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

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ABSTRACT

OBJECTIVE
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 (3.2%) 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.

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.

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.6 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: “pregnancy,” “gestatio*” or “matern*” together with “diabetes,” “hyperglycaemia,” “insulin,” “glucose,” or “glucose tolerance test*” to represent the exposed populations, and combined them with terms related to outcomes, such as “pregnanc* outcome*,” “obstetric* complicat*,” “pregnanc* disorder*,” “obstetric* outcome*,” “haemorrhage,” “induc*,” “instrumental,” “cesarean section,” “dystocia,” “hypertensi*,” “eclampsia,” “premature rupture of membrane,” “PROM,” “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 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.

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,
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 τ² 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.html), 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
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 count and the Hartung-Knapp adjustment for random effects meta models.20

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 7 506 061 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%
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 Apgar 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.

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**Outcomes**

<table>
<thead>
<tr>
<th>Maternal outcomes</th>
<th>Studies (No)</th>
<th>P value</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>1</td>
<td>0.12</td>
<td></td>
<td>1.24 (0.94 to 1.63)</td>
</tr>
<tr>
<td>Induction</td>
<td>2</td>
<td>0.33</td>
<td></td>
<td>1.83 (0.02 to 136.80)</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>1</td>
<td>0.17</td>
<td></td>
<td>0.52 (0.20 to 1.33)</td>
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<tr>
<td>Caesarean section</td>
<td>4</td>
<td>0.05</td>
<td></td>
<td>1.70 (0.99 to 2.90)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>1</td>
<td>0.21</td>
<td></td>
<td>1.29 (0.87 to 1.92)</td>
</tr>
<tr>
<td>Neonatal outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>1</td>
<td>0.30</td>
<td></td>
<td>1.62 (0.65 to 4.07)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>5</td>
<td>0.06</td>
<td></td>
<td>1.22 (0.99 to 1.50)</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>1</td>
<td>0.002</td>
<td></td>
<td>1.57 (1.19 to 2.08)</td>
</tr>
<tr>
<td>Low 1 minute Apgar score</td>
<td>1</td>
<td>0.12</td>
<td></td>
<td>1.63 (0.88 to 3.02)</td>
</tr>
<tr>
<td>Low 5 minute Apgar score</td>
<td>1</td>
<td>0.69</td>
<td></td>
<td>0.94 (0.70 to 1.27)</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>6</td>
<td>0.08</td>
<td></td>
<td>1.56 (0.92 to 2.66)</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>7</td>
<td>0.02</td>
<td></td>
<td>1.61 (1.09 to 2.37)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>2</td>
<td>0.18</td>
<td></td>
<td>0.87 (0.53 to 1.43)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>3</td>
<td>0.16</td>
<td></td>
<td>0.77 (0.46 to 1.29)</td>
</tr>
<tr>
<td>Neonatal jaundice</td>
<td>2</td>
<td>0.05</td>
<td></td>
<td>1.28 (1.02 to 1.62)</td>
</tr>
<tr>
<td>Admission to neonatal intensive care unit</td>
<td>4</td>
<td>0.005</td>
<td></td>
<td>2.29 (1.59 to 3.31)</td>
</tr>
</tbody>
</table>

**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.
Table 2 | 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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Country status*</th>
<th>Overall risk</th>
<th>Diagnostic criteria</th>
<th>Screening method</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Developed</td>
<td>Developing</td>
<td>P value</td>
<td>WHO 1999</td>
<td>CC</td>
</tr>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>1.31</td>
<td>1.48</td>
<td>0.64</td>
<td>1.45</td>
<td>1.40</td>
</tr>
<tr>
<td></td>
<td>(0.69 to 2.48)</td>
<td>(0.64 to 3.39)</td>
<td></td>
<td>(0.91 to 163.95)</td>
<td>(1.89 to 19.19)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>1.00</td>
<td>1.18</td>
<td>0.74</td>
<td>1.00</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>(0.91 to 1.53)</td>
<td>(0.95 to 1.38)</td>
<td></td>
<td>(0.71 to 1.41)</td>
<td>(0.95 to 1.40)</td>
</tr>
<tr>
<td>Neonatal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>1.17</td>
<td>1.09</td>
<td>0.60</td>
<td>1.18</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>(1.02 to 1.34)</td>
<td>(0.48 to 2.51)</td>
<td></td>
<td>(0.91 to 1.53)</td>
<td>(0.95 to 1.38)</td>
</tr>
<tr>
<td>Macrosomia</td>
<td>1.70</td>
<td>1.47</td>
<td>0.21</td>
<td>1.70</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>(0.81 to 3.56)</td>
<td>(1.17 to 1.84)</td>
<td></td>
<td>(1.06 to 2.12)</td>
<td>(0.30 to 5.24)</td>
</tr>
<tr>
<td>LGA</td>
<td>1.50</td>
<td>1.58</td>
<td>0.43</td>
<td>1.50</td>
<td>1.58</td>
</tr>
<tr>
<td></td>
<td>(0.99 to 2.53)</td>
<td>(1.16 to 2.72)</td>
<td></td>
<td>(1.09 to 2.53)</td>
<td>(0.99 to 2.53)</td>
</tr>
<tr>
<td>SGA</td>
<td>1.00</td>
<td>0.83</td>
<td>0.74</td>
<td>1.00</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>(0.55 to 1.23)</td>
<td>(0.55 to 1.23)</td>
<td></td>
<td>(0.95 to 1.40)</td>
<td>(0.95 to 1.40)</td>
</tr>
<tr>
<td>NICU admission</td>
<td>1.00</td>
<td>0.82</td>
<td>0.74</td>
<td>1.00</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>(0.48 to 1.35)</td>
<td>(0.55 to 1.23)</td>
<td></td>
<td>(0.95 to 1.40)</td>
<td>(0.95 to 1.40)</td>
</tr>
</tbody>
</table>

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; GGT=glycemic threshold test; GGA=large for gestational age; SGA=small for gestational age; NICU=neonatal intensive care unit; NA=calculation of effect estimates not applicable.

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

*Catalano et al18 was omitted when performing subgroup analysis of pre-eclampsia and large for gestational age according to country status because the study was conducted in multiple cross-national centres.

### Discussion

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 various adverse outcomes (10 studies).

To examine the heterogeneity conferred by different diagnostic criteria, we categorized the studies by use of insulin. Insulin is used to control glucose concentrations in the context of a positive linear association between glucose and adverse outcomes. We applied meta-regression models to evaluate the modification power of the proportion of patients who had received insulin use, insulin use, insulin use not reported. The meta-regression showed that the proportion of patients who had received insulin use, insulin use, insulin use not reported. The study was a comprehensive analysis, quantifying the associations between gestational diabetes mellitus and adverse outcomes of pregnancy, and would facilitate counselling of women with gestational diabetes mellitus and adverse outcomes of pregnancy. The study was a comprehensive analysis, quantifying the associations between gestational diabetes mellitus and adverse outcomes of pregnancy. 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 various adverse outcomes (10 studies).

We found evidence of a small study effect only for the modification power of the proportion of patients who had received insulin use, insulin use, insulin use not reported. The study was a comprehensive analysis, quantifying the associations between gestational diabetes mellitus and adverse outcomes of pregnancy. 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 various adverse outcomes (10 studies).

### Conclusion

The pooled estimate effect became not significantly different when a study was omitted, however (fig S5). We found evidence of a small study effect only for the modification power of the proportion of patients who had received insulin use, insulin use, insulin use not reported. The study was a comprehensive analysis, quantifying the associations between gestational diabetes mellitus and adverse outcomes of pregnancy. 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 various adverse outcomes (10 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)\textsuperscript{181} and the American Diabetes Association (2020).\textsuperscript{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,\textsuperscript{183,184} macrosomia,\textsuperscript{185,186} or respiratory distress syndrome.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\%\textsuperscript{191}). 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.\textsuperscript{126} Our study identified a 1.24-1.66-fold greater odds of pre-eclampsia between patients with and without gestational diabetes mellitus, which was similar to previous results.\textsuperscript{191}

### Strengths and limitations of the study

Our study included more studies than previous meta-analyses 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 pre-existing 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

### 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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Country status</th>
<th>Overall risk</th>
<th>Diagnostic criteria</th>
<th>Screening method</th>
<th>P value</th>
<th>Universal one step</th>
<th>Universal GCT</th>
<th>Selective</th>
<th>P value</th>
</tr>
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<tr>
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<td>Low</td>
<td>CC</td>
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<td>1.70</td>
<td>1.77</td>
<td>0.44</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
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<td>P value</td>
<td>IADPSG</td>
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<td>1.67</td>
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<td>1.10</td>
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</tr>
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<td>2</td>
<td>1.44</td>
<td>1.77</td>
<td>0.44</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

1 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.
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.

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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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