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Maternal gestational diabetes and infant feeding, nutrition and growth: a systematic review and meta-analysis

Komal Manerkar[1], Jane Harding[1], Cathryn Conlon[2] and Christopher McKinlay[1,3]*

[1]*Liggins Institute, University of Auckland, Auckland, New Zealand*
[2]*School of Sport, Exercise and Nutrition, Massey University, Auckland, New Zealand*
[3]*Counties Manukau Health, Auckland, New Zealand*

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Abstract

Gestational diabetes mellitus (GDM) is a major health problem, with increased risks of obesity and diabetes in offspring. However, little is known about the effect of GDM on infant feeding, nutrition and growth, and whether these factors play a role in mediating these risks. We systematically reviewed evidence for the effect of GDM on infant feeding, nutrition and growth. We searched MEDLINE, Web-of-Science, Embase, CINAHL and CENTRAL for studies that reported outcomes in infants <2 years who were and were not exposed to GDM. Studies of pre-gestational diabetes were excluded. Meta-analysis was performed for three epochs (1–6, 7–12, 13–24 months), using inverse-variance, fixed-effects methods. Primary outcomes were energy intake (kJ) and BMI (kg/m^2). Twenty-five studies and 308 455 infants were included. Infants exposed to GDM, compared with those not exposed, had similar BMI at age 1–6 months (standardised mean difference (SMD) = 0·01, 95 % CI −0·04, 0·06; P = 0·69) and 7–12 months (SMD = 0·04, 95 % CI −0·01, 0·10; P = 0·09), reduced length at 1–6 and 7–12 months, increased whole-body fat at 1–6 months, higher rates of formula supplementation in hospital, shorter duration of breast-feeding and decreased rates of continued breast-feeding at 12 months. Breast milk of women with GDM had lower protein content. There was no association between GDM and infant weight and skinfold thickness. No data were available for nutritional intake and outcomes at 13–24 months. Low- or very low-quality evidence suggests GDM is not associated with altered BMI in infancy, but is associated with increased fat mass, high rates of formula use and decreased duration of breast-feeding.

Key words: **Gestational diabetes: Infant feeding: Early life nutrition: Infant adiposity**

Gestational diabetes mellitus (GDM), defined as glucose intolerance first recognised during pregnancy, is a major public health issue, with an estimated 18·4 million births affected globally per annum[1]. In many countries, rates of GDM have increased steadily over recent decades[2], a trend that continues unabated in the absence of effective preventative strategies[3]. GDM not only increases the risk of major obstetric and perinatal complications, such as pre-eclampsia, stillbirth, macrosomia, shoulder dystocia, birth trauma and neonatal encephalopathy[4], but is also associated with long-term health risks for women and their infants. Infants exposed to GDM also have increased incidence of obesity and insulin resistance in childhood, and impaired glucose tolerance and type 2 diabetes mellitus in adulthood; risks that are further increased in those born large for gestational age[5–7].

The mechanisms underlying these long-term consequences for infants exposed to GDM are not well understood. Infancy is a critical period of development, characterised by rapid changes in growth, nutrition and feeding patterns, that have an important influence on growth and body composition throughout childhood and beyond[8,9]. For example, breast-feeding protects against childhood obesity[10], whereas early introduction of formula milk or bottle feeding is associated with more rapid infant weight gain and subsequent increased risk of childhood obesity[11,12]. Similarly, early introduction of solids and greater avidity for food at 3 months of age are associated with increased adiposity in later life[13–16]. Therefore, nutrition, growth and feeding behaviours in infancy appear to have a potential role in mediating the risk of later obesity and metabolic disease.

The association between GDM and offspring obesity and diabetes may be due to effects on growth, nutrition and appetite in infancy, either as a result of altered nutrition *in utero* or postnatally via breast milk composition. For example, rats exposed to maternal diabetes in pregnancy demonstrate hyperinsulinaemia, and exposure to breast milk of dams with GDM has been shown

Abbreviations: GDM, gestational diabetes mellitus; SMD, standardised mean difference.

* **Corresponding author:** Christopher McKinlay, email c.mckinlay@auckland.ac.nz

to alter hypothalamic function, which may influence satiety centres and regulation of body weight and metabolism[17,18]. In humans, GDM has been associated with lower breast-feeding duration, early introduction of cows' milk[19,20] and greater weight gain in the first 3 months of life[21,22].

To date, the association between GDM and feeding, nutrition and growth in infancy has not been systematically assessed. This information may be important in guiding clinical care of infants exposed to GDM and in designing intervention trials to reduce their risks of obesity and metabolic disease. Thus, we undertook a systematic review and meta-analysis to evaluate the impact of GDM on infant feeding patterns and behaviour, nutritional intake and growth in the first 2 years after birth.

Methods

This systematic review was conducted following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The protocol was registered in PROSPERO (CRD42018115212, http://www.crd.york.ac.uk/PROSPERO/).

Search strategy

We searched MEDLINE, Web of Science, Embase, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) database using key words, MeSH terms and Emtree headings including gestational diabetes, infant nutrition, breast-feeding, infant formula, weaning, appetite, feeding behaviour, energy intake, food frequency, body size, BMI, skinfold thickness and body composition. We also searched for alternative terms for the main concepts using phrasing and truncation (online Supplementary File S1). The search was limited to studies involving humans and with abstracts. We did not limit the search to any language or year of publication. We also hand searched references lists in eligible studies, review papers and conference abstracts to identify additional items. One author identified records through database searching and screened titles and abstracts for potential eligibility. Two authors then independently assessed the full text for eligibility. Discrepancies were resolved through discussion or consultation with the third author. We used a reference management software Covidence (https://www.covidence.org) to combine search results from different databases and to remove duplicates.

Inclusion criteria

We included all published studies (case–control, cohort and randomised trials) that reported one or more primary or secondary outcomes up to 2 years of age in infants exposed to GDM compared with those not so exposed. We included studies that reported GDM as diagnosed by oral carbohydrate challenge test (any diagnostic criteria), treated or untreated and maternal self-report. Studies that retrospectively collected data on GDM status from hospital records were also included in the review. We excluded uncontrolled case series, unpublished results, conference abstracts and studies primarily about pre-gestational diabetes. We did not limit studies by health care setting or country.

Outcomes

The primary outcomes were energy intake (kJ) and BMI (kg/m^2) *z*-score or standardised score. Secondary outcomes related to feeding patterns and behaviour were: (a) exclusive or predominant breast-feeding at ≥5 months of age, defined as the proportion of infants fed exclusively or predominantly with breast milk (can include medicines, vitamins, oral re-hydration solution and water-based liquids, in addition to breast milk) from birth to at least 5 months of age[23]; (b) introduction of formula milk before hospital discharge; (c) continued breast-feeding at 12 months of age, defined as the proportion of children fed any breast milk at 12–15 months of age[24]; (d) duration of breast-feeding[25]; (e) no breast milk feeding, defined as proportion of infants who did not receive any breast milk at ≤5 months[26]; (f) introduction of solid, semi-solid or soft foods before 5 months of age and (g) appetitive scores to assess the appetite-related feeding behaviours, for example, Baby Eating Behaviour Questionnaire for infants <6 months and Child Eating Behaviour Questionnaire for older infants[27,28]. Secondary outcomes related to nutritional intake were: (a) breast milk composition including energy (kJ/100 ml), lactose (g/100 ml), protein (g/100 ml) and fat (g/100 ml); (b) minimum diet diversity, defined as the proportion of children who received foods from ≥5 out of eight food groups during the previous day (breast milk, grains, roots and tubers, legumes and nuts, dairy products, flesh foods, eggs, vitamin-A-rich fruits and vegetables, and other fruits and vegetables)[29]; (c) food group frequency; and (d) macronutrient intake, including daily intake of protein (g), carbohydrate (g) and fat (g), and percentage of energy from protein, carbohydrates and fats. Secondary growth outcomes were weight (kg), length (cm), abdominal circumference (cm), head circumference (cm), skinfold thicknesses (mm), fat mass (g) and fat-free mass (g) *z*-scores or standardised scores.

Risk of bias

Two authors independently assessed the risk of bias of each study using the ROBINS-I tool for non-randomised studies of interventions[30], a modified version of the ROBINS-I tool for non-interventional observational studies[31], or the Cochrane Collaboration's risk of bias tool for randomised trials[32]. The following bias domains were assessed: (a) recruitment and selection of participants in the study; (b) confounding; (c) ascertainment of exposures; (d) measurement of outcomes; (e) missing data and (f) reporting of results. Discrepancies between authors were resolved through discussion or by consultation with the third reviewer.

Data extraction and analysis

Two authors independently extracted data from included studies using a pre-specified data form. We extracted year of publication, type of study, country of the study, study population, participant characteristics, definition of gestational diabetes used (including diagnostic criteria), treatment, inclusion and exclusion criteria, adjustment for confounding and outcomes specific for the review. Discrepancies between authors were resolved through discussion or by consultation with the third author.

Meta-analysis was performed separately across three age epochs (1–6, 7–12 and 13–24 months) using Review Manager (REVMAN) version 5.3[33]. An inverse variance, fixed-effects method was used, based on adjusted estimates where available. If adjusted estimates of exposure effect were not available, meta-analysis was performed using extracted summary statistics, either proportions or mean differences, as appropriate.

If there was more than one report from a single study, only the latest report within each epoch was used in analysis. Exposure effects are presented as OR or standardised mean difference (SMD) with 95 % CI. For continuous data, if median and inter-quartile range were reported, we estimated mean values and standard deviation to pool the results in meta-analysis[34]. Statistical heterogeneity was assessed by the χ^2 test and I^2 statistic values. If meta-analysis was not possible, we provided a narrative synthesis of findings.

We planned subgroup analysis for primary outcomes comparing higher and lower degrees of maternal dysglycaemia. We also planned sensitivity analysis, excluding studies with high risk of bias.

Quality of evidence

We used the GRADE approach to assess the quality of evidence for each outcome[35]. Two reviewers independently assessed the quality of evidence based on eight assessment criteria[36]. Observational studies were initially assigned a low quality of evidence and randomised controlled trials a high quality of evidence. The quality level was downgraded if: (a) one or more studies had uncertain or high risk of bias for several domains; (b) there was evidence of substantial heterogeneity (I^2 statistic value >50 % and low P value for χ^2 test)[36]; (c) there was indirectness in reporting of participants, exposure, comparison and outcomes or (d) there was imprecision of results due to a total number of events <300 (for dichotomous outcomes), total number of participants <400 (for continuous outcome) and wide confidence intervals. We upgraded the quality by one level if there were only observational studies with no major threats to validity and there was evidence of large exposure effect (for dichotomous outcomes, OR > 2 or <0·5; for continuous data, SMD > 0·8)

Results

Search results

We identified 5445 citations and removed 2121 duplicates. The remaining 3324 citations were screened for title and abstract. Of these, 3135 citations were irrelevant and were excluded. Following full-text screening of 189 citations, 163 were excluded and twenty-six publications (twenty-five studies) were included (Fig. 1). One study published in Chinese[37] and one published in German[38] were translated to English. Two studies reported secondary analysis of data from the Infant Feeding Practices study II[39,40]. Four publications (three studies) had no extractable data for any outcomes[37,41–43]; thus, twenty-two studies comprising 301 622 infants were included in the meta-analysis.

Characteristics of the selected studies

All the included studies were observational, with the majority being cohort studies; thirteen were prospective[19,37,44–54], eleven were retrospective[20,38–43,55–59] and one was a retrospective case–control study[60] (Table 1). All but three studies[38,44,45] were published after 2010. The studies were conducted in both developed and developing countries, including the USA, Germany, Finland, Sweden, Greece, Portugal, the UK, Canada, Australia, Singapore, Israel, China, India, Vietnam, Brazil, Colombia, Kenya and South Africa, and were carried out in various settings, such as tertiary hospitals, university hospitals, community clinics and research centres.

GDM was diagnosed using a one-step 2-h 75 g oral glucose tolerance test in six studies[37,43,51,52,54,60]; one-step 3-h oral glucose tolerance test in one study[45]; 50 g polycose screen followed by 2-h 75 g oral glucose tolerance test in two studies[49,55] and 3-h oral glucose tolerance test in four studies[41,42,44,46,53]; or by maternal report in six studies[39,40,50,56–58]. Diagnostic criteria for GDM were unclear in six studies[19,20,38,47,48,59].

No study had low risk of bias for all domains (Table 2). Only seven studies adjusted for potential confounding[19,39,40,50,52,54,59] and nine studies were at high risk of bias due to possible confounding[20,38,43,45–48,53,60]. Seven studies had high risk of bias relating to ascertainment of exposures[38,39,42,47,48,50,59] because exposures were not measured prior to outcomes of interest or were not well defined[38,47,48,59].

Primary outcomes

None of the included studies reported on energy intake. Very low-quality evidence showed that infants who were and were not exposed to GDM had similar BMI at both 1–6 months (SMD 0·01, 95 % CI −0·04, 0·06; $P = 0·69$, $I^2 = 81$ %; two studies, 23 587 infants)[55,60] and 7–12 months (SMD 0·04, 95 % CI −0·01, 0·10; $P = 0·09$, $I^2 = 37$ %; four studies, 22 612 infants)[44,45,55,60] (Table 3; online Supplementary Fig. S1). Data were not available for BMI in infants aged 13–24 months, nor for planned subgroup analyses. In sensitivity analyses, exclusion of two studies with high risk of bias[45,60] did not alter results.

Secondary outcomes

Feeding patterns and behaviour. Very low-quality evidence showed that infants who were and were not exposed to GDM had similar rates of exclusive or predominant breast-feeding at ≥5 months of age (19·5 % *v.* 21·0 %, OR 0·89, 95 % CI 0·79, 1·01; $P = 0·07$, $I^2 = 65$ %; five studies, 30 799 infants)[49,51,54,55,58] and rates of no breast milk under 5 months of age (18·9 % *v.* 17 %, OR 1·00, 95 % CI 0·96, 1·03; $P = 0·89$, $I^2 = 81$ %; seven studies, 263 755 infants)[39,49,51,55–58] (Table 3; online Supplementary Figs S2 and S3). However, infants born to mothers with GDM were more likely to receive formula milk/breast milk substitute before hospital discharge (OR 1·36, 95 % CI 1·22, 1·51; $P < 0·00001$, $I^2 = 56$ %; five studies, 29 089 infants)[40,47,50,52,59] (Table 3; online Supplementary Fig. S4).

Infants who were exposed to GDM compared with those not so exposed were less likely to have continued breast-feeding at 12 months (65·2 % *v.* 73·7 %, OR 0·66, 95 % CI 0·51, 0·85;

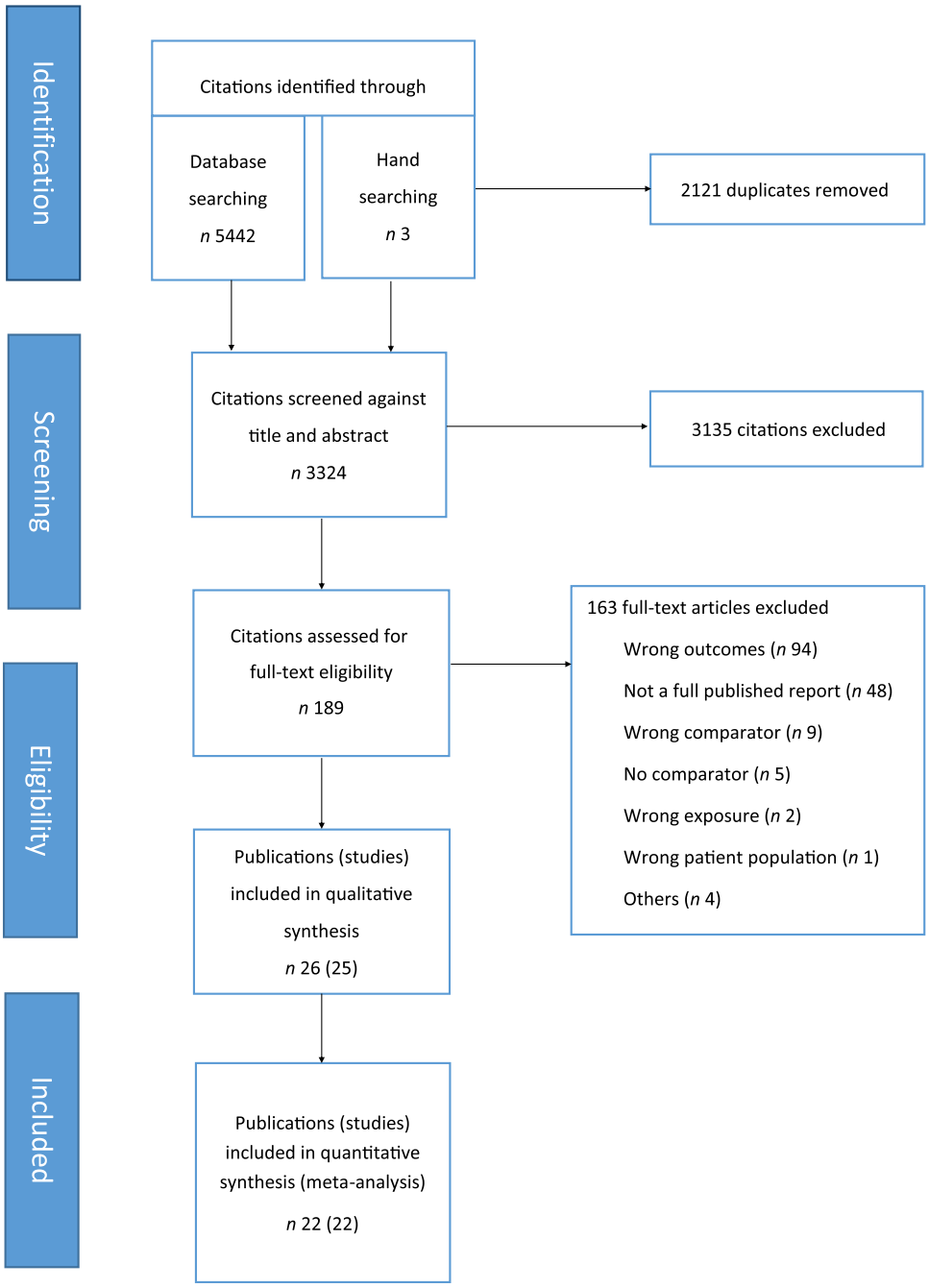

Fig. 1. Study identification, inclusion and exclusion.

$P = 0{\cdot}002$; one study, 1709 infants; low-quality evidence)[52] (Table 3; online Supplementary Fig. S5). Moreover, infants exposed to GDM compared with those not exposed to GDM had shorter duration of breast-feeding (months) (SMD −0·19, 95 % CI −0·26, −0·12; $P < 0{\cdot}00001$, $I^2 = 76\,\%$; five studies, 9176 infants; very low-quality evidence)[19,20,38,40,50] (Table 3; online Supplementary Fig. S6). No data were available for introduction of solid, semi-solid or soft foods before 5 months of age, nor for appetitive scores.

Nutritional intake. Very low-quality evidence showed that mature breast milk of women with GDM compared with women without GDM did not differ in total energy content, lactose and fat content but had lower protein content (SMD −0·36, 95 % CI −0·68, −0·04; $P = 0{\cdot}03$, $I^2 = 0\,\%$; two studies, 272 infants)[48,53] (Table 3; online Supplementary Fig. S7). No data were available for diet diversity, food group frequency and macronutrient intake.

Growth. At 1–6 months, low-quality evidence showed that infants who were exposed to GDM compared with those not exposed to GDM did not differ in weight but were shorter (SMD −0·09, 95 % CI −0·14, −0·04; $P = 0{\cdot}0008$, $I^2 = 0\,\%$; four studies, 25 365 infants)[46,49,54,55] (Table 3; online Supplementary Figs S8 and S9).

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Table 1. Characteristics of included studies

Study and location	Study design and setting	Exposure group	Control group	GDM testing and diagnostic criteria	Infant age at follow-up	Included in meta-analysis	Adjustment for potential confounding (covariates)
Vohr *et al.*[44], USA	Prospective cohort study Primary teaching hospital	*n* 94 Infants of GDM mothers LGA and AGA	*n* 99 Infants of non-GDM mothers LGA and AGA	Test: 2 step*; 3 h 100 g OGTT Diagnosis: 1 h 50 g glucose screen value ≥7·2 mmol/l and ≥2 abnormal PGC in OGTT (fasting ≥5·8 mmol/l, 1 h ≥ 10·6 mmol/l, 2 h ≥ 9·2 mmol/l, 3 h ≥ 8·1 mmol/l)[61,62]	1 year	Yes	No
Krishnaveni *et al.*[45], India	Prospective cohort study Tertiary hospital	*n* 41† Infants of diabetic mothers	*n* 548 Infants of non-diabetic mothers and fathers	Test: 1 step; 3 h 100 g OGTT Diagnosis: ≥2 abnormal PGC (fasting ≥5·3 mmol/l, 1 h ≥ 10·0 mmol/l, 2 h ≥ 8·7 mmol/l and 3 h ≥ 7·8 mmol/l)	1 year, 2 years and 5 years	Yes	No
Hummel *et al.*[38], Germany	Retrospective cohort study Diabetes research institute	*n* 257 Infants of mothers with GDM	*n* 527 Infants of non-diabetic healthy mothers but fathers with type 1 diabetes	Diagnosis unclear	9 months and 2 years	Yes	No
Crume *et al.*[41], USA The EPOCH study	Retrospective cohort study Tertiary hospital	*n* 95 Infants of diabetic mothers	*n* 409 Infants of non-diabetic mothers	Test: 2 step; 3 h 100 g OGTT Diagnosis: 1 h 50 g screen value ≥7·8 mmol/l and ≥2 abnormal PGC in OGTT (fasting ≥5·8 mmol/l, 1 h ≥ 10·6 mmol/l, 2 h ≥ 9·2 mmol/l and 3 h ≥ 8·1 mmol/l)[61]	8 months, 1 year, 26 months, 3 years, 6 years, 9 years and 13 years	No	No
Crume *et al.*[42], USA The EPOCH study	Retrospective cohort study Tertiary hospital	*n* 94 Infants of diabetic mothers	*n* 399 Infants of non-diabetic mothers	Test: 2 step; 3 h 100 g OGTT Diagnosis: 1 h 50 g screen value ≥7·8 mmol/l and ≥2 abnormal PGC in OGTT (fasting ≥5·8 mmol/l, 1 h ≥ 10·6 mmol/l, 2 h ≥ 9·2 mmol/l and 3 h ≥ 8·1 mmol/l)[61]	8 months, 1 year, 26 months, 3 years, 6 years, 9 years and 13 years	No	No
Finkelstein *et al.*[59], Canada	Retrospective cohort study Data from BORN Niday Perinatal Database, an Internet-based birth record system	*n* 1291 Infants of mothers with GDM	*n* 23 291 Infants of non-diabetic mothers	Diagnosis unclear	Post-birth hospital stay	Yes	Yes Maternal age, income, education, area of residence, parity, first trimester visit, antenatal classes, healthcare provider and small for gestational age
Hummel *et al.*[19], USA, Sweden, Finland, Germany The TEDDY birth cohort study	Prospective cohort study Clinical research centre	*n* 404‡ Infants born to mothers with GDM	*n* 5866 Infants of non-diabetic mothers with no family history of diabetes	Diagnosis unclear	3, 6, 9, 12, 18, 24 months	Yes	Yes Maternal smoking status, pre-pregnancy BMI, pregnancy weight gain, infant sex, maternal age, birth order, country and maternal education, delivery mode, gestational age, Apgar score and birth weight

Table 1. (*Continued*)

Study and location	Study design and setting	Exposure group	Control group	GDM testing and diagnostic criteria	Infant age at follow-up	Included in meta-analysis	Adjustment for potential confounding (covariates)
Konig *et al.*[60], Germany	Retrospective case–control study University hospital	*n* 130 Infants of diabetic mothers	*n* 77 Infants of non-diabetic mothers	Test: 1 step; 2 h 75 g OGTT Diagnosis: 1 or 2 abnormal values as recommended by 1) ADA and NDDG (fasting ≥5·8 mmol/l, 1 h ≥ 10·6 mmol/l, 2 h ≥ 9·2 mmol/l and 3 h ≥ 8·1 mmol/l)[62] or by 2) the Hesse Diabetes Society (fasting ≥5·0 mmol/l, 1 h postprandial ≥8·9 mmol/l, 2 h postprandial ≥7·8 mmol/l)	6–7 months, 10–12 months Outcomes were recorded from the child's medical check-up booklet	Yes	No
Kramer *et al.*[46], Canada	Prospective cohort study Tertiary hospital	*n* 90 Infants of mothers with GDM	*n* 250 Infants of mothers without GDM	Test: 2 step; 3 h 100 g OGTT Diagnosis: abnormal or normal 1 h 50 g GCT and ≥2 abnormal PGC (fasting ≥5·8 mmol/l; 1 h ≥ 10·6 mmol/l; 2 h ≥ 9·2 mmol/l or 3 h ≥ 8·1 mmol/l)[61]	3 months	Yes	No
Liu *et al.*[55], China	Retrospective cohort study Primary hospitals, health centres and tertiary hospitals	*n* 1420§ Infants of mothers with IGT or IFG and newly diagnosed DM	*n* 23 508 Infants of mothers with normal GCT	Test: 2 step; 2 h OGTT Diagnosis: 1 h 50 g GCT screen value ≥7·8 mmol/l and abnormal PGC in OGTT according to WHO diagnostic criteria[63], including women diagnosed with IGT (fasting <7·0 mmol/l and 2 h ≥ 7·8 to 11·1 mmol/l), IFG (fasting ≥6·1 mmol/l and <7·0 mmol/l and 2 h < 7·8 mmol/l) and new DM (fasting ≥7·0 mmol/l or 2 h ≥ 11·1 mmol/l)	3, 6, 9, 12 months	Yes	No
Uebel *et al.*[54], Germany GesA-Study	Prospective cohort study Tertiary hospital	*n* 16 Infants of obese women (BMI > 30 kg/m^2) with GDM	*n* 13‖ Infants of obese women without GDM	Test: 1 step; 2 h 75 g OGTT Diagnosis: ≥1 PGC (fasting ≥5·1 mmol/l or 1 h ≥ 10·0 mmol/l or 2 h ≥ 8·5 mmol/l)[64]	Week 6, 4 months, 1 year	Yes	Yes Infant sex, pregnancy duration, breast-feeding
Oza-Frank *et al.*[56], USA	Retrospective cohort study National sample from PRAMS	*n* 6652¶ Infants of mothers with GDM	*n* 64 702 Infants of mothers without diabetes	Self-report of GDM	2–4 months	Yes	No
Chertok *et al.*[47], Israel	Prospective cohort study Tertiary hospital	*n* 32 Infants of mothers with GDM	*n* 35 Infants of mothers without GDM	Diagnosis unclear	Post-birth hospital stay	Yes	No
Dritsakou *et al.*[48], Greece	Prospective cohort study Tertiary hospital	*n* 27 Infants of mothers with diet-controlled GDM	*n* 183 Infants of mothers without GDM	Diagnosis unclear	3rd, 7th, and 30th day of lactation	Yes	No

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Table 1. (*Continued*)

Study and location	Study design and setting	Exposure group	Control group	GDM testing and diagnostic criteria	Infant age at follow-up	Included in meta-analysis	Adjustment for potential confounding (covariates)
Hakanen *et al.*[43], Finland	Retrospective cohort study Clinics and school nurse	*n* 417** Infants of mothers with GDM	*n* 5688 Infants of mothers without GDM	Test: 1 step; 2 h 75 g OGTT Diagnosis: ≥1 abnormal PGC in OGTT (fasting ≥4·8 mmol/l, 1 h ≥ 10·0 mmol/l and 2 h ≥ 8·7 mmol/l)	6 months, 1 year, 2 years, 5 years, 7 years and 12 years	No	No
Logan *et al.*[49], UK	Prospective cohort study Tertiary hospital	*n* 42 Infants of mothers with GDM	*n* 44 Infants of mothers without GDM	Test: 2 step; 2 h 75 g OGTT Diagnosis: 1 h 50 g glucose screen PGC ≥ 7·8 mmol/l and fasting PGC ≥ 5·3 mmol/l or 2 h ≥ 7·8 mmol/l	2 weeks, 8–12 weeks	Yes	No
Oza-Frank *et al.*[50], USA Moms2Moms (M2M) study	Prospective cohort study University medical centre	*n* 34 Infants of mothers with GDM	*n* 398 Infants of mothers without GDM	Diagnosis by ICD-9 codes obtained from maternal medical records[65]	12 months	Yes	Yes Parity
Zhao *et al.*[58], Australia, Brazil, Canada, China, Colombia, Finland, India, Kenya, Portugal, South Africa, UK and USA The International Study of Childhood, Obesity, Lifestyle and the Environment (ISCOLE)	Retrospective cohort study Schools	*n* 206 Infants of mothers with GDM	*n* 4534 Infants of mothers without GDM	Self-report of GDM Two diagnostic criteria were used during the study period, either WHO (2 h 75 g OGTT, fasting PGC ≥ 7·0 mmol/l or 2 h ≥ 7·8 mmol/l)[66] or ADA (3 h 100 g OGTT, fasting PGC ≥ 5·3 mmol/l, 1 h ≥ 10·0 mmol/l, 2 h ≥ 8·6 mmol/l or 3 h ≥ 7·8 mmol/l)[67]	9–11 years	Yes	No
Zhao *et al.*[37], China	Prospective cohort study University hospital	*n* 70 Infants of mothers with GDM	*n* 154 Infants of mothers without GDM	Test: 1 step; 75 g OGTT at 28–30 weeks (also 12 weeks in high risk women) Diagnosis: included women with IGT (fasting PGC < 7·0 mmol/l and 2 h ≥ 7·8 to 11·1 mmol/l), IFG (fasting PGC ≥ 6·1 mmol/l and <7·0 mmol/l and 2 h < 7·8 mmol/l) and new DM (fasting PGC ≥ 7·0 mmol/l or 2 h ≥ 11·1 mmol/l)[63]	3, 6, 12 months	No	No
Aris *et al.*[51], Singapore GUSTO study	Prospective cohort study University hospital	*n* 181 Infants of mothers with GDM	*n* 835 Infants of mothers without GDM	Test: 1 step; 2 h 75 g OGTT Diagnosis: fasting PGC ≥ 7·0 mmol/l or 2 h ≥ 7·8 mmol/l	3, 6, 9, 12, 15, 18, 24, 36 months	Yes	No
Oza-Frank *et al.*[57] USA	Retrospective cohort study National sample from PRAMS	*n* 14 409 Infants of mothers with GDM	*n* 142 778 Infants of mothers without GDM	Self-report of GDM	2–6 months	Yes	No

Table 1. (*Continued*)

Study and location	Study design and setting	Exposure group	Control group	GDM testing and diagnostic criteria	Infant age at follow-up	Included in meta-analysis	Adjustment for potential confounding (covariates)
Wallenborn *et al.*[39], USA	Retrospective cohort study Data obtained from IFPS II study[68]	*n* 310 Infants of mothers with GDM	*n* 4134 Infants of mothers without GDM	Self-report of GDM	1 month–6 years	Yes	No
Weisband *et al.*[40], USA	Retrospective cohort study Data obtained from IFPS II study[68]	*n* 160 Infants of mothers with GDM	*n* 2139 Infants of mothers without GDM	Self-report of GDM	1 month–6 years	Yes	Yes Maternal age, race, WIC support, household income, smoking during third trimester, planning to go to birth, first birth, pregnancy BMI
Nguyen *et al.*[52], Vietnam	Prospective cohort study Tertiary hospital	*n* 373 Infants of mothers with GDM	*n* 1336 Infants of mothers without GDM	Test: 1 step; 2 h 75 g OGTT Diagnosis: ≥1 abnormal PGC in OGTT (fasting PCG ≥ 5·1 mmol/l, 1 h ≥ 10·0 mmol/l and 2 h ≥ 8·5 mmol/l)	At discharge, 1, 3, 6 and 12 months	Yes	Yes Maternal age, occupation, maternal education, parity, gestational age, birth weight, caesarean section and infant admission to NICU
Dugas *et al.*[20], Canada	Retrospective cohort study Research centre	*n* 62 Infants of mothers with GDM	*n* 32 Infants of mothers without GDM	Diagnosis unclear	2–14 years	Yes	No
Shapira *et al.*[53], Israel	Prospective cohort study	*n* 31 Infants of mothers with GDM	*n* 31 Infants of mothers without GDM	Test: 2 step; 100 g OGTT Diagnosis: 1 h 50 g screen PGC ≥ 7·8 mmol/l and ≥2 abnormal PGC in OGTT (fasting ≥5·8 mmol/l, 1 h ≥ 0·6 mmol/l, 2 h ≥ 9·2 mmol/l and 3 h ≥ 8·1 mmol/l)[62]	72 h after delivery, 7 d postpartum and 14 d postpartum	Yes	No

GDM, gestational diabetes mellitus; LGA, large for gestational age; AGA, appropriate for gestational age; OGTT, oral glucose tolerance test; PGC, plasma glucose concentration; EPOCH, Exploring Perinatal Outcomes among Children; BORN, The Better Outcomes Registry and Network; TEDDY, The Environmental Determinants of Diabetes in the Young; ADA, American Diabetic Association; NDDG, National Diabetes Data Group; GCT, glucose challenge test; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; DM, diabetes mellitus; PRAMS, The Pregnancy Risk Assessment Monitoring System; ICD, International Classification of Diseases; GUSTO, Growing Up in Singapore Towards Healthy Outcomes; IFPS, The Infant Feeding Practices Study; WIC, The Women, Infants and Children's program; NICU, neonatal intensive care unit; T1D, type 1 diabetes.

* In the two-step approach, women are screened at 24 to 28 weeks' gestation by a non-fasted 1 h, 50 g oral glucose challenge test; women who screen positive for this test subsequently undergo a diagnostic OGTT.

† *n* 41 Offspring of diabetic fathers.

‡ *n* 292 Infants born to mother with T1D, *n* 464 Infants who have mother without T1D but a father and/or sibling with T1D.

§ *n* 2229 Infants born to mothers with positive GCT and normal OGTT.

‖ *n* 15 Infants born to lean mothers without GDM.

¶ *n* 1401 Infants born to mothers with pre-gestational diabetes.

** *n* 53 Infants born to mother with T1D are included in the respective cohorts but not included for analysis.

Table 2. Risk of bias assessment of included studies

Authors	Domain					
	Selection of comparison of groups	Confounding	Ascertainment of exposures	Measurement of outcomes	Missing data	Reporting of results
Vohr *et al.*[44]	Low	Uncertain	Low	Uncertain	Uncertain	Low
Krishnaveni *et al.*[45]	Low	High	Low	Uncertain	Low	Low
Hummel *et al.*[38]	Uncertain	High	High	Uncertain	Low	Low
Crume *et al.*[41]	Low	Low	Uncertain	Uncertain	Uncertain	Low
Crume *et al.*[42]	Uncertain	Low	High	Uncertain	Uncertain	High
Finkelstein *et al.*[59]	Low	Low	High	Uncertain	Low	Low
Hummel *et al.*[19]	Low	Low	Uncertain	Uncertain	Low	Low
Konig *et al.*[60]	Uncertain	High	Low	Uncertain	Uncertain	Low
Kramer *et al.*[46]	Low	High	Low	Uncertain	Low	Low
Liu *et al.*[55]	Low	Low	Low	Uncertain	Low	Low
Uebel *et al.*[54]	Low	Low	Low	Uncertain	Uncertain	Low
Oza-Frank *et al.*[56]	Low	Low	Uncertain	Uncertain	Uncertain	Low
Chertok *et al.*[47]	Low	High	High	Uncertain	Uncertain	Low
Dritsakou *et al.*[48]	Uncertain	High	High	Uncertain	Uncertain	Low
Hakanen *et al.*[43]	Low	High	Uncertain	Low	Uncertain	Low
Logan *et al.*[49]	Low	Low	Low	Uncertain	Uncertain	Low
Oza-Frank *et al.*[50]	Low	Low	High	Uncertain	Uncertain	Uncertain
Zhao Pei *et al.*[58]	Low	Uncertain	Uncertain	Uncertain	Uncertain	Low
Zhao Y *et al.*[37]	Low	Uncertain	Uncertain	Uncertain	Uncertain	Low
Aris *et al.*[51]	Low	Low	Low	Uncertain	Uncertain	Low
Oza-Frank *et al.*[57]	Low	Low	Uncertain	Uncertain	Low	Low
Wallenborn *et al.*[39]	Low	Uncertain	High	Uncertain	Low	Low
Weisband *et al.*[40]	Low	Low	Uncertain	Uncertain	Uncertain	Low
Nguyen *et al.*[52]	Low	Low	Low	Uncertain	Uncertain	Low
Dugas *et al.*[20]	Low	High	Uncertain	Uncertain	Low	Uncertain
Shapira *et al.*[53]	Low	High	Low	Uncertain	Low	Low

Table 3. GRADE summary of quality of evidence for feeding and growth outcomes (Odds ratios or standardised mean differences (SMD) and 95 % confidence intervals)

Outcome	Infants	Studies	Exposure effect		Quality of evidence	Comments
			OR or SMD	95 % CI		
Epoch 1: infants 1–6 months*						
BMI *z*-score or standardised score	23 587	2	0·01	−0·04, 0·06	Very low	Initial level low; downgraded for substantial heterogeneity and indirectness in reporting of outcomes in one study†
Exclusive or predominant breast-feeding at ≥5 months of age	30 799	5	0·89	0·79, 1·01	Very low	Initial level low; downgraded for substantial heterogeneity and indirect exposure‡
Introduction of formula milk or breast milk substitute before hospital discharge	29 089	5	1·36	1·22, 1·51	Very low	Initial level low; downgraded for substantial heterogeneity and indirect exposure‡§
No breast milk feeding under 5 months	263 755	7	1·00	0·96, 1·03	Very low	Initial level low; downgraded for substantial heterogeneity and indirect exposure‡‖
Breast milk (mature milk) energy standardised score	272	2	0·15	−0·17, 0·47	Very low	Initial level low; downgraded for risk of bias, substantial heterogeneity, imprecise results and indirect exposure§
Breast milk (mature milk) lactose standardised score	272	2	−0·13	−0·44, 0·18	Very low	Initial level low; downgraded for risk of bias, imprecise results and indirect exposure§
Breast milk (mature milk) crude protein standardised score	272	2	−0·36	−0·68, −0·04	Very low	Initial level low; downgraded for risk of bias, imprecise results and indirect exposure§
Breast milk (mature milk) fat standardised score	272	2	−0·11	−0·42, 0·21	Very low	Initial level low; downgraded for risk of bias, substantial heterogeneity, imprecise results and indirect exposure§
Weight for age *z*-score or standardised score	25 365	4	−0·04	−0·09, 0·02	Low	No change to initial level of low
Length for age *z*-score or standardised score	25 365	4	−0·09	−0·14, −0·04	Low	No change to initial level of low
Head circumference for age *z*-score or standardised score	24	1	−0·07	−0·88, 0·73	Very low	Initial level low; downgraded for imprecise results and indirect population‖

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Table 3. (*Continued*)

Outcome	Infants	Studies	Exposure effect: OR or SMD	Exposure effect: 95 % CI	Quality of evidence	Comments
Skinfold thickness for age *z*-score or standardised score	24	1	0·51	−0·31, 1·32	Very low	Initial level low; downgraded for imprecise results and indirect population‖
Fat mass for length *z*-score or standardised score	97	2	0·53	0·13, 0·94	Very low	Initial level low; downgraded for imprecise results and indirect population‖
Epoch 2: infants 7–12 months¶						
BMI *z*-score or standardised score	22 612	4	0·04	−0·01, 0·10	Very low	Initial level low; downgraded for indirectness in reporting outcomes in one study†
Weight for age *z*-score or standardised score	25 736	4	0·00	−0·05, 0·06	Low	No change to initial level of low
Length for age *z*-score or standardised score	25 736	4	−0·07	−0·13, −0·02	Low	No change to initial level of low
Abdominal circumference for age *z*-score or standardised score	219	2	0·07	−0·20, 0·33	Very low	Initial level low; downgraded for risk of bias and imprecise results
Head circumference for age *z*-score or standardised score	26	1	0·06	−0·71, 0·83	Very low	Initial level low; downgraded for imprecise results and indirect population**
Total skinfold thickness for age *z*-score or standardised score	219	2	−0·04	−0·31, 0·22	Very low	Initial level low; downgraded for risk of bias and imprecise results.
Triceps skinfolds for age *z*-score or standardised score	589	1	0·18	−0·13, 0·50	Very low	Initial level low; downgraded for risk of bias
Subscapular skinfold for age *z*-score or standardised score	589	1	0·23	−0·08, 0·55	Very low	Initial level low; downgraded for risk of bias
Fat mass for length *z*-score or standardised score	26	1	−0·06	−0·83, 0·71	Very low	Initial level low; downgraded for imprecise results and indirect population**
Epoch 3: infants 13–24 months***						
Continued breast-feeding at ≥12 months	1709	1	0·66	0·51, 0·85	Low	No change to initial level low
Duration of breast-feeding standardised score	9716	5	−0·19	−0·26, −0·12	Very low	Initial level low; downgraded for risk of bias and indirect exposure‡

GDM, gestational diabetes mellitus; PRAMS, The Pregnancy Risk Assessment Monitoring System.
* No data available for energy intake; introduction of solid-semi solid or soft foods before 5 months of age; appetitive scores; abdominal circumference and fat-free/lean mass.
† Weight for length *z*-score used as BMI *z*-score not available[55].
‡ Self-reported GDM history recalled by parents[39,40,58].
§ Unclear diagnosis of GDM[48,59].
‖ Self-reported GDM history obtained from PRAMS questionnaire[56,57].
¶ No data available for energy intake; appetitive score; breast milk composition; minimum diet diversity; food group frequency; macronutrient intake; fat-free/lean mass.
** Infants born to obese women with GDM compared with infants born to obese women without GDM[54].
*** No data available for energy intake; BMI; appetitive score; breast milk composition; minimum diet diversity; food group frequency; macronutrient intake; weight; length; abdominal circumference; head circumference; skinfold thickness; fat mass; fat-free /lean mass.

Very low-quality evidence showed that at 1–6 months, infants who were exposed to GDM compared with those not exposed to GDM did not differ in head circumference or skinfold thickness (sum of four skinfolds)[54] but had greater fat mass (SMD 0·53, 95 % CI 0·13, 0·94; $P = 0·010$, $I^2 = 0$ %; two studies, ninety-seven infants)[49,54] (Table 3; online Supplementary Figs S10, S12 and S13). No data were available for abdominal circumference or fat-free mass at 1–6 months of age.

At 7–12 months, low-quality evidence showed that infants who were exposed to GDM compared with those not exposed to GDM did not differ in weight but were again shorter (SMD −0·07, 95 % CI −0·13, −0·02; $P = 0·005$, $I^2 = 0$ %; four studies, 25 736 infants)[44,45,54,55] (Table 3; online Supplementary Figs S8 and S9). Very low-quality evidence showed that at 7–12 months, infants who were exposed to GDM compared with those not exposed to GDM did not differ in abdominal circumference[44,54], head circumference, skinfold thickness (sum of four skinfolds)[44,54], triceps skinfold[45], subscapular skinfold[45] and fat mass[54] (Table 3; online Supplementary Figs S10, S11, S12 and S13). No data were available for fat-free mass at 7–12 months or for any growth outcomes at 13–24 months of age.

Studies not included in quantitative synthesis

In the EPOCH study, GDM was not associated with altered mean infant BMI or BMI growth trajectory from birth to 26 months (n 504)[41], and rates of adequate breast-feeding, that is, breast-feeding ≥ 6 months (44 % *v.* 47 %, n 493; $P = 0·54$)[42]. This study had uncertain to high risk of bias (Table 2). A Finnish study (n 6609) found no difference in mean peak BMI between infants who were and were not exposed to GDM, although infant BMI peaked slightly earlier in those exposed to GDM (9·9 *v.* 10·4 months; $P = 0·05$)[43]. The study had high risk of bias for potential confounding (Table 2). A Chinese study found that among boys who were born with appropriate birth weight for gestation, those exposed to GDM compared with those who were not so exposed had less gain in weight and length from 3 to 6 months of age (mean weight 1. 1 (SD 0·4) *v.* 1. 4 (SD 0·4) kg, $P = 0·040$; length 4·9 (SD 2·3) *v.* 6·3 (SD 1·2) cm, $P = 0·026$), but not from birth to 3 months or from 6 to 13 months. No differences in growth were seen in girls who were and were not exposed to GDM. The study had uncertain risk of bias (Table 2)[37].

Discussion

We found low- to very low-quality evidence that the infants exposed to GDM, compared with infants not exposed, had similar BMI and weight to 12 months of age but were slightly shorter (about 0·5 cm) at 1–6 and 7–12 months. Nevertheless, infants exposed to GDM had increased total fat mass at 1–6 months (about 200 g) but not at 7–12 months. Subcutaneous fat, as measured by skinfold thickness, also did not differ in the first year. With regard to feeding, we found low to very low-quality evidence that infants exposed to GDM, compared with control infants, were about 40 % more likely to receive formula milk/breast milk substitute before hospital discharge, about 30 % less likely to have continued breast-feeding at 12 months and had about 1 month shorter mean duration of breast-feeding. Further, breast milk of women with GDM compared with women without GDM was similar in energy, fat and carbohydrate content but had about 4 g/l lower protein concentration. No data were available on energy intake, complementary feeding, infant appetitive traits and nutritional intake.

Rapid weight gain during early infancy, especially in fat mass, is associated with increased risk of childhood obesity[69,70]. Thus, our finding that infants born to women with GDM had increased whole-body fat mass at 3–4 months provide one possible explanation for the association between GDM and childhood obesity. An increase in fat mass of ≥ 200 g represents 75 % of the average monthly gain in fat mass at 3–6 months and is likely to be clinically important[70,71]. For example, in a mixed population of infants, 38 % of whom were exposed to GDM, the odds of overweight or obesity in mid-childhood was increased 8-fold for every additional 100 g in fat mass gained per month up to 8 months[70]. The fact that weight and BMI were similar between infants who were and were not exposed to GDM suggests that the accelerated gain in fat mass is associated with slower growth in fat-free mass. Further, given similar skinfold thickness between exposure groups, the increased fat deposition may be intra-abdominal, which in adolescents and adults is associated with greater risk of cardio-metabolic disease, especially type 2 diabetes[72–74]. Although fat mass was similar between exposure groups at 7–12 months, this does not preclude future effects of GDM on offspring body composition, as several longitudinal cohorts have shown that BMI trajectories of GDM and non-GDM cohorts converge about 12 months and only to separate again after 6 years of age[41,75,76].

One potential pathway for the increased fat gain in early infancy associated with GDM is reduced breast-feeding. WHO recommends initiation of breast-feeding within 1 h of birth, exclusive breast-feeding up to 6 months of age and continuation of breast-feeding along with complementary foods until at least 24 months of age[77–79]. Importantly, breast-feeding, compared with formula feeding, is associated with reduced risk of childhood obesity and metabolic disorders in adult life[10]. This may be related to lower overall energy intake in breastfed infants[80], or the influence of breast milk hormones on appetitive traits[17,81] and growth. Although we did not find that GDM was associated with reduced exclusive/predominant breast-feeding in the first 5 months, overall duration of breast-feeding was reduced and use of formula in hospital was substantially increased. The latter may be an important risk factor, as even brief supplementation with formula or protein in preterm infants has been associated with increased risk of later obesity[14]. It is interesting that breast milk of women with GDM had lower protein content, which might be expected to be protective against excess adiposity in infancy and obesity in childhood[82,83], although some studies in preterm infants have shown that lower protein intake is associated with a transient increase in fat mass in early infancy[84].

Although the effect size was small, a consistent finding in infants exposed to GDM at both the 1–6 and 7–12 months epochs was shorter length. The reasons for and long-term significance of this is unclear. It is evident that insulin is important for bone and muscle growth[85–87]. However, it has also been demonstrated that preterm infants exposed to higher concentrations of insulin have shorter leg length at term corrected age and reduced stature at mid-childhood[88,89]. A similar response may occur with fetal hyperinsulinism in GDM.

Limitations

A key limitation of this systematic review is a lack of high-quality data. This was primarily due studies being observational with several at high risk of bias due to confounding and ascertainment of exposures. The quality of evidence was also limited by imprecise estimates and heterogeneity. Moreover, no data were available for several outcomes, including the primary outcome of energy intake. Given the importance of early nutrition for long-term metabolic health[90], it is surprising that no studies have assessed the effect of GDM on infant energy intake, nutrition, complementary feeding and appetitive traits. The latter may be particularly important in explaining associations between GDM and obesity in offspring. For example, in animals, consumption of breast milk from GDM mothers affects satiety centres in the infant brain[17], leading to consumption of larger and more frequent feeds, and increased energy intake, thereby increasing the risk of obesity. Additionally, for some outcomes, there was insufficient information to draw any conclusion due to inadequate sample size. Thus, results of this review must be interpreted cautiously, and higher-quality evidence from large well-designed prospective cohort studies is needed.

Another limitation is that studies included in this review provided few data on maternal treatment of GDM and the degree of glycaemic control that was achieved. Only six studies provided data on the proportion of women treated with either diet or with medications, such as insulin, metformin or sulphonylureas[45,46,49,53,54,60]. Variations in treatment of GDM may have contributed to the substantial heterogeneity seen for several outcomes, as infants whose mothers have well controlled *v.* poorly controlled GDM are likely to be different. The varying approaches to screening and diagnosis of GDM may have also contributed to heterogeneity, as women meeting different diagnostic thresholds are known to be at different risk for perinatal complications[91]. We planned to explore the effect of higher and lower degrees of maternal dysglycaemia on infant outcomes, including whether women met higher or lower glycaemic thresholds for diagnosis, were treated or untreated, or had tighter

or less tight glucose control, but data were unavailable for this pre-specified subgroup analysis.

The association between GDM and infant feeding and growth outcomes may be confounded by maternal BMI, as larger maternal size is a risk factor for both GDM and offspring obesity[92]. We planned to use adjusted estimates of exposure effect in meta-analysis, but only two studies included maternal BMI as a covariate in regression analysis. Thus, this remains a potential source of bias that should be addressed in future studies. Similarly, there is some evidence to suggest that management of GDM with metformin compared with insulin may be associated with greater gains in subcutaneous fat in early childhood[93,94] and it will be important that future studies explore the effect of maternal mode of treatment on infant growth outcomes.

Recommendations for research

Given that the population of infants exposed to GDM is continuously on the rise, it is important that the effects of GDM on infant growth, nutrition and feeding, and underlying mechanisms, are elucidated. This review has outlined key infant outcomes and mechanistic pathways that should be evaluated in large prospective studies, including potentially modifiable factors, such as breast-feeding, use of formula in hospital and complementary feeding. Nested cohort studies within relevant clinical trials are the most suitable design to provide the highest quality evidence for the effect of GDM on infant outcomes. For example, clinical trials of GDM screening and diagnosis provide an opportunity to prospectively evaluate infant outcomes after different degrees of maternal dysglycaemia, with adjustment for potential confounding, including maternal BMI, age and socio-economic status. One such large study is currently underway (ACTRN12615000290594). It is also important that infant outcomes are fully assessed in GDM treatment trials to investigate the extent to which any adverse effects of GDM on offspring are preventable.

Conclusions

There was low- to very low-quality evidence that infants exposed to GDM, compared with those not exposed, have similar BMI from 1 to 12 months of age. No data were reported on energy intake. However, infants exposed to GDM had reduced length at 1–6 and 7–12 months, increase whole-body fat at 1–6 months, higher rates of formula supplementation in hospital, shorter duration of breast-feeding and decreased rates of continued breast-feeding at 12 months. Breast milk of women with GDM had lower protein content. There was no association between GDM and infant weight, skinfold thickness at 1–6 and 7–12 months. No data were available to assess the effect of GDM on macronutrient intake, diet quality, complementary feeding, appetitive traits, fat-free mass or outcomes at 13–24 months. Large, well-designed prospective cohort studies are needed to determine if the association between GDM and later risk of obesity and diabetes is mediated by altered infant feeding, nutrition and growth. This is an important knowledge gap that must be addressed if effective strategies are to be found to reverse intergenerational risks of obesity and type 2 diabetes mellitus related to GDM.

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K. M. drafted the protocol, conducted the literature search, performed hand-searching to identify additional studies, screened title, abstracts and full-texts, extracted data, assessed risk of bias and quality of evidence, analysed data and interpreted results and drafted the manuscript. C. M. contributed to the protocol, assessed full-text eligibility, extracted data, assessed risk of bias and quality of evidence, assisted in analysis and interpretation of data and assisted with drafting of the manuscript. J. H. contributed to the protocol, assessed full-text eligibility, extracted the data, assessed the risk of bias and critically reviewed the manuscript. C. C. contributed to the protocol, assessed full text eligibility and critically reviewed the manuscript.

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Supplementary material

For supplementary materials referred to in this article, please visit https://doi.org/10.1017/S0007114520000264

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