Gestational diabetes mellitus and adverse maternal and perinatal outcomes in twin and singleton pregnancies: a systematic review and meta-analysis.

Elena GRECO, MD, PhD, Maria CALANDUCCI, MD, Kypros H. NICOLAIDES, Professor, Eleanor VH. BARRY, Mohammed SB. HUDA, Stamatina ILIODROMITI, MD, PhD

PII: S0002-9378(23)00545-8

DOI: https://doi.org/10.1016/j.ajog.2023.08.011

Reference: YMOB 15226

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 21 March 2023

Revised Date: 10 August 2023

Accepted Date: 10 August 2023

Please cite this article as: GRECO E, CALANDUCCI M, NICOLAIDES KH, BARRY EV, HUDA MS, ILIODROMITI S, Gestational diabetes mellitus and adverse maternal and perinatal outcomes in twin and singleton pregnancies: a systematic review and meta-analysis., *American Journal of Obstetrics and Gynecology* (2023), doi: https://doi.org/10.1016/j.ajog.2023.08.011.

TITLE PAGE

Gestational diabetes mellitus and adverse maternal and perinatal outcomes in twin and singleton pregnancies: a systematic review and meta-analysis.

Authors

Elena GRECO, MD, PhD* [1]

Maria CALANDUCCI, MD*[2,3]

Kypros H NICOLAIDES, Professor [3]

Eleanor VH BARRY[1]

Mohammed SB HUDA [2]

Stamatina ILIODROMITI, MD, PhD[1]

1. *Women's Health Research Unit, Wolfson Institute of Population Health, Queen Mary University of London, UK*
2. *The Royal London Hospital, Barts Health NHS Trust*
3. *The Harris Birthright Research Centre, King's College, London UK*

*Joint first authors.

Conflict of interest: The authors report no conflict of interest.

Funding: Dr Maria Calanducci was funded by the Fetal Medicine Foundation (UK Charity No: 1037116)

Review registration: PROSPERO CRD42020222733 on 13/06/2023

Corresponding author: Dr Elena Greco. Women's Health Research Unit, Wolfson Institute of Population Health, Queen Mary University of London, Mile End Road, London E1 4NS, United Kingdom. Tel (cell). +44 07854712987 e.greco@qmul.ac.uk

Word count (abstract): 385. **Word count (main text):** 4988

CONDENSATION PAGE

Tweetable statement: Gestational diabetes #GDM is associated with adverse maternal and perinatal outcomes in both #singleton and #twin pregnancies. Gestational diabetes is associated with lower risk of neonatal death in twins. @m_iliodromiti @CphpQmul @QMUL_WIPH

Short title: Adverse outcomes in twin and singleton pregnancies with Gestational diabetes

AJOG at a Glance:

A. Why was this study conducted?

- The impact of gestational diabetes mellitus (GDM) on pregnancy outcomes in twin pregnancies is not well studied.
- Screening and management of GDM in twins have been extrapolated from singletons where the beneficial impact of tight control on maternal and neonatal outcome is better studied.
- The aim of this study was to investigate whether twin and singleton pregnancies affected by GDM are at higher risk of adverse maternal and perinatal complications compared to the respective group without GDM.

B. What are the key findings?

- In both singleton and twin pregnancies, GDM is associated with increased risk of adverse maternal and perinatal outcomes.
- Unlike singletons, GDM in twin pregnancies may be associated with less adverse outcomes than twins without GDM, including a lower risk of neonatal death.

C. What does this study add to what is already known?

- In twin pregnancies the impact of GDM is milder than in singleton pregnancies. Different glycaemic targets might be considered in twin pregnancies.

ABSTRACT PAGE

Objective: To assess the risk of adverse maternal and perinatal complications in twin and singleton pregnancies affected by gestational diabetes mellitus (GDM), compared to the respective group without GDM.

Data sources: Medline, Embase and Cochrane (January 1980 to May 2023).

Study eligibility criteria: Observational studies reporting maternal and perinatal outcomes in singletons and/or twin pregnancies with GDM versus controls.

Study appraisal and synthesis methods: Systematic review and meta-analysis**.** Pooled estimate risk ratios (RR) with 95% confidence intervals (CI) were generated to determine the likelihood of adverse pregnancy outcomes between GDM and non-GDM in twin and singleton pregnancies. Heterogeneity between studies was evaluated in the model and expressed using the I2 statistic. A P-value < 0.05 was considered statistically significant. The meta-analyses were performed using Review Manager (Version 5.4). Meta-regression was used to compare RRs between singletons and twins. The addition of multiple covariates into the models was used to address lack of adjustments.

Results: Eighty-five studies in singletons and 27 in twins were included. In singletons with GDM, compared to controls, there was increased risk of hypertensive disorders of pregnancy (RR 1.85; 95%CI 1.69, 2.01), induction of labour (RR 1.36; 95%CI 1.05,1.77), caesarean delivery (RR 1.31; 95%CI 1.24,1.38), large for gestational age neonate (RR 1.61; 95%CI 1.46,1.77), preterm birth (RR 1.36; 95%CI 1.27,1.46), admission to neonatal unit (RR 1.43; 95%CI 1.38,1.49). In twins with GDM, compared to controls, there was increased risk of hypertensive disorders of pregnancy (RR 1.69; 95%CI 1.51,1.90),

caesarean delivery (RR 1.10; 95%CI 1.06,1.13) large for gestational age neonate (RR 1.29; 95%CI 1.03,1.60), preterm birth (RR 1.19; 95%CI 1.07,1.32), admission to neonatal unit (RR 1.20; 95%CI 1.09,1.32) and reduced risk of small for gestational age neonate (RR 0.89; 95% CI 0.81-0.97) and risk of neonatal death (RR 0.50; 95%CI 0.39,0.65). When comparing RRs in singleton versus twin pregnancies, there was sufficient evidence to suggest that twins have a lower RR of caesarean delivery than singletons (P=0.003) and with sufficient adjustment for confounders, also lower RR for admission to neonatal care unit (P= 0.005), stillbirths (P= 0.002) and neonatal death (P= 0.001).

Conclusions: In both singletons and twin pregnancies, GDM is associated with increased risk of adverse maternal and perinatal outcomes. In twins, GDM may have a milder impact on some adverse perinatal outcomes and may be associated with lower risk of neonatal death.

Keywords: *gestational diabetes, hypertension, maternal outcomes, perinatal outcomes, pregnancy, preterm, singletons, twins.*

MAIN TEXT

Introduction

Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance resulting in hyperglycaemia of variable severity, diagnosed for the first time during pregnancy [1]. Over the last decades the incidence of GDM has increased, mainly due to increasing prevalence of obesity and advanced maternal age [2, 3]. Twin pregnancies account for approximately 3% of all births with increasing incidence over the last decades mostly due to advanced maternal age and widespread use of *in vitro* fertilisation (IVF) [4 5].

The increasing prevalence of both GDM and twin pregnancies as well as the shared risk factors have led to the hypothesis that twinning may further increase the risk of GDM complications [6 7] . However, a meta-analysis by McGrath found the risks of adverse neonatal outcomes to be similar in twins born to mothers with GDM compared to controls[8]. In addition, there is some evidence that GDM in twins but not in singletons may actually be protective on some important perinatal outcomes such as lower Apgar score and perinatal death [9]. Conversely, a recent meta-analysis by Tu and Fei [10] aggregating data from eight studies comparing maternal and perinatal outcomes in singleton versus twin pregnancies with GDM found lower risk in singletons for several perinatal outcomes.

Screening and management for twin pregnancies with GDM are extrapolated from studies in singletons, although good quality evidence that treatment improves adverse outcomes is available only for singletons with GDM [11 12], and despite reports showing glucose tolerance to be different in mothers of twins [13 14 15]. At present, it remains unclear whether

GDM has different associations with maternal and perinatal outcomes in twin and singleton pregnancies.

Objectives

The aim of this systematic review and meta-analysis was to assess the risk of adverse maternal and perinatal complications in twin and singleton pregnancies affected by GDM, compared to the respective group without GDM.

Methods

Eligibility criteria, data sources and search strategy

This systematic review was performed in accordance with PRISMA statement for systematic reviews and meta-analysis [16] and registered with PROSPERO International prospective register of systematic review (CRD42020222733).

A literature search was carried out using Medline, Embase and Cochrane databases. The following search terms were used: 'GDM; or gestational diabetes; or diabetes in pregnancy; or glucose intolerance; or hyperglycaemia; AND twins; or multiple; or singleton; AND pregnancy; NOT type 1; or type 2; or t2DM'. Filters applied included 'humans, female'. A manual search of relevant study reference lists was completed to identify additional studies of interest. Search results were exported to EndNote X6 (Clarivate; http: //www.endnote.com) to organise and remove duplicate publications. Searches were carried out from January 1980 until May 2023. Start date of the search was set based on the time where GDM screening using thresholds adjusted for plasma became widespread [17]. Two authors (MC, EG) independently screened the titles and/or

abstracts of studies to determine eligibility for subsequent full paper appraisal. Disagreements were solved by consensus or by a third reviewer (SI).

Study selection

Papers were considered eligible for full manuscript review and data extraction if the study was a full paper observational study (either retrospective or prospective) comparing maternal and perinatal outcomes in pregnancies with GDM with pregnancies without GDM stratified to singleton or twins, published between January 1980 and May 2023. No language restriction was imposed.

Studies with insufficient data for interpretation, those without an adequate comparison group and those with inadequate distinction between pre-existing diabetes and GDM were excluded. If studies did not report data in sufficient detail, the corresponding author was contacted to request further information.

Data extraction

For data collection, an extraction sheet was developed on Microsoft Excel (Microsoft Corporation, 2018) including main data categories: study characteristics (study authors, year of publication, study design); details of GDM screening (method, approach, diagnostic criteria) and management (lifestyle modifications, diet, medical treatment with metformin and/or insulin); GDM prevalence (as reported in the study, or calculated as number of GDM cases over total number of cases screened); maternal demographics (non-GDM and GDM sample sizes, maternal age, main ethnicity, parity, body mass index

158 [BMI], smoking habit, mode of conception, chronic hypertension). In addition, for studies
159 in twins we extracted data on chorionicity.

160 Data were extracted from publications by one author (MC) and cross-checked by another
161 author (EG). For studies that separated groups (i.e., two control groups or two GDM
162 groups based on differences in blood glucose levels), the means and standard deviations
163 were combined using the formula provided by the Cochrane Handbook for Systematic
164 Reviews of Interventions Version 5.1.0 (Cochrane 2011) and the lower glucose threshold
165 used for diagnosis was selected.

166 *Outcomes*

167 Adverse maternal outcomes included any caesarean delivery (CD); induction of labour
168 (IOL); post-partum haemorrhage; hypertensive disorders of pregnancy (HDP) defined as
169 the sum of all adverse maternal outcomes related to high blood pressure including
170 pregnancy-induced hypertension, pre-eclampsia, eclampsia and HELLP syndrome;
171 premature, prelabour rupture of membranes; placental abruption.

172 Adverse perinatal outcomes included small-for-gestational-age (SGA) and large-for-
173 gestational-age (LGA), including definition and reference chart used; preterm birth,
174 including definition; low Apgar score, including definition ; admission to Neonatal Intensive
175 Care Unit (NICU); stillbirth, defined as any death between 24 weeks and birth; neonatal
176 death (NND), referred to as the death of a live born infant, regardless of gestational age
177 at birth, within the first 28 completed days of life; perinatal mortality, defined as the sum
178 of stillbirths and neonatal deaths.

179 *Assessment of risk of bias*

180 To assess the quality of the studies selected and the risk of bias, two authors (MC, EG)
181 classified them independently, according to the Newcastle - Ottawa scale (NOS) grading
182 and considering scores ≥ 7-9, 4-6, <4 low, medium, and high risk of bias, respectively.

183 *Data synthesis*

184 The primary end points of this study were to investigate the association of GDM in twin
185 and singleton pregnancies with paired adverse maternal and perinatal outcomes.

186 Unadjusted pooled estimate risk ratios (RRs) with 95% confidence intervals (CIs) were
187 generated to determine the likelihood of adverse pregnancy outcomes between GDM and
188 non-GDM. Heterogeneity between studies was evaluated in the model and expressed
189 using the I2 statistic. A P-value < 0.05 was considered statistically significant. The meta-
190 analyses were performed using Review Manager (Version 5.4). Meta-regression was
191 used to compare RRs between singletons and twins (RStudio version 3.4.1).

192 *Secondary analysis: Meta-regression*

193 To address the lack of adjustments of the studies included, multiple covariates were
194 added into a meta-regression model to investigate whether this altered our conclusions
195 regarding the difference in RRs between singletons and twins. The covariates included
196 number of fetuses (singleton or twin), diagnostic criteria for GDM (five most common
197 criteria and an additional 'other' category), and four demographic maternal characteristics
198 including ethnicity, age, BMI, and nulliparity. Ethnicity was considered as a categorical
199 variable depending on the most prevalent ethnicity; age and BMI were considered as

continuous variables and the means for each category were used; parity was defined by the percentage of nulliparous mothers out of the total number of mothers with and without GDM.

For this analysis, we have assumed that all women diagnosed with GDM (including those where data on screening methods and management were unavailable) received standard monitoring and treatment as appropriate. Therefore, outcomes presented herein, refer to singleton and twin pregnancies diagnosed with GDM and treated as per local policies.

RESULTS

Study selection

A total of 6190 studies were identified with the search. After removal of duplicate studies, 5898 studies were screened by title and/or abstract and 388 were deemed suitable for full paper appraisal. Following assessment of eligibility, 280 studies were excluded due to the following reasons: insufficient reported study data for interpretation (n = 42), inadequate comparison group (n = 66), inadequate distinction between pre-existing diabetes and GDM (n = 51), outcomes not of interest (n=121). Screening the study reference lists did not lead to additional studies being incorporated.

A total of 108 studies were included in the final meta-analysis, of which 81 in singleton pregnancies [18] [19] [20-22] [23] [24-26] [27, 28] [29] [30] [31-33] [34, 35] [36] [37, 38] [39-43] [44-46] [47] [48-52] [53-57] [58] [59] [60] [61] [62] [63] [64] [65] [66-68] [69] [70] [71] [72, 73] [74] [75-77] [78-82] [83] [84], [85] [86] [87] [88] [89] [90] [91] [92] [93] [94] [95], 23 in twins [96] [97] [98] [99] [100] [101] [102] [103] [104, 105] [106] [107] [108] [109] [110] [111] [112] [113] [114] [115] [62] [116] [117], and 4 [51] [37] [6] [118] reporting outcomes for both singletons and twins, thus included in both analyses (**Figure 1)**.

Characteristics of studies in singletons

A total of 14,033.990 pregnancies were examined, including 722,020 GDM singleton pregnancies and 13,308.855 singleton controls. All studies included were observational in design. Out of these 70 were cohort studies, of which 58 retrospective and 12 prospective, and 15 were case control, of which 9 retrospective and 6 prospective. Qualitative assessment using NOS identified a low risk of bias for 56 studies, a medium risk of bias for 21 studies and a high risk of bias for the remaining 7 studies (Supplementary Table 1).

Most studies were carried out in Asian women [34%], followed by White [31%], Hispanic [7%], Middle Eastern [6%], Black [3%], and in the remaining 19% ethnicity was other non-White or unspecified. The average age for GDM patients was 31.6 ± 4.7 years and 29.4 ± 4.8 years for controls. Mean BMI was 26.2 ± 4.6 Kg/m^2 for GDM patients and 24.4 Kg/m^2 ± 4.3 for controls. Paired parity data were available for 63% of the studies which showed a lower percentage of nulliparous amongst GDM patients compared to controls [47% vs 51%].

Screening strategy was universal in 59 studies, based on risk-factors in 12 studies, variable in 2 studies (universal or risk-factors) and unspecified in 12 studies. Out of the studies reporting a universal screening strategy, in 32 the screening approach was two-step (glucose challenge test [GCT] in all women, followed by glucose tolerance test [GTT] in those with positive results), in 25 one-step (GTT in all women), and in two the approach was variable (one-step or two-step). Out of the studies adopting a screening strategy

based on risk-factors, six used a one-step approach, four a two-step approach and two a variable or unspecified approach.

Methods of screening and criteria for diagnosis varied widely across studies with International Association of Diabetes and Pregnancy Study Group (IADPSG) (33% of the studies), Carpenter and Coustan (CC) (19%), National Diabetes Data Group (NDDG) (8%) and American Diabetes Association (ADA) (5%) being the most used. Half of the studies included details of management of GDM, with a combination of diet, self-monitoring, oral antihyperglycemic agents and insulin being the most common measures reported.

Study design, geographical setting, ethnic characteristics of the populations, screening strategy and GDM prevalence in studies on singletons are outlined in Supplementary Table 2.

Characteristics of studies in twins

A total of 167,991 twin pregnancies were examined, including 11,812 GDM pregnancies and 156,179 controls. All studies included were observational in design, of which 20 were cohort (all retrospective but one [115]) and 7 case-control (5 retrospective and 2 prospective). Qualitative assessment using NOS identified a low risk of bias for 21 studies, a medium risk of bias for two studies, and high risk of bias for four studies (Supplementary Table 3).

The most represented ethnicity in studies on twins was White [34%], followed by Asians [22%], however in 44% of cases ethnicity was unspecified. The average age for GDM

patients was 32.7 ± 5.0 years and 31.2 ± 5.0 years for controls. The mean BMI was 25 ± 5.0 kg/m^2 for GDM and 23.6 ± 4.5 kg/m^2 for controls. Paired parity data were available for 15 studies (56%) which showed the percentage of nulliparous women to be higher in the GDM group compared to controls (56% vs 55%). Twenty-one studies (78%) included all type of twins, five (18%) excluded complications in monochorionic diamniotic twins and all monochorionic monoamniotic pregnancies, and one (4%) included dichorionic twins only.

Screening strategy was universal in 20 studies, unspecified in six and based on risk factors in one. Out of studies adopting universal screening, 12 described a two-step approach, 7 one-step and one a variable approach (one-step or two-step). Criteria for diagnosis were the same as for singletons and varied widely across studies with CC (15%), NDDG (11%), CDA (15%) and Australasian Diabetes in Pregnancy Society (ADIPS) (26%) being the most used ones. Details of management of GDM in twins were available in 16 studies, of which self-monitoring, life-style measures and insulin treatment were common to 11 studies whereas oral antihyperglycemic were used in 5 studies only.

Study design, geographical setting, ethnic characteristics of the populations, screening strategy and GDM prevalence in studies in twins are outlined in Supplementary Table 4.

GDM and maternal outcomes

Hypertensive disorders of pregnancy

Fifty-two studies in singletons (including 194,224 GDM mothers and 4,909.973 controls) and 21 in twins (including 11646 GDM mothers and 155,030 controls) reported outcome data for HDP, with mean prevalence of 9.6% (0.5 to 65) and 18.3% (6.4 to 48) in GDM

mothers of singletons and twins, respectively. In singletons with GDM, compared to those without GDM, the risk of hypertensive disorders of pregnancy was increased (RR 1.85; 95%CI 1.69, 2.01; I2 94%; P<0.00001), and this was also true in twins (RR 1.69; 95%CI 1.51,1.90; I2 50%; P<0.00001) **(Figure 2: A, B).** The difference between the RRs for singletons and twins was not statistically significant (P=0.477) and the addition of covariates in meta-regression models did not change this.

Induction of labour

Eighteen studies in singletons (including 43,817 mothers with GDM and 704,228 controls) and seven in twins (including 1268 GDM mothers of twins versus 12,399 controls) reported data on IOL with a prevalence of 25.2% (3 to 60) in singletons and 18.5% (5.3 to 56.3) in twins. In singletons with GDM, compared to those without GDM, the risk of induction of labour was increased (RR 1.36; 95%CI 1.05,1.77; I2 99%; P=0.02); this was not the case in twins (RR 1.20; 95%CI 0.72,2.00; I2 94%; P=0.48). **(Figure 2: C, D).** The difference between the RRs for singleton and twins was not statistically significant (P=0.484) and the addition of covariates in meta-regression models did not change this.

Caesarean delivery

Sixty-seven studies in singletons (including 657,545 GDM mothers and 10,302.849 controls) and 23 in twins (including 11,503 GDM mothers and 153,455 controls) reported outcome data for CD, with mean prevalence of 36.4% (2.6-74) and 76% (44-100) in GDM mothers of singletons and twins, respectively. The risk of caesarean delivery was

increased both in singletons with GDM (RR 1.31; 95%CI 1.24,1.38; I2 99%, P<0.00001) and in twins with GDM (RR 1.10; 95%CI 1.06,1.13; I2 88%; P<0.00001) compared to their respective controls without GDM. (**Figure 2: E, F**).

The difference between the RRs for singleton and twins was statistically significant (P=0.003) and the addition of covariates in meta-regression models did not change this.

GDM and perinatal outcomes

Small for Gestational Age

Thirty-nine studies in singletons (including 124,873 babies from GDM mothers and 2,064.602 controls) and 16 studies in twins (including 4986 twins from GDM mothers and 35,591 twins controls) provided outcome data for small for gestational age neonates, with a mean prevalence of 7.3% (range 1.8 to 20) in singletons and 20% (range 7-63.2) in twins born to GDM mothers. SGA was mostly defined as birth weight below the 10th centile (70% of the studies in singletons and all but one study in twins[105]) or birth weight less than 2500g [18 57 68 70 74 80 119 105 23 46]. Most studies in singletons used reference charts adjusted for gender and gestational age; 53% of studies in twins used charts for multiples [101 112 103 113 100 115 51 114 104] , with the remaining using charts for singletons (41%) or unspecified (6%). In singletons with GDM, compared to those without GDM, the risk of small for gestational age was not reduced (RR 0.99; 95%CI 0.90,1.08; I2 92%; P=0.78). Conversely, in twins with GDM, compared to those without GDM, the risk of small for gestational age was reduced (RR 0.89; 95%CI 0.81,0.97; I2 27%; P=0.009) (**Figure 3: A, B**).

The difference between the RRs for singleton and twins was not statistically significant (P=0. 250) and the addition of covariates in meta-regression models did not change this.

Large for Gestational Age

Forty-six studies in singletons (including 508,648 babies from GDM mothers and 9,834.975 controls) and fourteen studies in twin pregnancies (including 4841 twins from GDM mothers and 34,205 twin controls) looked at large for gestational age, with a mean prevalence of 16.3% (range 3.5 to 37.7) in singletons and 14.1% (range 3.8 to 34.5) in twins born to GDM mothers. LGA was mostly defined as birth weight above the 90th centile (88% of studies in singletons and 100% studies in twins), or birth weight greater than two standard deviations [SD] above the mean [46] or birth weight greater than 4000g [64] . In singletons with GDM, compared to those without GDM, the risk of large for gestational age was increased (RR 1.61; 95%CI 1.46,1.77, I2 99%, P<0.00001). This was true also for twins born to mother with GDM (RR 1.29; 95%CI 1.03,1.60; I2 58%; P=0.02) compared to controls (**Figure 3: C, D**).

The difference between the RRs for singleton and twins was not statistically significant (P= 0.103) and the addition of covariates in meta-regression models did not change this.

Preterm birth

Fifty-three studies in singletons (including 508,766 GDM mothers and 10,151.968 controls) and 16 in twins (including 2804 GDM mothers of twins and 21,250 controls) reported outcome data for preterm birth (< 37 weeks), with a mean prevalence of 12.1%

(2.5 to 100) in singletons and 40.2% (13.6 to 73.8) in twins born to GDM mothers. Nine studies in twins reported also outcome data for preterm birth <34 weeks [105 113 100 96 118 37 102 98 114]; several studies both in singletons [18 21 33 37 38 42 53 61 83 94 89] and twins [96 37 98, 102 111 114 62 117 100 113] reported outcome data also for other categories of preterm birth which were insufficient for meta-analysis due to heterogeneity in outcomes. In singletons with GDM, compared to those without GDM, the risk of preterm birth was increased (RR 1.36 95%CI 1.27,1.46, I2 99%; P<0.00001) and this was also true for twins (RR 1.19; 95%CI 1.07,1.32; I2 90%; P=0.001) (**Figure 4: A, B**).

The difference between the RRs for singleton and twins was not statistically significant (P= 0.161) and the addition of covariates in meta-regression models did not change this.

In addition, we considered that in twins preterm birth < 34 weeks is clinically more relevant than <37 weeks, thus we produced RRs also for 9 studies in twins including the preterm birth category of < 33- or <34- weeks. However, these showed minimal change in the RR for twins (RR 1.24; 95%CI 1.04,1.48, I2 61%; P=0.02), and meta-regression analysis did not show a significant difference between singletons and twins (P=0.440).

Low Apgar score

Thirty studies in singletons (including 114,034 babies from GDM mothers and 4,243.611 controls) were examined and 11 studies in twins (including 3326 twins from GDM mothers and 25,277 twins controls) reported outcome data for low Apgar score, with a mean prevalence of 2.5% (range 0 to 11.7) in singletons and 2.5% (range 0 to 10.5) in twins born to GDM mothers. Low Apgar score was defined as below 7 at 5 minutes of life in all

but one study [113]; In singletons with GDM, compared to those without GDM, the risk of low Apgar score was not increased (RR 1.12; 95%CI 0.97,1.31; I2 76%, P= 0.13); this was also true for twin pregnancies (RR 0.90; 95%CI 0.68,1.19; I2 16%; P= 0.44) (**Figure 4: C, D**), but the direction of associations was opposite in the two groups. The difference between the RRs for singleton and twins was not statistically significant (P=0.129) and the addition of covariates in meta-regression models did not change this.

Admission to Neonatal Intensive Care Unit

Thirty-five studies in singletons (including 495,192 singletons from GDM mothers and 6,495.739 controls) and 15 in twins (including 4294 twins born from GDM mothers and 31,001 twins controls) reported outcome data on admission to NICU, with a mean prevalence of 14% (0.4 to 76) in singletons and 45.8% (22.8 to 100) in twins born to GDM mothers. In singletons with GDM, compared to those without GDM, the rate of NICU admission was increased (RR 1:43; 95% CI 1.38,1.49; I2 82%; P<0.0001); this was also true for twin pregnancies (RR 1.20; 95% CI 1.09,1.32; I2 80%; P=0.0002) (**Figure 4: E, F**). The difference between the RRs for singleton and twins was not statistically significant (P= 0.097) when additional covariates were not included. However, when BMI or parity were included in the model, the effect estimates for singletons versus twins became significant (P= 0.033 and P= 0.005, respectively).

Stillbirth

Twenty-two studies in singletons and 8 in twins reported outcome data for stillbirths, with a mean prevalence of 1.2% (0 to 8.3) in singleton and 2.4% (0.0 to 8.8) in twin pregnancies complicated with GDM. A total of 360,647 GDM singletons and 8,489.858 singleton controls were examined, versus 1531 twins from diabetic mother and 15362 twins controls. In singletons with GDM, compared to those without GDM, the risk of stillbirth was not significantly different (RR 1.00; 95%CI 0.80,1.25; I2 73%; P=0.99). Similarly, in twins with GDM, compared to those without GDM, the risk of stillbirth was not significantly different (RR 1.72; 95%CI 0.57,5.19; I2 68%, P=0.34) (**Figure 5: A, B**). The difference between the RRs for singletons and twins was not statistically significant (P= 0.3743). However, when age or diagnostic criteria were added in the meta-regression, the estimate effect of being a singleton versus twin was significant, implying that twins have a greater risk ratio compared to singletons (P= 0.002 and P=0.042, respectively).

Neonatal death

Sixteen studies in singletons (including 147107 babies from GDM mothers and 4434173 controls) and 10 studies in twins (including 19,299 twins from GDM mothers and 280,387 twins controls) reported data on neonatal deaths, with a mean prevalence of 0.9% (0 to 3) in singleton and 0.88% (0 to 2.3) in twin pregnancies complicated with GDM. In singletons with GDM, compared to those without GDM, the risk of neonatal death was not significantly different (RR 0.87, 95%CI 0.65,1.17, I2 78%; P=0.36). In twins with GDM, compared to those without GDM, the risk of neonatal death was markedly reduced (RR 0.50; 95% CI 0.39,0.65, I2 6%; P<0.00001) (**Figure 5: C, D**). The RRs for singletons and

418 twins did not differ substantially (P= 0.082), which remained unchanged after the inclusion
419 of most covariates in the meta-regression models. However, after including diagnostic
420 criteria for GDM in the meta-regression, the RRs for NND differed between singletons
421 and twins, with twins having a lower risk of NND compared to singletons (P= 0.0012).

422 *Perinatal mortality*

423 Fifteen studies in singletons (including 153099 babies from GDM mothers and 4214762
424 controls) and 5 studies in twins (including 1763 twins from GDM mothers and 13416 twins
425 controls) reported outcome data for perinatal mortality, with a mean prevalence of 1.0%
426 (0 to 6.8) in singletons and 3.8 (1.5 to 10.5) in twins born to GDM mothers. In singletons
427 with GDM, compared to those without GDM, the risk of perinatal mortality was not
428 significantly different (RR 0.89; 95%CI, 0.67,1.18; I2 88%; P= 0.41) and this was also true
429 for twin pregnancies (RR 1.04; 95%CI 0.47, 2.32; I2 75%; P=0.92) (**Figure 5: E, F**). The
430 difference between the RRs for singleton and twins was not statistically significant (P=
431 0.893) and the addition of covariates in meta-regression models did not change this.

432

433

434

COMMENT

Principal findings

This systematic review and meta-analysis have demonstrated that in singleton pregnancies with GDM, compared to those without GDM, there was increased risk of hypertensive disorders of pregnancy, induction of labour, caesarean delivery, birth of large for gestational age neonate, preterm birth, neonatal intensive care unit admission; there was no significant difference in risk of birth of small for gestational age neonate, low-Apgar score, stillbirth, neonatal death, and perinatal mortality.

In twin pregnancies with GDM, compared to those without GDM, there was increased risk of hypertensive disorders of pregnancy, caesarean delivery, birth of large for gestational age neonate, preterm birth, and admission to neonatal intensive care unit; there were reduction in the risk of small for gestational age neonate and a 50% reduction in the risk of neonatal death. There were no significant differences in risk of induction of labour, low-Apgar score, stillbirth, or perinatal mortality.

When comparing RRs in singleton versus twin pregnancies, there was sufficient evidence to suggest that twins have a lower RR of caesarean delivery than singletons. There was insufficient evidence to suggest a difference in hypertensive disorders of pregnancy, induction of labour, birth of large for gestational neonate, preterm birth, low-Apgar score, stillbirth, and perinatal mortality. With sufficient adjustment for confounders, there was evidence that twins have lower RR than singletons for admission to neonatal intensive care unit, stillbirth, and neonatal death.

Comparison with existing literature

The increased risk of adverse outcomes in singleton pregnancies with GDM is well established [120] and likely to be mediated by the substantial increase in the risk of LGA which, in turn, leads to increased risk of induction of labour and caesarean delivery and predisposes to other adverse outcomes, such as birth trauma and shoulder dystocia, which have been omitted in this review as were not reported for twins. In addition, GDM in singletons is known to be associated with placental dysfunction [121], chronic hypoxia, neonatal hypoglycaemia, all of which may contribute to increased perinatal risks. Conversely, in twins, the impact of hyperglycaemia is thought to provide a benefit in terms of fetal growth, by counterbalancing the inherent growth restricting effect of the inadequate uterine milieu in multiples [37] .

In our study, GDM was associated with a 50% reduction in the risk of neonatal death in twins but not in singletons. Our results were mostly driven by two good quality studies, which showed a positive impact of GDM on the risk of neonatal death [110] [51] in twins compared to controls without GDM. In the large US birth cohort study by Foeller, the trend towards reduced neonatal deaths in twins GDM versus controls (aOR 0.84, 95% CI 0.68–1.02) was justified by reduced risk of low Apgar score (aOR 0.8 95%CI 0.68, 0.94), reduced prematurity before 32 weeks (aOR 0.72, 95% CI 0.68–0.76), and reduced risk of SGA neonate (aOR 0.84, 95% CI 0.81–0.89) [110]. Lai et al also observed a reduced risk of neonatal death (OR 0.45 95%CI 0.21, 0.97 $p<0.05$) and low Apgar score (OR 0.54 95%CI 0.34, 0.87 $p<0.05$) in twins with GDM versus controls but not in singletons [51]. Of note both these studies reported data adjusted for multiple maternal and pregnancy confounders, except pre-pregnancy BMI, which is known to be an independent predictor of adverse

perinatal outcomes [122]. In addition, neither study presented chorionicity data. Interestingly, in our study, the risk of low Apgar score was not significantly reduced; both the risk of NICU admissions and preterm birth were increased in twin neonates with GDM compared to controls, thus they could not mediate the risk of neonatal death. It can be hypothesised that the positive effect of GDM on growth in twins is what confers them a real metabolic advantage, whereas low birth weight is one of the most frequent causes of morbidity in twins. Other contributing factors may include closer antenatal surveillance with multidisciplinary input in twin pregnancies with GDM compared to twins without GDM, lower threshold for delivery, higher rates of steroid administration for lung maturation and increased compliance to follow-up in this group.

Strengths and limitations

Strengths of our analysis include the large sample size and inclusion of studies from a wide number of geographical settings, ethnicities, and cultures without language restriction, which increase the applicability of our findings to different populations. The comprehensive outcome dataset, including paired perinatal and maternal adverse outcomes for singletons and twins helps comparability of findings between these two populations.

There are several limitations to this meta-analysis. Estimating risks of adverse outcomes for both twins and singletons affected by GDM based on aggregated data is subject to the heterogeneity of the primary studies with regards to the study design, demographics of the populations studied, methods of screening, and criteria for diagnosing GDM across the studies. The high between studies heterogeneity reflects great methodological

variation, thus suggesting that the findings should be interpreted cautiously. However, adopting a mixed methods approach accounts partially for the within studies heterogeneity. In addition, the inclusion of meta-regression models mitigates the risk of bias due to lack of adjustment for confounders by assessing whether the variation in confounders accounts for the within group difference in risk.

Finally, data from birth registry studies incorporated in this analysis included different approaches and/or methods of screening and provided no information on local policies for management of GDM; however, the inclusion of registry data minimises the risk of selection bias. Data reported in this meta-analysis pertain to women diagnosed and treated with GDM as per local policy, therefore the effect of treatment on the outcomes could not be measured. However, this was beyond the scope of this review.

Conclusions and Implications

We performed a meta-analysis of the association between GDM and adverse pregnancy outcomes in more than fourteen million women with singleton and nearly 170,000 with twin pregnancies. In singletons GDM is associated with increased risk of adverse maternal and perinatal outcomes, but the impact of GDM on twins was milder, with a remarkable reduced risk of neonatal death.

Our findings contribute to a more comprehensive understanding of adverse outcomes of pregnancy related to GDM in singletons and twins compared to their counterparts without GDM which will facilitate evidence-based counselling to the respective group of women. The impact of GDM treatment in mediating adverse outcomes in each group and the optimal thresholds for diagnosing GDM in twin pregnancies warrant further research.

CRediT author statement:

Elena Greco: *Investigation, Formal Analysis*, *Writing-Original Draft, Writing- Review & Editing, Visualization.* **Maria Calanducci:** *Investigation, Formal analysis, Data curation, Writing-Original Draft, Visualization.* **Kypros H Nicolaides:** *Methodology, Visualization, Writing- Review & Editing.* **Mohammed BS Huda:** *Visualization, Writing- Review & Editing*. **Eleanor VH Barry:** *Methodology, Formal analysis, Writing- Review & Editing*. **Stamatina Iliodromiti:** *Conceptualization, Methodology, Project administration, Supervision, Writing- Review & Editing.*

Data availability: The protocol and datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Figure Legends:

Figure 1. PRISMA study selection flowchart

Figure 2. Risk of adverse maternal outcomes in singleton pregnancies with GDM versus control and in twin pregnancies with GDM versus controls.

Risk of hypertensive disorders of pregnancy in singleton pregnancies with GDM versus controls (A) and in twin pregnancies with GDM versus controls (B); Risk of induction of labour in singleton pregnancies with GDM versus controls (C) and in twin pregnancies with GDM versus controls (D); Risk of caesarean delivery in singleton pregnancies with GDM versus controls (E) and in twin pregnancies with GDM versus controls (F)

Figure 3. Risk of adverse growth outcomes in singleton pregnancies with GDM with GDM versus controls and twin pregnancies with GDM versus controls. Risk of SGA in singleton pregnancies with GDM versus controls (A) and in twin pregnancies with GDM versus controls (B); Risk of LGA in singleton pregnancies with GDM versus controls (C) and in twin pregnancies with GDM versus controls (D).

Figure 4. Risk of preterm birth, low Apgar score and NICU admission in singleton pregnancies with GDM versus controls and twin pregnancies with GDM versus controls. Risk of preterm birth in singleton pregnancies with GDM versus controls (A) and in twin pregnancies with GDM versus controls (B); Risk of low-Apgar score in singleton pregnancies with GDM versus controls (C) and in twin pregnancies with GDM versus controls (D); Risk of NICU admission in singleton pregnancies with GDM versus controls (E) and in twin pregnancies with GDM versus controls (F).

Figure 5. Risk of stillbirth, neonatal death, and perinatal mortality in singleton pregnancies with GDM with GDM versus controls and twin pregnancies with GDM versus controls. Risk of stillbirth in singleton pregnancies with GDM versus controls (A) and in twin pregnancies with GDM versus controls (B); Risk of NND in singleton pregnancies with GDM versus controls (C) and in twin pregnancies with GDM versus controls (D); Risk of perinatal mortality in singleton pregnancies with GDM versus controls (E) and in twin pregnancies with GDM versus controls (F).

Supplementary material:

Table 1. Quality assessment for studies in singletons using Newcastle-Ottawa scale

567 **Table 2.** Characteristics of studies in singletons

568 **Table 3.** Quality assessment for studies in twins using Newcastle-Ottawa scale

569 **Table 4.** Characteristics of studies in twins

570

References

1. Practice Bulletin No. 180: Gestational Diabetes Mellitus. Obstetrics & Gynecology 2017;130:e17-e37.
2. Giannakou K, Evangelou E, Yiallouros P, et al. Risk factors for gestational diabetes: An umbrella review of meta-analyses of observational studies. PLoS One 2019;14:e0215372.
3. Benhalima K, Van Crombrugge P, Moyson C, et al. Risk factor screening for gestational diabetes mellitus based on the 2013 WHO criteria. Eur J Endocrinol 2019;180:353-63.
4. Spellacy WN, Handler A, Ferre CD. A case-control study of 1253 twin pregnancies from a 1982-1987 perinatal data base. Obstet Gynecol 1990;75:168-71.
5. Kiely JL, Kiely M. Epidemiological trends in multiple births in the United States, 1971-1998. Twin Res 2001;4:131-3.
6. Rauh-Hain JA, Rana S, Tamez H, et al. Risk for developing gestational diabetes in women with twin pregnancies. J Matern Fetal Neonatal Med 2009;22:293-9.
7. Yogev Y, Eisner M, Hiersch L, Hod M, Wiznitzer A, Melamed N. The performance of the screening test for gestational diabetes in twin versus singleton pregnancies. J Matern Fetal Neonatal Med 2014;27:57-61.
8. McGrath RT, Hocking SL, Scott ES, Seeho SK, Fulcher GR, Glastras SJ. Outcomes of twin pregnancies complicated by gestational diabetes: a meta-analysis of observational studies. J Perinatol 2017;37:360-68.
9. Luo ZC, Simonet F, Wei SQ, Xu H, Rey E, Fraser WD. Diabetes in pregnancy may differentially affect neonatal outcomes for twins and singletons. Diabet Med 2011;28:1068-73.
10. Tu F, Fei A. Maternal and neonatal outcomes of singleton versus twin pregnancies complicated by gestational diabetes mellitus: A systematic review and meta-analysis. PLoS One 2023;18:e0280754.
11. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477-86.

12. LANDON MB, SPONG CY, THOM E, et al. A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes. New England Journal of Medicine 2009;361:1339-48.
13. SCHWARTZ DB, DAOUD Y, ZAZULA P, et al. Gestational diabetes mellitus: metabolic and blood glucose parameters in singleton versus twin pregnancies. Am J Obstet Gynecol 1999;181:912-4.
14. REBARBER A, DOLIN C, FIELDS JC, et al. Screening approach for gestational diabetes in twin pregnancies. Am J Obstet Gynecol 2014;211:639.e1-5.
15. JUNG YJ, KWON JY, CHO HY, PARK YW, KIM YH. Comparison of the performance of screening test for gestational diabetes in singleton versus twin pregnancies. Obstet Gynecol Sci 2015;58:439-45.
16. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
17. BHAVADHARINI B, UMA R, SARAVANAN P, MOHAN V. Screening and diagnosis of gestational diabetes mellitus - relevance to low and middle income countries. Clin Diabetes Endocrinol 2016;2:13.
18. ALFADHLI EM, OSMAN EN, BASRI TH, et al. Gestational diabetes among Saudi women: prevalence, risk factors and pregnancy outcomes. Ann Saudi Med 2015;35:222-30.
19. AHLSSON F, LUNDGREN M, TUVEMO T, GUSTAFSSON J, HAGLUND B. Gestational diabetes and offspring body disproportion. Acta Paediatr 2010;99:89-93.
20. AVIRAM A, GUY L, ASHWAL E, HIERSCH L, YOGEV Y, HADAR E. Pregnancy outcome in pregnancies complicated with gestational diabetes mellitus and late preterm birth. Diabetes Res Clin Pract 2016;113:198-203.
21. BAR-HAVA I, BARNHARD Y, SCARPELLI SA, ORVIETO R, BEN R, DIVON MY. Gestational diabetes and preterm labour: is glycaemic control a contributing factor? Eur J Obstet Gynecol Reprod Biol 1997;73:111-4.
22. BASHIR M, IBRAHIM I, ELTAHER F, et al. Screening pregnant women in a high-risk population with WHO-2013 or NICE diagnostic criteria does not affect the prevalence of gestational diabetes. Sci Rep 2021;11:5604.

23. Blickstein I, Doyev R, Trojner Bregar A, Bržan Šimenc G, Verdenik I, Tul N. The effect of gestational diabetes, pre-gravid maternal obesity, and their combination ('diabesity') on outcomes of singleton gestations. J Matern Fetal Neonatal Med 2018;31:640-43.
24. Bo S, Menato G, Signorile A, et al. Obesity or diabetes: what is worse for the mother and for the baby? Diabetes Metab 2003;29:175-8.
25. Boriboonhirunsarn D, Waiyanikorn R. Emergency cesarean section rate between women with gestational diabetes and normal pregnant women. Taiwan J Obstet Gynecol 2016;55:64-7.
26. Bricelj K, Tul N, Lucovnik M, et al. Neonatal respiratory morbidity in late-preterm births in pregnancies with and without gestational diabetes mellitus. J Matern Fetal Neonatal Med 2017;30:377-79.
27. Casey BM, Lucas MJ, McIntire DD, Leveno KJ. Pregnancy outcomes in women with gestational diabetes compared with the general obstetric population. Obstet Gynecol 1997;90:869-73.
28. Catalano PM, McIntyre HD, Cruickshank JK, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care 2012;35:780-6.
29. Chou CY, Lin CL, Yang CK, Yang WC, Lee FK, Tsai MS. Pregnancy outcomes of Taiwanese women with gestational diabetes mellitus: a comparison of Carpenter-Coustan and National Diabetes Data Group criteria. J Womens Health (Larchmt) 2010;19:935-9.
30. Cosson E, Cussac-Pillegand C, Benbara A, et al. Pregnancy adverse outcomes related to pregravid body mass index and gestational weight gain, according to the presence or not of gestational diabetes mellitus: A retrospective observational study. Diabetes Metab 2016;42:38-46.
31. Das S, Irigoyen M, Patterson MB, Salvador A, Schutzman DL. Neonatal outcomes of macrosomic births in diabetic and non-diabetic women. Arch Dis Child Fetal Neonatal Ed 2009;94:F419-22.
32. Davis EM, Scifres CM, Abebe K, et al. Comparison of Birth Outcomes by Gestational Diabetes Screening Criteria. AJP Rep 2018;8:e280-e88.

33. DIAMOND MP, SALYER SL, VAUGHN WK, COTTON RB, ENTMAN SS, BOEHM FH. Continuing neonatal morbidity in infants of women with class A diabetes. South Med J 1984;77:1386-8, 92.
34. DUDHBHAI M, LIM L, BOMBARD A, et al. Characteristics of patients with abnormal glucose challenge test and normal oral glucose tolerance test results: comparison with normal and gestational diabetic patients. Am J Obstet Gynecol 2006;194:e42-5.
35. FADL HE, OSTLUND IK, MAGNUSON AF, HANSON US. Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. Diabet Med 2010;27:436-41.
36. GORTAZAR L, FLORES-LE ROUX JA, BENAIGES D, et al. Trends in prevalence of gestational diabetes and perinatal outcomes in Catalonia, Spain, 2006 to 2015: the Diagestcat Study. Diabetes Metab Res Rev 2019;35:e3151.
37. HIERSCH L, BERGER H, OKBY R, et al. Gestational diabetes mellitus is associated with adverse outcomes in twin pregnancies. Am J Obstet Gynecol 2019;220:102.e1-02.e8.
38. HILDÉN K, HANSON U, PERSSON M, MAGNUSON A, SIMMONS D, FADL H. Gestational diabetes and adiposity are independent risk factors for perinatal outcomes: a population based cohort study in Sweden. Diabet Med 2019;36:151-57.
39. HUIDOBRO A, FULFORD A, CARRASCO E. [Incidence of gestational diabetes and relationship to obesity in Chilean pregnant women]. Rev Med Chil 2004;132:931-8.
40. IJÄS H, KOIVUNEN S, RAUDASKOSKI T, KAJANTIE E, GISSLER M, VÄÄRÄSMÄKI M. Independent and concomitant associations of gestational diabetes and maternal obesity to perinatal outcome: A register-based study. PLoS One 2019;14:e0221549.
41. IKENOUE S, MIYAKOSHI K, SAISHO Y, et al. Clinical impact of women with gestational diabetes mellitus by the new consensus criteria: two year experience in a single institution in Japan. Endocr J 2014;61:353-8.
42. ISMAIL NA, ARIS NM, MAHDY ZA, et al. Gestational diabetes mellitus in primigravidae: a mild disease. Acta Medica (Hradec Kralove) 2011;54:21-4.

43. JOHNS K, OLYNIK C, MASE R, KREISMAN S, TILDESLEY H. Gestational diabetes mellitus outcome in 394 patients. J Obstet Gynaecol Can 2006;28:122-7.
44. KARI A, SAHHAF F, ABBASALIZADEH F. Maternal, Fetal and Neonatal Outcomes in Mothers With Diabetes Mellitus or Gestational Diabetes That Complicated With Preterm Premature Rupture of the Membrane (PPROM). International Journal of Women's Health and Reproduction Sciences 2017;5:66-71.
45. KAUL P, SAVU A, NERENBERG KA, et al. Impact of gestational diabetes mellitus and high maternal weight on the development of diabetes, hypertension and cardiovascular disease: a population-level analysis. Diabet Med 2015;32:164-73.
46. KAWAKITA T, BOWERS K, HAZRATI S, et al. Increased Neonatal Respiratory Morbidity Associated with Gestational and Pregestational Diabetes: A Retrospective Study. Am J Perinatol 2017;34:1160-68.
47. KIM MH, KWAK SH, KIM SH, et al. Pregnancy Outcomes of Women Additionally Diagnosed as Gestational Diabetes by the International Association of the Diabetes and Pregnancy Study Groups Criteria. Diabetes Metab J 2019;43:766-75.
48. KOIVUNEN S, TORKKI A, BLOIGU A, et al. Towards national comprehensive gestational diabetes screening - consequences for neonatal outcome and care. Acta Obstet Gynecol Scand 2017;96:106-13.
49. KWIK M, SEEHO SK, SMITH C, MCELDUFF A, MORRIS JM. Outcomes of pregnancies affected by impaired glucose tolerance. Diabetes Res Clin Pract 2007;77:263-8.
50. LAAFIRA A, WHITE SW, GRIFFIN CJ, GRAHAM D. Impact of the new IADPSG gestational diabetes diagnostic criteria on pregnancy outcomes in Western Australia. Aust N Z J Obstet Gynaecol 2016;56:36-41.
51. LAI FY, JOHNSON JA, DOVER D, KAUL P. Outcomes of singleton and twin pregnancies complicated by pre-existing diabetes and gestational diabetes: A population-based study in Alberta, Canada, 2005-11. J Diabetes 2016;8:45-55.
52. LAO TT, HO LF. Impaired glucose tolerance and pregnancy outcome in Chinese women with high body mass index. Hum Reprod 2000;15:1826-9.

53. LEON MG, MOUSSA HN, LONGO M, et al. Rate of Gestational Diabetes Mellitus and Pregnancy Outcomes in Patients with Chronic Hypertension. Am J Perinatol 2016;33:745-50.

54. LEYBOVITZ-HALELUYA N, WAINSTOCK T, LANDAU D, SHEINER E. Maternal gestational diabetes mellitus and the risk of subsequent pediatric cardiovascular diseases of the offspring: a population-based cohort study with up to 18 years of follow up. Acta Diabetol 2018;55:1037-42.

55. LI HP, WANG FH, TAO MF, HUANG YJ, JIA WP. Association between glycemic control and birthweight with glycated albumin in Chinese women with gestational diabetes mellitus. J Diabetes Investig 2016;7:48-55.

56. LI MF, MA L, YU TP, et al. Adverse maternal and neonatal outcomes in pregnant women with abnormal glucose metabolism. Diabetes Res Clin Pract 2020;161:108085.

57. LU MC, HUANG SS, YAN YH, WANG P. Use of the National Diabetes Data Group and the Carpenter-Coustan criteria for assessing gestational diabetes mellitus and risk of adverse pregnancy outcome. BMC Pregnancy Childbirth 2016;16:231.

58. LUCAS MJ, LOWE TW, BOWE L, MCINTIRE DD. Class A1 gestational diabetes: a meaningful diagnosis? Obstet Gynecol 1993;82:260-5.

59. MARTÍNEZ-CRUZ N, RAPISARDA AMC, SORIANO-ORTEGA KP, et al. Perinatal Outcomes in Mexican Women with Untreated Mild Gestational Diabetes Mellitus Diagnosed by the International Association of Diabetes and Pregnancy Study Groups Criteria. Diabetes Metab Syndr Obes 2019;12:2667-74.

60. MECACCI F, CARIGNANI L, CIONI R, et al. Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: comparison with non-diabetic pregnant women. Eur J Obstet Gynecol Reprod Biol 2003;111:19-24.

61. MEGHELLI L, VAMBERGUE A, DRUMEZ E, DERUELLE P. Complications of pregnancy in morbidly obese patients: What is the impact of gestational diabetes mellitus? J Gynecol Obstet Hum Reprod 2020;49:101628.

62. MIYAKOSHI K, TANAKA M, MATSUMOTO T, et al. Hypertensive disorders in Japanese women with gestational glucose intolerance. Diabetes Res Clin Pract 2004;64:201-5.

63. MORTIER I, BLANC J, TOSELLO B, GIRE C, BRETELLE F, CARCOPINO X. Is gestational diabetes an independent risk factor of neonatal severe respiratory distress syndrome after 34 weeks of gestation? A prospective study. Arch Gynecol Obstet 2017;296:1071-77.

64. NAYLOR CD, SERMER M, CHEN E, SYKORA K. Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? Toronto Trihospital Gestational Diabetes Investigators. Jama 1996;275:1165-70.

65. OKUN N, VERMA A, MITCHELL BF, FLOWERDEW G. Relative importance of maternal constitutional factors and glucose intolerance of pregnancy in the development of newborn macrosomia. J Matern Fetal Med 1997;6:285-90.

66. OSTLUND I, HAGLUND B, HANSON U. Gestational diabetes and preeclampsia. Eur J Obstet Gynecol Reprod Biol 2004;113:12-6.

67. OVESEN PG, JENSEN DM, DAMM P, RASMUSSEN S, KESMODEL US. Maternal and neonatal outcomes in pregnancies complicated by gestational diabetes. a nation-wide study. J Matern Fetal Neonatal Med 2015;28:1720-4.

68. PEIXOTO AB, CALDAS TM, SANTOS RO, LOPES KS, MARTINS WP, ARAUJO JÚNIOR E. The impact of gestational diabetes and hypothyroidism on the third-trimester ultrasound parameters and in adverse perinatal outcomes: a retrospective cohort study. J Matern Fetal Neonatal Med 2016;29:3416-20.

69. RAMACHANDRAN A, SNEHALATHA C, CLEMENTINA M, SASIKALA R, VIJAY V. Foetal outcome in gestational diabetes in south Indians. Diabetes Res Clin Pract 1998;41:185-9.

70. REMSBERG KE, MCKEOWN RE, MCFARLAND KF, IRWIN LS. Diabetes in pregnancy and cesarean delivery. Diabetes Care 1999;22:1561-7.

71. RICART W, LÓPEZ J, MOZAS J, et al. Potential impact of American Diabetes Association (2000) criteria for diagnosis of gestational diabetes mellitus in Spain. Diabetologia 2005;48:1135-41.

72. ROSEN H, SHMUELI A, ASHWAL E, HIERSCH L, YOGEV Y, AVIRAM A. Delivery outcomes of large-for-gestational-age newborns stratified by the presence or absence of gestational diabetes mellitus. Int J Gynaecol Obstet 2018;141:120-25.
73. SACKS DA, BLACK MH, LI X, MONTORO MN, LAWRENCE JM. Adverse Pregnancy Outcomes Using The International Association of the Diabetes and Pregnancy Study Groups Criteria: Glycemic Thresholds and Associated Risks. Obstet Gynecol 2015;126:67-73.
74. SOLIMAN A, SALAMA H, AL RIFAI H, et al. The effect of different forms of dysglycemia during pregnancy on maternal and fetal outcomes in treated women and comparison with large cohort studies. Acta Biomed 2018;89:11-21.
75. SRICHUMCHIT S, LUEWAN S, TONGSONG T. Outcomes of pregnancy with gestational diabetes mellitus. Int J Gynaecol Obstet 2015;131:251-4.
76. STELLA CL, O'BRIEN JM, FORRESTER KJ, et al. The coexistence of gestational hypertension and diabetes: influence on pregnancy outcome. Am J Perinatol 2008;25:325-9.
77. STONE CA, MCLACHLAN KA, HALLIDAY JL, WEIN P, TIPPETT C. Gestational diabetes in Victoria in 1996: incidence, risk factors and outcomes. Med J Aust 2002;177:486-91.
78. VAN HOORN J, DEKKER G, JEFFRIES B. Gestational diabetes versus obesity as risk factors for pregnancy-induced hypertensive disorders and fetal macrosomia. Aust N Z J Obstet Gynaecol 2002;42:29-34.
79. VILCHEZ GA, DAI J, HOYOS LR, GILL N, BAHADO-SINGH R, SOKOL RJ. Labor and neonatal outcomes after term induction of labor in gestational diabetes. J Perinatol 2015;35:924-9.
80. WAHABI HA, FAYED AA, ALZEIDAN RA, MANDIL AA. The independent effects of maternal obesity and gestational diabetes on the pregnancy outcomes. BMC Endocr Disord 2014;14:47.
81. WANG LF, WANG HJ, AO D, LIU Z, WANG Y, YANG HX. Influence of pre-pregnancy obesity on the development of macrosomia and large for gestational age in women with or without gestational diabetes mellitus in Chinese population. J Perinatol 2015;35:985-90.

82. WATERS TP, DYER AR, SCHOLTENS DM, et al. Maternal and Neonatal Morbidity for Women Who Would Be Added to the Diagnosis of GDM Using IADPSG Criteria: A Secondary Analysis of the Hyperglycemia and Adverse Pregnancy Outcome Study. Diabetes Care 2016;39:2204-10.
83. KYOZUKA H, YASUDA S, MURATA T, et al. Adverse obstetric outcomes in early-diagnosed gestational diabetes mellitus: The Japan Environment and Children's Study. J Diabetes Investig 2021;12:2071-79.
84. MUSTANIEMI S, NIKKINEN H, BLOIGU A, et al. Normal Gestational Weight Gain Protects From Large-for-Gestational-Age Birth Among Women With Obesity and Gestational Diabetes. Front Public Health 2021;9:550860.
85. RANDALL DA, MORRIS JM, KELLY P, GLASTRAS SJ. Are newly introduced criteria for the diagnosis of gestational diabetes mellitus associated with improved pregnancy outcomes and/or increased interventions in New South Wales, Australia? A population-based data linkage study. BMJ Open Diabetes Res Care 2021;9.
86. TESHOME AA, LI Q, GAROMA W, et al. Gestational diabetes mellitus, pre-pregnancy body mass index and gestational weight gain predicts fetal growth and neonatal outcomes. Clin Nutr ESPEN 2021;42:307-12.
87. WANG C, WEI Y, YANG Y, et al. Evaluation of the value of fasting plasma glucose in the first trimester for the prediction of adverse pregnancy outcomes. Diabetes Res Clin Pract 2021;174:108736.
88. WANG X, ZHANG X, ZHOU M, JUAN J, WANG X. Association of Gestational Diabetes Mellitus with Adverse Pregnancy Outcomes and Its Interaction with Maternal Age in Chinese Urban Women. J Diabetes Res 2021;2021:5516937.
89. CHUNG YS, MOON H, KIM EH. Risk of obstetric and neonatal morbidity in gestational diabetes in a single institution: A retrospective, observational study. Medicine (Baltimore) 2022;101:e30777.
90. PUNNOSE J, MALHOTRA RK, SUKHIJA K, et al. Gestational diabetes mellitus in early pregnancy amongst Asian Indian women: Evidence for poor pregnancy outcomes despite treatment. Diabet Med 2023;40:e14993.

844 91. TIAN ML, DU LY, MA GJ, et al. Secular increase in the prevalence of gestational
845 diabetes and its associated adverse pregnancy outcomes from 2014 to 2021 in
846 Hebei province, China. Front Endocrinol (Lausanne) 2022;13:1039051.
847 92. KAWASAKI M, ARATA N, SUGIYAMA T, et al. Risk of fetal undergrowth in the
848 management of gestational diabetes mellitus in Japan. J Diabetes Investig
849 2023;14:614-22.
850 93. LI J, YAN J, MA L, HUANG Y, ZHU M, JIANG W. Effect of gestational diabetes mellitus
851 on pregnancy outcomes among younger and older women and its additive
852 interaction with advanced maternal age. Front Endocrinol (Lausanne)
853 2023;14:1158969.
854 94. LI G, XING Y, WANG G, et al. Does recurrent gestational diabetes mellitus increase
855 the risk of preterm birth? A population-based cohort study. Diabetes Res Clin Pract
856 2023;199:110628.
857 95. REITZLE L, HEIDEMANN C, BAUMERT J, et al. Pregnancy Complications in Women
858 With Pregestational and Gestational Diabetes Mellitus. Dtsch Arztebl Int
859 2023;120:81-86.
860 96. GONZÁLEZ GONZÁLEZ NL, GOYA M, BELLART J, et al. Obstetric and perinatal outcome
861 in women with twin pregnancy and gestational diabetes. J Matern Fetal Neonatal
862 Med 2012;25:1084-9.
863 97. MOSES RG, WEBB AJ, LUCAS EM, DAVIS WS. Twin pregnancy outcomes for women
864 with gestational diabetes mellitus compared with glucose tolerant women. Aust N
865 Z J Obstet Gynaecol 2003;43:38-40.
866 98. OKBY R, WEINTRAUB AY, SERGIENKO R, EYAL S. Gestational diabetes mellitus in twin
867 pregnancies is not associated with adverse perinatal outcomes. Arch Gynecol
868 Obstet 2014;290:649-54.
869 99. CHO HJ, SHIN JS, YANG JH, et al. Perinatal outcome in twin pregnancies
870 complicated by gestational diabetes mellitus: a comparative study. J Korean Med
871 Sci 2006;21:457-9.
872 100. KIM Y, HONG SY, KIM SY, et al. Obstetric and neonatal outcomes of gestational
873 diabetes mellitus in twin pregnancies according to changes in its diagnostic criteria

from National Diabetes Data Group criteria to Carpenter and Coustan criteria: a retrospective cohort study. BMC Pregnancy Childbirth 2022;22:9.

101. SHEEHAN ACM, UMSTAD MP, COLE S, CADE TJ. Does Gestational Diabetes Cause Additional Risk in Twin Pregnancy? Twin Res Hum Genet 2019;22:62-69.

102. TWARD C, BARRETT J, BERGER H, et al. Does gestational diabetes affect fetal growth and pregnancy outcome in twin pregnancies? Am J Obstet Gynecol 2016;214:653.e1-8.

103. DINHAM GK, HENRY A, LOWE SA, et al. Twin pregnancies complicated by gestational diabetes mellitus: a single centre cohort study. Diabet Med 2016;33:1659-67.

104. SIMÕES T, QUEIRÓS A, CORREIA L, ROCHA T, DIAS E, BLICKSTEIN I. Gestational diabetes mellitus complicating twin pregnancies. J Perinat Med 2011;39:437-40.

105. SIMÕES T, QUEIRÓS A, VALDOLEIROS S, MARUJO AT, FELIX N, BLICKSTEIN I. Concurrence of gestational diabetes and pre-gravid obesity ("diabesity") in twin gestations. J Matern Fetal Neonatal Med 2017;30:1813-15.

106. BUHLING KJ, HENRICH W, STARR E, et al. Risk for gestational diabetes and hypertension for women with twin pregnancy compared to singleton pregnancy. Arch Gynecol Obstet 2003;269:33-6.

107. POULAIN C, DUHAMEL A, GARABEDIAN C, et al. Outcome of twin pregnancies associated with glucose intolerance. Diabetes Metab 2015;41:387-92.

108. GUILLÉN MA, HERRANZ L, BARQUIEL B, HILLMAN N, BURGOS MA, PALLARDO LF. Influence of gestational diabetes mellitus on neonatal weight outcome in twin pregnancies. Diabet Med 2014;31:1651-6.

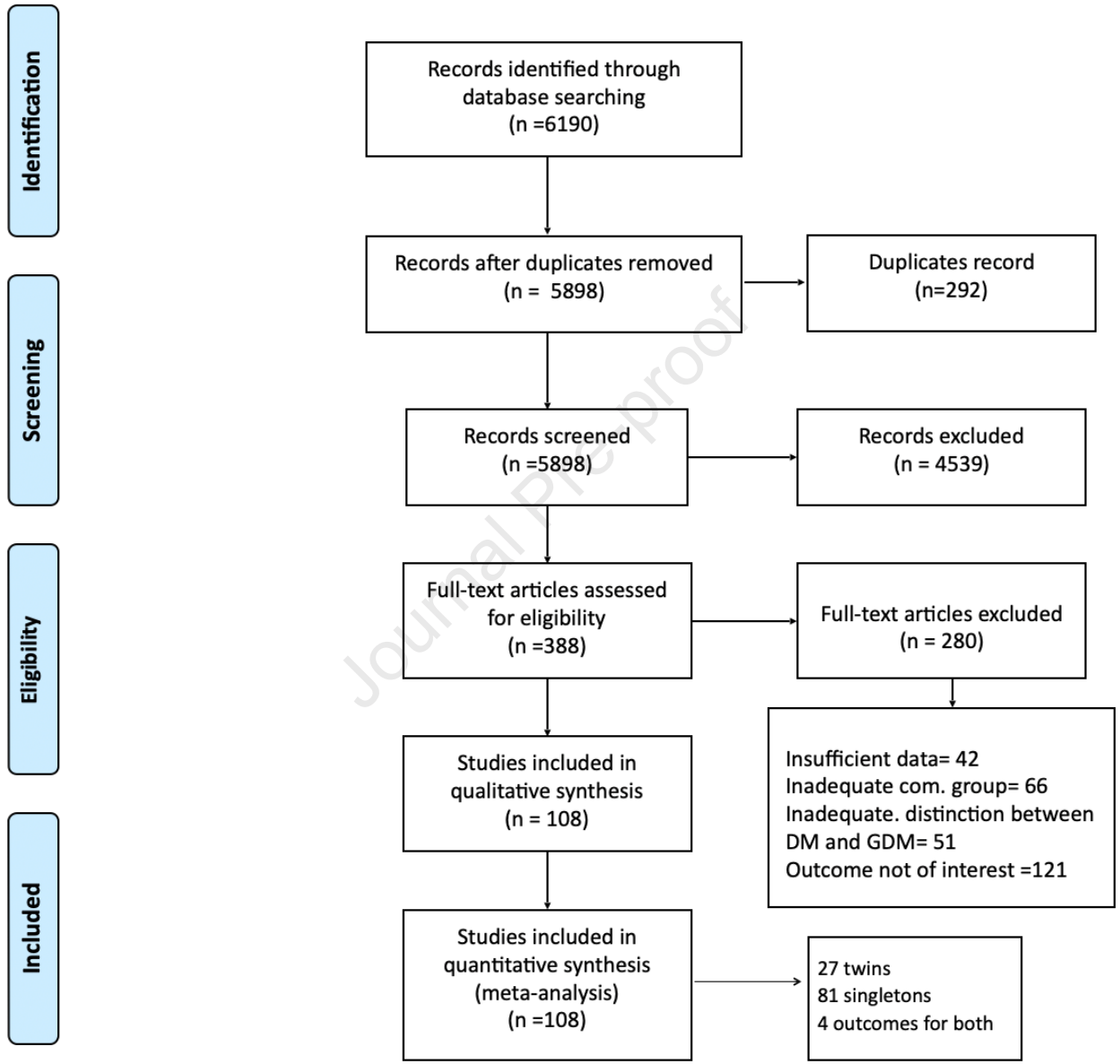
109. MOURAD M, TOO G, GYAMFI-BANNERMAN C, ZORK N. Hypertensive disorders of pregnancy in twin gestations complicated by gestational diabetes(). J Matern Fetal Neonatal Med 2021;34:720-24.

110. FOELLER ME, ZHAO S, SZABO A, CRUZ MO. Neonatal outcomes in twin pregnancies complicated by gestational diabetes compared with non-diabetic twins. J Perinatol 2015;35:1043-7.

111. ALKAABI J, ALMAZROUEI R, ZOUBEIDI T, et al. Burden, associated risk factors and adverse outcomes of gestational diabetes mellitus in twin pregnancies in Al Ain, UAE. BMC Pregnancy and Childbirth 2020;20:612.

112. DAVE ED, BODNAR LM, VANI K, HIMES KP. Perinatal outcomes in twin pregnancies complicated by gestational diabetes. Am J Obstet Gynecol MFM 2021;3:100396.
113. HUNG TH, HSIEH TT, SHAW SW, KOK SEONG C, CHEN SF. Risk factors and adverse maternal and perinatal outcomes for women with dichorionic twin pregnancies complicated by gestational diabetes mellitus: A retrospective cross-sectional study. J Diabetes Investig 2021;12:1083-91.
114. LIN D, FAN D, LI P, et al. Perinatal outcomes among twin pregnancies with gestational diabetes mellitus: A nine-year retrospective cohort study. Front Public Health 2022;10:946186.
115. MEI Y, YU J, WEN L, et al. Perinatal outcomes and offspring growth profiles in twin pregnancies complicated by gestational diabetes mellitus: A longitudinal cohort study. Diabetes Res Clin Pract 2021;171:108623.
116. MONTEIRO SS, FONSECA L, SANTOS TS, et al. Gestational diabetes in twin pregnancy: A predictor of adverse fetomaternal outcomes? Acta Diabetol 2022;59:811-18.
117. SUGIYAMA M, YAMAKAWA T, HARADA M, et al. Comparing the course and delivery outcomes of Japanese twin pregnancies with and without gestational diabetes mellitus: a single-center retrospective analysis. Endocr J 2022;69:1183-91.
118. ASHWAL E, BERGER H, HIERSCH L, et al. Gestational diabetes and fetal growth in twin compared with singleton pregnancies. Am J Obstet Gynecol 2021;225:420.e1-20.e13.
119. ZHAO D, YUAN S, MA Y, AN YX, YANG YX, YANG JK. Associations of maternal hyperglycemia in the second and third trimesters of pregnancy with prematurity. Medicine (Baltimore) 2020;99:e19663.
120. METZGER BE, LOWE LP, DYER AR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991-2002.
121. EHLERS E, TALTON OO, SCHUST DJ, SCHULZ LC. Placental structural abnormalities in gestational diabetes and when they develop: A scoping review. Placenta 2021;116:58-66.
122. SANTOS S, VOERMAN E, AMIANO P, et al. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data

936 meta-analysis of European, North American and Australian cohorts. Bjog
937 2019;126:984-95.
938
939



A.

Study or Subgroup	GDM Events	GDM Total	Controls Events	Controls Total	Weight	Risk Ratio IV, Random, 95% CI
Ashwal 2021	159	1893	1027	22877	2.5%	1.87 [1.59, 2.20]
Bashir et al. 2021	29	402	66	1429	1.7%	1.56 [1.02, 2.38]
Boriboonhirunsarn, D. et al 2016	4	237	1	237	0.1%	4.00 [0.45, 35.52]
Bo S. et al. 2003	19	250	16	450	1.1%	2.14 [1.12, 4.08]
Bricelj et al. 2017	44	363	623	7400	2.1%	1.44 [1.08, 1.92]
Casey aet al. 1997	146	874	7532	61209	2.5%	1.36 [1.17, 1.58]
Catalano et al. 2012	296	3746	820	19570	2.6%	1.89 [1.66, 2.14]
Chou et al. 2010	36	874	238	10116	1.9%	1.75 [1.24, 2.47]
Chung YS 2022	2	56	9	626	0.3%	2.48 [0.55, 11.22]
Cosson et al. 2016	269	2097	66	13436	2.2%	26.11 [20.03, 34.05]
Davis et al. 2018	53	452	493	5485	2.2%	1.30 [1.00, 1.70]
Dudhbhai et al. 2005	10	76	15	201	0.9%	1.76 [0.83, 3.75]
Fadl et al. 2010	821	10525	43742	1249772	2.7%	2.23 [2.09, 2.38]
Gortazar et al. 2019	916	35729	10115	704148	2.7%	1.78 [1.67, 1.91]
Hiersch et al. 2018	1312	16731	10153	250211	2.7%	1.93 [1.83, 2.04]
Huidobro et al. 2004	3	24	6	219	0.4%	4.56 [1.22, 17.08]
Ikenoue et al. 2014	6	141	38	852	0.8%	0.95 [0.41, 2.22]
Ismail et al. 2011	2	113	17	503	0.3%	0.52 [0.12, 2.23]
Johns et al. 2006	97	394	9	100	1.1%	2.74 [1.43, 5.22]
Kaul et al. 2014	216	8731	3180	231352	2.6%	1.80 [1.57, 2.06]
Kawakita et al. 2017	1325	11327	15002	208355	2.7%	1.62 [1.54, 1.71]
Kawasaki 2023	69	878	57	825	1.9%	1.14 [0.81, 1.59]
Kim et al. 2019	1	200	11	1838	0.2%	0.84 [0.11, 6.44]
Kwik et al. 2007	22	265	35	410	1.4%	0.97 [0.58, 1.62]
Kyozuka 2021	174	2286	2845	98090	2.5%	2.62 [2.26, 3.04]
Lai et al. 2016	625	18137	5308	306576	2.7%	1.99 [1.83, 2.16]
Leon 2015	3	129	20	634	0.4%	0.74 [0.22, 2.44]
Leybovitz-Haleluya et al. 2018	704	10184	8062	206013	2.7%	1.77 [1.64, 1.90]
Li J. 2023	407	4975	2571	100708	2.6%	3.20 [2.90, 3.54]
Li M. et al. 2020	70	787	92	2367	2.1%	2.29 [1.69, 3.09]
Lucas et al. 1993	32	159	18	151	1.3%	1.69 [0.99, 2.88]
Lu et al. 2016	46	708	337	10778	2.1%	2.08 [1.54, 2.80]
Martinez-Cruz et al. 2019	31	282	34	282	1.6%	0.91 [0.58, 1.44]
Meghelli et al. 2019	18	121	35	233	1.4%	0.99 [0.59, 1.67]
Miyakoshi et al. 2003	17	188	101	2463	1.5%	2.21 [1.35, 3.61]
Naylor et al. 1996	22	258	175	3520	1.6%	1.72 [1.12, 2.62]
Ostlund et al. 2004	210	3448	11795	427404	2.6%	2.21 [1.93, 2.52]
Ovesen et al. 2014	739	9014	15195	389609	2.7%	2.10 [1.96, 2.26]
Punnose 2022	42	722	82	1916	1.9%	1.36 [0.95, 1.95]
Resemberg et al. 1999	74	1216	1617	40555	2.3%	1.53 [1.22, 1.91]
Ricart et al. 2005	43	1082	150	8188	1.9%	2.17 [1.55, 3.03]
Rosen et al. 2018	81	2236	688	43876	2.3%	2.31 [1.84, 2.90]
Sacks 2015	119	1892	352	7943	2.4%	1.42 [1.16, 1.74]
Shindo 2020	10	503	50	2789	1.0%	1.11 [0.57, 2.17]
Soliman et al. 2018	165	3027	312	8995	2.4%	1.57 [1.31, 1.89]
Srichumchit et al. 2017	151	1350	1325	20421	2.5%	1.72 [1.47, 2.02]
Stella et al. 2008	199	927	2604	13953	2.6%	1.15 [1.01, 1.31]
Stone et al.2002	428	2169	7454	58231	2.7%	1.54 [1.41, 1.68]
Tian 2022	2803	25995	15758	340217	2.7%	2.33 [2.24, 2.42]
Van Horn et al. 2002	33	51	153	334	2.3%	1.41 [1.12, 1.78]
Wahabi et al. 2014	12	415	21	2286	1.0%	3.15 [1.56, 6.35]
Wang C. 2021	158	4446	376	14800	2.4%	1.40 [1.17, 1.68]
Waters et al. 2016	137	1139	285	5020	2.4%	2.12 [1.75, 2.57]
Total (95% CI)		**194224**		**4909973**	**100.0%**	**1.85 [1.69, 2.01]**
Total events	13410		171086			

Heterogeneity: Tau² = 0.07; Chi² = 875.59, df = 52 (P < 0.00001); I² = 94%
Test for overall effect: Z = 13.87 (P < 0.00001)

Risk Ratio IV, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Controls GDM

B.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alkaabi 2020	7	109	16	295	1.5%	1.18 [0.50, 2.80]
Ashwal 2021	33	180	114	1701	5.7%	2.74 [1.92, 3.90]
Dave 2021	54	167	440	2406	8.5%	1.77 [1.40, 2.24]
Dinham 2016	17	86	104	896	4.1%	1.70 [1.07, 2.70]
Foeller et al 2015	1317	8281	11001	129429	13.1%	1.87 [1.78, 1.97]
González González 2012	36	257	22	277	3.7%	1.76 [1.07, 2.92]
Guillen 2014	51	106	25	166	4.8%	3.19 [2.12, 4.82]
Hiersch 2019	38	326	311	3575	6.5%	1.34 [0.98, 1.84]
Hung 2021	6	57	27	588	1.6%	2.29 [0.99, 5.32]
Kim 2022	13	130	175	1634	3.3%	0.93 [0.55, 1.59]
Lai 2016	38	405	299	5097	6.4%	1.60 [1.16, 2.21]
Lin 2022	55	472	168	1679	7.2%	1.16 [0.87, 1.55]
Mei 2021	18	103	16	230	2.6%	2.51 [1.34, 4.73]
Mourad 2019	14	44	102	570	4.1%	1.78 [1.11, 2.84]
Okby 2013	52	341	345	4055	7.6%	1.79 [1.37, 2.35]
Poulain 2015	20	177	40	509	3.6%	1.44 [0.86, 2.39]
Santos Monteiro 2022	6	42	8	83	1.2%	1.48 [0.55, 3.99]
Sheehan 2019	4	39	22	194	1.1%	0.90 [0.33, 2.48]
Simões 2011	29	105	58	315	5.2%	1.50 [1.02, 2.21]
Simões 2016	8	31	24	126	2.2%	1.35 [0.67, 2.72]
Tward 2015	36	188	138	1205	6.2%	1.67 [1.20, 2.33]
Total (95% CI)		**11646**		**155030**	**100.0%**	**1.69 [1.51, 1.90]**
Total events	1852		13455			

Heterogeneity: Tau² = 0.02; Chi² = 39.92, df = 20 (P = 0.005); I² = 50%
Test for overall effect: Z = 9.18 (P < 0.00001)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Control GDM

C.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Aviram 2016	6	132	107	1717	3.9%	0.73 [0.33, 1.63]
Bashir et al. 2021	61	402	151	1429	5.8%	1.44 [1.09, 1.89]
Boriboonhirunsarn, D. et al 2016	43	237	32	237	5.3%	1.34 [0.88, 2.05]
Casey aet al. 1997	122	874	5994	61209	6.0%	1.43 [1.21, 1.68]
Hiersch et al. 2018	6536	16731	58174	250211	6.2%	1.68 [1.65, 1.71]
Ijas et al. 2019	1630	5680	3658	18897	6.1%	1.48 [1.41, 1.56]
Kari et al. 2017	21	99	14	135	4.6%	2.05 [1.10, 3.82]
Kaul et al. 2014	1126	8731	68583	231352	6.1%	0.44 [0.41, 0.46]
Kim et al. 2019	6	200	161	1838	3.9%	0.34 [0.15, 0.76]
Kwik et al. 2007	83	265	97	410	5.8%	1.32 [1.03, 1.70]
Meghelli et al. 2019	43	121	77	233	5.7%	1.08 [0.80, 1.45]
Mortier et al. 2017	19	60	75	384	5.3%	1.62 [1.06, 2.48]
Punnose 2022	433	722	1079	1916	6.1%	1.06 [0.99, 1.14]
Rosen et al. 2018	867	2236	4330	43876	6.1%	3.93 [3.70, 4.17]
Soliman et al. 2018	506	3027	797	8995	6.1%	1.89 [1.70, 2.09]
Stone et al.2002	809	2169	13218	58231	6.1%	1.64 [1.55, 1.74]
Total (95% CI)		**43817**		**704228**	**100.0%**	**1.36 [1.05, 1.77]**
Total events	13008		161613			

Heterogeneity: Tau² = 0.29; Chi² = 3224.04, df = 17 (P < 0.00001); I² = 99%
Test for overall effect: Z = 2.33 (P = 0.02)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Controls GDM

D.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ashwal 2021	28	180	278	1701	14.5%	0.95 [0.67, 1.36]
Dinham 2016	23	86	194	896	14.4%	1.24 [0.85, 1.79]
Hiersch 2019	68	326	1070	3575	15.2%	0.70 [0.56, 0.87]
Kim 2022	41	130	133	1634	14.8%	3.87 [2.87, 5.24]
Moses 2003	8	28	13	29	12.0%	0.64 [0.31, 1.30]
Okby 2013	25	341	162	4055	14.2%	1.84 [1.22, 2.76]
Poulain 2015	41	177	133	509	14.8%	0.89 [0.65, 1.20]
Total (95% CI)		**1268**		**12399**	**100.0%**	**1.20 [0.72, 2.00]**
Total events	234		1983			

Heterogeneity: Tau² = 0.43; Chi² = 94.62, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.71 (P = 0.48)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Controls GDM

E.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alfadhli et al. 2015	140	292	103	281	1.4%	1.31 [1.08, 1.59]
Ashwal 2021	895	1893	6788	22877	1.7%	1.59 [1.51, 1.68]
Aviram 2016	67	132	546	1717	1.5%	1.60 [1.33, 1.91]
Bashir et al. 2021	168	402	503	1429	1.6%	1.19 [1.04, 1.36]
Blickstein I. et al 2017	472	1525	3316	13937	1.7%	1.30 [1.20, 1.41]
Boriboonhirunsarn, D. et al 2016	75	237	46	237	1.1%	1.63 [1.18, 2.25]
Bo S. et al. 2003	104	250	145	450	1.4%	1.29 [1.06, 1.58]
Bricelj et al. 2017	92	363	1793	7400	1.5%	1.05 [0.87, 1.25]
Casey aet al. 1997	260	874	10233	61209	1.7%	1.78 [1.60, 1.97]
Chou et al. 2010	347	874	3671	10116	1.7%	1.09 [1.00, 1.19]
Chung YS 2022	28	56	242	626	1.2%	1.29 [0.98, 1.71]
Cosson et al. 2016	569	2097	2696	13454	1.7%	1.35 [1.25, 1.46]
Das et al. 2009	27	41	78	262	1.2%	2.21 [1.66, 2.95]
Davis et al. 2018	146	452	1442	5485	1.6%	1.23 [1.07, 1.41]
Dudhbhai et al. 2005	20	76	37	201	0.7%	1.43 [0.89, 2.30]
Fadl et al. 2010	2284	10525	153722	1249772	1.8%	1.76 [1.70, 1.83]
Gortazar et al. 2019	10592	35729	180690	704148	1.8%	1.16 [1.14, 1.17]
Hiersch et al. 2018	6183	16731	67211	250211	1.8%	1.38 [1.35, 1.40]
Huidobro et al. 2004	12	24	37	219	0.7%	2.96 [1.80, 4.86]
Ijas et al. 2019	1219	5680	3196	18897	1.7%	1.27 [1.20, 1.35]
Ismail et al. 2011	28	113	125	503	1.0%	1.00 [0.70, 1.42]
Johns et al. 2006	143	394	23	100	0.9%	1.58 [1.08, 2.31]
Kari et al. 2017	65	99	70	135	1.4%	1.27 [1.02, 1.57]
Kaul et al. 2014	3094	8731	56400	231352	1.8%	1.45 [1.41, 1.50]
Kawakita et al. 2017	4825	11327	55839	208355	1.8%	1.59 [1.55, 1.63]
Kawasaki 2023	318	878	285	825	1.6%	1.05 [0.92, 1.19]
Kim et al. 2015	1533	8820	30775	133863	1.7%	0.75 [0.72, 0.79]
Kim et al. 2019	21	200	629	1838	0.9%	0.31 [0.20, 0.46]
Kyozuka 2021	660	2286	18049	98090	1.7%	1.57 [1.47, 1.68]
Laatira et al. 2016	294	669	997	2902	1.7%	1.28 [1.16, 1.41]
Lai et al. 2016	6698	18137	76460	306576	1.8%	1.48 [1.45, 1.51]
Lao et al. 2000	27	128	33	128	0.8%	0.82 [0.52, 1.28]
Leon 2015	52	129	212	634	1.3%	1.21 [0.95, 1.53]
Leybovitz-Haleluya et al. 2018	2677	10184	27289	206013	1.8%	1.98 [1.92, 2.05]
Li J. 2023	2384	4975	31749	100708	1.8%	1.52 [1.47, 1.57]
Li M. et al. 2020	371	787	869	2367	1.7%	1.28 [1.17, 1.41]
Lucas et al. 1993	52	159	38	151	1.0%	1.30 [0.91, 1.85]
Lu et al. 2016	294	708	3338	10778	1.7%	1.34 [1.22, 1.47]
Martinez-Cruz et al. 2019	210	282	208	282	1.7%	1.01 [0.92, 1.11]
Mecacci et al. 2003	13	49	8	50	0.4%	1.66 [0.75, 3.65]
Meghelli et al. 2019	45	121	96	233	1.2%	0.90 [0.68, 1.19]
Mortier et al. 2017	22	60	83	384	0.9%	1.70 [1.16, 2.49]
Naylor et al. 1996	82	258	721	3520	1.4%	1.55 [1.28, 1.88]
Ovesen et al. 2014	2794	9014	76753	389609	1.8%	1.57 [1.52, 1.62]
Punnose 2022	320	722	739	1916	1.7%	1.15 [1.04, 1.27]
Ramachandran et al. 1998	118	211	216	851	1.5%	2.20 [1.87, 2.60]
Randall 2021	1883	71740	27991	806155	1.8%	0.76 [0.72, 0.79]
Rauh-Hain et al. 2009	183	521	5539	21982	1.6%	1.39 [1.24, 1.57]
Reitzle 2023	108444	283210	1390595	4661460	1.8%	1.26 [1.25, 1.27]
Resemberg et al. 1999	418	1216	9083	40555	1.7%	1.53 [1.42, 1.66]
Ricart et al. 2005	262	1082	1612	8188	1.6%	1.23 [1.10, 1.38]
Rosen et al. 2018	211	2236	1857	43876	1.6%	2.23 [1.95, 2.55]
Sacks 2015	647	1892	2102	7943	1.7%	1.29 [1.20, 1.39]
Shindo 2020	136	503	662	2789	1.5%	1.14 [0.97, 1.33]
Soliman et al. 2018	1115	3027	2584	8995	1.7%	1.28 [1.21, 1.36]
Srichumchit et al. 2017	457	1350	4226	20421	1.7%	1.64 [1.51, 1.77]
Stella et al. 2008	376	927	3981	13953	1.7%	1.42 [1.31, 1.54]
Stone et al.2002	692	2169	10889	58231	1.7%	1.71 [1.60, 1.82]
Tian 2022	10525	25995	165234	340217	1.8%	0.83 [0.82, 0.85]
Van Horn et al. 2002	16	51	92	334	0.8%	1.14 [0.73, 1.77]
Vilchez et al. 2015	5426	96964	7908	176079	1.8%	1.25 [1.20, 1.29]
Wahabi et al. 2014	110	415	473	2286	1.5%	1.28 [1.07, 1.53]
Wang C. 2021	2436	4446	7804	14800	1.8%	1.04 [1.01, 1.07]
Wang et al. 2015	252	587	185	478	1.6%	1.11 [0.96, 1.28]
Wang X. 2021	737	1229	3488	7615	1.7%	1.31 [1.24, 1.38]
Yang et al. 2018	125	234	477	998	1.6%	1.12 [0.98, 1.28]
Zhao et al. 2020	30	57	300	603	1.2%	1.06 [0.82, 1.37]
Total (95% CI)		**657545**		**10302849**	**100.0%**	**1.31 [1.24, 1.38]**
Total events	183321		2465581			

Heterogeneity: Tau² = 0.04; Chi² = 6815.15, df = 66 (P < 0.00001); I² = 99%
Test for overall effect: Z = 9.97 (P < 0.00001)

Risk Ratio IV, Random, 95% CI
0.2 0.5 1 2 5
Controls GDM

F.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alkaabi 2020	83	109	205	295	3.8%	1.10 [0.96, 1.25]
Ashwal 2021	123	180	822	1701	4.5%	1.41 [1.27, 1.58]
Dinham 2016	63	86	597	896	3.6%	1.10 [0.96, 1.26]
Foeller 2016	6650	8281	96554	129429	8.2%	1.08 [1.06, 1.09]
González González 2012	158	257	159	277	3.5%	1.07 [0.93, 1.23]
Hiersch 2019	229	326	2121	3575	5.9%	1.18 [1.10, 1.28]
Hung 2021	47	57	528	588	4.1%	0.92 [0.81, 1.04]
Kim 2022	115	130	1456	1634	6.4%	0.99 [0.93, 1.06]
Lai 2016	288	405	3032	5097	6.4%	1.20 [1.12, 1.28]
Lin 2022	465	472	1657	1679	8.2%	1.00 [0.99, 1.01]
Mei 2021	103	103	224	230	7.9%	1.02 [1.00, 1.05]
Moses 2003	14	28	4	29	0.1%	3.63 [1.36, 9.68]
Mourad 2019	34	44	348	570	2.7%	1.27 [1.06, 1.50]
Myszkowski 2023	32	33	155	177	5.7%	1.11 [1.02, 1.20]
Okby 2013	217	341	2149	4055	5.5%	1.20 [1.10, 1.31]
Poulain 2015	78	177	257	509	2.4%	0.87 [0.72, 1.05]
Rauh-Hain 2009	18	22	321	531	2.1%	1.35 [1.10, 1.67]
Santos Monteiro 2022	32	42	47	83	1.5%	1.35 [1.04, 1.73]
Sheehan 2019	30	39	143	194	2.3%	1.04 [0.86, 1.26]
Simões 2011	76	105	216	315	3.5%	1.06 [0.92, 1.21]
Simões 2016	22	31	89	126	1.5%	1.00 [0.78, 1.29]
Sugiyama 2022	41	47	234	260	4.3%	0.97 [0.86, 1.09]
Tward 2015	151	188	839	1205	5.7%	1.15 [1.06, 1.25]
Total (95% CI)		**11503**		**153455**	**100.0%**	**1.10 [1.06, 1.13]**
Total events	9069		112157			

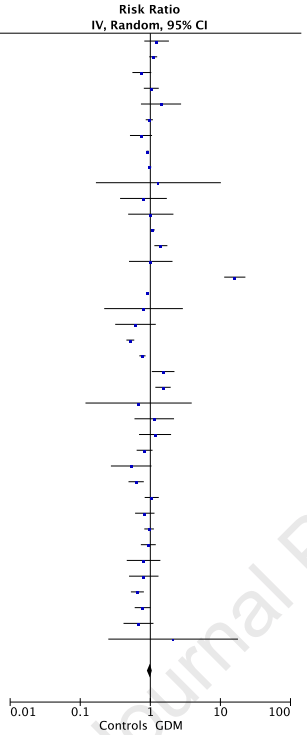
Heterogeneity: Tau² = 0.00; Chi² = 188.86, df = 22 (P < 0.00001); I² = 88%
Test for overall effect: Z = 5.17 (P < 0.00001)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Controls GDM

A.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alfadhli et al. 2015	46	292	36	281	2.4%	1.23 [0.82, 1.84]
Ashwal 2021	222	1893	2438	22877	3.9%	1.10 [0.97, 1.25]
Bashir et al. 2021	43	402	202	1429	2.9%	0.76 [0.55, 1.03]
Blickstein I. et al 2017	68	1525	602	13937	3.3%	1.03 [0.81, 1.32]
Bo S. et al. 2003	15	250	19	450	1.4%	1.42 [0.74, 2.75]
Cosson et al. 2016	277	2097	1837	13454	4.0%	0.97 [0.86, 1.09]
Davis et al. 2018	29	452	478	5485	2.6%	0.74 [0.51, 1.06]
Gortazar et al. 2019	2882	35729	62038	704148	4.2%	0.92 [0.88, 0.95]
Hiersch et al. 2018	1514	16731	23069	250211	4.2%	0.98 [0.93, 1.03]
Huidobro et al. 2004	1	24	7	219	0.2%	1.30 [0.17, 10.15]
Ikenoue et al. 2014	7	141	53	852	1.1%	0.80 [0.37, 1.72]
Johns et al. 2006	32	394	8	100	1.2%	1.02 [0.48, 2.13]
Kawakita et al. 2017	985	11327	16668	208355	4.2%	1.09 [1.02, 1.16]
Kawasaki 2023	176	878	117	825	3.5%	1.41 [1.14, 1.75]
Kim et al. 2019	7	69	197	1969	1.2%	1.01 [0.50, 2.07]
Kyozuka 2021	43	2286	115	98090	2.7%	16.04 [11.33, 22.72]
Lai et al. 2016	1701	18137	31439	306576	4.2%	0.91 [0.87, 0.96]
Lao et al. 2000	4	128	5	128	0.5%	0.80 [0.22, 2.91]
Leon 2015	9	129	72	634	1.4%	0.61 [0.32, 1.20]
Leybovitz-Haleluya et al. 2018	232	10184	9053	206013	3.9%	0.52 [0.46, 0.59]
Li J. 2023	359	4975	9413	100708	4.1%	0.77 [0.70, 0.85]
Li M. et al. 2020	40	787	79	2367	2.6%	1.52 [1.05, 2.21]
Lu et al. 2016	61	708	612	10778	3.3%	1.52 [1.18, 1.95]
Mecacci et al. 2003	2	49	3	50	0.3%	0.68 [0.12, 3.90]
Meghelli et al. 2019	13	121	22	233	1.4%	1.14 [0.59, 2.18]
Miyakoshi et al. 2003	14	188	157	2463	1.8%	1.17 [0.69, 1.98]
Mustaniemi 2021	94	1055	111	1032	3.2%	0.83 [0.64, 1.08]
Peixoto et al. 2016	8	70	160	747	1.4%	0.53 [0.27, 1.04]
Resemberg et al. 1999	59	1216	3135	40555	3.3%	0.63 [0.49, 0.81]
Ricart et al. 2005	76	1082	549	8188	3.4%	1.05 [0.83, 1.32]
Shindo 2020	40	503	266	2789	2.9%	0.83 [0.61, 1.15]
Soliman et al. 2018	192	3027	594	8995	3.8%	0.96 [0.82, 1.12]
Srichumchit et al. 2017	65	1350	1050	20421	3.3%	0.94 [0.73, 1.20]
Teshome 2021	13	293	164	2960	1.7%	0.80 [0.46, 1.39]
Wahabi et al. 2014	18	415	123	2286	2.0%	0.81 [0.50, 1.31]
Wang C. 2021	99	4446	504	14800	3.5%	0.65 [0.53, 0.81]
Wang X. 2021	61	1229	487	7615	3.2%	0.78 [0.60, 1.01]
Yang et al. 2018	17	234	107	998	2.0%	0.68 [0.41, 1.11]
Zhao et al. 2020	1	57	5	603	0.2%	2.12 [0.25, 17.80]
Total (95% CI)		**124873**		**2064621**	**100.0%**	**0.99 [0.90, 1.08]**
Total events	9525		165994			

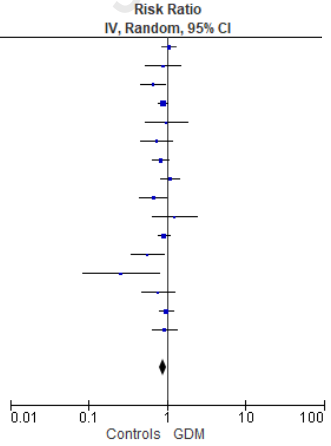
Heterogeneity: Tau² = 0.05; Chi² = 461.95, df = 38 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.27 (P = 0.78)



B.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ashwal 2021	76	360	676	3402	10.9%	1.06 [0.86, 1.31]
Dinham 2016	14	172	164	1792	2.7%	0.89 [0.53, 1.50]
González González 2012	40	514	65	554	4.8%	0.66 [0.46, 0.97]
Hiersch 2019	152	649	1865	7099	15.9%	0.89 [0.77, 1.03]
Hung 2021	10	114	106	1176	2.0%	0.97 [0.52, 1.81]
Kim 2022	17	260	290	3266	3.3%	0.74 [0.46, 1.18]
Lai 2016	68	810	1029	10194	9.6%	0.83 [0.66, 1.05]
Lin 2022	66	944	228	3558	8.2%	1.09 [0.84, 1.42]
Mei 2021	27	206	90	460	4.4%	0.67 [0.45, 1.00]
Mourad 2019	9	88	93	1140	1.8%	1.25 [0.66, 2.40]
Poulain 2015	122	354	382	1018	14.2%	0.92 [0.78, 1.08]
Santos Monteiro 2022	16	84	56	166	3.1%	0.56 [0.35, 0.92]
Sheehan 2019	3	78	58	388	0.6%	0.26 [0.08, 0.80]
Simões 2011	18	210	70	630	3.0%	0.77 [0.47, 1.26]
Simões 2016	36	57	158	246	10.4%	0.98 [0.79, 1.22]
Sugiyama 2022	24	86	151	502	5.0%	0.93 [0.64, 1.34]
Total (95% CI)		**4986**		**35591**	**100.0%**	**0.89 [0.81, 0.97]**
Total events	698		5481			

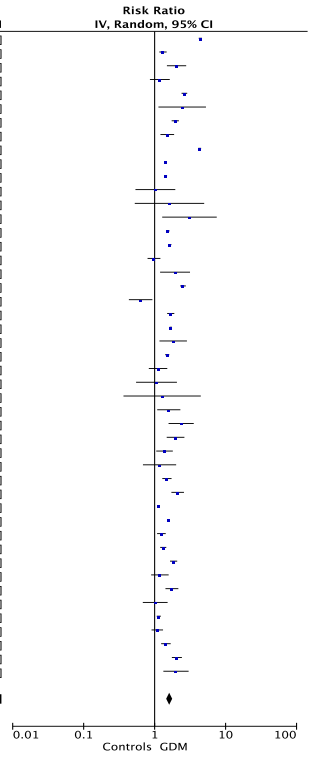
Heterogeneity: Tau² = 0.01; Chi² = 20.54, df = 15 (P = 0.15); I² = 27%
Test for overall effect: Z = 2.59 (P = 0.009)



C.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ahlsson et al. 2009	1232	7817	31637	884267	2.6%	4.41 [4.18, 4.64]
Ashwal 2021	259	1893	2387	22877	2.5%	1.31 [1.16, 1.48]
Bashir et al. 2021	55	402	96	1429	2.1%	2.04 [1.49, 2.78]
Bo S. et al. 2003	50	250	76	450	2.0%	1.18 [0.86, 1.63]
Casey aet al. 1997	310	874	8273	61209	2.6%	2.62 [2.39, 2.88]
Chung YS 2022	7	56	32	626	1.0%	2.45 [1.13, 5.29]
Cosson et al. 2016	313	2097	1028	13454	2.5%	1.95 [1.74, 2.20]
Davis et al. 2018	74	452	596	5485	2.3%	1.51 [1.21, 1.88]
Fadl et al. 2010	1589	10525	43742	1249772	2.6%	4.31 [4.12, 4.52]
Gortazar et al. 2019	6549	35729	89517	704148	2.6%	1.44 [1.41, 1.47]
Hiersch et al. 2018	2188	16731	22770	250211	2.6%	1.44 [1.38, 1.50]
Ikenoue et al. 2014	10	141	59	852	1.2%	1.02 [0.54, 1.95]
Ismail et al. 2011	4	113	11	503	0.6%	1.62 [0.52, 4.99]
Johns et al. 2006	61	394	5	100	0.8%	3.10 [1.28, 7.50]
Kaul et al. 2014	1287	8731	22149	231352	2.6%	1.54 [1.46, 1.62]
Kawakita et al. 2017	1314	11327	14793	208355	2.6%	1.63 [1.55, 1.72]
Kawasaki 2023	150	878	144	825	2.3%	0.98 [0.79, 1.21]
Kim et al. 2019	14	69	206	1969	1.6%	1.94 [1.19, 3.15]
Koivunen et al. 2016	565	11858	1977	104132	2.6%	2.51 [2.29, 2.75]
Kwik et al. 2007	32	265	78	410	1.9%	0.63 [0.43, 0.93]
Kyozuka 2021	262	2286	6670	98090	2.5%	1.69 [1.50, 1.89]
Lai et al. 2016	2766	18137	27703	306576	2.6%	1.69 [1.63, 1.75]
Lao et al. 2000	42	128	23	128	1.7%	1.83 [1.17, 2.85]
Li J. 2023	779	4975	10489	100708	2.6%	1.50 [1.41, 1.61]
Lucas et al. 1993	60	159	51	151	2.1%	1.12 [0.83, 1.51]
Martinez-Cruz et al. 2019	17	282	16	282	1.2%	1.06 [0.55, 2.06]
Mecacci et al. 2003	5	49	4	50	0.5%	1.28 [0.36, 4.47]
Meghelli et al. 2019	37	121	45	233	1.9%	1.58 [1.09, 2.30]
Miyakoshi et al. 2003	24	188	133	2463	1.8%	2.36 [1.57, 3.56]
Mustaniemi 2021	129	1055	64	1032	2.1%	1.97 [1.48, 2.63]
Naylor et al. 1996	48	258	475	3520	2.2%	1.38 [1.05, 1.80]
Okun et. al 1997	11	50	178	949	1.5%	1.17 [0.68, 2.01]
Punnose 2022	201	722	358	1916	2.5%	1.49 [1.28, 1.73]
Ramachandran et al. 1998	90	118	78	216	2.4%	2.11 [1.72, 2.59]
Randall 2021	8035	71740	79003	806155	2.6%	1.14 [1.12, 1.17]
Reitzle 2023	40897	283210	429530	4661460	2.6%	1.57 [1.55, 1.58]
Ricart et al. 2005	189	1082	1148	8188	2.5%	1.25 [1.08, 1.43]
Rosen et al. 2018	353	2236	5241	43876	2.6%	1.32 [1.20, 1.46]
Sacks 2015	346	1892	785	7943	2.5%	1.85 [1.65, 2.08]
Shindo 2020	52	503	243	2789	2.1%	1.19 [0.89, 1.58]
Stella et al. 2008	89	927	765	13953	2.3%	1.75 [1.42, 2.16]
Teshome 2021	24	293	238	2960	1.8%	1.02 [0.68, 1.52]
Wang C. 2021	920	4446	2677	14800	2.6%	1.14 [1.07, 1.22]
Wang et al. 2015	182	587	136	478	2.4%	1.09 [0.90, 1.31]
Wang X. 2021	172	1229	739	7615	2.5%	1.44 [1.24, 1.68]
Waters et al. 2016	184	1139	394	5020	2.4%	2.06 [1.75, 2.42]
Yang et al. 2018	30	234	64	998	1.8%	2.00 [1.33, 3.01]
Total (95% CI)		**508648**		**9834975**	**100.0%**	**1.61 [1.46, 1.77]**
Total events	72007		806826			

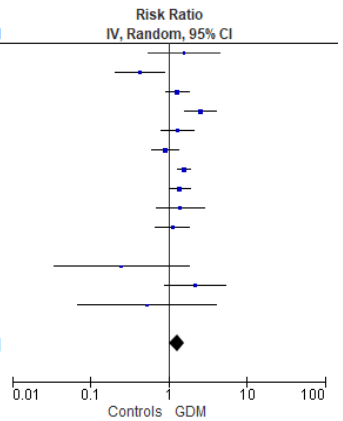
Heterogeneity: Tau² = 0.09; Chi² = 4719.27, df = 46 (P < 0.00001); I² = 99%
Test for overall effect: Z = 9.52 (P < 0.00001)



D.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ashwal 2021	4	360	24	3402	3.4%	1.57 [0.55, 4.51]
Dinham 2016	7	172	171	1792	5.7%	0.43 [0.20, 0.89]
González González 2012	63	514	53	554	11.8%	1.28 [0.91, 1.81]
Hiersch 2019	21	649	90	7099	9.5%	2.55 [1.60, 4.08]
Hung 2021	16	114	126	1176	9.2%	1.31 [0.81, 2.12]
Kim 2022	25	260	350	3266	11.0%	0.90 [0.61, 1.32]
Lai 2016	113	810	905	10194	15.1%	1.57 [1.31, 1.89]
Lin 2022	56	944	152	3558	12.8%	1.39 [1.03, 1.87]
Mei 2021	12	206	19	460	6.1%	1.41 [0.70, 2.85]
Poulain 2015	20	354	51	1018	8.9%	1.13 [0.68, 1.86]
Santos Monteiro 2022	0	84	0	166		Not estimable
Sheehan 2019	1	78	20	388	1.1%	0.25 [0.03, 1.83]
Simões 2011	8	210	11	630	4.3%	2.18 [0.89, 5.35]
Sugiyama 2022	1	86	11	502	1.1%	0.53 [0.07, 4.06]
Total (95% CI)		**4841**		**34205**	**100.0%**	**1.29 [1.03, 1.60]**
Total events	347		1983			

Heterogeneity: Tau² = 0.07; Chi² = 28.65, df = 12 (P = 0.004); I² = 58%
Test for overall effect: Z = 2.27 (P = 0.02)



A.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alfadhli et al. 2015	27	292	37	281	1.2%	0.70 [0.44, 1.12]
Ashwal 2021	277	1893	2035	22877	2.5%	1.64 [1.46, 1.85]
Bar-Hava I. et al. 1997	34	550	68	14552	1.4%	13.23 [8.84, 19.79]
Bashir et al. 2021	69	402	158	1429	2.0%	1.55 [1.20, 2.01]
Blickstein I. et al 2017	110	1525	835	13937	2.2%	1.20 [0.99, 1.46]
Bo S. et al. 2003	22	250	31	450	1.1%	1.28 [0.76, 2.16]
Bricelj et al. 2017	363	363	7400	7400	2.7%	1.00 [1.00, 1.00]
Chou et al. 2010	60	874	708	10116	2.0%	0.98 [0.76, 1.26]
Chung YS 2022	16	56	74	626	1.2%	2.42 [1.52, 3.85]
Cosson et al. 2016	175	2097	1032	13454	2.4%	1.09 [0.93, 1.27]
Das et al. 2009	6	41	0	262	0.1%	81.40 [4.67, 1418.53]
Davis et al. 2018	53	452	506	5485	1.9%	1.27 [0.97, 1.66]
Diamond et al. 1984	8	51	0	102	0.1%	33.67 [1.98, 572.10]
Fadl et al. 2010	905	10525	62489	1249772	2.7%	1.72 [1.62, 1.83]
Gortazar et al. 2019	5597	35729	84760	704148	2.7%	1.30 [1.27, 1.33]
Hiersch et al. 2018	1395	16731	13146	250211	2.7%	1.59 [1.51, 1.67]
Hilden et al. 2018	1409	14833	70892	1440834	2.7%	1.93 [1.84, 2.03]
Ijas et al. 2019	290	5680	675	18897	2.5%	1.43 [1.25, 1.63]
Ismail et al. 2011	18	113	65	503	1.2%	1.23 [0.76, 1.99]
Kawakita et al. 2017	1846	11327	22711	208355	2.7%	1.50 [1.43, 1.56]
Kawasaki 2023	77	878	47	825	1.6%	1.54 [1.08, 2.18]
Kim et al. 2015	441	8820	9595	133633	2.6%	0.70 [0.63, 0.76]
Kim et al. 2019	5	200	105	1838	0.5%	0.44 [0.18, 1.06]
Koivunen et al. 2016	594	11858	4460	104132	2.6%	1.17 [1.08, 1.27]
Kwik et al. 2007	12	265	19	410	0.7%	0.98 [0.48, 1.98]
Kyozuka 2021	176	2286	5885	98090	2.4%	1.28 [1.11, 1.48]
Laafira et al. 2016	90	669	267	2902	2.1%	1.46 [1.17, 1.83]
Lai et al. 2016	1926	18137	21761	306576	2.7%	1.50 [1.43, 1.56]
Lao et al. 2000	5	128	3	128	0.2%	1.67 [0.41, 6.83]
Leon 2015	47	129	342	634	2.0%	0.68 [0.53, 0.86]
Leybovitz-Haleluya et al. 2018	845	10184	12819	206013	2.7%	1.33 [1.25, 1.43]
Li G. 2023	870	16806	3271	88722	2.6%	1.40 [1.31, 1.51]
Li J. 2023	491	4975	5909	100708	2.6%	1.68 [1.54, 1.84]
Li M. et al. 2020	66	787	141	2367	1.9%	1.41 [1.06, 1.86]
Lu et al. 2016	81	708	708	10778	2.1%	1.74 [1.40, 2.16]
Martinez-Cruz et al. 2019	23	282	28	282	1.0%	0.82 [0.49, 1.39]
Meghelli et al. 2019	15	121	12	233	0.7%	2.41 [1.16, 4.98]
Mortier et al. 2017	5	60	20	384	0.4%	1.60 [0.62, 4.10]
Punnose 2022	157	722	198	1916	2.2%	2.10 [1.74, 2.55]
Ramachandran et al. 1998	11	211	9	851	0.5%	4.93 [2.07, 11.74]
Reitzle 2023	21072	283210	305814	4661460	2.7%	1.13 [1.12, 1.15]
Resemberg et al. 1999	82	1216	3295	40555	2.2%	0.83 [0.67, 1.03]
Ricart et al. 2005	64	1082	429	8188	2.0%	1.13 [0.87, 1.46]
Sacks 2015	174	1892	491	7943	2.4%	1.49 [1.26, 1.76]
Soliman et al. 2018	271	3027	573	8995	2.5%	1.41 [1.22, 1.61]
Srichumchit et al. 2017	201	1350	2853	20421	2.5%	1.07 [0.93, 1.22]
Tian 2022	2112	25995	17792	340217	2.7%	1.55 [1.49, 1.62]
Wang C. 2021	292	4446	737	14800	2.5%	1.32 [1.16, 1.50]
Wang et al. 2015	40	587	20	478	1.1%	1.63 [0.97, 2.75]
Wang X. 2021	116	1229	670	7615	2.3%	1.07 [0.89, 1.29]
Waters et al. 2016	104	1139	301	5020	2.2%	1.52 [1.23, 1.89]
Yogev et al. 2007	163	1526	1193	10560	2.4%	0.95 [0.81, 1.10]
Zhao et al. 2020	8	57	56	603	0.7%	1.51 [0.76, 3.01]
Total (95% CI)		**508766**		**10151968**	**100.0%**	**1.36 [1.27, 1.46]**
Total events	43316		667445			

Heterogeneity: Tau² = 0.04; Chi² = 3603.67, df = 52 (P < 0.00001); I² = 99%
Test for overall effect: Z = 8.77 (P < 0.00001)

Risk Ratio IV, Random, 95% CI
0.2 0.5 1 2 5
Controls GDM

B.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alkaabi 2020	67	109	174	295	6.6%	1.04 [0.87, 1.24]
Ashwal 2021	122	180	709	1701	7.3%	1.63 [1.45, 1.82]
Dinham 2016	62	86	578	896	7.0%	1.12 [0.97, 1.29]
González González 2012	160	257	39	277	4.8%	4.42 [3.26, 6.01]
Hiersch 2019	184	326	1737	3575	7.5%	1.16 [1.05, 1.29]
Hung 2021	41	57	362	588	6.6%	1.17 [0.98, 1.39]
Kim 2022	86	130	1014	1634	7.2%	1.07 [0.94, 1.21]
Lai 2016	241	405	2870	5097	7.6%	1.06 [0.97, 1.15]
Lin 2022	345	472	1170	1679	7.8%	1.05 [0.98, 1.12]
Mei 2021	28	103	48	230	3.7%	1.30 [0.87, 1.95]
Myszkowski 2023	20	33	113	177	5.0%	0.95 [0.71, 1.28]
Okby 2013	249	341	3090	4055	7.8%	0.96 [0.90, 1.02]
Poulain 2015	109	177	293	509	7.1%	1.07 [0.93, 1.23]
Santos Monteiro 2022	31	42	60	83	5.9%	1.02 [0.82, 1.28]
Sheehan 2019	16	39	61	194	3.5%	1.30 [0.85, 2.01]
Sugiyama 2022	23	47	121	260	4.7%	1.05 [0.76, 1.45]
Total (95% CI)		**2804**		**21250**	**100.0%**	**1.19 [1.07, 1.32]**
Total events	1784		12439			

Heterogeneity: Tau² = 0.04; Chi² = 147.99, df = 15 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.18 (P = 0.001)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Controls GDM

C.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Aviram 2016	1	132	32	1717	0.5%	0.41 [0.06, 2.95]
Blickstein I. et al 2017	9	1525	146	13937	3.0%	0.56 [0.29, 1.10]
Bricelj et al. 2017	11	363	258	7400	3.4%	0.87 [0.48, 1.57]
Casey aet al. 1997	0	874	120	61209	0.3%	0.29 [0.02, 4.66]
Chung YS 2022	4	56	22	626	1.7%	2.03 [0.73, 5.69]
Das et al. 2009	0	41	1	262	0.2%	2.09 [0.09, 50.39]
Fadl et al. 2010	42	10525	3749	1249772	5.7%	1.33 [0.98, 1.80]
Hiersch et al. 2018	296	16731	4094	250211	7.1%	1.08 [0.96, 1.22]
Hilden et al. 2018	94	14833	4939	1440834	6.5%	1.85 [1.51, 2.27]
Ijas et al. 2019	59	5680	156	18897	5.7%	1.26 [0.93, 1.70]
Kawasaki 2023	19	878	15	825	3.0%	1.19 [0.61, 2.33]
Koivunen et al. 2016	245	11858	2023	104132	7.0%	1.06 [0.93, 1.21]
Kwik et al. 2007	3	265	9	410	1.1%	0.52 [0.14, 1.89]
Lai et al. 2016	363	18137	5381	306576	7.1%	1.14 [1.03, 1.27]
Lao et al. 2000	1	128	1	128	0.3%	1.00 [0.06, 15.82]
Leon 2015	3	634	29	129	1.4%	0.02 [0.01, 0.07]
Leybovitz-Haleluya et al. 2018	37	10184	629	206013	5.4%	1.19 [0.85, 1.66]
Li J. 2023	29	4975	735	100708	5.1%	0.80 [0.55, 1.16]
Lu et al. 2016	1	708	36	10778	0.5%	0.42 [0.06, 3.08]
Meghelli et al. 2019	9	121	13	233	2.3%	1.33 [0.59, 3.03]
Mortier et al. 2017	7	60	6	384	1.6%	7.47 [2.60, 21.46]
Ovesen et al. 2014	74	9014	2338	389609	6.3%	1.37 [1.09, 1.72]
Peixoto et al. 2016	1	70	59	747	0.6%	0.18 [0.03, 1.29]
Punnose 2022	39	722	64	1916	5.0%	1.62 [1.10, 2.39]
Ricart et al. 2005	15	1082	101	8188	3.8%	1.12 [0.66, 1.93]
Rosen et al. 2018	8	2236	160	43876	2.8%	0.98 [0.48, 1.99]
Shindo 2020	39	503	195	2789	5.5%	1.11 [0.80, 1.54]
Srichumchit et al. 2017	35	1350	633	20421	5.4%	0.84 [0.60, 1.17]
Zhao et al. 2020	1	57	1	603	0.3%	10.58 [0.67, 166.89]
Total (95% CI)		**114034**		**4243611**	**100.0%**	**1.12 [0.97, 1.31]**
Total events	1468		25948			

Heterogeneity: Tau² = 0.08; Chi² = 120.24, df = 29 (P < 0.00001); I² = 76%
Test for overall effect: Z = 1.51 (P = 0.13)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Controls GDM

D.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Cho 2006	0	66	0	132		Not estimable
González González 2012	8	514	7	554	6.9%	1.23 [0.45, 3.37]
Hiersch 2019	21	649	282	7099	25.2%	0.81 [0.53, 1.26]
Hung 2021	2	114	5	1176	2.8%	4.13 [0.81, 21.03]
Kim 2022	8	260	89	3266	12.5%	1.13 [0.55, 2.30]
Lai 2016	22	810	495	10194	26.3%	0.56 [0.37, 0.85]
Mei 2021	3	206	4	460	3.4%	1.67 [0.38, 7.42]
Poulain 2015	2	354	8	1018	3.1%	0.72 [0.15, 3.37]
Simões 2011	3	210	10	630	4.5%	0.90 [0.25, 3.24]
Simões 2016	1	57	7	246	1.8%	0.62 [0.08, 4.91]
Sugiyama 2022	9	86	42	502	13.4%	1.25 [0.63, 2.48]
Total (95% CI)		**3326**		**25277**	**100.0%**	**0.90 [0.68, 1.19]**
Total events	79		949			

Heterogeneity: Tau² = 0.03; Chi² = 10.75, df = 9 (P = 0.29); I² = 16%
Test for overall effect: Z = 0.77 (P = 0.44)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Controls GMD

E.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alfadhli et al. 2015	76	292	52	281	1.3%	1.41 [1.03, 1.92]
Aviram 2016	31	132	409	1717	1.3%	0.99 [0.72, 1.36]
Bashir et al. 2021	58	402	114	1429	1.4%	1.81 [1.35, 2.43]
Blickstein I. et al 2017	97	1525	822	13937	2.5%	1.08 [0.88, 1.32]
Boriboonhirunsarn, D. et al 2016	4	237	3	237	0.1%	1.33 [0.30, 5.89]
Casey aet al. 1997	45	874	3214	61209	1.5%	0.98 [0.74, 1.31]
Chung YS 2022	20	56	137	626	0.9%	1.63 [1.11, 2.39]
Dudhbhai et al. 2005	8	76	3	201	0.1%	7.05 [1.92, 25.89]
Hiersch et al. 2018	2799	16731	25983	250211	7.3%	1.61 [1.55, 1.67]
Ijas et al. 2019	736	5680	1615	18897	5.8%	1.52 [1.40, 1.65]
Ismail et al. 2011	5	113	30	503	0.2%	0.74 [0.29, 1.87]
Johns et al. 2006	48	394	2	100	0.1%	6.09 [1.51, 24.64]
Kari et al. 2017	76	99	105	135	3.9%	0.99 [0.86, 1.14]
Kaul et al. 2014	1454	8731	23299	231352	6.9%	1.65 [1.58, 1.74]
Kawakita et al. 2017	1948	11327	23961	208355	7.1%	1.50 [1.43, 1.56]
Kawasaki 2023	118	878	67	825	1.5%	1.65 [1.25, 2.20]
Kim et al. 2019	9	69	190	1969	0.4%	1.35 [0.72, 2.52]
Koivunen et al. 2016	1695	11858	9194	104132	6.9%	1.62 [1.54, 1.70]
Kwik et al. 2007	9	265	22	410	0.3%	0.63 [0.30, 1.35]
Laafira et al. 2016	142	669	512	2902	3.2%	1.20 [1.02, 1.42]
Lai et al. 2016	2960	18137	32774	306576	7.3%	1.53 [1.47, 1.58]
Lucas et al. 1993	84	708	705	10778	2.4%	1.81 [1.47, 2.24]
Lu et al. 2016	5	159	5	151	0.1%	0.95 [0.28, 3.21]
Meghelli et al. 2019	11	121	9	233	0.2%	2.35 [1.00, 5.52]
Punnose 2022	165	722	268	1916	3.1%	1.63 [1.37, 1.94]
Rauh-Hain et al. 2009	63	521	1451	21982	2.0%	1.83 [1.45, 2.32]
Reitzle 2023	40033	283210	428401	4661460	7.7%	1.54 [1.52, 1.55]
Rosen et al. 2018	165	2236	2770	43876	3.6%	1.17 [1.00, 1.36]
Shindo 2020	25	503	109	2789	0.8%	1.27 [0.83, 1.94]
Soliman et al. 2018	483	3027	1076	8995	5.2%	1.33 [1.21, 1.47]
Stella et al. 2008	78	927	837	13953	2.2%	1.40 [1.12, 1.75]
Tian 2022	116	25995	1665	340217	2.8%	0.91 [0.76, 1.10]
Vilchez et al. 2015	4102	96964	5011	176079	7.1%	1.49 [1.43, 1.55]
Wahabi et al. 2014	24	415	109	2286	0.8%	1.21 [0.79, 1.86]
Waters et al. 2016	96	1139	313	5020	2.3%	1.35 [1.09, 1.68]
Total (95% CI)		**495192**		**6495739**	**100.0%**	**1.43 [1.38, 1.49]**
Total events	57788		565237			

Heterogeneity: Tau² = 0.01; Chi² = 178.07, df = 34 (P < 0.00001); I² = 81%
Test for overall effect: Z = 18.02 (P < 0.00001)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Controls GDM

F.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Buhling 2003	6	6	54	172	5.1%	2.95 [2.18, 3.98]
González González 2012	252	514	289	554	8.9%	0.94 [0.83, 1.06]
Hiersch 2019	349	649	3287	7099	9.7%	1.16 [1.08, 1.25]
Hung 2021	33	114	231	1176	4.9%	1.47 [1.08, 2.01]
Kim 2022	104	260	1253	3266	8.1%	1.04 [0.89, 1.22]
Lai 2016	401	810	4928	10194	9.8%	1.02 [0.95, 1.10]
Lin 2022	397	944	1324	3558	9.6%	1.13 [1.04, 1.23]
Mei 2021	52	206	95	460	5.2%	1.22 [0.91, 1.64]
Mourad 2019	53	88	516	1140	7.5%	1.33 [1.11, 1.60]
Poulain 2015	117	354	269	1018	7.5%	1.25 [1.04, 1.50]
Rauh-Hain 2009	23	44	393	1062	5.2%	1.41 [1.05, 1.89]
Santos Monteiro 2022	27	84	64	166	4.1%	0.83 [0.58, 1.20]
Sheehan 2019	48	78	206	388	7.1%	1.16 [0.95, 1.41]
Simões 2016	13	57	51	246	2.4%	1.10 [0.64, 1.88]
Sugiyama 2022	31	86	153	502	4.9%	1.18 [0.87, 1.61]
Total (95% CI)		**4294**		**31001**	**100.0%**	**1.20 [1.09, 1.32]**
Total events	1906		13113			

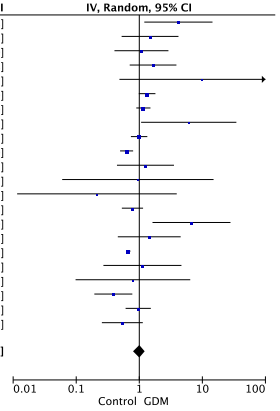
Heterogeneity: Tau² = 0.02; Chi² = 69.14, df = 14 (P < 0.00001); I² = 80%
Test for overall effect: Z = 3.74 (P = 0.0002)

Risk Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Controls GDM

A.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alfadhli et al. 2015	13	292	3	281	2.4%	4.17 [1.20, 14.48]
Bashir et al. 2021	5	402	12	1429	3.2%	1.48 [0.52, 4.18]
Casey aet al. 1997	4	874	259	61209	3.4%	1.08 [0.40, 2.90]
Chou et al. 2010	6	874	42	10116	4.1%	1.65 [0.70, 3.88]
Diamond et al. 1984	2	51	0	102	0.5%	9.90 [0.48, 202.54]
Fadl et al. 2010	42	10525	3749	1249772	9.0%	1.33 [0.98, 1.80]
Hilden et al. 2018	58	14833	4852	1440834	9.4%	1.16 [0.90, 1.50]
Huidobro et al. 2004	2	24	3	219	1.4%	6.08 [1.07, 34.62]
Kawakita et al. 2017	45	11327	833	208355	9.0%	0.99 [0.74, 1.34]
Lai et al. 2016	70	18137	1880	306576	9.6%	0.63 [0.50, 0.80]
Li M. et al. 2020	5	787	12	2367	3.2%	1.25 [0.44, 3.55]
Lucas et al. 1993	1	159	1	151	0.6%	0.95 [0.06, 15.05]
Meghelli et al. 2019	0	121	4	233	0.5%	0.21 [0.01, 3.93]
Ovesen et al. 2014	26	9014	1442	389609	8.1%	0.78 [0.53, 1.15]
Ramachandran et al. 1998	5	211	3	851	2.0%	6.72 [1.62, 27.90]
Rauh-Hain et al. 2009	3	521	88	21982	2.7%	1.44 [0.46, 4.53]
Reitzle 2023	635	283210	15638	4661460	10.7%	0.67 [0.62, 0.72]
Rosen et al. 2018	2	2236	35	43876	1.9%	1.12 [0.27, 4.66]
Shindo 2020	1	503	7	2789	1.0%	0.79 [0.10, 6.42]
Soliman et al. 2018	9	3027	69	8995	5.2%	0.39 [0.19, 0.78]
Srichumchit et al. 2017	19	1350	299	20421	7.3%	0.96 [0.61, 1.52]
Stone et al.2002	7	2169	349	58231	4.8%	0.54 [0.26, 1.14]
Total (95% CI)		**360647**		**8489858**	**100.0%**	**1.00 [0.80, 1.25]**
Total events	960		29580			

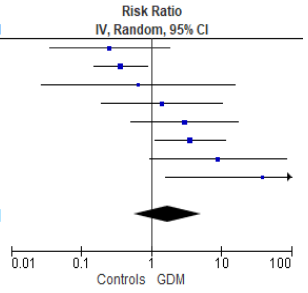
Heterogeneity: Tau² = 0.12; Chi² = 77.18, df = 21 (P < 0.00001); I² = 73%
Test for overall effect: Z = 0.02 (P = 0.99)



B.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Dinham 2016	1	172	41	1792	12.5%	0.25 [0.04, 1.84]
Lai 2016	5	810	173	10194	18.3%	0.36 [0.15, 0.88]
Santos Monteiro 2022	0	84	1	166	7.6%	0.65 [0.03, 15.91]
Rauh-Hain 2009	1	44	17	1062	12.4%	1.42 [0.19, 10.43]
Cho 2006	3	66	2	132	13.6%	3.00 [0.51, 17.52]
Simões 2016	5	57	6	246	16.9%	3.60 [1.14, 11.37]
Simões 2011	3	210	1	630	11.1%	9.00 [0.94, 86.06]
Mourad 2019	1	88	0	1140	7.6%	38.46 [1.58, 937.27]
Total (95% CI)		**1531**		**15362**	**100.0%**	**1.72 [0.57, 5.19]**
Total events	19		241			

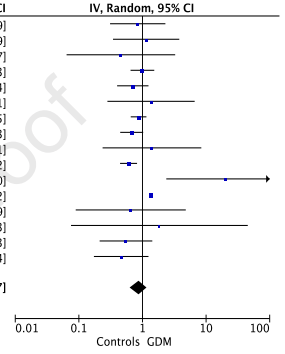
Heterogeneity: Tau² = 1.53; Chi² = 21.61, df = 7 (P = 0.003); I² = 68%
Test for overall effect: Z = 0.96 (P = 0.34)



C.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alfadhli et al. 2015	7	292	8	281	5.3%	0.84 [0.31, 2.29]
Blickstein I. et al 2017	3	1525	24	13937	4.2%	1.14 [0.34, 3.79]
Casey aet al. 1997	1	874	153	61209	1.9%	0.46 [0.06, 3.27]
Fadl et al. 2010	21	10525	2500	1249772	10.6%	1.00 [0.65, 1.53]
Hilden et al. 2018	12	14833	1654	1440834	9.1%	0.70 [0.40, 1.24]
Kari et al. 2017	3	99	3	135	2.8%	1.36 [0.28, 6.61]
Kaul et al. 2014	49	8731	1495	231352	12.1%	0.87 [0.65, 1.15]
Kawakita et al. 2017	23	11327	625	208355	10.7%	0.68 [0.45, 1.03]
Kawasaki 2023	3	878	2	825	2.3%	1.41 [0.24, 8.41]
Lai et al. 2016	42	18137	1175	306576	11.9%	0.60 [0.44, 0.82]
Ramachandran et al. 1998	5	211	1	851	1.7%	20.17 [2.37, 171.70]
Randall 2021	2152	71740	17735	806155	13.6%	1.36 [1.30, 1.42]
Rosen et al. 2018	1	2236	30	43876	1.9%	0.65 [0.09, 4.79]
Shindo 2020	0	503	1	2789	0.8%	1.85 [0.08, 45.23]
Soliman et al. 2018	5	3027	27	8995	5.6%	0.55 [0.21, 1.43]
Stone et al.2002	4	2169	232	58231	5.4%	0.46 [0.17, 1.24]
Total (95% CI)		**147107**		**4434173**	**100.0%**	**0.87 [0.65, 1.17]**
Total events	2331		25665			

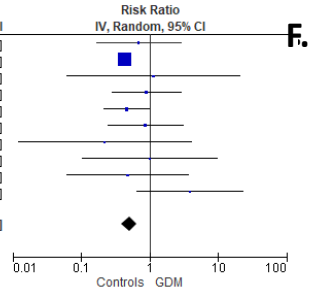
Heterogeneity: Tau² = 0.17; Chi² = 67.48, df = 15 (P < 0.00001); I² = 78%
Test for overall effect: Z = 0.92 (P = 0.36)



D.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Dinham 2016	2	172	30	1792	3.2%	0.69 [0.17, 2.88]
Foeller 2016	121	16562	4331	258857	70.8%	0.44 [0.36, 0.52]
Hung 2021	0	114	4	1176	0.8%	1.14 [0.06, 20.99]
Kim 2022	3	260	42	3266	4.7%	0.90 [0.28, 2.88]
Lai 2016	7	810	191	10194	10.7%	0.46 [0.22, 0.98]
Lin 2022	3	944	13	3558	4.1%	0.87 [0.25, 3.05]
Santos Monteiro 2022	0	84	4	166	0.8%	0.22 [0.01, 4.01]
Simões 2011	1	210	3	630	1.3%	1.00 [0.10, 9.56]
Simões 2016	1	57	9	246	1.6%	0.48 [0.06, 3.71]
Sugiyama 2022	2	86	3	502	2.1%	3.89 [0.66, 22.95]
Total (95% CI)		**19299**		**280387**	**100.0%**	**0.50 [0.39, 0.65]**
Total events	140		4630			

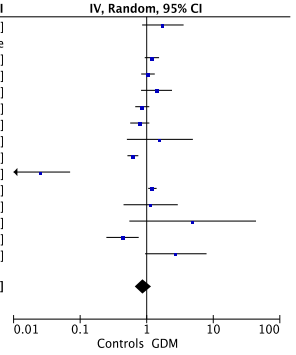
Heterogeneity: Tau² = 0.02; Chi² = 9.53, df = 9 (P = 0.39); I² = 6%
Test for overall effect: Z = 5.20 (P < 0.00001)



E.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alfadhli et al. 2015	20	292	11	281	6.3%	1.75 [0.85, 3.58]
Aviram 2016	0	132	0	1717		Not estimable
Fadl et al. 2010	63	10525	6249	1249772	9.8%	1.20 [0.93, 1.53]
Hilden et al. 2018	70	14833	6506	1440834	9.9%	1.05 [0.83, 1.32]
Ijas et al. 2019	19	5680	45	18897	7.7%	1.40 [0.82, 2.40]
Kawakita et al. 2017	68	11327	1459	208355	9.9%	0.86 [0.67, 1.09]
Koivunen et al. 2016	38	11858	424	104132	9.3%	0.79 [0.57, 1.10]
Laafira et al. 2016	4	669	11	2902	3.9%	1.58 [0.50, 4.94]
Lai et al. 2016	112	18137	3055	306576	10.2%	0.62 [0.51, 0.75]
Leon 2015	4	634	32	129	4.5%	0.03 [0.01, 0.07]
Randall 2021	201	71740	1854	806155	10.4%	1.22 [1.05, 1.41]
Ricart et al. 2005	5	1082	33	8188	4.9%	1.15 [0.45, 2.93]
Rosen et al. 2018	1	2236	4	43876	1.4%	4.91 [0.55, 43.87]
Soliman et al. 2018	14	3027	96	8995	7.5%	0.43 [0.25, 0.76]
Stella et al. 2008	4	927	22	13953	4.3%	2.74 [0.95, 7.93]
Total (95% CI)		**153099**		**4214762**	**100.0%**	**0.89 [0.67, 1.18]**
Total events	623		19801			

Heterogeneity: Tau² = 0.20; Chi² = 104.49, df = 13 (P < 0.00001); I² = 88%
Test for overall effect: Z = 0.82 (P = 0.41)



F.

Study or Subgroup	GDM Events	GDM Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Dinham 2016	3	172	71	1792	17.8%	0.44 [0.14, 1.38]
González González 2012	16	514	10	554	22.0%	1.72 [0.79, 3.77]
Lai 2016	12	810	364	10194	24.4%	0.41 [0.23, 0.73]
Simões 2011	4	210	4	630	15.3%	3.00 [0.76, 11.89]
Simões 2016	6	57	15	246	20.6%	1.73 [0.70, 4.25]
Total (95% CI)		**1763**		**13416**	**100.0%**	**1.04 [0.47, 2.32]**
Total events	41		464			

Heterogeneity: Tau² = 0.60; Chi² = 16.08, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 0.10 (P = 0.92)