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Cardiovascular risk factors in offspring exposed to gestational diabetes mellitus *in utero*: systematic review and meta-analysis

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Review

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Abstract

Gestational diabetes mellitus (GDM) is a pregnancy complication that affects one in seven pregnancies. Emerging evidence demonstrates that children born of pregnancies complicated by GDM may be at increased risk of cardiovascular disease (CVD) in adulthood. Therefore, the aim of this study was to determine cardiovascular risk factors in offspring exposed to GDM *in utero*. PubMed, CINAHL, SCOPUS, and EMBASE databases were searched. Information was extracted on established CVD risk factors including blood pressure, lipids, blood glucose, fasting insulin, body mass index (BMI), and endothelial/microvascular function. The review protocol is registered in PROSPERO (CRD42018094983). Prospective and retrospective studies comparing offspring exposed to GDM compared to controls (non-GDM pregnancies) were considered. We included studies that defined GDM based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) definition, or prior definitions. The PRISMA guidelines were followed in conducting this systematic review. Methodological quality was assessed using the Newcastle–Ottawa Quality Assessment Scale. Study selection, data extraction, and quality assessment were done by two independent reviewers. The data were pooled using a random-effects model. Of 59 eligible studies, 24 were included in the meta-analysis. Offspring exposed to GDM had higher systolic blood pressure (mean difference (MD): 1.75 mmHg, 95% CI 0.57–2.94; eight studies, 7264 participants), BMI *z*-score (MD 0.11, 95% CI 0.02–0.20; nine studies, 8759 participants), and glucose (standard MD 0.43, 95% CI 0.08–0.77; 11 studies, 6423 participants) than control participants. In conclusion, offspring exposed to GDM have elevated systolic blood pressure, BMI, and glucose. Those exposed to GDM *in utero* may benefit from early childhood blood pressure measurements.

Introduction

The incidence of cardiovascular disease (CVD) has shown a rapid increase over the last decade. In 2012, there were an estimated 17.6 million deaths from CVD, accounting for 31.43% of global mortality.[1] Emerging evidence demonstrates an association between gestational diabetes mellitus (GDM) and CVD with risk factors for CVD being more prevalent among women who experienced gestational diabetes (GDM) compared to those who did not.[1,2]

Prevalence of GDM varies between populations, but it is estimated to affect one in seven pregnancies.[3] The definition of GDM has changed over recent years, as it has become apparent that mild glucose intolerance in pregnancy which was not formerly considered as GDM increases the risk of developing type 2 diabetes mellitus (T2DM) and CVD in later life.[4] A recent meta-analysis showed a 7.5-fold increase in the risk of T2DM among women who experience GDM.[2]

Emerging evidence also suggests that children born after pregnancies complicated by GDM may also be at increased risk of CVD in adult life. Tam *et al.* showed that for every 1-SD (standard deviation) increase in maternal glycemic level, there was an increase in the adjusted odds ratio for impaired glucose tolerance in the offspring.[5] A meta-analysis conducted by Aceti *et al.* and colleagues demonstrated that systolic blood pressure (SBP) was higher in offspring of women who experienced GDM than controls.[6]

At present, there is no systematic review comparing the main conventional CVD risk factors between offspring exposed to GDM *in utero* compared to controls. Both vascular and metabolic CVD risk factors constitute metabolic syndrome which is a well-established risk factor for CVD.[1] Therefore, synthesizing evidence on all CVD risk factors will provide important information that can guide preventive strategies to reduce the global burden of CVD.

The primary objective of this study was to conduct a comprehensive systematic review and meta-analyses of all relevant studies published until October 2018 to assess conventional CVD risk factors including SBP and diastolic blood pressure (DBP), body mass index (BMI), lipids,

blood glucose, and insulin levels. As a secondary objective, we aimed to assess all relevant studies that assessed microvascular function.

Methods

Search strategy

All studies describing the association between GDM and offspring CVD risks were identified by searching the following electronic databases: PubMed CINAHL, SCOPUS, and EMBASE with an end of search date of April 18, 2018. Subsequently, we updated the literature search to include all relevant articles published until October 17, 2018. The review protocol is registered in PROSPERO (CRD42018094983). No amendments have been made to the current protocol.

The review was undertaken with reference to the PRISMA guidelines.[7] The search strategy is as follows: ("gestational diabetes*" OR "pregnancy induced diabetes" OR "diabetic pregnancy") AND (offspring OR newborn OR baby OR babies OR children OR infant OR neonate* OR adolescent* OR adult) AND ("blood pressure" OR diabetes OR cardiovascular OR metabolic OR hypertension OR BMI or "body mass index" OR obesity OR overweight OR lipids OR lipid OR cholesterol OR triglyceride* OR glucose OR insulin OR vascular). We included case–control studies, cohort studies, and clinical trials. Conference abstracts were also screened. Previous systematic reviews and meta-analyses on relevant topics were identified, and references from eligible reviews were checked for additional studies. All identified studies were assessed for relevance by two independent authors (MMP and PHA). Data were independently extracted by two authors (MMP and PHA). Discrepancies were resolved by discussion.

Inclusion criteria

The population of interest and exposure were offspring at any follow-up visit born to women who experienced GDM during pregnancy. We selected studies that assessed conventional CVD risk factors in offspring exposed to GDM *in utero* compared to offspring not exposed to GDM *in utero*. The CVD risk factor outcomes were blood pressure, BMI, serum and cord blood lipids, and serum and cord blood insulin and glucose.

We included studies that defined GDM based on the IADPSG. However, as diagnostic criteria have recently changed, we included studies that used prior diagnostic criteria of GDM including the 1999 World Health Organization definition, and other regional definitions. The definitions of GDM of included studies are detailed in Table 1. Studies that did not have the above definition/s of GDM, those that did not define study groups, and those that compared GDM and another risk group collectively were excluded. Studies that compared offspring exposed to GDM with offspring exposed to impaired glucose tolerance *in utero* were included in the review but were not included in the meta-analysis. The data from these studies are presented in Supplementary Table S1.

Data were extracted independently and in duplicate for outcomes SBP, DBP, BMI, serum and cord lipid levels (total cholesterol, low-density lipoprotein (LDL) high-density lipoprotein (HDL), non-HDL, and triglycerides), blood glucose, fasting insulin, and measures of vascular/endothelial function. When the same cohort was reported in multiple publications at different ages, the study reporting on the older age group was included in the meta-analysis. We considered both studies published in English and studies that could be translated to English. We contacted authors via email for missing information or data clarification if necessary, and if authors did not respond, then any relevant data from their respective studies are included in Supplementary Table S1.

Statistical analysis

The following data were collected from each included study: definition of GDM, age of offspring at follow-up, number of cases/exposed to GDM *in utero* and controls/not exposed to GDM *in utero*, and birthweight and gestational age at birth of cases and controls. For each outcome measure, mean and SD were used in meta-analyses. When mean and SD were not reported, standard error of mean and 95% CI were converted to SD via statistical software.[8] For studies reporting using median and interquartile range, the results are detailed in Supplementary Table S1. The standard mean difference (SMD) or mean difference (MD) and the 95% CI were calculated using a random-effects model. SMD was used when the outcome was measured in different units across trials and MD when units were consistent.

The meta-analysis was performed using Cochrane Collaborations RevMan software (Review Manager, Version 5.3, The Nordic Cochrane Centre, Copenhagen) based on an inverse variance method. As per protocol, the random-effects model was selected to account for the variation in different criteria used to diagnose GDM among the studies. However, to ensure that the results were not influenced by the choice of model, each analysis was repeated using a fixed-effects model. No difference in results was seen between the two models (results not shown). Substantial heterogeneity was considered when I^2 statistic exceeded 50%, and the χ^2 P value was less than 0.1. To assess publication bias, funnel plots were used. The methodological quality and risk of bias were assessed using Newcastle–Ottawa Quality Assessment Scale (Supplementary Table S2).[9] Sensitivity analyses were performed to evaluate heterogeneity for outcomes when omitting low-quality studies. Two authors (MMP, PHA) independently assessed the quality of each study included in the review. The discrepancies were resolved through discussions.

Results

A total of 4359 articles were identified from the literature search. One hundred and twelve articles were eligible for full-text review. Of these, 59 were included in the review and 25 were included in the meta-analyses. The reasons for excluding 53 studies are detailed in Fig. 1. We contacted nine authors for additional data, with responses from four authors (44.4% response); however, the authors of these four studies did not have data that could be used in the meta-analyses and hence are included in Supplementary Table S1.

The assessment of methodological quality identified 25 studies of high quality (scored 7–8), 25 studies of moderate quality (scored 4–6), and 9 studies of low quality (scored 1–3) (Supplementary Table S2). No publication bias was evident for relevant outcomes. Studies were found for all relevant outcomes, except microvascular function, and therefore, we could not report on this outcome in the review.

Systolic blood pressure

SBP data were available from 15 studies, of which 8 were included in the meta-analysis. The age of follow-up of offspring ranged from 3 to 16 years. Based on quantitative summary measures, the meta-analysis demonstrated that offspring exposed to GDM *in utero*

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Table 1. Characteristics of the included studies

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Kaseva *et al.*[79]	2018	Multicohort study	Finland	(Both cohorts): OGTT at 26–28 weeks: indications for screening: glycosuria, prior GDM, suspected fetal macrosomia, previous macrosomic infant (birthweight 4500 g), maternal prepregnancy BMI ≥25 kg/m^2, and maternal age ≥40 years Overnight fasting by using a 75-g oral glucose load. Cutoff limits for GDM were used for venous blood glucose: >5.5mmol/l at fasting, >11.0 mmol/l and >8.0mmol/l, 1 and 2 h after the glucose load, respectively. A diagnosis of GDM was made with one abnormal value in the OGTT	191/547	ESTER cohort: 3651 (601)/3519 (466) ALYS cohort: 3881 (648)/3555 (462)	ESTER cohort: 39.0 (1.8)/39.8 (1.5) ALYS cohort: 39.0 (1.5)/40.0 (1.3)	23–25 years after delivery	BMI (kg/m^2)
Kearney *et al.*[26]	2017	Cohort study	USA	Based on hospital records from two major hospitals with a neonatal care unit in the metropolitan area of Québec City (Hôpital Saint-François d'Assise, Centre Hospitalier de l'Université Laval – CHUL) or according to administrative data from the provincial health plan registry (Régie de l'assurance maladie du Québec)	56/30	3346 ± 442/3267 ± 558	38.8 ± 1.4/ 39.5 ± 1.2	Between 3 and 12 years after delivery	BMI (kg/m^2) BMI *z*-score
Le Moullec *et al.*[47]	2018	Cohort study	France	Confirmed based on hospital, medical records with following criteria: positive screening for GDM based on a OGTT (1-h postload 50-g plasma glucose, 11.1 mmol/l), had a diagnosis of GDM based on a 100-g OGTT (OGTT with at least two pathologic values defined as: fasting, −5.3 mmol/l; 1 h, 10.0 mmol/l; 2 h, 8.6 mmol/l; 3 h, 7.8 mmol/l), and/or had received insulin treatment during pregnancy. A small number of participants (<0.5%; $n = 6$) with no available data were also classified into the GDM group if they combined high fasting (or postprandial) glycemic values with intense medical monitoring during pregnancy	600/600	3183 ± 563/ 3047 ± 500	Not reported	Average 6 years after delivery	BMI centile
Miettinen *et al.*[50]	2018	Cohort study	Finland	An oral 75-g, 2-h glucose tolerance test (OGTT) was performed for all subjects at weeks 22–29 of pregnancy, with the exception of three subjects with OGTT performed at weeks 31–33. OGTT was considered diagnostic for GDM if any of the measures were pathological. The following diagnostic thresholds were used: fasting plasma glucose >5.3 mmol/ l, 1-h plasma glucose (10.0 mmol/l) or 2-h plasma glucose (8.6 mmol/l)	15/13	3500 ± 120/ 3540 ± 130	39.8 ± 0.33/ 40.54.7 ± 0.32	After birth	Cord blood total cholesterol, lipids (mmol/l)

Table 1. (*Continued*)

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Wang *et al.*[78]	2019	Population-based cohort study	China	Based on American diabetes association	1500/23,471	Not reported	39.1 ± 1.1/ 39.3 ± 1.1	6 years	BMI *z*-score
Hammoud *et al.*[80]	2017	Cohort study	The Netherlands	75-g OGTT or elevated fasting glucose (exact cutoffs not shown)	24/T1D: 27, T2D: 22	3582 ± 576/T1D: 3506 ± 556, T2D: 3701 ± 509	39 ± 2.0/T1D: 37 ± 1.3, T2D: 38 ± 1.7	5 years after delivery	Overweight/obese
Li *et al.*[37]	2017	Prospective cohort study	USA	Self-reported questionnaire	756/14,253	No mean reported	Not reported	11 years after delivery	BMI
Tam *et al.*[5]	2017	Longitudinal cohort study	Hong Kong	All women underwent a standard 75-g OGTT between 24 and 32 weeks of gestation, GDM diagnosed based on *HAPO criteria*	132/794	Not reported	Not reported	7 years after delivery	BMI (kg/m^2) BMI percentile SBP (mmHg) DBP (mmHg) Glucose (mmol/l) Lipids (mmol/l)
Bozkurt *et al.*[53]	2016	Descriptive study	Austria	Fourth International Workshop Conference on GDM criteria	32/DM: (26), Control: (18)	63.0 ± 24.0/DM: (71.3 ± 29.3), Control: (66.6 ± 22.1)[a]	Not reported	Average 6 years after birth	BMI-SDS, insulin (µU/ml)
Hakanen *et al.*[81]	2016	Longitudinal study	Finland	Diagnosed by hospital records	520/T1D: 67, Control: 6316	3600 (600)/Control: 3500 (500), T1D: 3700 (700)	39.4 (2.5)/Control: 39.7 (2.4), T1D: 38.5 (2.0)	Average 1–12 after delivery	BMI peak (kg/m^2)
López Morales *et al.*[49]	2016	Cross sectional	Spain	Diagnosed in medical records	38/women with normal gestation (still pregnant) = 38	Not reported	Not reported	Infant (after birth)	Cord blood glucose (mg/dl) Cord blood insulin (U/ml) Cord blood lipids (mg/dl)
Zhao *et al.*[36]	2016	Cross-sectional	Multicenter (Australia, Brazil, Canada, China Colombia, Finland, India, Kenya, Portugal, South Africa, UK, USA)	Varied between international centers but included WHO, ADA, modified ADA, and modified WHO definitions – women would self-report GDM and the research team confirmed the diagnostic criteria at the time of diagnosis	206/4.354	3415 (623)/ 3274 (576)	38.3 (2.1)/ 38.6 (2.2)	9–11 years after delivery	BMI
Chang *et al.*[12]	2015	Retrospective cohort study	China	*American Diabetes Association:* Women with abnormal 50-g OGTT (>7.8 mmol/l) underwent further fasting 3-h 75-g OGTT. GDM diagnosed with criteria: (BG > 5.3 mmol/l at baseline, >10 mmol/l at 1 h, >8.6 mmol/l at 2 h, 7.8 mmol/l at 3 h	356/500	3700 ± 120/3200 ± 800	Not reported	6 years after birth	BMI (kg/m^2) SBP (mmHg)
Krishnaveni *et al.*[13]	2015	Cohort study	India	*Carpenter and Coustan:* two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min) (reported in 2005 study)	26/CTRL: 165, Offspring of diabetic fathers: 22	Not reported	Not reported	13.5 years after delivery	BMI (kg/m^2) SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l) Lipids (mmol/l)
Page *et al.*[82b]	2015	Cohort study	USA	Based on protocol[31]	10/9	Not reported	Not reported	Average 9–10 years after delivery	BMI (kg/m^2) BMI percentile
Rutkowska *et al.*[46b]	2015	Prospective cohort	Poland	Not specified	261/153	3330 ± 53/3420 ± 54	Not reported	Approximately 3 years after delivery	BMI percentile

Wilk *et al.*[57]	2015	Cohort study	Poland	Hospital records	50/46	Not reported	Not reported	7–15 years after delivery	BMI SDS BMI percentile Glucose (mg/dl) Insulin (mg/dl)
Zhao *et al.*[83]	2015	Cohort study	China	Women with risk factors for GDM underwent 85-g OGTT at <12-week gestation, OGTT repeated at 24–28 weeks if normal results. All women with low risk for GDM did normal 24- to 32-week gestation. 1999 WHO diagnostic criteria for GDM since January 1, 2003. GDM diagnosis based on IGT (fasting blood glucose <7.0 mmol/l and 2-h postprandial blood glucose ≥7.8–11.0 mmol/l) or DM (fasting blood glucose ≥7.0 mmol/l or 2-h postprandial blood glucose ≥11.1 mmol/l) positive results	LGA: 149/284 AGA: 771/1401 SGA: 148/180	GDM (followed) 3256 ± 405, GDM (not followed) 3172 ± 509/ Control followed: 3261 ± 391, Control not followed: 3254 ± 417	GDM (followed) 38.9 ± 0.9 (not followed) 38.4 ± 1.5/Control followed: 39.5 ± 1.0, Control not followed: 39.1 ± 0.7	5–10 years after delivery	BMI percentile
Holder *et al.*[25]	2014	Cohort study	USA	Self-reported	45/210	3242.54 ± 959.59/ 3297.93 ± 603.99	Not reported	Average 15 years after delivery	BMI (kg/m^2) BMI *z*-score Plasma glucose (mmol/l)
Köing *et al.*[35]	2014	Retrospective case-control	Germany	Three women were diagnosed with *Hesse Diabetes Society diagnosis:* Fasting: ≥90 mg/dl, 1-h postprandial: ≥160 mg/dl, 2-h postprandial ≥140 mg/dl in venous plasma. Some women were diagnosed who exceeded only one of these three threshold values in a venous blood specimen. Other women referred to by clinicians, based on DDG and AGA values: GDM was diagnosed if at least two measured values exceeded the limits of *Carpenter and Coustan* after ingestion of 75-g glucose, only one exceeded value was declared as impaired glucose tolerance. GDM can also be diagnosed if only one of the predetermined cutoffs is exceeded, whereas these values – based on the results of the *HAPO Study* – differ slightly from the former criteria: Fasting: ≥92 mg/dl, 1-h postprandial: ≥180 mg/dl, 2-h postprandial: ≥153 mg/dl	130/77	3406.62 ± 463.69/ 3456.09 ± 463.25	Not reported	6 months after delivery	BMI (kg/m^2) BMI percentile
Page *et al.*[27]	2014	Cohort study	USA	Based on protocol[31]	37/25	3186 ± 113/ 3454 ± 79	Not reported	5–16 years old (average 7–9 years after delivery)	BMI (kg/m^2) BMI *z*-score BMI percentile
Davis *et al.*[24]	2013	Longitudinal cohort	USA	Self-reported	47/163	3900 (800)/ 3700 (600)	Not reported	Average 10–11 years after birth	BMI (kg/m^2) BMI percentile BMI *z*-score Glucose (mg/dl) Insulin (μU/ml)

Table 1. (*Continued*)

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Eslamian *et al.*[33]	2013	Cohort study	Iran	*World Health Organization*, diagnosed as either: fasting plasma glucose 5.1–6.9 mmol/l or: 1-h plasma glucose 10.0 mmol/l. Following a 75-g oral glucose load 2-h plasma glucose 8.5–11.0 mmol/l following a 75-g oral glucose load	112/159	3336.07 ± 630/ 3259.75 ± 490	37.72 ± 1.7/ 39.1.33	Infant (after birth)	BMI (kg/m^2) Cord blood glucose (mg/dl) Cord blood insulin (µU/ml) Cord blood lipids (mg/dl)
Farfel *et al.*[45b]	2013	Cohort study	Israel	159 males, 113 females/diagnosed by hospital records	Female (113), male (159)/PGDM male (34) female (23) control, male (198), control (147)	Male 3423 ± 537, female 3230 ± 510, PGDM male 3451 ± 535, female 3210 ± 364. CTRL male 3344 ± 372, female 3228 ± 324	Not reported	17 years after delivery	BMI >85th percentile
Nehring *et al.*[39]	2013	Retrospective cohort study	Germany	GDM cases found from medical records	195/7160	3479 (3417–3540)/ 3413 (3403–3424)	3413 (3403–3424)/ 39.4 (39.3–39.4)	Average 5.8 years after delivery	BMI (kg/m^2)
Nielsen *et al.*[40]	2012	Population-based cohort study	Denmark	*Rigshospitalet University Hospital modification of the White classification:* Oral glucose challenge test (OGTT) in gestational weeks 24–26 if they met one of the following criteria: (1) previous birth of a baby with birthweight >4500 g; (2) maternal overweight >130%; (3) family history of diabetes; (4) glycosuria; or (5) previous obstetrical complications or late miscarriage (diagnostic values not specified)	34/previous GDM (185), control (737)	3803 (780)/PREGDM: 3327 (648), control: 3482 (551)	38.9 (1.9)/PREGDM: 36.5 (1.8), control: 38.8 (2.0)	18–20 years after delivery	BMI (kg/m^2)
Page *et al.*[20b]	2013	Cohort study	USA	Based on protocol[31]	10/19	Not reported	Not reported	Average 9 years after delivery	BMI *z*-score SBP (mmHg) Glucose (mg/dl) Insulin (ulU/ml)
Pham *et al.*[84]	2013	Retrospective cohort study	USA	Normal screening at 24–28 weeks (unless considered at risk, tested in first trimester). 50-g, 1-h glucose challenge test of greater/equal to 140 mg/dl, then given a 100-g, 3-h glucose tolerance test if 1-h challenge was positive. Needed 1/4 of the possible measurements to be diagnosed. Diagnosis followed *National Diabetes Data Group* prior to April 2007, then changed to *Carpenter and Coustan* criteria after April 2007	459/2185	3406 ± 496/3404 ± 442	39.3 ± 1.0/ 39.6 ± 0.9	2–4 years after delivery	BMI percentile
Retnakaran *et al.*[32]	2013	Substudy of prospective observational study	Canada	Those with and without an abnormal 50-g glucose challenge screening test undergo 3-h, 100-g OGTT for ascertainment of antepartum glucose intolerance status (i.e., either GDM or non-GDM) based on NDDG, measurements at 20 min 1, 2, and 3 h	36/68	3411 (3110–3635)/ 3415 (3144–3628)	Not reported	1 year after delivery	BMI *z*-score Fasting glucose (mmol/l) Lipids (mmol/l)

Baptise-Roberts *et al.*[29]	2012	Prospective cohort	USA	All women provided fasting blood specimen if it was 120 mg/dl or higher, or if it rose to over 175 mg/dl at the end of 1 h and did not return to normal in the 2- and 3-h specimens. GDM diagnosed based on these criteria: (1) she was newly diagnosed with diabetes during pregnancy; (2) she initiated insulin during pregnancy; (3) she displayed an abnormal glucose tolerance test result; or (4) she had a blood glucose level of 200 mg/dl or more at any time during pregnancy	484/27,874	3302 ± 584/ 3190 ± 484	Not reported	7 years after birth	BMI (kg/m^2) BMI *z*-score BMI percentile
Borgoño *et al.*[52]	2012	Prospective cohort	Canada	*National Diabetes Data Group* criteria	36/68	3411 (3110–3635)/ 3415 (3144–3628)	Not included	1 year after birth	Fasting glucose (mmol/l) Fasting insulin (pmol/l)
Chandler Laney *et al.*[51]	2012	Cohort study	USA	Self-reported, confirmed with hospital records	Normal weight: (11), Overweight: (13)/Normal weight: (19), Overweight: (8)	Not reported	Not reported	Average 7–8 years after birth	BMI percentile Glucose (mg/dl)^2 Insulin (mg/dl)^2
Page *et al.*[31b]	2012	Cohort study	USA	Not reported in abstract (based on protocol): Fasting glucose <126 mg/dl (7 mM) from families of a proband with GDM diagnosed within the previous 5 years)	35/14	Not reported	Not reported	Average 8 years after delivery	BMI (kg/m^2) BMI *z*-score
Patel *et al.*[14]	2012	Prospective population-based cohort study	England	GDM was defined as any record of a diagnosis of gestational diabetes at any time during the pregnancy in women without existing diabetes at the start of pregnancy. (At time of study recruitment: all pregnant women to have urine tested for glycosuria and proteinuria at every antenatal clinic visit. Glycosuria was defined as a record of at least ++ (equal to 13.9 mmol/l or 250 mg/100 ml) on at least two occasions at any time during the pregnancy.) GDM was tested further to these results, diagnosed in the medical records as GDM with no history of existing diabetes.	27/Control: (4384), existing diabetes: (23), glycosuria: (154)	1.45 (1.28)/Control: 0.038 (0.97), existing diabetes: 0.28 (1.32), glycosuria: 0.18 (1.04)	38.6 (1.48)/control: 39.4 (1.85), existing diabetes: 37.5 (1.86), glycosuria: 39.7 (1.63)	15 years after delivery	BMI *z*-score SBP and DBP (mmHg) Glucose (mmol/l) Insulin (IU/l) Lipids (mmol/l)
Jahan *et al.*[85]	2011	Cohort study	Bangladesh	Diagnosed with fasting blood glucose, and 2 h after 75-g OGTT. Women who had repeatedly elevated fasting (>7.0 mmol/l) or postprandial (9 mmol/l) blood glucose values.	30/DM: ($n = 45$), control: ($n = 30$)	3000 (2100–4500)/ DM: 3100 (1700–4800), NDM: 2700 (2000–3800)	Not reported	Infant (after birth)	Insulin (mmol/l)
Tsadok *et al.*[22]	2011	Population-based cohort	Israel	Reported on hospital records	293/59,499	3411 ± 616/3301 ± 483	Not reported	17 years after delivery	BMI (kg/m^2) SBP and DBP

Table 1. (*Continued*)

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Boerschmann *et al.*[86]	2010	Prospective cohort	Germany	*German Diabetes Association* – an OGTT with a 75-g glucose load. Women were considered to have GDM if two of three capillary blood glucose values exceeded the following limits: >5 mmol/l (fasting) before an OGTT, >10 mmol/l after 60 min, and >8.6 mmol/l after 120 min	232	Not reported	Not reported	11	BMI percentile
Krishnaveni *et al.*[18]	2010	Cohort study	India	*Carpenter and Coustan:* two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min)	Female (23), Male (12)/Control: female (191) male (190), Offspring of diabetic fathers male: (20), female: (19)	Not reported	Not reported	9.5 years after delivery	BMI (kg/m^2) BMI percentile SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l) Lipids (mmol/l)
Lawlor *et al.*[30]	2010	Longitudinal cohort	England	GDM was defined as any record of a diagnosis of gestational diabetes at any time during the pregnancy in women without existing diabetes at the start of pregnancy. (At time of study recruitment: all pregnant women to have urine tested for glycosuria and proteinuria at every antenatal clinic visit. Glycosuria was defined as a record of at least ++ (equal to 13.9 mmol/l or 250 mg/100 ml) on at least two occasions at any time during the pregnancy.) GDM was tested further to these results, diagnosed in the medical records as GDM with no history of existing diabetes	53/control: (10,126) Existing diabetes (40) Glycosuria (372)	3711 (655)/control: 3416 (536), existing diabetes: 3248 (787), glycosuria: 3511 (534)	38.2 (1.9)/control: 39.5 (1.9), existing diabetes: 37.5 (2.6), glycosuria: 39.5 (1.8)	Average 9–11 years after delivery	BMI *z*-score
Pirkola *et al.*[41]	2010	Longitudinal cohort study	Finland	GDM risk factors; 40 years, BMI 25 kg/m^2, prior GDM, previous delivery of a macrosomia infant (birthweight 4500 g), glycosuria, and suspected fetal macrosomia in the current pregnancy. Glucose tolerance testing, performed after an overnight fast, conducted by administering a 2-h, 75-g OGTT: 5.5, 11.0, and 8.0 mmol/l at fasting and at 1 h and 2 h after the glucose load, respectively. Diagnosis of GDM was set after one abnormal value in the OGTT, according to prevailing national guidelines	Normal weight: (n = 49), Overweight: (n = 35)/Control total: (657) Normal weight: (503), Overweight (n = 154)	Overweight: 3700 (3490–3920) Normal 3670 (3530–3820)/ Overweight = 3780 (3680–3880), Normal weight: 3690 (3640–3740), Total: 3480 (3460–3500)	Overweight: 38.5 (37.8–39.1), Normal 39.0 (38.6–39.5)/ Overweight 39.4 (39.1–39.6), Normal weight 39.5 (39.4–39.7) Total 39.5 (39.4–39.5)	16 years after delivery	BMI (kg/m^2)
Tam *et al.*[15]	2010	Longitudinal cohort	Hong Kong	GDM defined based on *WHO criteria*: Gestational IGT (i.e., fasting PG level of 7.0 mmol/l and 2-h PG level of 7.8–11.1 mmol/l, and GDM (i.e., fasting PG level of 7.0 mmol/l and/or 2-h PG level of 11.1 mmol/l). WHO criteria states that "pregnant women who meet WHO criteria for diabetes mellitus of IGT are classified as having GDM"	42/87	3248 (351)/ 3273 (454)	Based on Tam *et al.*[21] with larger (n =): 39.6 ± 0.2/ 39.5 ± 0.2	15 years after delivery	BMI (kg/m^2) SBP and DBP (mmHg) Glucose (mmol/l) Lipids (mmol/l)

Catalano *et al.*[11]	2009	Prospective cohort	USA	NDDG	25/38	3373 ± 532/ 3376 ± 496	38.7 ± 1.3/ 39.4 ± 1.2	Average 8.8 years after birth	BMI (kg/m^2) BMI *z*-score SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l) HOMA-IR Lipids (mmol/l)
Vaarasmaki *et al.*[23]	2009	Prospective cohort study	England	Risk factors: glycosuria, prior gestational diabetes, suspected fetal macrosomia (birthweight 4500 g) in the current pregnancy, previous delivery of a macrosomic infant, BMI 25 kg/m^2 and age more than 40 years. A history of prior gestational diabetes or glycosuria in the current pregnancy warrants an earlier OGTT. Diagnosed with 2-h, 75-g OGTT usually at 26–28 week of gestation: one or more abnormal OGTT values (cutoff values for venous blood samples are 4.8 mmol/l at 0 min, 10.0 mmol/l at 60 min, and 8.7 mmol/l at 120 min)	96/3909	3727 (577)/ 3517 (471)	38.8 (1.7)/ 39.5 (1.5)	16 years after delivery	BMI SBP and DBP (mmHg) Glucose (mmol/l) Insulin (milliunits/l) Lipids (mmol/l)
Wright *et al.*[16]	2009	Cohort study	USA	Screening at 26–28 weeks with nonfasting 50-g 1-h oral glucose challenge. If test result was abnormal (i.e., blood glucose value of >140 mg/dl), then women were referred for fasting 3-h 100 OGTT. Two or more abnormal results were a diagnosis for GDM: a blood glucose >95 mg/dl at baseline, >180 mg/dl at 1 h, >155 mg/dl at 2 h, or >140 mg/dl at 3 h	51/control $n = 1035$, IGT $n = 152$	3510 (52)/ control = 3510/52, IGT 3600 (52)	Not reported	3 years after delivery	BMI (kg/m^2) BMI percentile BMI *z*-score SBP (mmHg)
Buzinaro *et al.*[10]	2008	Cohort study	Brazil	Based on OGTT values (cutoffs not specified)	23/Control (17) Hyperglycemia (23)	Not reported	Not reported	Average 12–16 years after birth	BMI (kg/m^2) SBP and DBP (mmHg) Glucose (mg/dl) Lipids (mg/dl)
Clausen *et al.*[56]	2008	Retrospective cohort study	Denmark	OGTT – GDM was based on risk indicators: family history of diabetes, overweight (20%) prepregnancy, prior GDM, delivery of macrosomic baby, glycosuria. Women with these risk indicators and two capillary blood glucose measurements > 4.1 mmol/l were offered a 3-h 50-g OGTT. OGTT was abnormal if more than two of seven values during the test exceeded mean 3 SDs for a reference group of normal weight nonpregnant women without family history of diabetes (Until September 1982 venous plasma used for OGTT, after then capillary whole blood)	168/128	3410 (530)/ 3474 (481)	273 (247–284)/ 280 (253–298)	18–27 years after delivery	Glucose (mmol/l)

Table 1. (*Continued*)

Study	Year	Study design	Country	Definition of GDM	Exposed/ nonexposed (*n*=)	Birthweight cases/control (g)	Gestational age cases/control (weeks)	Follow-up (years)	Outcome measure considered
Pirkola *et al.*[17]	2008	Cohort study	Finland	Risk factors for diagnosis: glycosuria, prior gestational diabetes, suspected fetal macrosomia (birthweight 4500 g) in the current pregnancy, previous delivery of a macrosomic infant, BMI 25 kg/m^2 and age more than 40 years. A history of prior gestational diabetes or glycosuria in the current pregnancy warrants an earlier OGTT. Diagnosed with 2-h, 75-g OGTT usually at 26–28 week of gestation: one or more abnormal OGTT values (cutoff values for venous blood samples are 4.8 mmol/l at 0 min, 10.0 mmol/l at 60 min, and 8.7 mmol/l at 120 min)	22/T1D: 16, control: 25	3.708 (3.538–3.886)/ T1D: 3.818 (3.482–4.185), Control: 3.666 (3.452–3.893)	39.2 (38.7–39.7)/ T1D: 37.5 (36.8–38.2), 39.3 (38.8–39.8)	Mean 4.9 years after delivery	SBP and DBP (mmHg) Cord blood insulin (pmol/l)
Tam *et al.*[21]	2008	Longitudinal cohort study	Hong Kong	DM defined based on *WHO criteria*: Gestational IGT (i.e., fasting PG level of 7.0 mmol/l and 2-h PG level of 7.8–11.1 mmol/l, and GDM (i.e., fasting PG level of 7.0 mmol/l and/or 2-h PG level of 11.1 mmol/l). WHO criteria states that "pregnant women who meet WHO criteria for diabetes mellitus of IGT are classified as having GDM"	63/101	3292 ± 52/3245 ± 45	39.6 ± 0.2/ 39.5 ± 0.2	Average 7–8 years after delivery	BMI (kg/m^2) BMI percentile SBP and DBP (mmHg) Glucose (mmol/l) Insulin (pmol/l) Lipids (mmol/l)
Lee *et al.*[19]	2007	Cohort study	South Korea	*National Diabetes Data Group:* 50-g glucose challenge test was performed; if the 1-h plasma glucose value was 130 mg/dl (7.2 mmol/l), a 3-h OGTT was performed during 28–32 weeks of gestation	202/96	3344.6 ± 585.0/ 3286.6 ± 612.4	38.6 ± 1.5/ 38.7 ± 2.2	Average 4 years after delivery	BMI (kg/m^2) SBP and DBP (mmHg) Lipids (mmol/l) Glucose (mmol/l) Insulin (mg/ml)
Boney *et al.*[87]	2005	Longitudinal cohort	USA	*National Diabetes Data Group* criteria described by *Carpenter and Coustain*	LGA: 42/43 AGA: 52/42	LGA: 4107 (386)/ 4132 (285) AGA: 3316 (310)/ 3370 (282)	Not reported	11 years after birth	BMI percentile BP >90th percentile (BP is either SBP or DBP) (mmHg) Glucose (mmol/l) Lipids (mmol/l)
Jaber *et al.*[34]	2006	Cohort study	Saudi Arabia	Venous fasting glucose concentration of >5.5 mol/l or of >8.0 mmol/l 2 h after a 75-g oral glucose load or both	26/Control (n = 32), FDM (n = 21)	3640 ± 690/CTRL: 3.30 ± 0.59, FDM: 3.18 ± 0.86	37.38 ± 0.64/CTRL: 37.28 ± 0.73, FDM: 37.48 ± 0.60	Approximately 2 weeks after delivery	BMI (kg/m^2) Glucose range (mmol/l) Insulin range (pmoL/l)
Krishnaveni *et al.*[38]	2005	Cohort study	India	*Carpenter and Coustan:* two or more plasma glucose concentrations 5.3 (fasting), 10.0 (60 min), 8.7 (120 min), and 7.8 mmol/l (180 min)	41/Control: 588, Offspring of diabetic fathers: 41	3344 ± 421/CTRL: 2973 ± 408, ODF: 2869 ± 305	39.1 ± 1.2/CTRL 39.0 ± 1.8, ODF: 39.1 ± 1.2	1 and 5 years after delivery	Fasting plasma glucose (pmol/l)
Gillman *et al.*[88]	2003	Prospective Cohort	USA	Self-reported questionnaire	Female (246), male (219)/ female (n = 7735), male (n = 6681)	Female: 3.55 (0.56), male 3.68 (0.61)/ female 3.44 (0.48), male 3.58 (0.51)	Not reported	Average 9–14 years after delivery	BMI percentile

Vohr *et al.*[44]	1999	Prospective observational study	USA	24- to 28-week screening, GDM diagnosis made on initial 1-h 50-g glucose screen >130 mg/dl, followed by two abnormal values in a 100-g OGTT. *Criteria of O'Sullivan et al. modified by Carpenter and Coustan (recent 1999):* fasting plasma glucose >95 mg/dl and 1-h >180 mg/dl, 2-h >155 mg/dl, and 3-h >140 mg/dl	LGA: 47/46 AGA: 59/55	LGA: 4100 ± 3800/ 4200 ± 2900 AGA: 3300 ± 300/ 3400 ± 3000	LGA: 39.4 ± 1/ 40.0 ± 1, AGA: 39.4 ± 1/ 39.7 ± 1	4–7 years after delivery	BMI (kg/m^2)
Silverman *et al.*[42c]	1998	Long-term prospective cohort	USA	Unclear – from hospital records (From Silverman *et al.*[89])	Unclear	Not reported	Not reported	14–17 years after delivery	BMI (kg/m^2)
Whitaker *et al.*[28]	1998	Cohort study	USA	24- to 32-week screening, 1-h 50-g oral glucose load – glucose screening values >7.77mmol/l (140mg/dl) called back for 3-h 100-g OGTT. GDM diagnosed based on calculations *Carpenter and Coustan (recent 1998)*	63/Control: (257), Normal OGTT = 159, No OGTT = 45	Not reported	Not reported	5–10 years after delivery	BMI *z*-score BMI percentile
Plagemann *et al.*[55]	1997	Retrospective study	Germany	Diagnosed 26- to 28-week gestation by Furmann: a 50-g OGTT using the following criteria (two or more abnormal values): fasting venous blood glucose over 5.55 mmol/l, 1-h value over 8.88 mmol/l, 2-h value over 7.22 mmol/l	57/156	3500.8 ± 50.8 (117)/ 3443.5 ± 45.5 (200)	Not reported	Average 1–9 years delivery	Plasma insulin (mIU/ml)
Plagemann *et al.*[54]	1997	Cohort study	Germany	Diagnosed 26- to 28-week gestation by Furmann: a 50-g OGTT using the following criteria (two or more abnormal values): fasting venous blood glucose over 5.55 mmol/l, 1-h value over 8.88 mmol/l, 2-h value over 7.22 mmol/l	69/129	3460.1 ± 50.7/ 3411.2 ± 56.8	Not reported	Average 1–9 years after delivery	Glucose (mmol/l) Insulin (pmol/l)
Vohr *et al.*[43]	1995	Prospective cohort study	USA	Screening 24–28 weeks, GDM diagnosis made on initial 1-h 50-g glucose screen >130 mg/dl, followed by two abnormal values in a 100-g OGTT. *Criteria of O'Sullivan* et al. *modified by Carpenter and Coustan:* fasting plasma glucose >95 mg/dl and 1 h >180 mg/dl, 2 h >155 mg/dl, and 3 h >140 mg/dl	LGA: 57/74 AGA: 62/69	LGA: 4064 ± 305/ 4095 ± 267 AGA: 3301 ± 280/ 3282 ± 238	LGA: 39 ± 1/40 ± 1, AGA: 39 ± 1/39 ± 1	20 h after delivery	BMI (kg/m^2)
Teng *et al.*[48]	2017	Longitudinal cohort	India	*IADPSG criteria:* 75 g OGTT and if serum glucose level was over 1 mmol/l at 0 h, or 10.0 mmol/l at 1 h, or 8.5 mmol/l at 2 h, GDM was diagnosed	123/80	Not reported	Not reported	14 years after delivery	Glucose (mmol/l) Lipids (mmol/l)

IGT, impaired glucose tolerant; NDDG, National Diabetes Dat ` a Group; OGTT, oral glucose tolerance test; SDS, Standard Deviation Score; ADA, American Diabetes Association; BG, blood glucose; CTRL, control; LGA, large for gestational age; AGA, average for gestational age; SGA, small for gestational age; PGDM, previous gestational diabetes mellitus; PREGDM, previous GDM; NDM, nondiabetic mothers; PG, plasma glucose; HOMA-IR, homeostatic model assessment of insulin resistance; FDM, frank diabetic mothers; ODF, offspring of diabetic fathers.

[a]Birthweight centiles used rather than birthweight.

[b]Abstract only.

[c](*n*=) not known for GDM or non-GDM group.

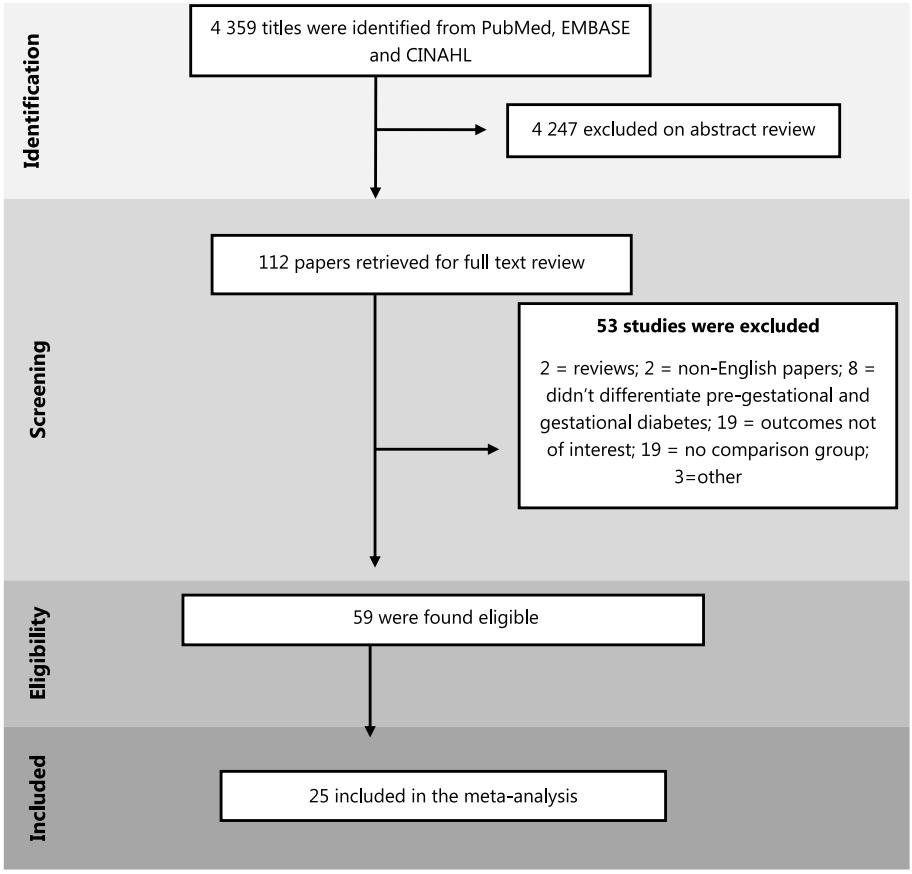

Fig. 1. PRISMA flow diagram of study selection.

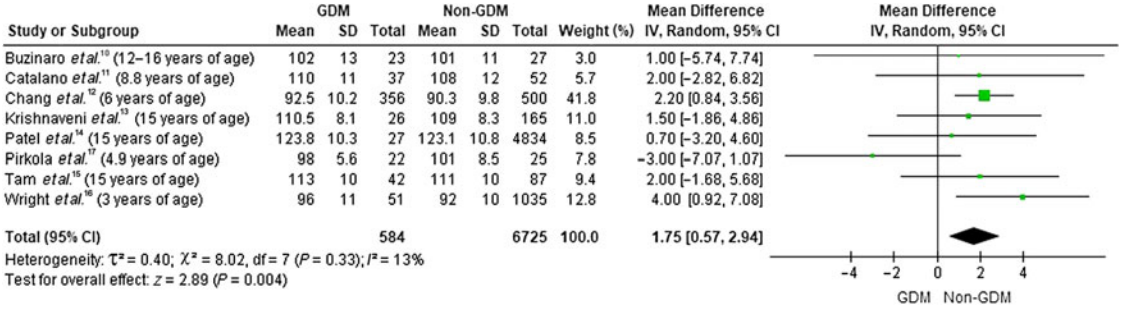

Fig. 2. Mean difference in systolic blood pressure (mmHg) in those exposed to GDM *in utero* and controls.

have 1.75 mmHg (95% CI 0.57–2.94) higher SBP compared to controls (n(total) = 7309, n(exposed to GDM) = 584; $P = 0.33$, $I^2 = 13\%$) (Fig. 2).[10–17] Sensitivity analyses were not performed as no low-quality studies were included in the analysis. Of the seven studies not included in the meta-analysis,[5,18–23] four reported a significant increase in SBP among offspring exposed to GDM compared to controls (Supplementary Table S1).[5,18,21,22]

Diastolic blood pressure

DBP data were available from 13 studies of which 6 were included in the meta-analysis. The age at follow-up ranged between 8 and 16 years. The meta-analysis demonstrated no difference in DBP among GDM-exposed offspring and controls (MD −0.24, 95% CI −2.33 to 1.85; n(total) = 5367, n(exposed to GDM) = 177; $P = 0.08$, $I^2 = 50\%$[10,11,13–15]; Supplementary Fig. S1). Sensitivity analyses were not performed as no low-quality studies were included in the analysis. Seven studies were not included in the meta-analysis,[5,17–23] of which two reported a significantly higher DBP in GDM offspring compared to controls (Supplementary Table S1).[21,22]

Body mass index

BMI data (i.e., BMI z-score, BMI (kg/m^2), and/or BMI percentile, BMI peak, BMI SD) were available from 48 studies. BMI z-score and BMI (kg/m^2) are reported in the meta-analysis, and other BMI data are reported in the nonmeta-analysis (Supplementary Table S1).

BMI z-score data were reported in 14 studies, of which 9 were included in the meta-analysis. The age at follow-up ranged from 3 to 15 years. Offspring exposed to GDM *in utero* showed an

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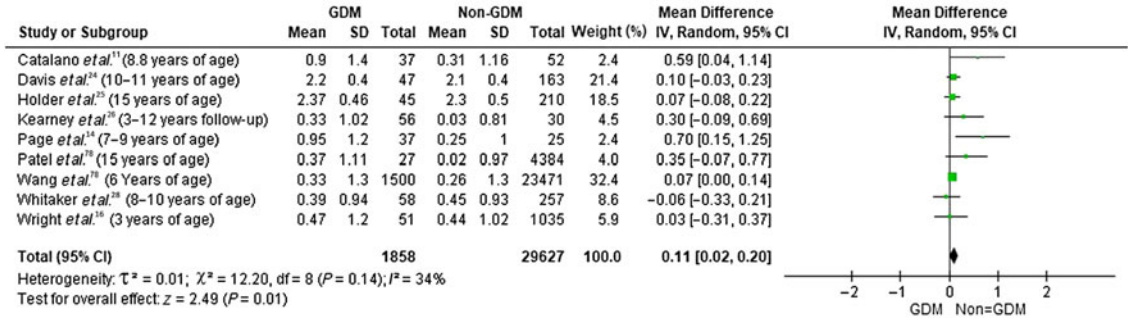

Fig. 3. Mean difference in BMI *z*-score in those exposed to GDM *in utero* and controls.

increase in BMI *z*-score compared to controls (MD 0.11, 95% CI 0.02–0.20; *n*(total) = 31,485, *n*(exposed to GDM) = 1858; $P = 0.14$, $I^2 = 34\%$)[11,14,16,24–28] (Fig. 3). Five studies were not included in the meta-analysis,[20,29–32] with two reporting significantly higher BMI *z*-scores in GDM-exposed offspring compared to controls[29,31] (Supplementary Table S1). Sensitivity analysis showed no difference in heterogeneity when removing low-quality studies (Supplementary Table S3A).

BMI (kg/m^2) data were available from 31 studies. Sixteen studies were included in the meta-analysis, with the age at follow-up ranging broadly from <48 h after birth to 25 years. Quantitative summary measures obtained through meta-analysis showed a 1.06-kg/m^2 increase in BMI among those exposed to GDM *in utero* compared to controls (95% CI 0.40–1.73; *n*(total) = 23,864, *n*(exposed to GDM) = 2154; $P < 0.00001$, $I^2 = 95\%$; Supplementary Fig. S2).[10–13,15,16,24–27,33–37] Sensitivity analysis showed no difference in heterogeneity when removing low-quality studies (Supplementary Table S3B). Fifteen studies were not included in the meta-analysis,[5,18,19,21,23,29,31,36,38–44] of which seven studies showed significantly higher BMI among offspring exposed to GDM compared to controls[18,22,29,31,36,38,42] (Supplementary Table S1). Krishnaveni *et al.* reported a significant association between females exposed to GDM *in utero* compared to female controls ($P < 0.001$).[18] One study that showed statistical significance did not report on the sample size for either GDM or control groups.[42]

BMI percentiles were reported in 21 studies. Of these, five reported a higher BMI within obese/overweight BMI percentiles among those exposed to GDM *in utero* compared to controls (i.e., ≥85th percentile)[5,29,45–47] (Supplementary Table S1).

Lipids

Studies on cord blood and serum lipids (i.e., total cholesterol, LDL, HDL, and triglycerides) were included.

Total cholesterol

Total cholesterol data were available from 12 studies (9 serum cholesterol and 3 cord blood cholesterol). Five studies on total serum cholesterol were included in the meta-analysis. The age of follow-up ranged from 8 to 16 years. There was no significant difference in total serum cholesterol between GDM and control groups (SMD −0.01, 95% CI −0.28 to 0.25; *n*(total) = 662, *n*(exposed to GDM) = 251; $P = 0.07$, $I^2 = 54\%$; Supplementary Fig. S3A).[10,11,13,15,48] The four studies that were not included in the meta-analysis showed no difference in total cholesterol between those exposed to GDM and controls (Supplementary Table S1).[5,19,21,23] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Three studies on cord blood total cholesterol were included in the meta-analysis. Quantitative summary measures did not show a significant difference in total cord blood cholesterol between GDM and control groups (SMD −0.90, 95% CI −2.41 to 0.61; *n*(total) = 374, *n*(exposed to GDM) = 164; $P < 0.00001$, $I^2 = 96\%$; Supplementary Fig. S3B).[33,49] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

LDL cholesterol

LDL cholesterol data were available from 10 studies (8 serum LDL cholesterol, 2 cord blood cholesterol).

Four studies on serum LDL cholesterol were included in the meta-analysis. The age of follow-up ranged from 8 to 16 years. There was no difference in serum LDL cholesterol between those exposed to GDM and controls (SMD −0.03, 95% CI −0.44 to 0.38; *n*(total) = 5129, *n*(exposed to GDM) = 129; $P = 0.01$, $I^2 = 73\%$; Supplementary Fig. S4A).[10,11,14,15] Four studies that were not included in the meta-analysis showed no difference in LDL between GDM and control groups[5,21,23,32] (Supplementary Table S1). Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Two studies on cord blood LDL were included in the meta-analysis. Quantitative summary measures did not show a significant difference in cord blood LDL between GDM and control groups (SMD −0.60, 95% CI −1.57 to 0.38; *n*(total) = 298, *n*(exposed to GDM) = 126; $P = 0.01$, $I^2 = 84\%$; Supplementary Fig. S4B).[49,50] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

HDL cholesterol

HDL cholesterol data were available from 15 studies (12 serum HDL cholesterol, 3 cord blood HDL cholesterol).

Six studies on serum HDL cholesterol were included in the meta-analysis. The age of follow-up ranged from 8 to 16 years. Quantitative summary measures showed no significant difference in serum HDL cholesterol between those exposed to GDM and controls (SMD 0.08, 95% CI −0.07 to 0.24; *n*(total) = 5073, *n*(exposed to GDM) = 278; $P = 0.77$, $I^2 = 0\%$; Supplementary Fig. S5A).[10,11,13–15,48] Sensitivity analyses were not performed as no low-quality studies were included in the analysis. Six studies were not included in the meta-analysis.[5,18,19,21,23,32] Of these, one reported lower serum HDL cholesterol in the GDM group compared to controls (Supplementary Table S1).[21] Three studies on cord blood HDL were included in the meta-analysis. Quantitative summary measures showed no difference in cord blood HDL between GDM and controls groups (SMD −0.13, 95% CI −0.84 to 0.59; *n*(total) = 374, *n*(exposed to GDM) = 164; $P = 0.0006$, $I^2 = 87\%$; Supplementary Fig. S5B).[33,49,50] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

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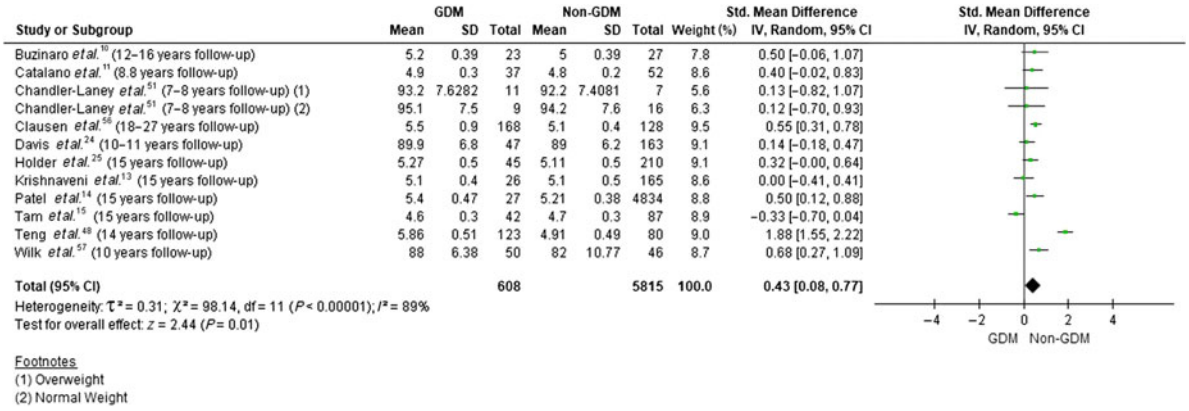

Fig. 4. Standard mean difference in fasting glucose in those exposed to GDM *in utero* and controls.

Triglycerides

Triglyceride data were available from 14 studies (11 serum triglycerides and 3 cord blood triglycerides). Six studies on serum triglycerides were included in the meta-analysis. The age at follow-up ranged from 7 to 16 years. Quantitative summary measures showed no difference in the level of serum triglycerides between GDM and control groups (SMD 0.50, 95% CI −0.14 to 1.14; n(total) = 5523, n(exposed to GDM) = 278; $P < 0.00001$, $I^2 = 93\%$; Supplementary Fig. S6A).[10,11,13–15,48] Sensitivity analyses were not performed as no low-quality studies were included in the analysis. Five studies that were not included in the meta-analysis also showed no significant difference in serum triglycerides in GDM and control groups (Supplementary Table S1).[5,18,19,21,23] Three studies on cord blood triglycerides were included in the meta-analysis. There was no difference in cord blood triglycerides in the GDM group compared to controls (SMD 0.02, 95% CI −0.67 to −0.71; n(total) = 374, n(exposed to GDM) = 164; $P = 0.001$, $I^2 = 86\%$; Supplementary Fig. S6B).[33,49,50] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Insulin

Data for fasting serum insulin were collected for 20 studies (16 serum insulin and 4 cord blood insulin).

Four studies on serum insulin were included in the meta-analysis. The age at follow-up ranged from 8 to 15 years. The meta-analysis showed no difference in insulin between the two groups (SMD −0.02, 95% CI −0.70 to 0.67; n(total) = 5136, n(exposed to GDM) = 131; $P < 0.00001$, $I^2 = 89\%$; Supplementary Fig. S7A).[11,14,24,51] Sensitivity analyses showed no difference in heterogeneity when poor-quality studies were omitted (Supplementary Table S4)

Twelve studies were not included in the meta-analysis,[5,13,18–21,23,34,51–55] of which five reported significantly elevated insulin levels in the GDM group compared to controls[13,18,34,54,55] (Supplementary Table S1). Two of these studies showed a significant difference in fasting insulin between offspring exposed to pre-GDM (i.e., diabetes diagnosed before pregnancy) and GDM.[54,55] Two studies were included in a meta-analysis on cord blood insulin; however, there was no difference between the GDM and control groups (SMD −4.74 95%, CI −14.99 to 5.51; n(total) = 123, n(exposed to GDM) = 60; $P < 0.00001$, $I^2 = 99\%$; Supplementary Fig. S7B).[17,49] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Glucose

Glucose data were available from 25 studies (23 serum glucose and 2 cord blood glucose). Eleven studies on serum glucose were included in the meta-analysis, in which the age at follow-up ranged from 8 to 27 years. Based on quantitative summary measures, the meta-analysis showed an increase in glucose in offspring exposed to GDM *in utero* compared to controls, demonstrating a 0.43 SMD (95% CI 0.08–0.77; n(total) = 6423 n(exposed to GDM) = 608; $P = 0.00001$, $I^2 = 89\%$ (Fig. 4).[10,11,13–15,24,25,48,51,56,57] Sensitivity analysis showed no difference in heterogeneity when removing low-quality studies (Supplementary Table S5). Twelve studies were not included in the meta-analysis.[5,18–21,23,32,34,38,44,52] One study reported significantly higher serum glucose in the GDM group than controls.[20] One study reported a significantly lower serum glucose value in those exposed to GDM compared to controls.[34] Two studies assessed cord blood glucose with both newborn cohorts;[33,49] however, no difference was seen between the GDM and non-GDM groups (MD −2.69, 95% CI −5.80 to 0.42; n(total) = 346, n(exposed to GDM) = 149; $P = 0.19$, $I^2 = 42\%$; Supplementary Fig. S8).[33,49] Sensitivity analyses were not performed as no low-quality studies were included in the analysis.

Discussion

This systematic review aimed to assess the prevalence of conventional cardiovascular risk factors in those exposed to GDM *in utero* compared to those not exposed to GDM. There is an established link between pregnancy complications and vascular outcomes such as elevated markers of inflammation and impaired fetal aortic intimal media thickness (aIMT).[58,59] Many reviews on GDM focus on cardiovascular endpoints including myocardial infarction and coronary heart disease. Identifying risk factors for CVD is vital in planning screening strategies to identify those at risk of future CVD with the aim of targeting preventive interventions. Hence, this review is a comprehensive synthesis of evidence from published studies comparing the main conventional cardiovascular risk factors in those born after pregnancies complicated by GDM compared to controls and includes outcomes that have not been recently reviewed in the literature such as serum and cord blood lipids.

Our meta-analysis showed that offspring exposed to GDM *in utero* have 1.75 mmHg higher SBP than controls (95% CI 0.57–2.94, $n = 7309$, eight studies). Aceti *et al.* showed a similar association for offspring of GDM pregnancies (1.39 mmHg, 95% CI 0.00–2.77); 10 studies, $P = 0.05$).[6] They also showed a smaller,

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nonsignificant increase in DBP for GDM offspring (0.75 mmHg, 95% CI −0.47–1.97; nine studies, $P = 0.23$).[6]

This meta-analysis primarily consists of adolescent cohorts (i.e., 10–19 years) with one 3-year-old cohort. Therefore, the existing literature is not sufficient to show the trend in blood pressure throughout childhood and adolescence. These trends have been previously reported in a few large cohort studies. Krishnaveni *et al.* demonstrated that SBP remains elevated in those exposed to GDM compared to unexposed controls throughout ages 5, 9.5, and 13.5 years.[13,18,38] A similar association was seen in another cohort at ages 8 and 15.[15,21] Therefore, it is important to assess childhood cohorts to affirm any trends seen in long-term cohort studies.

Blood pressure that is elevated in childhood and adolescence is predictive of adult hypertension.[60] Raitakari *et al.* found a positive correlation between SBP at 12–16 years with carotid artery intima medial thickness (C-IMT), which is a predictive factor of future CVD.[61] The association was weaker in males at 3–9 years age, but not among females. In a study by Oikonen et al., two abnormal child or youth blood pressure observations were shown to predict risk for hypertension in adulthood.[62] While the effect size in our meta-analysis is small and blood pressure for all studies is generally within normal reference range, it is known that even a 2-mmHg increase in SBP is associated with 10% higher mortality from stroke, and 7% higher mortality from ischemic heart disease in middle age.[63] Therefore, offspring exposed to GDM may benefit from frequent blood pressure monitoring throughout childhood and adolescence. Dietary interventions during gestation, such as implication of a low glycemic index (GI) diet, may benefit offspring and reduce the risk of high blood pressure. It has been demonstrated that children at 12 months old born to mothers at risk of GDM with a low GI diet have significantly thinner aIMT than those children whose mothers had a standard high fiber diet.[64]

Among 31,485 participants, it was shown that BMI *z*-score is marginally higher in those exposed to GDM offspring compared to controls (MD 0.11, 95% CI 0.02–0.20, $n = 31{,}485$, nine studies). We also observed a higher BMI in those exposed to GDM compared to controls (Supplementary Fig. S2); however, BMI is not an accurate predictor of childhood obesity. As an indicator of adiposity, BMI varies greatly based on fat and muscle mass; hence, it may be accurate for fatter children but not those who are lean.[65] The findings of this meta-analysis on BMI *z*-scores are consistent with the findings reported in the review by Kawasaki *et al.* (pooled MD 0.14, 95% CI 0.04–0.24, seven studies).[66]

Higher BMI in youth is associated with dyslipidemia, hypertension, and reduced insulin sensitivity.[67] Jago *et al.* showed that a change in BMI *z*-score at ages 11–14 was associated in a change in cardiovascular risk factors including an increase in SBP and DBP, HDL-C, LDL-C, and triglycerides at the same age.[67] The results of this meta-analysis support previous findings of higher BMI in those exposed to GDM *in utero* compared to controls.[5,24,45] GDM is associated with newborn fat mass, indicative of the intrauterine environment in the final trimester of pregnancy.[68,69] Higher birthweight is associated with markers of subclinical atherosclerosis such as mean carotid IMT.[70] Therefore, those who are exposed to GDM *in utero* appear to have risk factors for CVD very early in life. We could not assess the age distribution in very young children as majority of published studies were in adolescence. Hence, more studies among young children are required to support the association between gestational diabetes and increasing BMI *z*-score in offspring.

Our meta-analysis demonstrated that those exposed to GDM *in utero* have marginally higher fasting blood glucose levels (SMD 0.43, 95% CI 0.08–0.77, $n = 6423$, 11 studies), but not fasting insulin compared to controls. Kawasaki *et al.* showed no difference in fasting plasma glucose among 7–10 and 15 year olds exposed to GDM compared to controls.[66] Plasma glucose was significantly higher at age 20 years among those exposed to GDM compared to controls (MD 0.4 mmol/l, 95% CI 0.25–0.55, seven studies).[66] Our meta-analysis showed a similar association in predominantly childhood–adolescent cohorts, with one cohort during adulthood. We can support an association between exposure to GDM *in utero* and impaired glucose tolerance in offspring; however, as the effect size is minimal, further studies are required to support this association.

Abnormal plasma glucose is a requisite for prediabetes, and if untreated and coupled with increasing obesity may lead to early onset T2DM, which progresses at a faster rate in children and adolescence than in adults.[71] Adolescents diagnosed with T2DM are predicted to lose 15 years from their life expectancy compared to those without T2DM.[72] Hence, frequent fasting blood glucose monitoring in those exposed to GDM *in utero* may reduce the risk of T2DM in the future. Also, interventions during pregnancy may be beneficial as evidenced by studies showing that infants born to mothers with diet or insulin controlled GDM have lower fasting blood glucose than controls.[34]

We acknowledge some limitations of our analyses. Both GDM and CVD are multifactorial diseases, influenced by genetic and environmental factors. Smoking during pregnancy is shown to have significant effects on childhood adiposity and elevated blood pressure.[73,74] High prepregnancy BMI is associated with elevated SBP and DBP in offspring.[75] GDM is shown to cluster in families, and variants of different genes are associated with increased risk of GDM.[76] We could not adjust for such important covariates due to limitations in the data that were available. We were unable to examine female and male subgroups due to lack of power; however, it may be of interest for future studies to consider this as Li *et al.* showed that male offspring of GDM pregnancy had higher BMI than male controls and an increased risk of obesity, while there was no significant association in the cohort of females exposed to GDM compared to female controls.[37]

We did not identify any studies that looked at microvascular function in offspring of GDM. West *et al.* found that offspring of diabetic pregnancies had increased levels of circulating cellular adhesion molecules such as E-selectin and VCAM1, even when adjusted for maternal prepregnancy BMI.[77] Therefore, further studies on this topic are required.

Most of the studies that we assessed in the meta-analysis are follow-up at adolescence, there were few studies that conducted follow-up during early childhood as well as in adulthood, therefore, we are unable to show age distributions in outcomes assessed.

Observational studies may be subject to publication bias, although visual analysis of funnel plots for BMI and glucose showed a low chance of publication bias (Supplementary Fig. S9). However, these outcomes showed high heterogeneity based on I^2, and hence need to be interpreted with caution. We performed sensitivity analysis for relevant outcomes; however, we observed no difference in heterogeneity for the outcomes assessed (Supplementary Tables S3–S5).

Conclusion

Offspring exposed to GDM *in utero* demonstrate risk factors for CVD in childhood and adolescence, including elevated SBP, BMI *z*-score, and fasting plasma glucose that are evident from early life. These outcomes at a young age, if not monitored, can lead to

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adverse vascular and metabolic health parameters resulting in CVD in adulthood. Regular blood pressure monitoring and weight control from a young age may benefit offspring exposed to GDM. Further long-term cohort studies also need to be established, which can adjust for important covariates and allow for affirmation of effect sizes.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174419000850.

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Conflict of Interest. None.

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