 women with a history of GDM based on biochemical and medical history data	Preexisting T2DM and metabolic syndrome, parous, current pregnant or BF, missing information.	Status (at 1 mo post partum) - 62 BF - 22 no BF	7, 10, 15, 20 y	Metabolic syndrome (the National Cholesterol Education Programme, adult	Race, time-dependent parity, study centre, age, education, smoking, time-dependent physical activity.	Increased BF duration was associated with lower metabolic syndrome incidence rates

(Continues)

TABLE 1 (Continued)

First Author, Year, Country, Reference	Design; Study Name	Study Population and Testing for GDM	Major Exclusion Criteria	BF Measure and Comparison Group	Follow-up Time Point (Postpartum)	Outcomes Studied (Diagnostic Criteria)	Adjusted Factors	Conclusions
Nelson 2008, USA ³⁹	Cross-sectional study	592 women with a history of GDM by a 3-h 100 g OGTT.	Once diagnosed with T2DM, they were excluded in the subsequent follow-up.	Status (at first postpartum visit) - 379 BF - 193 no BF	First visit (before pregnancy Medicaid ends), 1, 2 y	Pre-diabetes, T2DM (ADA criteria)	None	BF did not protect women from worsening of glucose tolerance. Shorter BF was not associated with a significant difference in the rate of deterioration in glucose metabolism.
Stuebe 2005, USA ⁴⁰	Cohort study; the Nurses' health Study II	266 women who ever reported having GDM (self-report).	With missing baseline information on parity, duration of BF, or age at last birth.	Status (at 3 mo post partum) - 183 BF - 83 no BF	15 y	T2DM (NDDG criteria)	Parity, BMI at age 18 y, current BMI, dietary score quintile, physical activity, family history of diabetes, smoking status, birth weight of mother, and multivitamin use.	BF had no effect on T2DM risk in the GDM group, with a covariate-adjusted HR of 0.96 (95% CI, 0.84–1.09) per additional year of BF.
McManus 2001, Canada ⁴¹	Cohort study	26 women with a history of GDM (ADA criteria) and vaginal delivery of a live singleton infant after 36 weeks gestation.	NR	Status (at 3 mo post partum) - 14 BF - 12 no BF	3 mo	T2DM, IGT (ADA), fasting insulin, cholesterol, triglycerides, insulin sensitivity, glucose effectiveness, disposition index, visceral fat, subcutaneous fat.	Age, weight, weight gain of pregnancy, weight at delivery, weight loss by 3 months post partum, BMI, size of infant, duration of GDM diagnosis, blood pressure, waist-hip ratios, and exercise habits.	BF for at least 3 mo in a population with previous GDM was associated with improved pancreatic b-cell function ($P = 0.03$), but not with any difference in measures of adiposity (all $P > 0.05$).
MacNeill 2001, Canada ⁴²	Cohort study	640 women had a pregnancy with a diagnosis of GDM by a 50 g OGTT from 1980 to 1996.	Preexisting T2DM diagnosed before their index pregnancy.	Status (index pregnancy) - 347 BF - 293 no BF	NR	GDM (O'Sullivan criteria)	None	BF status at the index pregnancy was not significantly associated with the rate of recurrence of GDM (RR = 1.1; 95% CI, 0.89–1.36).
Kjos 1998, USA ⁴³					7.5 y	T2DM (NDDG criteria)		

(Continues)

TABLE 1 (Continued)

First Author, Year, Country, Reference	Design; Study Name	Study Population and Testing for GDM	Major Exclusion Criteria	BF Measure and Comparison Group	Follow-up Time Point (Postpartum)	Outcomes Studied (Diagnostic Criteria)	Adjusted Factors	Conclusions
Buchanan 1998, USA ⁴⁴	Cohort study; HRFPC	443 women (nonhormonal only) with a recent history of GDM by NDDG criteria between Jan 1987 and Mar 1994.	T2DM at 4-16 wk post partum.	Status (at 4-16 wk post partum) - 183 BF - 260 no BF	1-6 mo	IGT, T2DM (ADA criteria).	Insulin treatment during the index pregnancy, glucose AUC at the initial postpartum OGTT, weight change from the initial postpartum weight, prior use of oral contraceptive.	BF was not significantly associated with T2DM risk in women who elected non-hormonal contraception (adjusted RR = 1.16, 95% CI, 0.72-1.92).
Buchanan 1998, USA ⁴⁴	Cross-sectional study	122 women with a history of GDM (recommendations of the Third International Workshop-Conference) between Aug 1993 and Mar 1995.	Islet autoantibody-positive, current or prior insulin therapy.	Status (at least 6 wk post partum) - 70 BF - 52 no BF	1-6 mo	IGT, T2DM (ADA criteria).	None	The proportion of BF was significant different between the normal glucose tolerance, IGT and diabetes groups ($P = 0.03$).
Kjos 1993, USA ⁴⁵	Cohort study	809 women whose pregnancies were complicated by GDM according to NDDG criteria.	NR	Status (at 4-12 wk post partum) - 404 BF - 405 no BF	4-12 wk	T2DM (NDDG criteria), fasting glucose, 2-h glucose, AUC, cholesterol, HDL, LDL, triglycerides.	Maternal age, BMI, mean arterial pressure, use of insulin.	BF had a beneficial effect on glucose and lipid metabolism in women with GDM; T2DM incidence was twice as common in non-BF women compared with BF women (9.4% versus 4.2%, adjusted $P = 0.01$).
Oats 1990, Australia ⁴⁶	Cross-sectional study	149 women with a recent history of GDM by mercy maternity hospital criterion.	NR	Intensity (at 6 wk post partum) - 110 fully BF - 4 mixed BF - 35 no BF	6 wk	Abnormal postnatal glucose tolerance, IGT, T2DM (1985 ADA criteria).	None	The method of infant feeding had no significant influence on the prevalence of abnormal glucose tolerance.

Abbreviations: ADA, the American diabetes association; AUC, area under the curve; BCAA, branched-chain amino acid; BF, breastfeed; BMI, body mass index; CARDIA, coronary artery risk development in young adults; CI, confidence interval; GDM, gestational diabetes mellitus; HRFPC, high-risk family planning clinic; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of assessment of insulin resistance, calculated as [fasting insulin \times fasting plasma glucose]/405; HR, hazard ratio; hr, hours; IADPSG, the international association of diabetes and pregnancy study group; ICD, international classification of diseases; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ISI, insulin sensitivity index, calculated as $10,000/\text{square root of [fasting glucose} \times \text{fasting insulin]} \times$ [mean glucose \times mean insulin during OGTT]; LDL, low-density lipoprotein; mo, months; NDDG, the national diabetes data group; OGTT, oral glucose tolerance test; OR, odd ratio; PINGUIN, postpartum intervention in women with gestational diabetes using insulin; POGO, postpartum outcomes in women with gestational diabetes and their offspring; RR, relative risk; SWIFT, study of women, infant feeding and type 2 diabetes after GDM pregnancy; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; WHO, the world health organization; wk, weeks; y, years.

^aStudies not included in the quantitative meta-analysis.

no information about the dropouts and protocol, which resulted that attrition bias (18 studies) and reporting bias (19 studies) were judged to be “unclear.”

3.3 | Progression to T2DM

In overall analysis of 9290 participants from 15 studies,^{23,24,26,28,29,31,35,37,39-41,43-46} there appeared to be a reduced possibility of progression to T2DM among women with longer BF of any intensity after GDM pregnancy (OR = 0.79; 95% CI, 0.68-0.92; $P = 0.002$), with slight heterogeneity ($I^2 = 33.3\%$, $P = 0.090$) (Figure 2). Subgroup analyses of 12 cohorts (from 10 studies^{23,24,26,28,29,35,40,41,43,45}) showed a consistent effect in longer BF (OR = 0.77; 95% CI, 0.67-0.89; $P < 0.001$), while pooled result of five cross-sectional studies^{31,37,39,44,46} did not find the significant relationship between longer BF and progression to T2DM (OR = 1.15; 95% CI, 0.52-2.55; $P = 0.723$) (Figure S1). Results from subgroup analyses stratified by follow-up period (1-6 months, 1-5 years, >5 years) are showed in Figure 2. The effect of longer BF was not obvious when T2DM was evaluated in early post partum (1-6 months; $I^2 = 54.9\%$; OR = 0.93; 95% CI, 0.52-1.67; $P = 0.800$) but became prominent with longer follow-up period ($I^2 = 0.8\%$; OR = 0.67; 95% CI, 0.47-0.96; $P = 0.028$ for subgroup with follow-up time between 1 and 5 years; and $I^2 = 17.2\%$; OR = 0.81; 95% CI, 0.72-0.90; $P < 0.001$ for follow-up time longer than 5 years). Only four studies^{24, 26, 37, 46} measured BF using intensity could be synthesized (Figure S2). Meta-analyses indicated that the association between longer BF and lower possibility of T2DM became more clear, with the extension of BF intensity and follow-up period, while the association was just significantly in the subgroup comparing fully BF with none, evaluated between 1 and

5 years after delivery (two studies, $I^2 = 0\%$; OR = 0.53; 95% CI, 0.29-0.95; $P = 0.033$).

Sensitivity analysis indicated that the pooled result was robust when omitted any one record alone. After restricting the distinction point of BF measure to 4 to 14 weeks, the association was stable through inverse variance fixed-effects model ($I^2 = 45.0\%$; OR = 0.74; 95% CI, 0.61-0.91; $P = 0.003$) but lost significance in DerSimonian-Laird random-effects model (OR = 0.81; 95% CI, 0.60-1.11; $P = 0.196$). For those combined analyses with I^2 lower than 50%, replacing the random-effects model with a fixed-effects model did not essentially change the conclusion. There was no evidence of publication bias in the overall analysis, either with Begg test ($P = 0.434$) or Egger test ($P = 0.563$).

3.4 | Progression to pre-DM

A total of 16 studies^{20,21,25-29,31-34,37,39,41,44,46} evaluated the risk of pre-DM, IGT, or IFG in 4266 women after GDM pregnancy. Meta-analyses (Figure 3) indicated that longer BF was significantly associated with a lower probability of pre-DM ($I^2 = 41.1\%$; OR = 0.66; 95% CI, 0.51-0.86; $P = 0.002$), which was identified in the subgroup analyses stratified by follow-up period (OR = 0.65; 95% CI, 0.49-0.86; $P = 0.003$ for 1-6 months; OR = 0.55; 95% CI, 0.33-0.91; $P = 0.020$ for 1-5 years). When it came to IFG, the results were similar, except that the effect of longer BF was not significant when IFG was evaluated in later post partum (1-5 years, $I^2 = 47.9\%$; OR = 0.71; 95% CI, 0.27-1.90; $P = 0.497$). However, no significant association was found between longer BF and possibility of progression to IGT, either in the overall analysis or subgroup analyses (all $P > 0.05$). Additionally, no publication bias was found in the analyses involving more than 10 studies in this section.

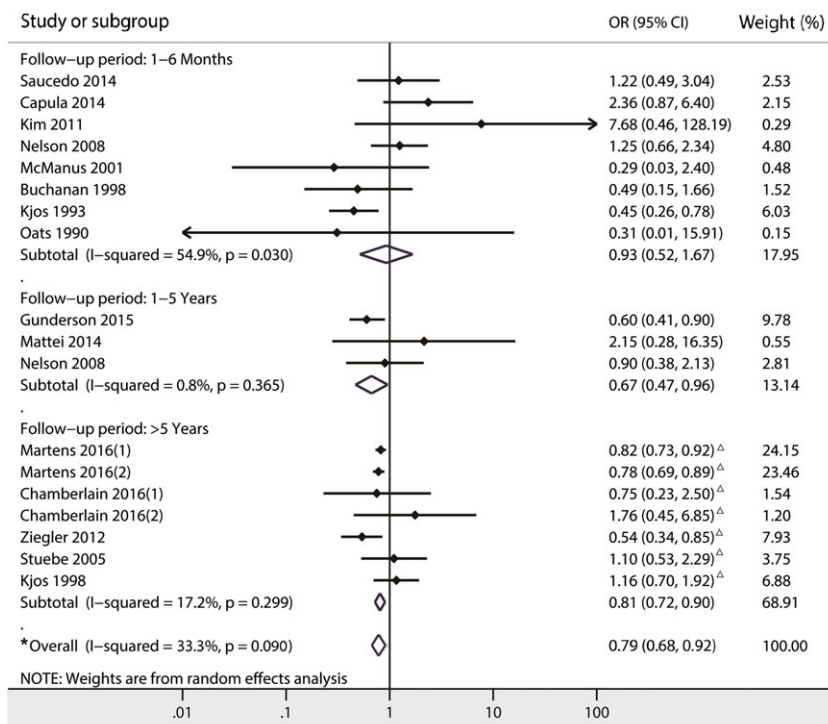


FIGURE 2 Forest plot of the association between longer breastfed and the incidence of diabetes mellitus in women with prior gestational diabetes mellitus, based on three different follow-up periods. *Only the result with longer follow-up period (Nelson et al³⁹) was included in the overall analysis. ^ΔAdjusted estimates and 95% confidence intervals

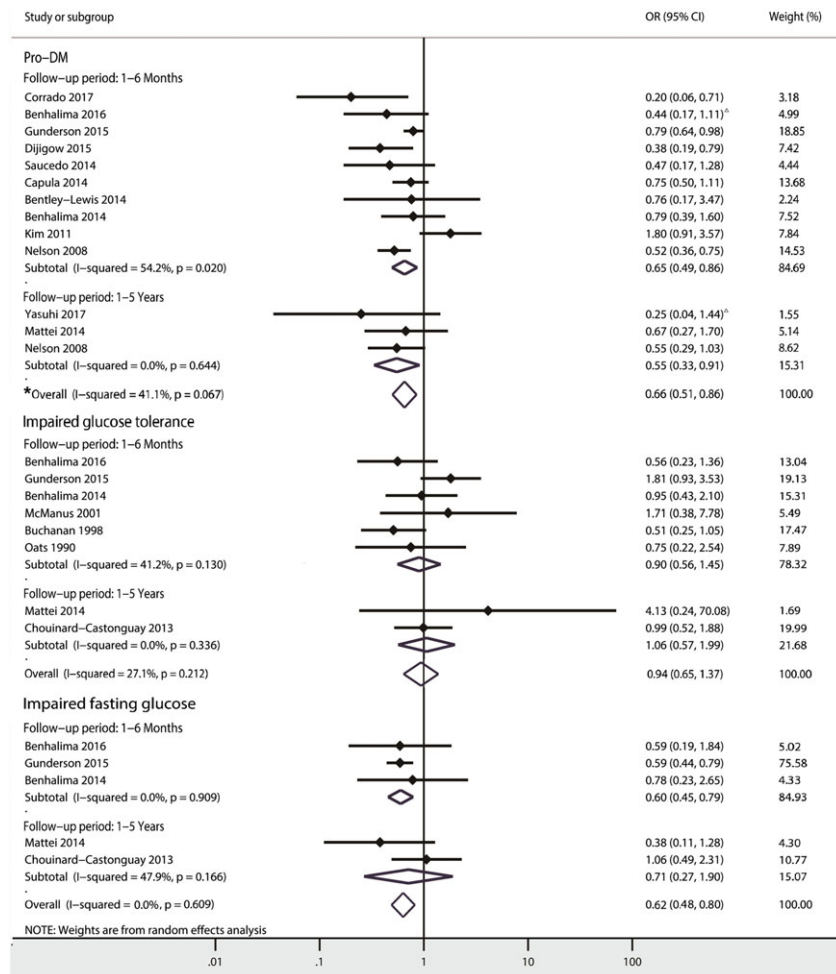


FIGURE 3 Forest plot of the associations between longer breastfed and the incidence of pre-diabetes, impaired glucose tolerance, impaired fasting glucose in women with prior gestational diabetes mellitus, based on two different follow-up periods. [△]Only the result with longer follow-up period (Nelson et al³⁹) was included in the overall analysis. [△]Adjusted estimates and 95% confidence intervals

3.5 | Pooled results of metabolic parameters

Results of meta-analyses of selected metabolic parameters are summarized in Table 2. BMI was found to be significantly lower among women with longer BF of any intensity after GDM pregnancy, both in the pooled and subgroup analyses (all $P < 0.05$). Pooled analyses of glucose metabolic parameters indicated that longer BF after delivery appeared to be statistically associated with lower fasting glucose (WMD = -3.77 ; 95% CI, -4.96 to -2.58 ; $P < 0.001$), lower HOMA-IR (WMD = -0.74 ; 95% CI, -1.33 to -0.15 ; $P = 0.014$), and higher ISI (WMD = 2.20 ; 95% CI, 0.54 - 3.87 ; $P = 0.009$). Result of fasting glucose was conformed when it was evaluated in early post partum (1-6 months), while result of HOMA-IR was the opposite. The association between longer BF and fasting insulin appeared to be existent, but only be significant in the subgroup of longer follow-up period (WMD = -17.68 ; 95% CI, -26.87 to -8.49 ; $P < 0.001$). For lipid metabolic parameters, only triglyceride was found to be associated with longer BF (WMD = -30.89 ; 95% CI, -43.03 to -18.71 ; $P < 0.001$), mainly when it was evaluated in early post partum.

Sensitivity analysis using SMD as the statistic shows a similar trend (Table S3), except for the following detailed differences. First, pooled analysis had indicated the significant association between longer BF and fasting insulin (SMD = -0.43 ; 95% CI, -0.74 to -0.12 ; $P = 0.006$). Second, result for the subgroup analyses of HOMA-IR was opposite, and the effect of longer BF was significant only when

HOMA-IR was evaluated in early post partum (SMD = -0.39 ; 95% CI, -0.71 to -0.08 ; $P = 0.015$). Third, longer BF seemed not to be statistically associated with lower triglyceride (SMD = -0.99 ; 95% CI, -2.08 to 0.09 ; $P = 0.073$).

3.6 | Other metabolic-related outcomes

To determine the rates and risk factors of recurrent GDM, MacNeill et al conducted a retrospective longitudinal study, using a perinatal database to identify 640 women with prior GDM and then had at least one subsequent pregnancy.⁴² The authors concluded that BF status at the index pregnancy was not significantly associated with the rate of recurrent GDM (RR = 1.1 ; 95% CI, 0.89 - 1.36).⁴² Prospective findings from a cohort of 84 US women with GDM history showed marked differences in metabolic syndrome incidence rate following the BF duration increased from 0-1 month to >9 months (relative hazard range 0.14 - 0.56 ; $P = 0.03$).³⁸

A prospective cohort study of 835 women with GDM history found that BF for an average of 15 minutes during oral glucose tolerance test might modestly lower (5% on average) plasma 2-hour post load glucose, as well as insulin concentrations in response to ingestion of glucose.³⁶ More recently, Much et al²² evaluated metabolic signatures before and after a glucose challenge in women with prior GDM, with a targeted metabolomics approach. Compared analyses indicated that BF for >3 months was associated with changes in metabolomics

TABLE 2 Pooled estimates for the associations of breastfeeding with metabolic parameters using weighted mean difference as effect measure

Index	Pooled Analysis				Follow-up Period: 1-6 mo				Follow-up Period: 1-5 y			
	Study no.	WMD (95% CI)	P	I ² (%)	Study No.	WMD (95% CI)	P	I ² (%)	Study No.	WMD (95% CI)	P	I ² (%)
	BMI	4	-1.91 (-2.85 to -0.98)	<0.001	0	2	-2.19 (-3.27 to -1.12)	<0.001	0	3	-1.47 (-2.81 to -0.14)	0.031
Fasting glucose (mg/dL)	8	-3.77 (-4.96 to -2.58)	<0.001	14.4	6	-4.15 (-5.24 to -3.07)	<0.001	0	3	-2.54 (-6.14 to 1.06)	0.167	46.9
2-h post load glucose (mg/dL)	6	-4.62 (-11.36 to 2.13)	0.180	68.1	4	-6.57 (-15.06 to 1.91)	0.129	79.6	2	1.58 (-9.35 to 12.52)	0.777	0
Fasting insulin (pmol/L)	4	-22.14 (-48.23 to 3.94)	0.096	93.5	3	-20.38 (-55.87 to 15.11)	0.260	95.6	2	-17.68 (-26.87 to -8.49)	<0.001	0
HOMA-IR	5	-0.74 (-1.33 to -0.15)	0.014	70.2	4	-0.66 (-1.36 to 0.04)	0.065	81.0	2	-0.63 (-1.06 to -0.20)	0.004	0
ISI	2	2.20 (0.54 to 3.87)	0.009	39.3					2	2.20 (0.54 to 3.87)	0.009	39.3
Triglyceride (mg/dL)	6	-30.89 (-43.03 to -18.71)	<0.001	59.5	5	-30.29 (-43.62 to -16.95)	<0.001	67.2	1	-39.40 (-83.24 to 4.44)	0.078	-
Cholesterol (mg/dL)	6	2.53 (-4.83 to 9.89)	0.501	79.4	5	3.91 (-3.89 to 11.70)	0.326	82.5	1	-11.5 (-31.79 to 8.79)	0.267	-

Abbreviations: BMI, body mass index; CI, confidence interval; HOMA-IR, homeostasis model of assessment of insulin resistance, calculated as [fasting insulin × fasting plasma glucose]/405; ISI, insulin sensitivity index, calculated as 10,000/square root of [fasting glucose × fasting insulin] × [mean glucose × mean insulin during oral glucose tolerance test]; WMD, weighted mean difference.

profile (total lysophosphatidylcholine/phosphatidylcholine ratio, branched-chain amino acids concentrations) that had been linked to the early pathogenesis of T2DM.²²

4 | DISCUSSION

Among women with prior GDM, a reduced possibility of progression to T2DM was found in women with longer BF of any intensity (OR = 0.79; 95% CI, 0.68-0.92). Since the definition of longer and shorter BF varied from article to article, potential bias was present. Sensitivity analysis restricting the distinction point of BF measure to 4 to 14 weeks found that the association was still visible. In addition, the benefit in studies measuring BF at discharge was likely to be underestimated because of the delayed lactogenesis in women with GDM.⁴⁷

Similarly, meta-analyses suggested an inverse association of longer BF with incidence of pre-DM (OR = 0.66; 95% CI, 0.51-0.86), which might largely result from the benefit on the progression to IFG (OR = 0.62; 95% CI, 0.48-0.80). Correspondingly, compared with women with shorter BF, those with longer BF manifested more favourable metabolic parameters, including lower BMI (WMD = -1.91; 95% CI, -2.85 to -0.98), fasting glucose (WMD = -3.77; 95% CI, -4.96 to -2.58), HOMA-IR (WMD = -0.74; 95% CI, -1.33 to -0.15), triglyceride (WMD = -30.89; 95% CI, -43.03 to -18.71), and higher ISI (WMD = 2.20; 95% CI, 0.54-3.87), but statistical significance was not reached in 2-hour post load glucose WMD = -4.62; 95% CI, -11.36 to 2.13.

In addition to the beneficial effects induced by the energy expenditure required by BF,⁴⁸ these synthesized results suggested that BF itself may be able to improve glucose tolerance through the enhancement of insulin sensitivity and/or preservation of pancreatic β cell function in women with prior GDM.⁴⁹ However, the detailed metabolic pathways underlying the protective effects of BF are still unclear; several assumptions have been raised via the studies on both animal models and human, including the increased glucose disposal by mammary gland,⁵⁰ downregulation of menin,⁵¹ elevated prolactin level,⁵² and increased levels of maternal adipokines (like ghrelin and protein peptide YY).⁵³

Subgroup analyses found that the positive effect of longer BF on progression to T2DM gradually became prominent with the extension of follow-up period (OR = 0.93 [95% CI, 0.52-1.67]; OR = 0.67 [95% CI, 0.47-0.96]; OR = 0.81 [95% CI, 0.72-0.90]; 1-6 months, 1-5 years, >5 years, respectively), which prompts that risk of T2DM after GDM pregnancy may increase with time⁵⁴; the beneficial effects of BF require at least several years to judge. Moreover, the underlying aetiology may be different between those develop T2DM in early post partum and later, which needs further biochemical evidence to elucidate. Subgroup analyses stratified by BF intensity (four studies) showed that the association between longer lactation of fully BF and lower possibility of T2DM might be present, but only significantly reflected in the subgroup with longer follow-up period, while the imprecise estimates here might owe to the small number of studies and individuals.

Strengths of our study include the systematic strategy, broad search terms, large sample size with increased statistical power to detect the effect of BF on risk of glucose intolerance, and quantitative

analyses of the associations between BF and multiple metabolic parameters. However, several limitations still need to be addressed and merit further discussion. First, adjustments of potential confounders were not conducted because of the most included crude data, nonuniform considered variables, inconsistent observations, and varying follow-up periods. As some confounders (eg, weight loss,²⁶ insulin treatment, and severity of GDM during pregnancy⁵⁵) may have modifying effects on the associations between BF and risk of glucose intolerance in women after GDM pregnancy, the results should be interpreted with caution, although heterogeneity between studies was not significant in most analyses. Second, subgroup analyses stratified by characteristics of participants (like BMI or ethnicity), diagnostic criteria of GDM, standardized BF measures were unavailable owing to the inadequate information, which may complicate the interpretation of results, further deter the extrapolation in real practice. Third, although evidence of publication bias were not found in the overall analyses, attrition bias and reporting bias might be present in majority of included studies, according to the quality assessments using RoBANS.

Based on the available evidence, BF is likely to be a modifiable behaviour that may play an important role in women's future health after GDM pregnancy, including protection against the development of metabolic diseases in midlife.⁵⁶ A recent Centers for Disease Control study reported that among all children born in the United States during 2010-2013, the national estimates for BF initiation exclusivity through 6 months and duration at 12 months were 79.2%, 20.0%, and 27.8%, respectively.⁵⁷ Women with history of GDM usually lactate less frequently and for shorter durations.^{58,59} Thus, better prenatal counselling and education about BF should be made available to women with prior GDM during pregnancy and post partum. In addition, BF discussions to an obstetric clinic at the first prenatal visit are reported to be infrequent (just 29% of visits), brief (mean duration 39 seconds), and usually initiated by clinicians in an ambivalent manner,⁶⁰ which requires that health care professionals should be knowledgeable with respect to the benefits of BF and provide comfortable assistance and appropriate evidence-based care for women with GDM history.⁶¹ In light of the higher risk of maternal and paediatric complications,⁶² BF promotion may be a safe and practical low-cost intervention during the postpartum period to prevent the development of metabolic diseases in women with GDM history, especially in those with a low socio-economic status.^{7,26,56}

Admittedly, the observational nature limits the identification of causal relationship, but randomization of BF is infeasible both technically and ethically;¹⁴ hence, well-controlled, prospective longitudinal studies with complete measures of BF intensity, duration, and potential confounders, as well as better standardized testing and clarity of definitions, are needed to conclusively determine the metabolic effects of BF among women with prior GDM. Moreover, researches on metabolic pathways underlying the protective effects of BF are warranted to substantiate this epidemiologic evidence.

5 | CONCLUSION

This synthesized review and meta-analysis suggest that BF is beneficial to glucose metabolism and longer BF is associated with reduced

risk of glucose intolerance and metabolic syndrome in women with prior GDM. BF promotion and support are essential for women with recent GDM to prevent the development of metabolic diseases. Simultaneously, further studies are needed to reveal the etiological mechanism.

AUTHOR CONTRIBUTION

Shujuan Ma reviewed the literature, screened the records, assessed the quality of studies, extracted the data, performed the statistical analysis, and wrote the manuscript. Shimin Hu screened the records, assessed the quality of studies, extracted the data, performed the statistical analysis, and reviewed/edited the manuscript. Huiling Liang and Yan-Ni Xiao contributed to the discussion and reviewed/edited the manuscript. Hongzhuan Tan contributed to the discussion and reviewed/edited the manuscript.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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