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Cite this as: *BMJ* 2022;377:e067946 http://dx.doi.org/10.1136/ bmi-2021-067946

Accepted: 18 April 2022

Gestational diabetes mellitus and adverse pregnancy outcomes: systematic review and meta-analysis

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ABSTRACT

OBIECTIVE

To investigate the association between gestational diabetes mellitus and adverse outcomes of pregnancy after adjustment for at least minimal confounding factors.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

Web of Science, PubMed, Medline, and Cochrane Database of Systematic Reviews, from 1 January 1990 to 1 November 2021.

REVIEW METHODS

Cohort studies and control arms of trials reporting complications of pregnancy in women with gestational diabetes mellitus were eligible for inclusion. Based on the use of insulin, studies were divided into three subgroups: no insulin use (patients never used insulin during the course of the disease), insulin use (different proportions of patients were treated with insulin), and insulin use not reported. Subgroup analyses were performed based on the status of the country (developed or developing), quality of the study, diagnostic criteria, and screening method. Meta-regression models were applied based on the proportion of patients who had received insulin.

RESULTS

156 studies with 7 506 061 pregnancies were included, and 50 (32.1%) showed a low or medium risk of bias. In studies with no insulin use, when

adjusted for confounders, women with gestational diabetes mellitus had increased odds of caesarean section (odds ratio 1.16, 95% confidence interval 1.03 to 1.32), preterm delivery (1.51, 1.26 to 1.80), low one minute Apgar score (1.43, 1.01 to 2.03), macrosomia (1.70, 1.23 to 2.36), and infant born large for gestational age (1.57, 1.25 to 1.97). In studies with insulin use, when adjusted for confounders, the odds of having an infant large for gestational age (odds ratio 1.61, 1.09 to 2.37), or with respiratory distress syndrome (1.57, 1.19 to 2.08) or neonatal jaundice (1.28, 1.02 to 1.62), or requiring admission to the neonatal intensive care unit (2.29. 1.59 to 3.31), were higher in women with gestational diabetes mellitus than in those without diabetes. No clear evidence was found for differences in the odds of instrumental delivery, shoulder dystocia, postpartum haemorrhage, stillbirth, neonatal death, low five minute Apgar score, low birth weight, and small for gestational age between women with and without gestational diabetes mellitus after adjusting for confounders. Country status, adjustment for body mass index, and screening methods significantly contributed to heterogeneity between studies for several adverse outcomes of pregnancy.

CONCLUSIONS

When adjusted for confounders, gestational diabetes mellitus was significantly associated with pregnancy complications. The findings contribute to a more comprehensive understanding of the adverse outcomes of pregnancy related to gestational diabetes mellitus. Future primary studies should routinely consider adjusting for a more complete set of prognostic factors.

REVIEW REGISTRATION

PROSPERO CRD42021265837.

Introduction

Gestational diabetes mellitus is a common chronic disease in pregnancy that impairs the health of several million women worldwide. Formally recognised by O'Sullivan and Mahan in 1964, gestational diabetes mellitus is defined as hyperglycaemia first detected during pregnancy. With the incidence of obesity worldwide reaching epidemic levels, the number of pregnant women diagnosed as having gestational diabetes mellitus is growing, and these women have an increased risk of a range of complications of pregnancy. Quantification of the risk or odds of possible adverse outcomes of pregnancy is needed for prevention, risk assessment, and patient education.

In 2008, the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study recruited a large multinational cohort and clarified the risks of adverse outcomes associated with hyperglycaemia.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The incidence of gestational diabetes mellitus is gradually increasing and is associated with a range of complications for the mother and fetus or neonate Pregnancy outcomes in gestational diabetes mellitus, such as neonatal death and low Apgar score, have not been considered in large cohort studies Comprehensive systematic reviews and meta-analyses assessing the association between gestational diabetes mellitus and adverse pregnancy outcomes are lacking

WHAT THIS STUDY ADDS

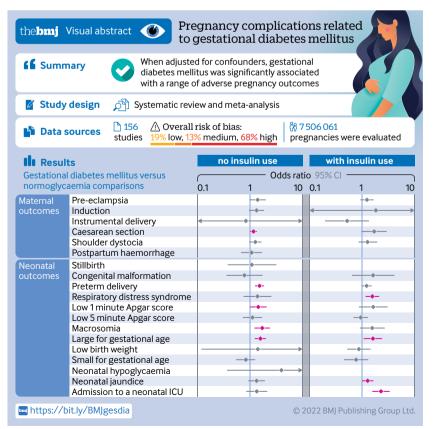
This systematic review and meta-analysis showed that in studies where insulin was not used, when adjusted for confounders, women with gestational diabetes mellitus had increased odds of caesarean delivery, preterm delivery, low one minute Apgar score, macrosomia, and an infant large for gestational age in the pregnancy outcomes

In studies with insulin use, when adjusted for confounders, women with gestational diabetes mellitus had increased odds of an infant large for gestational age, or with respiratory distress syndrome or neonatal jaundice, or requiring admission to the neonatal intensive care unit

Future primary studies should routinely consider adjusting for a more complete set of prognostic factors

The findings of the study showed that maternal hyperglycaemia independently increased the risk of preterm delivery, caesarean delivery, infants born large for gestational age, admission to a neonatal intensive care unit, neonatal hypoglycaemia, and hyperbilirubinaemia. The obstetric risks associated with diabetes, such as pregnancy induced hypertension, macrosomia, congenital malformations, and neonatal hypoglycaemia, have been reported in several large scale studies.⁷⁻¹² The HAPO study did not adjust for some confounders, however, such as maternal body mass index, and did not report on stillbirths and neonatal respiratory distress syndrome, raising uncertainty about these outcomes. Other important pregnancy outcomes, such as preterm delivery, neonatal death, and low Apgar score in gestational diabetes mellitus, were poorly reported. No comprehensive study has assessed the relation between gestational diabetes mellitus and various maternal and fetal adverse outcomes after adjustment for confounders. Also, some cohort studies were restricted to specific clinical centres and regions, limiting their generalisation to more diverse populations.

By collating the available evidence, we conducted a systematic review and meta-analysis to quantify the short term outcomes in pregnancies complicated by gestational diabetes mellitus. We evaluated adjusted associations between gestational diabetes mellitus and various adverse outcomes of pregnancy.



Methods

This meta-analysis was conducted according to the recommendations of Cochrane Systematic Reviews, and our findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (table S16). The study was prospectively registered in the international database of prospectively registered systematic reviews (PROSPERO CRD42021265837).

Search strategy and selection criteria

We searched the electronic databases PubMed, Web of Science, Medline, and the Cochrane Database of Systematic Reviews with the keywords: "pregnan*," "gestatio*" or "matern*" together with "diabete*," "hyperglycaemia," "insulin," "glucose," or "glucose tolerance test*" to represent the exposed populations, and combined them with terms related to outcomes, such as "pregnan* outcome*," "obstetric* complicat*," disorder*," "pregnan* "obstetric* outcome*," "haemorrhage," "induc*," "instrumental," "caesarean section," "dystocia," "hypertensi*," "eclampsia," "premature rupture of membrane," "preter*," "macrosomia," and "malformation," as well as some abbreviated diagnostic criteria, such as "IADPSG," "DIPSI," and "ADIPS" (table S1). The search strategy was appropriately translated for the other databases. We included observational cohort studies and control arms of trials, conducted after 1990, that strictly defined non-gestational diabetes mellitus (control) and gestational diabetes mellitus (exposed) populations and had definite diagnostic criteria for gestational diabetes mellitus (table S2) and various adverse outcomes of pregnancy.

Exclusion criteria were: studies published in languages other than English; studies with no diagnostic criteria for gestational diabetes mellitus (eg, self-reported gestational diabetes mellitus, gestational diabetes mellitus identified by codes from the International Classification of Diseases or questionnaires); studies published after 1990 that recorded pregnancy outcomes before 1990; studies of specific populations (eg, only pregnant women aged 30-34 years, ¹³ only twin pregnancies ¹⁴⁻¹⁶); studies with a sample size <300, because we postulated that these studies might not be adequate to detect outcomes within each group; and studies published in the form of an abstract, letter, or case report.

We also manually retrieved reference lists of relevant reviews or meta-analyses. Three reviewers (WY, CL, and JH) independently searched and assessed the literature for inclusion in our meta-analysis. The reviewers screened the titles and abstracts to exclude ineligible studies. The full texts of relevant records were then retrieved and assessed. Any discrepancies were resolved after discussion with another author (FL).

Data extraction

Three independent researchers (WY, CL, and JH) extracted data from the included studies with a predesigned form. If the data were not presented, we

contacted the corresponding authors to request access to the data. We extracted data from the most recent study or the one with the largest sample size when a cohort was reported twice or more. Sociodemographic and clinical data were extracted based on: year of publication, location of the study (country and continent), design of the study (prospective or retrospective cohort), screening method and diagnostic criteria for gestational diabetes mellitus, adjustment for conventional prognostic factors (defined as maternal age, pregestational body mass index, gestational weight gain, gravidity, parity, smoking history, and chronic hypertension), and the proportion of patients with gestational diabetes mellitus who were receiving insulin. For studies that adopted various diagnostic criteria for gestational diabetes mellitus, we extracted the most recent or most widely accepted one for

subsequent analysis. For studies adopting multivariate logistic regression for adjustment of confounders, we extracted adjusted odds ratios and synthesised them in subsequent analyses. For unadjusted studies, we calculated risk ratios and 95% confidence intervals based on the extracted data.

Outcomes

Studies of women with gestational diabetes mellitus that evaluated the risk or odds of maternal or neonatal complications were included. We assessed the maternal outcomes pre-eclampsia, induction of labour, instrumental delivery, caesarean section, shoulder dystocia, premature rupture of membrane, and postpartum haemorrhage. Fetal or neonatal outcomes assessed were stillbirth, neonatal death, congenital malformation, preterm birth, macrosomia,

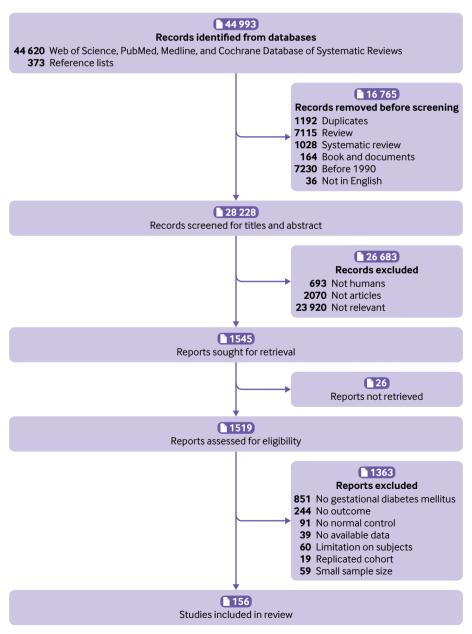


Fig 1 | Search and selection of studies for inclusion

Table 1 Characteristics	of study populati	ion						
	Whole population	on (156 studies)	No insulin use	* (35 studies)	Insulin use* (6	3 studies)	Insulin use not (58 studies)	reported*
Characteristic	GDM (n=338746)	Non-GDM (n=7170770)	GDM (n=26998)	Non-GDM (n=281 546)	GDM (n=75 551)	Non-GDM (n=984 997)	GDM (n=236197)	Non-GDM (n=5 904 227)
Insulin uset	_		No		Yes		Not reported	
Country status (No (%))								
Developed	272 564 (80.5)	6799221 (94.8)	19 996 (74.1)	218 675 (77.7)	53 968 (71.4)	898 144 (91.2)	198 600 (84.1)	5 682 402 (96.2
Developing	62 456 (18.4)	352 058 (4.9)	3276 (12.1)	43 380 (15.4)	21 583 (28.6)	86 853 (8.8)	37 597 (15.9)	221825 (3.8)
Other	3726 (1.1)	19491 (0.3)	3726 (13.8)	19 491 (6.9)	0 (0)	0 (0)	0 (0)	0 (0)
Diagnostic criteria (No (%))								
WHO 1999	5747 (1.7)	20 218 (0.3)	289 (1.1)	2596 (0.9)	5313 (7.0)	15 815 (1.6)	145 (0.1)	1807 (0.03)
Carpenter and Coustan	8100 (2.4)	148 202 (2.1)	3347 (12.4)	90 213 (32.0)	4179 (5.5)	51012 (5.2)	574 (0.2)	6977 (0.1)
IADPSG	78 851 (23.3)	773 220 (10.8)	23 362 (86.5)	188737 (67.0)	22824 (30.2)	277 678 (28.2)	32 665 (13.8)	306805 (5.2)
Other	246 048 (72.6)	6 229 130 (86.9)	0 (0)	0 (0)	43 235 (57.2)	640 492 (65.0)	202813 (85.9)	5588638 (94.7
Screening method (No (%))								
Universal one step	71 359 (21.1)	527 318 (7.4)	7338 (27.2)	48 012 (17.1)	36 282 (48.0)	329 052 (33.4)	27 7 39 (11.7)	150254 (2.5)
Universal GCT	209 840 (61.9)	3899872 (54.4)	18 406 (68.2)	226 127 (80.3)	30 869 (40.9)	475 367 (48.3)	160 565 (68.0)	3198378 (54.2
Selective	39 181 (11.6)	1 277 643 (17.8)	1254 (4.6)	7407 (2.6)	7813 (10.3)	166816 (16.9)	30 114 (12.7)	1103420 (18.7
Not reported	18 366 (5.4)	1 465 937 (20.4)	0	0	587 (0.8)	13762 (1.4)	17 779 (7.5)	1452175 (24.6
Risk of bias (No (%))								
High	315 058 (93.0)	7 003 302 (97.7)	23 447 (86.8)	248 364 (88.2)	62 966 (83.3)	910 508 (92.4)	228 645 (96.8)	5844430 (99.0
Medium	18 576 (5.5)	144 674 (2.0)	2773 (10.3)	21 064 (7.5)	10 488 (13.9)	67 162 (6.8)	5315 (2.3)	56 448 (1.0)
Low	5112 (1.5)	22794 (0.3)	778 (2.9)	12 118 (4.3)	2097 (2.8)	7327 (0.7)	2237 (0.9)	3349 (0.1)
Adjustment (No (%))‡								
Yes	193 230 (57.0)	5 108 276 (71.2)	21 875 (81.0)	220 886 (78.5)	4,134 (5.5)	44 567 (4.5)	167 221 (70.8)	4842823 (82.0
No	145 516 (43.0)	2062494 (28.8)	5123 (19.0)	60 660 (21.5)	71 417 (94.5)	940 430 (95.5)	68 976 (29.2)	1061404 (18.0

GDM=gestational diabetes mellitus; WHO=World Health Organization; IADPSG=International Association of Diabetes and Pregnancy Study Groups; GCT=glucose challenge test.
*Studies were divided into three subgroups: no insulin use (patients never used insulin during the course of the disease), insulin use (different proportions of patients were treated with insulin), and insulin use not reported.

low birth weight, large for gestational age, small for gestational age, neonatal hypoglycaemia, neonatal jaundice, respiratory distress syndrome, low Apgar score, and admission to the neonatal intensive care unit. Table S3 provides detailed definitions of these adverse outcomes of pregnancy.

Risk-of-bias assessment

A modified Newcastle-Ottawa scale was used to assess the methodological quality of the selection, comparability, and outcome of the included studies (table S4). Three independent reviewers (WY, CL, and JH) performed the quality assessment and scored the studies for adherence to the prespecified criteria. A study that scored one for selection or outcome, or zero for any of the three domains, was considered to have a high risk of bias. Studies that scored two or three for selection, one for comparability, and two for outcome were regarded as having a medium risk of bias. Studies that scored four for selection, two for comparability, and three for outcome were considered to have a low risk of bias. A lower risk of bias denotes higher quality.

Data synthesis and analysis

Pregnant women were divided into two groups (gestational diabetes mellitus and non-gestational diabetes mellitus) based on the diagnostic criteria in each study. Studies were considered adjusted if they adjusted for at least one of seven confounding factors (maternal age, pregestational body mass index, gestational weight gain, gravidity, parity, smoking history, and chronic hypertension). For each adjusted

study, we transformed the odds ratio estimate and its corresponding standard error to natural logarithms to stabilise the variance and normalise their distributions. Summary odds ratio estimates and their 95% confidence intervals were estimated by a random effects model with the inverse variance method. We reported the results as odds ratio with 95% confidence intervals to reflect the uncertainty of point estimates. Unadjusted associations between gestational diabetes mellitus and adverse outcomes of pregnancy were quantified and summarised (table S6 and table S14). Thereafter, heterogeneity across the studies was evaluated with the τ^2 statistics and Cochran's Q test. $^{17\ 18}$ Cochran's Q test assessed interactions between subgroups. 18

We performed preplanned subgroup analyses for factors that could potentially affect gestational diabetes mellitus or adverse outcomes of pregnancy: country status (developing or developed country according to the International Monetary Fund (www. imf.org/external/pubs/ft/weo/2020/01/weodata/ groups.htm), risk of bias (low, medium, or high), screening method (universal one step, universal glucose challenge test, or selective screening based on risk factors), diagnostic criteria for gestational diabetes mellitus (World Health Organization 1999, Carpenter-Coustan criteria, International Association of Diabetes and Pregnancy Study Groups (IADPSG), or other), and control for body mass index. We assessed small study effects with funnel plots by plotting the natural logarithm of the odds ratios against the inverse of the standard errors, and asymmetry was assessed with Egger's test. 19 A meta-regression model was used

tinsulin use in the gestational diabetes mellitus group.

[‡]Adjustment for core confounding factors, including maternal age, pregestational body mass index, gestational weight gain, smoking status, gravity, parity, and chronic hypertension.

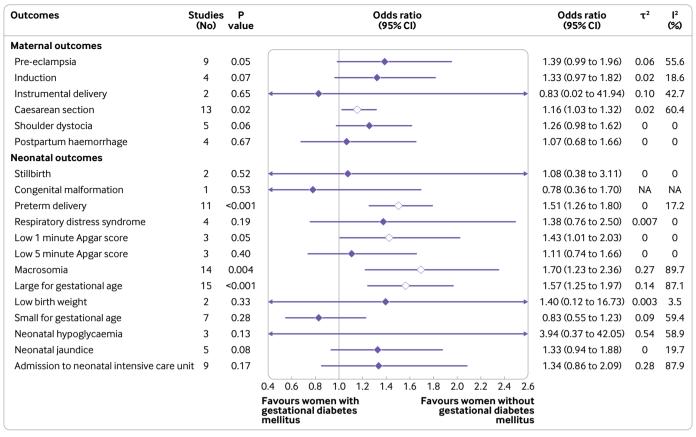


Fig 2 | Findings of meta-analysis of association between gestational diabetes mellitus and adverse outcomes of pregnancy after adjusting for at least minimal confounding factors, in studies in patients who never used insulin during the course of the disease (no insulin use). NA=not applicable

to investigate the associations between study effect size and proportion of patients who received insulin in the gestational diabetes mellitus population. Next, we performed sensitivity analyses by omitting each study individually and recalculating the pooled effect size estimates for the remaining studies to assess the effect of individual studies on the pooled results. All analyses were performed with R language (version 4.1.2, www.r-project.org) and meta package (version 5.1-0). We adopted the treatment arm continuity correction to deal with a zero cell count²⁰ and the Hartung-Knapp adjustment for random effects meta models. ^{21 22}

Patient and public involvement

The experience in residency training in the department of obstetrics and the concerns about the association between gestational diabetes mellitus and health outcomes inspired the author team to perform this study. We also asked advice from the obstetrician and patients with gestational diabetes mellitus about which outcomes could be included. The covid-19 restrictions meant that we sought opinions from only a limited number of patients in outpatient settings.

Results

Characteristics of included studies

Of the 44993 studies identified, 156 studies, ²³⁻¹⁷⁸ involving 7506061 pregnancies, were eligible for

the analysis of adverse outcomes in pregnancy (fig 1). Of the 156 primary studies, 133 (85.3%) reported maternal outcomes and 151 (96.8%) reported neonatal outcomes. Most studies were conducted in Asia (39.5%), Europe (25.5%), and North America (15.4%). Eighty four (53.8%) studies were performed in developed countries. Based on the Newcastle-Ottawa scale, 50 (32.1%) of the 156 included studies showed a low or medium risk of bias and 106 (67.9%) had a high risk of bias. Patients in 35 (22.4%) of the 156 studies never used insulin during the course of the disease and 63 studies (40.4%) reported treatment with insulin in different proportions of patients. The remaining 58 studies did not report information about the use of insulin. Table 1 summarises the characteristics of the study population, including continent or region, country, screening methods, and diagnostic criteria for the included studies. Table S5 lists the key excluded studies.

Associations between gestational diabetes mellitus and adverse outcomes of pregnancy

Based on the use of insulin in each study, we classified the studies into three subgroups: no insulin use (patients never used insulin during the course of the disease), insulin use (different proportions of patients were treated with insulin), and insulin use not reported. We reported odds ratios with 95%

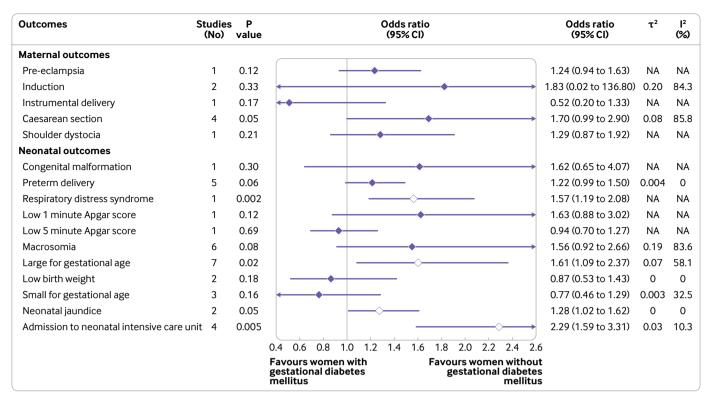


Fig 3 | Findings of meta-analysis of association between gestational diabetes mellitus and adverse outcomes of pregnancy after adjusting for at least minimal confounding factors, in studies where different proportions of patients were treated with insulin (insulin use). NA=not applicable

confidence intervals after controlling for at least minimal confounding factors. In studies with no insulin use, women with gestational diabetes mellitus had increased odds of caesarean section (odds ratio 1.16, 95% confidence interval 1.03 to 1.32), preterm delivery (1.51, 1.26 to 1.80), low one minute Appar score (1.43, 1.01 to 2.03), macrosomia (1.70, 1.23 to 2.36), and an infant born large for gestational age (1.57, 1.25 to 1.97) (fig 2 and fig S1). In studies with insulin use, adjusted for confounders, the odds of an infant born large for gestational age (odds ratio 1.61, 95% confidence interval 1.09 to 2.37), or with respiratory distress syndrome (1.57, 1.19 to 2.08) or neonatal jaundice (1.28, 1.02 to 1.62), or requiring admission to the neonatal intensive care unit (2.29, 1.59 to 3.31) were higher in women with than in those without gestational diabetes mellitus (fig 3). In studies that did not report the use of insulin, women with gestational diabetes mellitus had increased odds ratio for pre-eclampsia (1.46, 1.21 to 1.78), induction of labour (1.88, 1.16 to 3.04), caesarean section (1.38, 1.20 to 1.58), premature rupture of membrane (1.13, 1.06 to 1.20), congenital malformation (1.18, 1.10 to 1.26), preterm delivery (1.51, 1.19 to 1.93), macrosomia (1.48, 1.13 to 1.95), neonatal hypoglycaemia (11.71, 7.49 to 18.30), and admission to the neonatal intensive care unit (2.28, 1.26 to 4.13) (figs S3 and S4). We found no clear evidence for differences in the odds of instrumental delivery, shoulder dystocia, postpartum haemorrhage, stillbirth, neonatal death, low five minute Apgar score,

low birth weight, and infant born small for gestational age between women with and without gestational diabetes mellitus in all three subgroups (fig 2, fig 3, and figs S1-S4). Table S6 shows the unadjusted associations between gestational diabetes mellitus and adverse outcomes of pregnancy.

Subgroup, meta-regression, and sensitivity analyses

Subgroup analyses, based on risk of bias, did not show significant heterogeneity between the subgroups of women with and without gestational diabetes mellitus for most adverse outcomes of pregnancy (table 2 and table 3), except for admission to the neonatal intensive care unit in studies where insulin use was not reported (table S7). Significant differences between subgroups were reported for country status and macrosomia in studies with (P<0.001) and without (P=0.001) insulin use (table 2 and table 3), and for macrosomia (P=0.02) and infants born large for gestational age (P<0.001) based on adjustment for body mass index in studies with insulin use (table S8). Screening methods contributed significantly to the heterogeneity between studies for caesarean section (P<0.001) and admission to the neonatal intensive care unit (P<0.001) in studies where insulin use was not reported (table S7). In most outcomes, the estimated odds were lower in studies that used universal one step screening than those that adopted the universal glucose challenge test or selective screening methods (table 2 and table 3). Diagnostic criteria were not related to heterogeneity

	Country status*	*		Overallrisk			Diagnostic criteria	ria			Screening method	thod		
						_				۵	Universal one			
Outcomes	Developed	Developing	P value	P value Medium	Low	value	WHO 1999	S	IADPSG	value	step	Universal GCT Selective	Selective	Pvalue
Maternal														
Pre-eclampsia	9 1	2	0.64	2	7	96.0	0	1	8	92.0	7	5	0	0.40
	1.31	1.48			1.40	•	AN	1.60	1.38	I	1.26	1.66	AN	
	(0.69 to 2.48)	(0.64 to 3.39)		(0.01 to 163.95)	(0.89 to 2.19)			(0.66 to 3.87)	- 1		(0.73 to 2.18)	(0.75 to 3.69)		
Caesarean	10	3	0.74	5	8	0.82	1	8	6	0.70	3	∞	2	06.0
section	1.17	1.09		1.18	1.15		1.00	1.15	1.17	ı	1.11	1.16	1.21	
	(1.02 to 1.34)	(0.48 to 2.51)		(0.91 to 1.53)	(0.95 to 1.38)		(0.71 to 1.41)	(0.71 to 1.86)	(0.99 to 1.40)		(0.72 to 1.71)	(0.95 to 1.42)	(0.13 to 11.13)	
Neonatal														
Preterm	6	2	0.81	4	7	0.92	1	3	7	0.83	3	7	1	0.79
delivery	1.48	1.52		1.43	1.47		1.70	1.26	1.48		1.57	1.42	1.70	
	(1.15 to 1.92)	(1.46 to 1.59)		(0.73 to 2.83)	(1.17 to 1.84)		(0.81 to 3.56)	(0.30 to 5.24)	(1.18 to 1.86)		(1.34 to 1.85)	(0.99 to 2.05)	(0.81 to 3.56)	
Macrosomia	12	2	0.001	3	11	0.43	1	4	6	0.93	7	6	1	0.31
	1.61	2.80		1.48	1.78		1.50	1.58	1.67	ı	1.29	2.03	1.50	
	(1.12 to 2.31)	(1.92 to 4.07)		(0.85 to 2.59)	(1.16 to 2.72)		(1.06 to 2.12)	(0.99 to 2.53)	(1.00 to 2.81)		(0.39 to 4.20)	(1.41 to 2.90)	(1.06 to 2.12)	
LGA	12	2	0.15	4	11	0.42	1	2	12	0.39	4	6	2	0.43
	1.57	1.31		1.42	1.61		1.70	1.38	1.60		1.24	1.78	1.58	
	(1.18 to 2.09)	(1.25 to 1.37)		(1.16 to 1.73)	(1.17 to 2.22)		(1.15 to 2.51)	(0.73 to 2.61)	(1.20 to 2.14)		(0.53 to 2.88)	(1.33 to 2.37)	(0.76 to 3.32)	
SGA	9	1	0.74	0	7	N A	0	0	7	NA	3	4	0	0.10
	0.80	0.89		ı	0.83		NA	NA	0.83		1.05	99.0	NA	
	(0.48 to 1.35)	(0.58 to 1.37)			(0.55 to 1.23)				(0.55 to 1.23)		(0.42 to 2.63)	(0.37 to 1.18)		
NICU	7	2	0.84	2	7	0.46	0	1	8	0.48	4	5	0	0.13
admission	1.31	1.40		2.00	1.20		NA	1.61	1.29		1.80	1.04	NA	
	(0.71 to 2.41)	(0.15 to 13.27)		(0.00 to 11371.92)	(0.80 to 1.80)			(1.05 to 2.46)	(0.77 to 2.16)		(0.66 to 4.95)	(0.64 to 1.71)		

gestational diabetes mellitus

diagnostic criteria, screening method, and risk of bias for adverse outcomes of pregnancy in women with

Subgroup analysis according to country status,

glucose challenge test; LGA=large for and Coustan; IADPSG=International Association of Diabetes and Pregnancy Study; GCT, gestational age according to country status because the study was conducted in multiple cross national centres. between the studies for all of the study subgroups (no insulin use, insulin use, insulin use not reported). The subgroup analysis was performed only for outcomes including ≥6 studies.

We applied meta-regression models to evaluate the modification power of the proportion of patients with insulin use when sufficient data were available. Significant associations were found between effect size estimate and proportion of patients who had received insulin for the adverse outcomes caesarean section (estimate=0.0068, P=0.04) and preterm delivery (estimate=-0.0069, P=0.04) (table S9).

In sensitivity analyses, most pooled estimates were not significantly different when a study was omitted, suggesting that no one study had a large effect on the pooled estimate. The pooled estimate effect became significant (P=0.005) for low birth weight when the study of Lu et al⁹⁹ was omitted, however (fig S5). We found evidence of a small study effect only for caesarean section (Egger's P=0.01, table S10). Figure S6 shows the funnel plots of the included studies for various adverse outcomes (≥10 studies).

Discussion

Principal findings

We have provided quantitative estimates for the associations between gestational diabetes mellitus and adverse outcomes of pregnancy after adjustment for confounding factors, through a systematic search and comprehensive meta-analysis. Compared with patients with normoglycaemia during pregnancy, patients with gestational diabetes mellitus had increased odds of caesarean section, preterm delivery, low one minute Apgar score, macrosomia, and an infant born large for gestational age in studies where insulin was not used. In studies with insulin use, patients with gestational diabetes mellitus had an increased odds of an infant born large for gestational age, or with respiratory distress syndrome or neonatal jaundice, or requiring admission to the neonatal intensive care unit. Our study was a comprehensive analysis, quantifying the adjusted associations between gestational diabetes mellitus and adverse outcomes of pregnancy. The study provides updated critical information on gestational diabetes mellitus and adverse outcomes of pregnancy and would facilitate counselling of women with gestational diabetes mellitus before delivery.

To examine the heterogeneity conferred by different severities of gestational diabetes mellitus, we categorised the studies by use of insulin. Insulin is considered the standard treatment for the management of gestational diabetes mellitus when adequate glucose levels are not achieved with nutrition and exercise.¹⁷⁹ Our meta-regression showed that the proportion of patients who had received insulin was significantly associated with the effect size estimate of adverse outcomes, including caesarean section (P=0.04) and preterm delivery (P=0.04). This finding might be the result of a positive linear association between glucose concentrations and adverse outcomes of pregnancy, as previously reported.¹⁸⁰ However, the proportion

Table 3 | Subgroup analysis according to country status, diagnostic criteria, screening method, and risk of bias for adverse outcomes of pregnancy in women with gestational diabetes mellitus compared with women without gestational diabetes mellitus in studies with insulin use

	Country status			Overall risk			Diagnostic criteria					Screening method			
Outcomes	Developed	Developing	P value	Medium	Low	P value	WHO 1999	СС	IADPSG	Other	P value	Universal one step	Universal GCT	Selective	P value
Neonatal															
Macrosomia	2	4	<0.001	2	4	0.78	1	1	2	2	0.27	3	2	1	0.26
	0.89	2.05		1.77	1.51		3.30	1.10	1.70	1.44		1.27	1.77	2.67	
	(0.43 to	(1.30 to		(0.00 to	(0.68 to		(1.36 to	(0.59 to	(1.16 to	(0.00 to		(0.44 to	(0.00 to	(1.26 to	
	1.86)	3.23)		1090.44)	3.35)		6.75)	2.06)	2.48)	1590.41)		3.68)	1090.44)	5.65)	
LGA	4	3	0.19	1	6	0.65	1	1	3	2	0.14	4	1	2	0.11
	1.43	2.33		1.40	1.67		0.87	1.40	1.81	2.04		1.43	1.40	2.36	
	(0.84 to	(0.56 to		(0.71 to	(1.01 to		(0.52 to	(0.71 to	(0.70 to	(0.01 to		(1.06 to	(0.71 to	(0.14 to	
	2.43)	9.69)		2.75)	2.76)		1.45)	2.75)	4.67)	339.27)		1.92)	2.75)	41.03)	

Data are number of studies, and odds ratios (95% confidence intervals). WHO=World Health Organization; CC=Carpenter and Coustan; IADPSG=International Association of Diabetes and Pregnancy Study; GCT, glucose challenge test; LGA=large for gestational age; NA=calculation of effect estimates not applicable.

P value measures intergroup interaction. Subgroup analyses were performed only for outcomes including ≥6 studies.

of patients who were receiving insulin indicates the percentage of patients with poor glycaemic control in the population and cannot reflect glycaemic control at the individual level.

Screening methods for gestational diabetes mellitus have changed over time, from the earliest selective screening (based on risk factors) to universal screening by the glucose challenge test or the oral glucose tolerance test, recommended by the US Preventive Services Task Force (2014)¹⁸¹ and the American Diabetes Association (2020).¹⁸² The diagnostic accuracy of these screening methods varied, contributing to heterogeneity in the analysis.

Several studies have tried to pool the effects of gestational diabetes mellitus on pregnancy outcomes, but most focused on one outcome, such as congenital malformations, 183 184 macrosomia, 185 186 or respiratory distress syndrome. 187 Our findings of increased odds of macrosomia in gestational diabetes mellitus in studies where insulin was not used, and respiratory distress syndrome in studies with insulin use, were similar to the results of previous meta-analyses. 188 189 The increased odds of neonatal respiratory distress syndrome, along with low Apgar scores, might be attributed to disruption of the integrity and composition of fetal pulmonary surfactant because gestational diabetes mellitus can delay the secretion of phosphatidylglycerol, an essential lipid component of surfactants. 190

Although we detected no significant association between gestational diabetes mellitus and mortality events, the observed increase in the odds of neonatal death (odds ratio 1.59 in studies that did not report the use of insulin) should be emphasised to obstetricians and pregnant women because its incidence was low (eg, 3.75%⁸⁷). The increased odds of neonatal death could result from several lethal complications, such as respiratory distress syndrome, neonatal hypoglycaemia (3.94-11.71-fold greater odds), and jaundice. These respiratory and metabolic disorders might increase the likelihood of admission to the neonatal intensive care unit.

For the maternal adverse outcomes, women with gestational diabetes mellitus had increased odds of

pre-eclampsia, induction of labour, and caesarean section, consistent with findings in previous studies. 126 Our study identified a 1.24-1.46-fold greater odds of pre-eclampsia between patients with and without gestational diabetes mellitus, which was similar to previous results. 191

Strengths and limitations of the study

Our study included more studies than previous metaanalyses and covered a range of maternal and fetal outcomes, allowing more comprehensive comparisons among these outcomes based on the use of insulin and different subgroup analyses. The odds of adverse fetal outcomes, including respiratory distress syndrome (P=0.002), neonatal jaundice (P=0.05), and admission to the neonatal intensive care unit (P=0.005), were significantly increased in studies with insulin use, implicating their close relation with glycaemic control. The findings of this meta-analysis support the need for an improved understanding of the pathophysiology of gestational diabetes mellitus to inform the prediction of risk and for precautions to be taken to reduce adverse outcomes of pregnancy.

The study had some limitations. Firstly, adjustment for at least one confounder had limited power to deal with potential confounding effects. The set of adjustment factors was different across studies, however, and defining a broader set of multiple adjustment variables was difficult. This major concern should be looked at in future well designed prospective cohort studies, where important prognostic factors are controlled. Secondly, overt diabetes was not clearly defined until the IADPSG diagnostic criteria were proposed in 2010. Therefore, overt diabetes or preexisting diabetes might have been included in the gestational diabetes mellitus groups if studies were conducted before 2010 or adopted earlier diagnostic criteria. Hence we cannot rule out that some adverse effects in newborns were related to prolonged maternal hyperglycaemia. Thirdly, we divided and analysed the subgroups based on insulin use because insulin is considered the standard treatment for the management of gestational diabetes mellitus and can reflect the

level of glycaemic control. Accurately determining the degree of diabetic control in patients with gestational diabetes mellitus was difficult, however. Finally, a few pregnancy outcomes were not accurately defined in studies included in our analysis. Stillbirth, for example, was defined as death after the 20th or 28th week of pregnancy, based on different criteria, but some studies did not clearly state the definition of stillbirth used in their methods. Therefore, we considered stillbirth as an outcome based on the clinical diagnosis in the studies, which might have caused potential bias in the analysis.

Conclusions

We performed a meta-analysis of the association between gestational diabetes mellitus and adverse outcomes of pregnancy in more than seven million women. Gestational diabetes mellitus was significantly associated with a range of pregnancy complications when adjusted for confounders. Our findings contribute to a more comprehensive understanding of adverse outcomes of pregnancy related to gestational diabetes mellitus. Future primary studies should routinely consider adjusting for a more complete set of prognostic factors.

Contributors: WY and FL developed the initial idea for the study, designed the scope, planned the methodological approach, wrote the computer code and performed the meta-analysis. WY and CL coordinated the systematic review process, wrote the systematic review protocol, completed the PROSPERO registration, and extracted the data for further analysis. ZL coordinated the systematic review update. WY, JH, and FL defined the search strings, executed the search, exported the results, and removed duplicate records. WY, CL, ZL, and FL screened the abstracts and texts for the systematic review, extracted relevant data from the systematic review articles, and performed quality assessment. WY, ZL, and FL wrote the first draft of the manuscript and all authors contributed to critically revising the manuscript. ZL and FL are the study guarantors. ZL and FL are senior and corresponding authors who contributed equally to this study. All authors had full access to all the data in the study, and the corresponding authors had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: The research was funded by the National Natural Science Foundation of China (grants 82001223 and 81901401), and the Natural Science Foundation for Young Scientist of Hunan Province, China (grant 2019)J50952). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the National Natural Science Foundation of China and the Natural Science Foundation for Young Scientist of Hunan Province, China for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: Table S11 provides details of adjustment for core confounders. Supplementary data files contain all of the raw tabulated data for the systematic review (table S12). Tables S13-15 provide the raw data and R language codes used for the meta-analysis.

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The dissemination plan targets a wide audience, including members of the public, patients, patient and public

communities, health professionals, and experts in the specialty through various channels: written communication, events and conferences, networks, and social media.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix: Appendix