Gestational diabetes mellitus and development of intergenerational overall and subtypes of cardiovascular diseases: a systematic review and meta-analysis

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Abstract

Objective　We aimed to summarize the association between gestational diabetes mellitus (GDM) and its intergenerational cardiovascular diseases (CVDs) impacts in both mothers and offspring post-delivery in existing literature.

Methods　PubMed, Embase, Web of Science, and Scopus were utilized for searching publications between January 1980 and June 2024, with data extraction and meta-analysis continuing until 31 July 2024. Based on a predefined PROSPERO protocol, studies published as full-length, English-language journal articles that reported the presence of GDM during pregnancy and its association with any CVD development post-delivery were selected. All studies were evaluated using the Newcastle-Ottawa Scale. Maximally adjusted risk estimates were pooled using random-effects meta-analysis to assess the risk ratio (RR) of GDM, and overall and subtypes of CVDs in both mothers and offspring post-delivery.

Results　The meta-analysis was based on 38 studies with a total of 77,678,684 participants. The results showed a 46% increased risk (RR 1.46, 95% CI 1.34–1.59) for mothers and a 23% increased risk (1.23, 1.05–1.45) for offspring of developing overall CVDs after delivery, following a GDM-complicated pregnancy. Our subgroup analysis revealed that mothers with a history of GDM faced various risks (20% to 2-fold) of developing different subtypes of CVDs, including cerebrovascular disease, coronary artery disease, heart failure, and venous thromboembolism.

Conclusions　These findings underscore the heightened risk of developing various CVDs for mothers and offspring affected by GDM, emphasizing the importance of preventive measures even right after birth to mitigate the burden of CVDs in these populations.

Keywords　Gestational diabetes mellitus, Cardiovascular diseases, Pregnancy, Intergenerational, Mothers, Offspring, Systematic review, Meta-analysis

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Background

Gestational Diabetes Mellitus (GDM) is characterized by elevated blood sugar levels. It is primarily diagnosed during the second or third trimester of pregnancy in women who do not have a pre-existing diabetic condition [1]. It is a prevalent metabolic disorder, affecting approximately 1% to over 30% of pregnancies [2]. In the year 2021, the American Heart Association (AHA) issued a statement underscoring the importance of considering adverse outcomes during pregnancy, such as hypertensive disorders, gestational diabetes, preterm delivery, small-for-gestational-age delivery, pregnancy loss, and placental abruption, when evaluating the risk of cardiovascular diseases (CVDs) in individuals with a history of pregnancy [3]. Notably, the risk remains elevated up to 25 years after pregnancy, particularly in the window of 8 to 15 years after delivery [4].

Emerging evidence suggests that offspring born to pregnancies complicated by GDM are at elevated risk of developing cardiovascular disorders later in life [5, 6]. Exposure to GDM *in utero* has been linked to cardiovascular risks, including elevated levels of total cholesterol and systolic blood pressure in offspring from mid-childhood to adolescence [5, 7]. However, data on the intergenerational impact of GDM on CVDs remains scarce, let alone a notable absence of a comprehensive systematic review and meta-analysis examining these impacts on overall and various subtypes of CVDs among mother-offspring pairs affected by GDM-complicated pregnancies.

Our review sought to explore the connections between GDM and the subsequent occurrence of overall CVDs as well as distinct types of CVDs in both mothers and offspring following childbirth. Specifically, considering that the existing body of literature primarily originates from Western populations, our objective is to evaluate the potential differences in outcomes for the Asian demographic. We put forth the hypothesis that women with a history of GDM and their offspring might be confronted with an elevated risk of CVD development. Due to the intimate interplay between maternal and offspring health throughout the pregnancy period, our findings could offer valuable insights into the underlying pathophysiology linking GDM and the emergence of intergenerational CVDs, and subsequently raise public awareness regarding postnatal care, particularly emphasizing early intervention, to enhance cardiovascular well-being for both mothers and offspring.

Methods

Search Strategy and Selection Criteria

We conducted the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for standard protocols [8]. An investigator (L.-J.L.) oversaw the search strategy. References for this systematic review were identified through searches of four main databases (i.e., PubMed, Embase, Web of Science, and Scopus) for articles published between January 1, 1980, and June 30, 2024. Grey literature including case reports, working papers, government documents, white papers and evaluations were not included. Since we were interested in the intergenerational impact of maternal GDM on cardiovascular outcomes, we included two topics in our review. They are "Topic 1—maternal GDM and postpartum maternal CVD" and "Topic 2—maternal GDM and offspring CVD". Search terms for these two topics are described in detail in Supplementary Table 1. Articles resulting from these searches and relevant references cited in those articles were reviewed, among which those reporting non-human subjects, written in non-English language or without full-text available were excluded. Flow charts of detailed literature searching on each topic are shown in Supplementary Fig. 1. This review was registered at PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO/) with the registration No. CRD42023438259.

Data Extraction and Assessment of Quality

During the literature searching phase, two investigators (C.S. & B.T.) independently selected eligible studies (based on title and abstract, followed by full-text articles) and extracted the relevant data. Results were verified and discrepancies (if any) were evaluated by a third investigator (L.-J.L.). A clear set of pre-specified inclusion criteria and exclusion criteria was established prior to the data extraction. Studies published as full-length and English-language articles in peer-reviewed journals that reported the presence of GDM during pregnancy and its association with any CVD development post-delivery were included. Excluded studies were those published as case reports, reviews, letters, and conference abstracts. Non-full-length articles, non-English publications, and studies conducted on animal models were also excluded. The first phase was conducted in title and abstract screening (C.S., & B.T.), and the second phase was conducted in full-text screening (C.S., & B.T.). Subsequently, two investigators (C.S. & B.T.) performed the quality assessments for all papers based on the Newcastle-Ottawa Scale Criteria (NOSC) [9, 10] and a third investigator (L.-J.L.) assessed the findings independently. The maximum score of 9 points in the NOSC is distributed in three aspects based on the study groups, namely selection of study groups (four points), comparability of groups (two points), and ascertainment of exposure and outcomes (three points) for case–control and cohort studies. We used the points to further categorize the publication quality into low risk of bias (between 7 and 9 points), high risk of bias (between 4 and 6 points), and very high

risk of bias (between 0 and 3 points) [9, 10]. The inter-rater agreement between the two investigators, C.S. and B.T., was 95% for the data extraction phase and 90% for the quality assessment phase. In cases of disagreement, the senior investigator, L.-J.L., reviewed the discrepancies and made the final decision.

Once all papers were identified for both topics, study characteristics such as the name of the first author, country of study conduction, number of participants, mean age, race/ethnicity, years of follow-up, GDM diagnostic guidelines, assessment of CVDs outcomes, effect size, and adjustments model were tabulated. Studies that detailed information on maternal GDM during index pregnancy and intergenerational CVDs diagnosis after delivery were further included in the meta-analysis. Studies that were identified to be at higher risk of bias were assigned a lower weightage in the calculation for overall effect size.

Data synthesis and analysis
Data analysis was conducted between 1st August 2023 and 31 July 2024. Due to the various effect sizes reported in papers, we calculated risk ratio (RR) using random-effects meta-analysis to represent estimates reported from different studies, including hazard ratio (HR), incidence rate ratio (IRR), and odds ratio (OR). For studies' estimates stratified by comorbidity of type 2 diabetes (T2D) or overweight/obesity, an overall estimate was calculated based on the prevalence of within population T2D or overweight/obesity [9].

The risk estimate with the greatest degree of statistical adjustment was included in the meta-analysis. Statistical heterogeneity was assessed with the Cochran Q-test [10] and I^2 statistic, defining levels as mild, moderate, substantial, and high heterogeneity based on I^2 values falling within the ranges of 0–25%, 25–50%, 50–75%, and 75–100%, respectively [11, 12]. Publication bias was assessed visually with funnel plots and with the Egger [13, 14] (linear regression method) and Begg-Mazumdar [15] regression tests (rank correction method), and a p-value < 0.05 was considered representative of statistically significant publication bias [13, 15]. All analyses were conducted with Stata, version 17.0 (Stata Corporation, College Station, Texas, USA). All P values were from 2-sided tests, and the results were deemed statistically significant at *p* < 0.05 unless stated otherwise.

Subgroup Analysis
To comprehensively explore subgroup differences and potential sources of observed heterogeneity, we conducted a series of subgroup analyses based on various study characteristics. Firstly, we presented overall CVDs outcomes, and stratified further based on subtypes of CVDs outcomes based on individual studies. We categorized different CVDs conditions into the following subtypes: coronary artery disease (CAD), angina pectoris, heart failure, arrhythmia, valve disorders, peripheral artery disease, venous thromboembolism (VTE), cardiovascular procedures, cerebrovascular disease (CeVD) and aortic dissection (Supplementary Table 2). Secondly, based on the overall CVDs, we performed stratified meta-analyses based on study characteristics, such as study race/ethnicity (exclusive Asian vs. mixed population yet primarily composed of Caucasians), median duration of follow-up (>10 years vs. ≤ 10 years), method for ascertaining GDM (medical code vs. self-reporting), and study quality (low risk of bias vs. moderate-to-high risk of bias). To assess the potential mediating role of subsequent development of T2D underlying the association between GDM and overall CVDs, we examined the risk ratio for overall CVDs in women who had T2D comorbidity and those who did not specify. Thirdly, we conducted subgroup analyses in associations of overall CVDs stratified by major covariates, such as BMI, lifestyle factors, socioeconomic status, pregnancy complications, and systemic comorbidities. Q-test based on one-way ANOVA was conducted using the R package (R 4.2.2), and statistical significance for any difference in estimates between subgroups was determined with a two-sided p-value threshold of < 0.10.

Results
Study characteristics and summaries in systematic review
Supplementary Table 3 summarizes the characteristics and quality scores of the 36 studies involving mothers (*n* = 74,890,936, follow-up range: 1 day to 46 years after index pregnancy) and the 6 studies involving offspring (*n* = 14,260,765, follow-up range: at birth to 40 years after index pregnancy) within the context of GDM-related pregnancies. The majority of these studies were cohort studies (*n* = 33), with a small subset being cross-sectional studies (*n* = 7), and two identified as case-control studies. These studies were further analysed to categorize the studied outcomes of interest into overall CVD outcomes and various subtypes of CVDs, as illustrated above.

GDM and overall CVD outcomes in mothers
Among the studies that presented CVDs outcomes in mothers, fourteen out of the 33 studies were conducted in the US [16–29], four in Canada [4, 30–32], five in Sweden [33–37], two in Iran [38, 39], three in the UK [40–42], while the remaining six were in Denmark [43], France [44], Netherlands [45], South Korea [46], China [47], Israel [48], and New Zealand [49], respectively. The sample sizes in these studies ranged from 391 to 2,201,352, and the ages of the study populations spanned from under 20 to over 65 years old. The reported incidence rates of overall CVDs varied from 14 to 1,818 cases

per 1000 person-years (Supplementary Table 3). GDM was defined based on either medical reports/diagnostic codes or self-reported. Aside from medical reports and self-reported CVDs definition, clinical diagnostic assessments for CVDs included coronary computed tomography angiography [34, 38], electrocardiogram findings [19, 24, 38], echocardiogram [50], and cardiac-specific enzymes [19]. While the majority of articles reported a positive association between GDM and a 1.04- to 3.18-fold increased risk of maternal overall CVD outcomes post-index pregnancy, five studies reported a null association [22, 27, 29, 38, 45].

GDM and overall CVD outcomes in offspring

The six papers that reported CVD outcomes amongst offspring were conducted in the United States [51], the Czech Republic [52], Canada [53], Denmark [54], Israel [55], and France [56], respectively. The sample sizes ranged from 128 to 11,318,691, and the ages of the study populations spanned from birth to 40 years. The reported incidence rates ranged from 22 to 94 cases per 100,000 person-years (Supplementary Table 3). GDM at index pregnancy was all defined via clinical guidelines or diagnostic codes [51–56], while offspring CVDs outcomes were defined via national registries [51, 53, 54], hospital databases [55], or clinical diagnostic assessments such as two-dimensional electrocardiography [52] and neuroimaging or pathohistological examination [56].

All studies demonstrated a positive association between GDM-complicated pregnancy and a 1.19 to 2.24-fold increased risk of offspring overall CVDs following birth. Notably, Leybovitz-Haleluya et al. [55] observed a 60% higher risk of CVDs development in offspring born to mothers managed with oral treatment of insulin compared to those managed with diet and exercise alone. Moreover, Darmency-Stamboul et al. [56] reported a higher incidence of perinatal arterial ischemic stroke among boys compared to girls (59% vs. 41%), while Guillemette et al. [53] did not find any significant interaction between the sex of offspring and CVDs outcomes.

Meta-analysis of GDM and postpartum CVDs development in mothers

Table 1; Fig. 1A summarizes key study characteristics, including study population details, locations, follow-up periods, pre-pregnancy BMI, sample sizes, methods for defining GDM and CVDs, and effect sizes with 95% confidence intervals. Most studies made statistical adjustments for maternal age, race/ethnicity, and BMI. In a meta-analysis of thirty-three studies, women with GDM were found to have a higher risk of developing overall CVDs (RR 1.46, 95% CI 1.34–1.59) over follow-up periods from one day to 46 years. Among these studies, 19 had low bias risk [4, 16, 18, 19, 23, 29–32, 34, 36, 38,

40–43, 45, 46, 48], while 13 had high bias risk [17, 20, 21, 24, 27, 28, 34, 35, 37, 39, 44, 47, 49], and one had very high bias risk [26] (Table 1). The analysis showed significant heterogeneity ($I^2=95.44\%$), and a p-value less than 0.001 from Cochran's Q test, indicating significantly substantial variability among all publications (Fig. 1A). Publication bias assessment using Egger's and Begg's tests, along with a funnel plot (Supplementary Fig. 2), indicated no evidence of bias, with Egger's test result ($p=0.76$) and Begg's test result ($p=0.61$) supporting this conclusion.

For various CVDs subtypes, women with GDM exhibited significantly elevated risks in different categories: coronary artery disease (1.53; 1.32–1.76), heart failure (1.38; 1.17–1.62), venous thromboembolism (1.18; 1.00-1.39), cardiovascular procedures (2.10; 1.63–2.70), peripheral artery disease (2.00; 1.62–2.48), arrhythmia (1.48; 1.46–1.50), angina pectoris (2.03; 1.44–2.85), as well as overall CeVDs (1.27; 1.11–1.44) including ischemic stroke/TIA (1.52; 1.30–1.78), and haemorrhagic stroke/intracranial haemorrhage (1.44; 1.15–1.78), compared to women without a history of GDM (Fig. 2).

Subgroup analyses based on study characteristics such as race/ethnicity, sample size, follow-up duration, diagnostic methods for GDM, comorbidities of Type 2 Diabetes (T2D), overweight or obesity, and study quality grading did not show significant differences in pooled risk ratios (Supplementary Fig. 3) (all Q-test $p>0.10$). For instance, studies indicated a similar heightened risk of overall CVDs outcomes in women who are overweight or obese (1.51; 1.27–1.80) compared to the general population of women (1.47; 1.34–1.62) ($p=0.44$). Additionally, findings revealed that women with T2D did not have an increased risk of overall CVDs outcomes (1.40, 1.13–1.75) in comparison to those without T2D (1.47, 1.34–1.62) ($p=0.69$).

Further subgroup analyses revealed significant differences between subgroups when adjusting for major confounders. Notably, it showed significant differences if certain key confounders were not adjusted for in the association between GDM and postpartum CVDs in mothers, namely maternal pre-pregnancy BMI at study entry (Yes vs. No: 1.39, 1.32–1.56 vs. 1.63, 1.36–1.94; $p=0.06$), parity (Yes vs. No: 1.36, 1.25–1.48 vs. 1.55, 1.34–1.81; $p=0.095$), and comorbidities (Yes vs. No: 1.37, 1.26–1.49 vs. 1.60, 1.37–1.86; $p=0.07$) (Supplementary Fig. 4).

Meta-analysis of GDM and CVDs development in offspring

Table 2; Fig. 1B summarizes key characteristics of the five included studies, detailing study population, location, follow-up years, pre-pregnancy BMI, offspring BMI, ascertainment methods, sample sizes for GDM in mothers and CVDs in offspring, and effect sizes with 95% CI. The meta-analysis revealed that offspring born to mothers

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Table 1 Characteristics of studies on maternal gestational diabetes Mellitus and Postpartum overall Cardiovascular diseases included for Meta-Analysis

Author (Year)	Study*, Location	Follow-up (Year)	Total Samples (n)	Maternal Age at index pregnancy (year), (mean, SD)	Pre-pregnancy BMI at index pregnancy (kg/m²) (mean, SD)	Ascertainment of GDM (n cases)	Maternal Age at endpoint (year), (mean, SD)	Maternal BMI (kg/m²) (mean, SD)	Ascertainment of overall CVD (n cases)	Incidence rate (per 100,000 person years)	Effect size (HR/OR/RR, with 95% CI)	Adjustment	Grading score
Ackerman-Banks et al. [29] 2024	Prospective cohort, United States	1 year	84,746	Nil	Nil	6057	Nil	Nil	781	122	HR 1.16 95% CI 0.59–2.29	Maternal age at time of delivery, prepregnancy depression preexisting chronic hypertension, obesity and smoking, pregnancy number in data set, year of delivery, Medicaid coverage during pregnancy, rurality of maternal residence at time of delivery HDP, and prenatal depression	6
Michalopoulou et al. [44] 2024	Cohort, United Kingdom	Nil	220,726	GDM vs. non-GDM (27.7±6.2 vs. 25.9±5.1)	Nil	1225	Nil	GDM vs. non-GDM (29.2±6.0 vs. 27.1±5.1)	26,873	Nil	HR: 1.50 95% CI: 1.30–1.74	Age, sociodemographics, family history of CVD, diabetes and hypertension, body mass index (BMI), health behaviours	8
Bucci et al. [30] 2024	Retrospective observational, United States	5 years	944,880	GDM vs. no GDM (31.1±5.5 vs. 30.7±6.3)	Nil	63,770	Nil	Nil	1124	14	HR 1.73 95% CI 1.52–1.96	Age at index event, ethnicity, obesity, smoking habits, arterial hypertension, diabetes, and dyslipidemia, previous pregnancy with abortive outcome and previous complications of labor and delivery	5
Daly et al. [51] 2024	Retrospective cohort, New Zealand	10–20 years	68,628	GDM vs. non GDM (32.3±5.7 vs. 32.3±5.7)	Nil	11,459	Nil	Nil	720	52	HR 1.33 95% CI 1.10–1.61	Ethnicity, age, delivery period, maternal deprivation status, Regional Health Authority, resident status, unregistered with lead maternity carer, number of previous births, pre-eclampsia, smoking, cardiovascular medications 1 year prior to delivery, preterm birth, time-dependent T2DM	6
Countouris et al. [31] 2023	Retrospective cohort, United States	Max 20 years	391	Nil	Nil	28	GDM vs. non-GDM (51 (IQR 44–55) vs 53 (IQR 43–56))	Nil	391	Nil	HR 1.28 95% CI 0.74–2.22	Age at delivery, self-reported race, diabetes, hypertension, and BMI	7
Hildén et al. [39] 2023	Retrospective cohort, Sweden	Mean 9.1±4.3 years	15,949	Nil	Nil	210	40.7 (7.3)	Nil	2639	1818	OR 1.47 95% CI 1.04–2.09	BMI, chronic hypertension, smoking, ethnicity, education level and parity	6
Sederholm Lawesson et al. [36] 2023	Cross-sectional, Sweden	Nil	10,528	Nil	GDM 21.50 (IQR 20.05–23.09) vs. normal pregnancy 20.75 (IQR 19.38–22.31)	144	50–65 (median 57.3)	27.50 (IQR 24.75–30.45) vs. normal pregnancy 25.40 (IQR 23.00–28.6)	Any coronary atherosclerosis: 4,371	Nil	OR 0.92 95% CI: 0.62–1.36	Age, smoking, reported body mass index at age 20 years, educational level, financial strain, family history of myocardial infarction, family history of stroke, and total number of deliveries	7
Crump et al. [38] 2023	Prospective cohort, Sweden	Median 24.8	2,201,352	27.6 (5.2)	Nil	36,269	52.1 (13.2)	Nil	IHD: 83,881	154	HR 1.40 95% CI: 1.29, 1.51	Maternal age, calendar year of delivery, parity, education level, employment status in the year before delivery, country of origin, BMI, smoking, history of hypertension, diabetes or hyperlipidemia	8
Yu et al. [45] 2022	Retrospective cohort study, Denmark	Median 16.2 years (IQR 7.7–25.4)	1,002,486	Median 27 (IQR 24–30)	Nil	21,353	Nil	Pre-pregnancy obesity: GDM vs. non-GDM (18% vs. 4%)	185,820	1144	HR 1.40 95% CI 1.35–1.45	Time period of first delivery, parity, age at first delivery, education, smoking during pregnancy, cohabitation, residence, pre-pregnancy obesity, country of origin, maternal and paternal CVD history	8
Mao et al. [19] 2022	Prospective cohort, United States	Nil	12,025	Nil	Nil	926	GDM 45-45 (12.31) vs. non-GDM 53.49 (16.76)	Obesity: GDM vs. non-GDM (55.97% vs. 43.08%)	CHD: 933	Nil	OR 1.82 95% CI: 1.21–2.72	Age, race/ethnicity, BMI, socio-economic status, alcohol drinking, smoking, recreational physical activity, dietary factors (energy, fat, fiber, vitamin C, vitamin B6 and vitamin D)	4
Taufer Cederlof et al. [35] 2022	Retrospective cohort, Sweden	Median 22.7 years	2,134,239	27.0 (5.1)	Nil	22,991	Nil	Nil	Hospitalized ischemic stroke/TIA: 28,514	59	HR 1.24 95% CI: 0.92–1.68	Maternal age, BMI, smoking, family situation, comorbidities in any pregnancy and at first-time hospitalization of CVD (diabetes, hypertension, chronic kidney failure, and venous thrombosis), parity, and decade at first at first pregnancy	7
Lee et al. [42] 2022	Prospective cohort, UK	Median 10.3 years	219,330	Nil	Nil	1,390	GDM 52.1 (8.1) vs. non-GDM 56.9 (7.8)	Nil	13,094	580	HR 1.36 95% CI: 1.18–1.55	Age, race, BMI, smoking, early menopause, hysterectomy, prevalent diseases (hypertension, diabetes, or dyslipidemia), medication (aspirin, antihypertensive, cholesterol-lowering agent), early menopause, and hysterectomy	7

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Table 1 (continued)

Author (Year)	Study*, Location	Follow-up (Year)	Total Samples (n)	Maternal Age at index pregnancy (year), (mean, SD)	Pre-pregnancy BMI at index pregnancy (kg/m²) (mean, SD)	Ascertainment of GDM (n cases)	Maternal Age at endpoint (year), (mean, SD)	Maternal BMI (kg/m²) (mean, SD)	Ascertainment of overall CVD (n cases)	Incidence rate (per 100,000 person years)	Effect size (HR/OR/RR, with 95% CI)	Adjustment	Grading score
Zahid et al. [23] 2022	Cross-sectional, United States	Nil	63,115,002	Median and IQR of GDM 32 [27–36] vs. non-GDM 28 [23–32]	GDM vs. non-GDM (13.0% vs. 3.6%)	2,435,301	Nil	Nil	318,522	Nil	OR 1.48 95% CI: 1.46, 1.5	Age, race or ethnicity, comorbidities, insurance, and income	5
Sun et al. [48] 2021	Retrospective cohort, South Korea	Median 12.8 years	1,500,168	Nil	Nil	159,066	20–49 years	Nil	13,222	69	HR 1.08 95% CI: 1.02–1.14	Age, parity, household income, history of preeclampsia or hypertension, polycystic ovary syndrome, and dyslipidemia	8
Echouffo-Tcheugui et al. [33] 2021	Retrospective cohort, Canada	Median 7 years	906,319	30 (5.6)	Nil	50,193	Nil	Nil	763	12	HR 1.39 95% CI: 1.09, 1.79	Age at index delivery, socioeconomic status, rurality of residence, ethnicity, parity, pregestational hypertension, preeclampsia at the index pregnancy, preterm delivery, preexisting CVD, chronic kidney disease, postpartum progression to diabetes, hypertension, or coronary artery disease as time-varying covariates	7
Hadaegh et al. [41] 2021	Prospective cohort, Iran	Up to 10 years	1,204	Nil	Nil	Nil	57.5 (10)	Nil	73	606	HR 3.18 95% CI: 1.05–9.65	Atherosclerotic cardiovascular disease pooled cohort equations (ASCVD-PCE)	5
Wen et al. [49] 2020	Cross-sectional, China	Nil	1,474	Nil	Nil	117	Median 63 years (IQR 57, 67)	Nil	Obstructive CAD (OBCAD+): 881	Nil	OR 1.01 95% CI: 0.59–1.73	Age, history of hypertension, history of diabetes mellitus, TC, TG, HDL-C, LDL-C, E peak/A peak, LVEF, age at menarche, age at menopause and HDP	4
Wichmann et al. [22] 2019	Retrospective cohort, United States	Nil	884	GDM 23 (7) vs. non-pregnancy complications 21 (8)	GDM 30.9 (9.1) vs. non-pregnancy complications 31.8 (10)	148	Nil	Nil	Any CAD (≥20% luminal narrowing): 262	Nil	OR 3.26 95% CI: 2.03–5.22	BMI, smoking status, T2D, HTN, hyperlipidemia, age at first birth, and age when undergoing the CCTA examination	4
Arnaout et al. [18] 2019	Retrospective cohort, United States	Median 2.68 years	1,662,045	28	Obesity: GDM vs. uncomplicated pregnancies (7% vs. 2%)	107,636	Nil	Nil	3,284	74	HR 1.3 95% CI: 1.1–1.4	Age, race, insurance status, median household income, chronic kidney disease, pre-existing diabetes, obesity, drug abuse, smoking, multiple gestations, as well as each of the exposures (PPCM [Peripartum cardiomyopathy], HDP subtypes, preterm birth and IUGR)	7
Kabootari et al. [41] 2019	Prospective cohort, Iran	Median 14.1 years	4,308	Nil	Nil	477	Nil	Nil	314	517	HR 1.29 95% CI: 0.96–1.75	Age, BMI, maternal parity, history of miscarriage, physical activity, hypertension, hypercholesterolemia	7
Perera et al. [26] 2019	Prospective cohort, United States	Nil	8262	At study entry: GDM (39.1, 95%CI: 37.8–41.6) Non-GDM (45.4, 95%CI: 44.9–46.1)	At study entry: GDM (32.1, 95%CI: 31.1–32.9) Non-GDM (30.3, 95%CI: 30.1–30.5)	305	Nil	Nil	CHD without self-reported angina: 744	Nil	OR 1.2 95% CI: 0.5–2.6	Age, race/ethnicity, education, family income to poverty ratio, smoking status, alcohol intake, physical activity, total energy intake, and BMI	4
Daly et al. [43] 2018	Retrospective cohort, UK	Median 2.9 years	46,399	GDM 33 (5.4) vs. non-GDM 33 (5.4)	Obesity: GDM vs. non-GDM (39% vs. 14%)	9,118	Nil	Nil	Stroke/TIA: 64	48	IRR 0.91 95% CI: 0.48–1.70	Age, Townsend quintile, BMI, smoking, prescribed lipid-lowering medication, and hypertension, ethnicity	7
McKenzie-Sampson et al. [4] 2018	Retrospective cohort, Canada	Up to 25.2 years	1,070,667	<20 years: 5.9% 20–34: 84.2% >34: 9.9%	Nil	67,356	Nil	Nil	38,268	142	HR 1.66 95% CI: 1.60–1.73	Age, parity, socioeconomic deprivation, time period, and preeclampsia	8
Shostrom et al. [24] 2017	Prospective cohort, United States	Mean 22.9 years	8,127	Nil	Nil	555	GDM: 44.9 (0.62) Non GDM: 29.1 (0.12)	GDM: 31.7 (0.36) Non GDM: 29.1 (0.12)	829	445	OR 1.52 95% CI 0.95, 2.44	Age, race/ethnicity, education, family income to poverty ratio, smoking status, alcohol intake, physical activity, total energy intake, and BMI	6

Table 1 (continued)

Author (Year)	Study*, Location	Follow-up (Year)	Total Samples (n)	Maternal Age at index pregnancy (year), (mean, SD)	Pre-pregnancy BMI at index pregnancy (kg/m²) (mean, SD)	Ascertainment of GDM (n cases)	Maternal Age at endpoint (year), (mean, SD)	Maternal BMI (kg/m²) (mean, SD)	Ascertainment of overall CVD (n cases)	Incidence rate (per 100,000 person years)	Effect size (HR/OR/RR, with 95% CI)	Adjustment	Grading score
Tobias et al. [21] 2017	Prospective cohort, United States	Median 25.7 years	89,479	GDM: 27.5 (4.8) Non GDM: 26.5 (4.5)	Pre-pregnancy BMI: GDM: 21.5 (3.6) Non GDM: 21.0 (3.0)	5,292	GDM: 33.8 (4.4) Non GDM: 34.9 (4.7)	Nil	1,161	50	HR 1.29 95% CI 1.01–1.65	Age, years since first birth age, menopausal status, current hormone therapy use, white race/ethnicity, family history of MI or stroke, history of pregnancy, HDP, BMI and parity, pregnancy weight gain, current lifestyle factors	7
Retnakaran et al. [32] 2017	Population cohort, Canada	Median 10 years	1,515,079	Median ranges: 30–32 years	Nil	56,884	Nil	Nil	32,674	215	GDM-no-T2D: HR 1.30 95% CI: 1.07–1.59 GDM-then-T2D: HR 2.82 95% CI: 2.41–3.30	Age, income, region of residence	8
Goueslard et al. [46] 2016	Retrospective cohort, France	Median 7 years	1,518,990	Nil	Nil	62,958	Nil	Nil	3,629	34	OR: 1.25 95% CI: 1.09–1.43	Age, obesity, subsequent diabetes, hypertensive disorders of pregnancy	6
Heida et al. [47] 2015	Prospective cohort, Netherlands	Nil	22,265	At study entry: GDM: 51.2 (10.4) Non-GDM: 53.7 (9.2)	At study entry: GDM: 26.9 (5.2) Non-GDM: 25.7 (4.1)	1,089	Nil	Nil	2,557	Nil	HR 1.04 95% CI: 0.78–1.38	Cohort, age, BMI, current smoking, and current alcohol consumption at study enrollment, total cholesterol/high-density lipoprotein ratio, and prevalent hypertension and T2D	7
Kaul et al. [34] 2015	Retrospective cohort, Canada	Mean 5.3 years (IQR 2.2–8.4)	240,083	28.7 (5.6)	Nil	8,731	Nil	Nil	1,012	80	GDM and overweight (n = 1399): HR 2.1 95% CI: 1.1–1.35 GDM and non-overweight (n = 7332): HR 1.4 95% CI: 1.0–1.9	Maternal age, pre-eclampsia, parity, smoking status during pregnancy, ethnicity, socio-economic status, gestational diabetes during a subsequent pregnancy	7
Fadl et al. [37] 2014	Case-control, Sweden	Nil	15,949	Nil	Nil	209	40.7 (7.3)	Nil	2639	Nil	OR 1.51 95% CI: 1.07, 2.14	Chronic HTN, smoking, BMI, ethnicity, education level, and parity	6
Savitz et al. [20] 2014	Prospective cohort, United States	1 year	849,639	Nil	Nil	Nil	Nil	Nil	259	30	OR: 1.5 95% CI: 1.0–2.2	Gestational hypertension, preeclampsia, and gestational diabetes, parity, multiple gestations (subsequently relaxed inclusion criteria of only singleton births), calendar time, maternal age, maternal race/ethnicity, insurance status, maternal education, prenatal smoking, and pre-pregnancy weight	7
Kessous et al. [50] 2013	Retrospective cohort, Israel	Mean 15 years	47,909	GDM: 32.4 (6) Non-GDM: 29.4 (6)	Nil	4,928	Nil	Nil	1,771	246	OR: 2.6 95% CI: 2.3–2.9	Maternal age, ethnicity, current lifestyle factors	7
Carr et al. [28] 2016	Cross sectional, United States	Nil	994	Nil	Nil	332	At study entry GDM: 48.6 (0.7) Non-GDM: 52.4 (0.6)	At study entry GDM: 34.4 (1.2) Non-GDM: 33.7 (0.6)	132	Nil	OR 1.85 95% CI: 1.21–2.82	Age, menopausal status, race/ethnicity and proband status (account for subjects who were family members)	2

GDM gestational diabetes mellitus, *CVDs* cardiovascular diseases, *HR* hazard ratio, *OR* odds ratio, *RR* relative risk, *CI* confidence interval, *IQR* inter-quartile range, *SD* standard deviation, *BMI* body mass index

with GDM showed a 20% higher risk of developing overall CVDs (1.23; 1.05–1.45) over 0 to 40 years of follow-up period, with high heterogeneity ($I^2 = 78.07\%$) (Fig. 1B) and high publication bias, which was supported the funnel plot (Supplementary Fig. 5). Due to few publications, subgroup analysis was only successful for CeVD, in which the increased risk of CeVD outcomes in offsprings of mothers with GDM was not statistically significant (1.26; 0.88–1.80) (Fig. 2).

Discussion

This systematic review and meta-analysis synthesized available evidence on GDM and its association with a higher incidence of CVDs in both mothers and offspring post-delivery. Our analysis revealed a 45% increased risk of postpartum CVDs in mothers and a 31% increased risk in offspring over follow-up periods ranging from day 1 to over 40 years after delivery. In mothers, subtypes of CVDs such as coronary artery disease, heart failure, cardiovascular procedures, peripheral artery disease, arrhythmia, and angina pectoris showed increased risks ranging from 45% to 2-fold, while the risk of stroke was enhanced by 20%.

GDM and postpartum CVDs development in mothers

The mechanisms involved in GDM-associated CVDs development among mothers are related to cardiovascular risk factors, endothelial dysfunction, and myocardial remodelling [19, 40, 57]. To begin with, an elevated cardiovascular risk profile that includes conditions such as dyslipidaemia [58] and metabolic syndrome [59, 60], characterizes women with a history of GDM. These predisposing factors heighten their risk of developing CVDs in comparison to their non-GDM counterparts. Additionally, women with GDM have a seven to tenfold higher risk of transitioning to T2D in their later years [61–63]. This increased risk has been attributed to elevated markers of inflammation and reduced levels of adiponectin present in women with prior GDM [64].

Secondly, vascular dysfunction is recognized as an independent risk factor for CVDs [65]. It has been strongly suggested that even though GDM induces a temporary phase of significant glucose intolerance during pregnancy, it might result in substantial and irreversible changes within the endothelium [4]. Research indicates that women with a history of GDM exhibit decreased coronary flow reserve [66], which is a marker of potential cardiovascular issues. They also have a higher incidence of impaired endothelial vasodilation [30, 67], and increased carotid intima-media thickness (cIMT) [30, 64] when compared to their counterparts.

Thirdly, although normal pregnancy brings hemodynamic and physiological changes to the cardiovascular system [68], these are more pronounced in GDM. Advanced glycation end products in GDM can lead to critical alterations like altered preload, contractility, and heart rate, causing physiological left ventricular (LV) remodelling [69], endothelial damage, and reduced arterial elasticity [70]. These changes can persist after delivery, potentially leading to overt CVDs in women with GDM [71]. Emerging evidence has shown that women with a history of GDM manifested lower LV diastolic and systolic function during late pregnancy [72], and greater left ventricular mass, impaired LV relaxation, and lower LV systolic function years after delivery [73], compared with their counterparts.

GDM and CVDs development in offspring

Although research exploring the link between GDM and the subsequent development of CVDs in offspring is relatively limited, our analysis revealed a consistent and strong positive correlation across the five studies included in our review. Notably, some evidence even indicated the early onset of CVDs soon after birth in infants born to mothers with GDM [74].

Firstly, the intrauterine environment characterized by hyperglycemic level can adversely affect placental morphology and vasculature, leading to conditions such as villous immaturity, villous edema, villous fibrinoid necrosis, and chorangiosis [75]. These changes could cause fetal hypoxia, which prompts the release of reactive oxygen and nitrogen species, ultimately resulting in an overstimulation of nitrogen oxide [76]. Such pathological changes can increase inflammation [77] and lead to vascular endothelial dysfunction [78] in the fetoplacental unit, culminating in intrauterine growth restriction (IUGR) [79]. This has been concluded to be the underlying mechanism of the development of hypertension and other types of CVDs [65, 80].
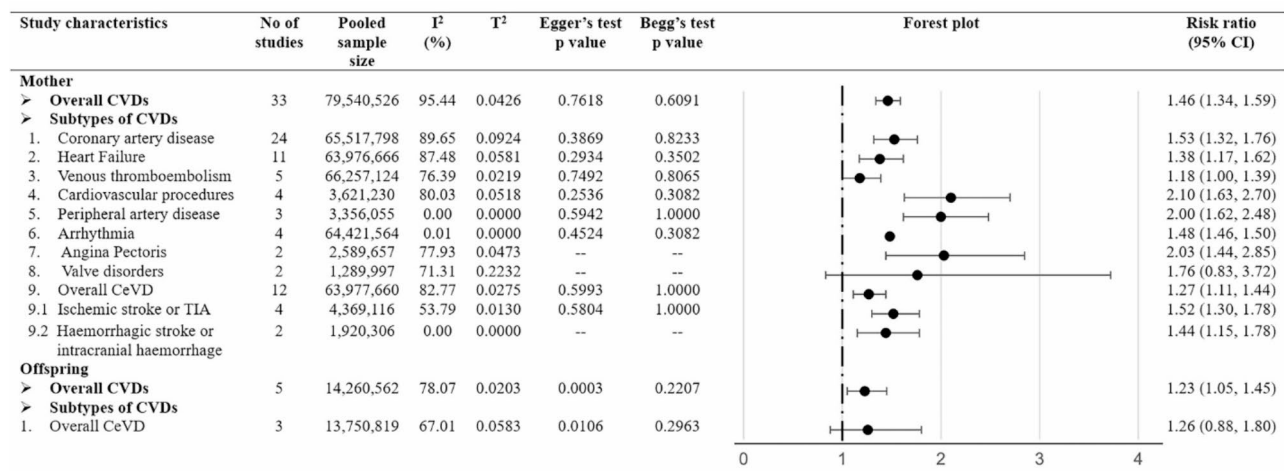
Secondly, fetal hyperinsulinemia can occur as a result of constant maternal hyperglycemia experienced *in utero* [81]. Over time, this sustained elevation in insulin production within the fetoplacental circulation may harm the fetal pancreatic islet beta cells, diminishing their ability to respond to hyperglycemia by secreting insulin [82]. This state of hyperinsulinemia could subsequently contribute to cardiac dysfunction in the offspring. For instance, studies indicated that up to 40% of pregnancies complicated by diabetes will result in offspring with myocardial hypertrophy, characterized by a thickened interventricular septum and ventricular walls, along with systolic and diastolic dysfunction [83].

Thirdly, maternal hyperglycemia may induce fetal hypoxia that results in an increased release of reactive oxygen species in both the fetus and placenta [76]. This can trigger oxidative damage to membrane lipids and deteriorate mitochondrial DNA [84]. Research has demonstrated that placentas impacted by GDM exhibit
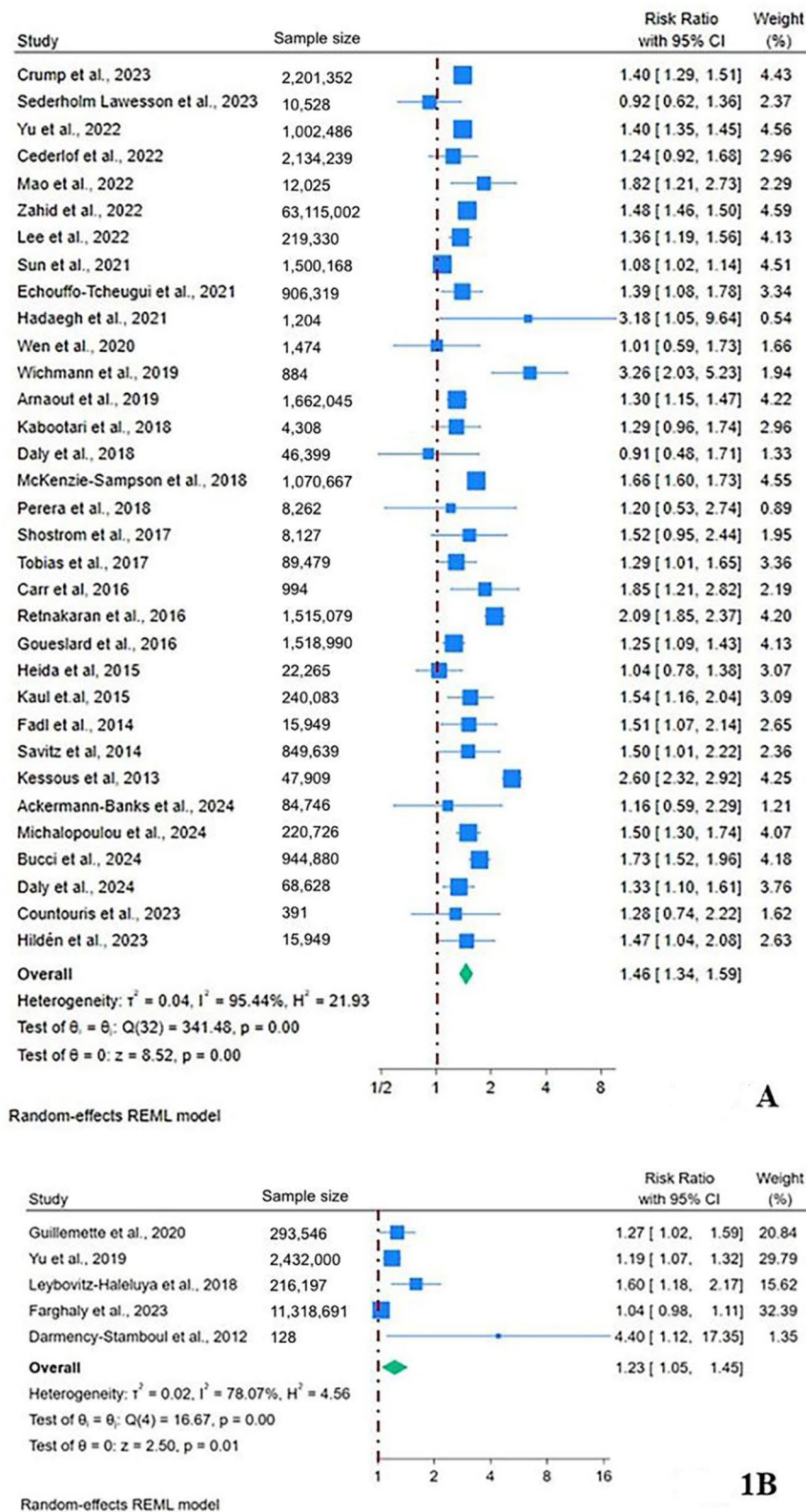
Fig. 1 Meta-analysis Results. Evidence of risk ratio (RR) and 95% confidence interval (CI) of maternal GDM and maternal postpartum overall CVDs (A) and offspring overall CVDs (B), using unadjusted random-effects model. Heterogeneity was presented in both I^2 (describing the percentage of variation across studies that is due to heterogeneity rather than chance) and T^2 (reflecting the variance of the true effect sizes). Abbreviations: RR: risk ratio; confidence interval; %, percentage

Study characteristics	No of studies	Pooled sample size	I² (%)	T²	Egger's test p value	Begg's test p value	Forest plot	Risk ratio (95% CI)
Mother								
➤ **Overall CVDs**	33	79,540,526	95.44	0.0426	0.7618	0.6091		1.46 (1.34, 1.59)
➤ **Subtypes of CVDs**								
1. Coronary artery disease	24	65,517,798	89.65	0.0924	0.3869	0.8233		1.53 (1.32, 1.76)
2. Heart Failure	11	63,976,666	87.48	0.0581	0.2934	0.3502		1.38 (1.17, 1.62)
3. Venous thromboembolism	5	66,257,124	76.39	0.0219	0.7492	0.8065		1.18 (1.00, 1.39)
4. Cardiovascular procedures	4	3,621,230	80.03	0.0518	0.2536	0.3082		2.10 (1.63, 2.70)
5. Peripheral artery disease	3	3,356,055	0.00	0.0000	0.5942	1.0000		2.00 (1.62, 2.48)
6. Arrhythmia	4	64,421,564	0.01	0.0000	0.4524	0.3082		1.48 (1.46, 1.50)
7. Angina Pectoris	2	2,589,657	77.93	0.0473	--	--		2.03 (1.44, 2.85)
8. Valve disorders	2	1,289,997	71.31	0.2232	--	--		1.76 (0.83, 3.72)
9. Overall CeVD	12	63,977,660	82.77	0.0275	0.5993	1.0000		1.27 (1.11, 1.44)
9.1 Ischemic stroke or TIA	4	4,369,116	53.79	0.0130	0.5804	1.0000		1.52 (1.30, 1.78)
9.2 Haemorrhagic stroke or intracranial haemorrhage	2	1,920,306	0.00	0.0000	--	--		1.44 (1.15, 1.78)
Offspring								
➤ **Overall CVDs**	5	14,260,562	78.07	0.0203	0.0003	0.2207		1.23 (1.05, 1.45)
➤ **Subtypes of CVDs**								
1. Overall CeVD	3	13,750,819	67.01	0.0583	0.0106	0.2963		1.26 (0.88, 1.80)

Fig. 2 Subgroup analyses stratified by subtypes of CVDs. Evidence of risk ratio (RR) and 95% confidence interval (CI) of maternal GDM and subtypes of CVDs in both mothers and offspring using unadjusted random-effects model. Heterogeneity was presented in both I² (describing the percentage of variation across studies that is due to heterogeneity rather than chance) and T² (reflecting the variance of the true effect sizes)

reduced gene and protein expression of markers associated with mitochondrial fusion and proteins related to mitochondrial biogenesis [84]. Such mitochondrial dysfunction can also extend to the myocardiocytes in the fetal heart, disrupting normal cardiac development [85].

Clinical implications

As a result of endothelial dysfunction and cardiac remodelling, against a background of CVD risks, women with a history of GDM have elevated risks of developing CVDs in the postpartum period and years after. Our study presents substantial evidence indicating that not only mothers with GDM but also their offspring face a similarly elevated risk of developing CVDs after birth. These findings underscore the importance of developing early prevention strategies that prevent the development of CVDs in GDM-complicated pregnancies. Future public health policies might incorporate these insights, by considering a history of GDM as a unique standalone CVD risk factor for both the mother and the offspring. The inclusion of GDM as a risk factor in CVD risk scoring systems might form the initial steps into public health strategies. Further assessment strategies might include targeted cardiac evaluation via easy-to-use tools such as measures of arterial stiffness, ultrasonography, or cardiac biomarkers.

Strengths and limitations

The primary strength of this systematic review lies in its extensive analysis of research evidence regarding the association of GDM and overall and subtypes of CVDs in both maternal and offspring. The robustness of our study is fortified by a meticulous search strategy, ensuring the thorough identification of all eligible studies, and subgroup analyses. However, the study is not without its

limitations. Firstly, our paper exclusively incorporated pertinent papers procured from four distinct search engines, limited to English-language publications. This approach could potentially introduce information bias if pertinent content is present but published in languages other than English or not covered within the predetermined quartet of databases. Secondly, there may be significant heterogeneity observed across studies. This variance stems from divergent follow-up durations, distinct protocols for data collection and screening methodologies, as well as variations in the diagnostic criteria or self-reported definition for GDM and CVDs. Thirdly, reporting risk over such an extended time frame, drawn from various papers without assessing the stability of risk over time, may complicate the contextualization of the reported estimates. Fourthly, pooled risk ratios derived from only two studies in the subgroup analysis should be interpreted with caution. Lastly, while GDM not only heightens the risk of CVDs, it also increases the likelihood of overweight/obesity and type 2 diabetes (T2D) in both mothers and their children, potentially mediating the development of CVDs in both generations. Nonetheless, our subgroup analyses, stratified by overweight/obesity status or T2D comorbidity, did not support these hypotheses. Further investigations utilizing a prospective longitudinal study design with more frequent follow-ups are essential to comprehensively grasp the potential mediating role of metabolic disorders underlying GDM and the development of intergenerational CVDs.

Conclusion

Our systematic review and meta-analysis unveiled increased risks of developing overall and subtypes of CVDs in both mothers and offspring impacted by GDM.

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Table 2 Characteristics of studies on maternal gestational diabetes Mellitus and overall Cardiovascular diseases in offspring included for Meta-Analysis

Author (Year)	Study *, Location	Fol- low- up (Year)	Total Samples (n)	Maternal Age at index preg- nancy (year), (mean, SD)	Pre-pregnancy BMI at index pregnancy (kg/ m²) (mean, SD)	Ascer- tainment of GDM (n cases)	Offspring Age at end- point (year), (mean, SD)	Maternal BMI (kg/ m²) (mean, SD)	Ascertain- ment of overall CVD (n cases)	Incidence rate (per 100,000 per- son years)	Effect size (HR/OR/RR, with 95% CI)	Adjustment	Grad- ing score
Fargha- ly et al. [53] 2023	United States	Nil	11,318,691	Nil	Nil	338,765	Nil	Nil	40,470	Nil	OR 1.60 95% CI: 1.11–2.10	Sex, race, GA, BW, type of insurance coverage, hospital type (rural, non- teaching urban, and teaching urban), maternal hypertension, chorioamnionitis, breech presentation, placenta previa, placental abruption, nuchal cord, cord prolapse, vacuum delivery, forceps delivery, RDS, TTN, sepsis, pulmonary hemorrhage, and pneumothorax	6
Guil- lemette et al. [55] 2020	Popula- tion-based cohort, Canada	Nil	293,546	GDM: 28.5 (6.1) Non GDM: 27.0 (5.5)	Nil	8,210	20.5 (6.4) (range 10–35 years)	Nil	2,765	Nil	HR 1.27 95% CI: 1.02–1.59	Maternal age at delivery, socioeco- nomic factor index, rural residence, birth weight, smaller for gestational age, large for gestational age, and preterm birth	5

Table 2 (continued)

Author (Year)	Study*, Location	Follow-up (Year)	Total Samples (n)	Maternal Age at index pregnancy (year), (mean, SD)	Pre-pregnancy BMI at index pregnancy (kg/m²) (mean, SD)	Ascertainment of GDM (n cases)	Offspring Age at endpoint (year), (mean, SD)	Maternal BMI (kg/m²) (mean, SD)	Ascertainment of overall CVD (n cases)	Incidence rate (per 100,000 person years)	Effect size (HR/OR/RR, with 95% CI)	Adjustment	Grading score
Yu et al. [56] 2019	Retrospective cohort, Denmark	Up to 40 years follow up	2,432,000	Nil	Nil	26,272	11 (up to 21)	Nil	91,672	92	HR: 1.19 95% CI: 1.07–1.32	Offspring's age as time scale, calendar year, sex, singleton status, parity, maternal smoking, maternal education, maternal cohabitation, maternal residence at birth, maternal history of CVD before childbirth, paternal history of CVD before birth of the child, and maternal age	8
Leybovitz-Haleluya et al. [57] 2018	Retrospective cohort, Israel	Mean (SD): GDM (diet/PA): 15.8 (3.5) GDM (treatment): 11.6 (5.5) Non-GDM: 10.2 (5.9)	216,197	GDM (diet/PA): 33.7 (5.6) GDM (treatment): 32.1 (5.8) Non-GDM: 28.0 (5.7)	Nil	10,184	Nil	Nil	736	22	HR: 1.6 95% CI 1.2–2.2	Maternal age at delivery, maternal obesity, hypertension, and cardiovascular morbidities, birth year of offspring	8
Darmency-Stamboul et al. [58] 2012	Case control, France	Nil	128	Cases: 29.9 (5.0) Controls: 29.8 (4.9)	Cases: 25.1 (6.0) Controls: 23.8 (4.7)	9	Nil	Nil	Perinatal arterial ischemic stroke: 32	Nil	OR: 4.4 95% CI: 1.1–17.7	Nil	8

GDM gestational diabetes mellitus, *CVDs* cardiovascular diseases, *HR* hazard ratio, *OR* odds ratio, *RR* relative risk, *SD* standard deviation, *CI* confidence interval, *BMI* body mass index, *PA* physical activity

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These staggering and enduring risks of GDM across two generations highlight an urgent public health need to increase awareness of CVD risks associated with GDM. Future population health strategies that include dedicated CVD risk assessment and cardiac evaluation represent crucial next steps for the field of GDM.

Abbreviations

AHA	American Heart Association
CAD	Coronary Artery Disease
CeVD	Cerebrovascular Disease
CI	Confidence Interval
cIMT	Carotid Intima-media Thickness
CVD	Cardiovascular disease
GDM	Gestational Diabetes Mellitus
HR	Hazard Ratio
IRR	Incidence Rate Ratio
IUGR	Intrauterine Growth Restriction
LV	Left Ventricular
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RR	Risk Ratio
T2D	Type 2 Diabetes
VTE	Venous Thromboembolism

Supplementary Information

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Supplementary Figure 1: Flow chart of systematic review literature searching scheme for both mothers and offspring

Supplementary Figure 2: Funnel plot regarding meta-analysis of maternal GDM and postpartum overall CVDs

Supplementary Figure 3: Subgroup analysis stratified by study features. Evidence of risk ratio (RR) and 95% confidence interval (CI) of maternal GDM and maternal postpartum overall CVDs was reported in all subgroups, using unadjusted random-effects model. Heterogeneity was presented in both I^2 (describing the percentage of variation across studies that is due to heterogeneity rather than chance) and T^2 (reflecting the variance of the true effect sizes). Cochran's Q test is used to determine if there are differences of overall CVDs within subgroups or between subgroups. P value < 0.10 for Q-test is considered significant. Abbreviations: CI: confidence interval; GDM, gestational diabetes mellitus; CVDs, cardiovascular diseases; T2D, type 2 diabetes; NOSC, Newcastle-Ottawa Scale

Supplementary Figure 4: Subgroup analysis stratified by covariates adjustment. Evidence of risk ratio (RR) and 95% confidence interval (CI) of maternal GDM and maternal postpartum overall CVDs was reported in all subgroups, using unadjusted random-effects model. Heterogeneity was presented in both I^2 (describing the percentage of variation across studies that is due to heterogeneity rather than chance) and T^2 (reflecting the variance of the true effect sizes). Cochran's Q test is used to determine if there are differences of overall CVDs within subgroups or between subgroups. P value < 0.10 for Q-test is considered significant. Abbreviations: CI, confidence interval; BMI, body mass index, HDP, hypertensive disorder during pregnancy; HTN, hypertension; T2D, type 2 diabetes

Supplementary Figure 5: Funnel plot regarding meta-analysis of maternal GDM and offspring overall CVDs

Supplementary material 6

Supplementary material 7

Supplementary material 8

Author contributions
L.-J.L. conceived the idea of the study; C.A., T.B. & L.-J.L. screened the studies and extracted the data; R.D. carried out the statistical analysis; L.-J.L. supervised the analysis. C.A., T.B. & L.-J.L. interpreted the findings and drafted the manuscript. C.Y.S., C.Z., K.A., and L.-J.L. edited and revised the manuscript. All authors critically revised and revised the manuscript for final submission. All authors have approved the final draft of the manuscript. L.-J.L. is guarantor. L.-J.L accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
Not required.

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