Hyperglycaemia and risk of adverse perinatal outcomes: A systematic review and meta-analysis

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, 5 sup File 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 and 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7 and Supp File

PRISMA 2009 Checklist

			2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, Figure 1and Table 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supp Fig 1-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary File 1. Full MEDLINE Search strategy

1 (pregnancy adj4 diabetes).ti,ab. (4082)
2 (gestational adj4 diabetes).ti,ab. (8108)
3 exp DIABETES, GESTATIONAL/ (7439)
4 gdm.ti,ab. (3272)
5 (glucose adj4 (pregnan* or gestation* or natal or maternal)).ti,ab. (3469)
6 1 or 2 or 3 or 4 or 5 (15075)
7 macrosomia.ti,ab. (2314)
8 exp FETAL MACROSOMIA/ (1826)
9 7 or 8 (3157)
10 exp BIRTH INJURIES/ (4937)
11 ((perinatal or labor or labour or birth) adj4 trauma).ti,ab. (1355)
12 ((perinatal or labor or labour or birth) adj4 injur*).ti,ab. (2542)
13 ((perinatal or labor or labour or birth) adj4 complication*1).ti,ab. (4372)
14 exp OBSTETRIC LABOR COMPLICATIONS/ (53369)
15 *DYSTOCIA/ (1902)
16 (shoulder adj4 dystocia).ti,ab. (1021)
17 (fracture*1 adj4 clavicle*1).ti,ab. (1218)
18 (fracture*1 adj4 humerus).ti,ab. (3451)
19 (fracture*1 adj4 shoulder*1).ti,ab. (753)
20 (fracture*1 adj4 arm*1).ti,ab. (454)
21 "erb* palsy".ti,ab. (185)
22 neuropath*.ti,ab. (97784)
23 exp BRACHIAL PLEXUS NEUROPATHIES/ (2817)
24 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (168258)
25 (preeclampsia or pre-eclampsia).ti,ab. (20669)
26 exp PRE-ECLAMPSIA/ (24509)
27 25 or 26 (31679)
28 (heart adj4 (disorder*1 or disease*1)).ti,ab. (142562)
29 (cardiovascular adj4 (disorder*1 or disease*1)).ti,ab. (119950)
30 (cardiac adj4 (disorder*1 or disease*1)).ti,ab. (26958)
31 exp CARDIOVASCULAR DISEASES/ (1944605)
32 exp HEART DISEASES/ (922916)
33 28 or 29 or 30 or 31 or 32 (2024083)
34 exp HYPOGLYCEMIA/ (22500)
35 hypoglyc*.ti,ab. (42033)
36 34 or 35 (48692)
37 exp DIABETES MELLITUS, TYPE 2/ (90640)
38 (("type 2" or "' type AND two" or "type II") adj4 diabet*).ti,ab. (87156)
39 37 or 38 (121847)
40 exp OBESITY/ (152662)
41 (obesity or obese or bmi or "body mass" or overweight).ti,ab. (311123)

42 40 or 41 (343012)
43 9 or 24 or 27 or 33 or 36 or 39 or 42 (2561831)
44 (offspring or son*1 or daughter*1 or child or children or pediatric*1 or paediatric*1).ti,ab. (1177569)
45 exp CHILD OF IMPAIRED PARENTS/ (4392)
46 exp CHILD/ (1595153)
47 (maternal or mother*2).ti,ab. (288181)
48 exp MOTHERS/ (27857)
49 44 or 45 or 46 or 47 or 48 (2246955)
50 43 and 49 (274768)
51 6 and 50 (4840)
52 51 not (animals/ not humans/) (4622)

Supplementary File 2. Statistical methods

To model the associations between outcomes and glucose levels a log-linear relationship between risk and outcome was assumed; that is, the log odds of the outcome was assumed to vary linearly with glucose level. This association was modelled separately for each outcome and glucose test. Formally the models had the form:

$$\log\left(\frac{p_{ijkl}}{1-p_{ijkl}}\right) = \phi_{ijkl} + \theta_{ijkl} G_{ijkl}$$
$$\theta_{ijkl} \sim N\left(\theta^{*}_{jkl}, \tau^{2}_{jkl}\right)$$

where i indicates study, j glucose test (eg. fasting 75g OGTT), k the outcome of interest (eg. macrosomia) and l the glucose category. Then p_{ijkl} is the probability of having the outcome in the relevant glucose category, G_{ijkl} is the typical glucose level in that category. Hence ϕ_{ijkl} is the baseline log odds of the outcome in study I, which are assumed to be independent across stuidies. Also, $\theta_{i\,ijkl}$ is the association between glucose and outcome, in terms of the log odds of outcome per 1 mmol/L increase in glucose, assumed to have a random effect across studies to allow for heterogeneity in the trend. The model was fitted in R using the lme4 package for mixed effect regression modelling.

For outcomes reported in only one study the same logistic regression model was used without the meta-analysis across studies or the random effects. That is:

$$\log\left(\frac{p_l}{1-p_l}\right) = \phi_l + \theta_l G_l$$

To test the assumption of linearity a term in glucose squared was added to each model:

$$\log\left(\frac{p_{ijkl}}{1-p_{ijkl}}\right) = \phi_{ijkl} + \theta_{ijkl} G_{ijkl} + \gamma_{jkl} G^{2}_{ijkl}$$
$$\theta_{ijkl} \sim N\left(\theta^{*}_{jkl}, \tau^{2}_{jkl}\right)$$

With the glucose squared terms γ modelled as fixed effects. Any deviation from linearity would be indicated by finding a statistically significant γ term.

Supplementary Table 1. Results of the risk of bias assessment

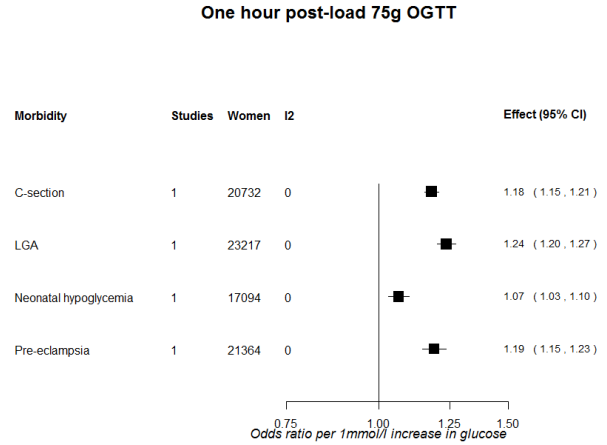
Study	Year of publication	Prospective or retrospective	Representative population	Loss to follow up	Consistent glucose measurement	Consistent outcome measurement	'Blinding'		Selective reporting	Adjusted results presented
							of glucose measurements	of outcomes		
Atlantic DIP	N/A	P	Low	Low	Low	Low	High	High	Low	Low
Aris	2014	P	Low	Low	Low	Low	Unclear	Unclear	Low	Low
BiB	N/A	P	Low	Low	Low	Low	High	High	Low	Low
Carr	2011	R	Low/moderate	Low	Low	Low	High	High	Low	Low
Chadna	2006	R	Unclear	Low	Unclear	Unclear	High	High	Unclear	High
Cheng	2007	R	Low	Low	Low	Unclear	High	High	Unclear	Low
Figueroa	2013	Secondary analysis of RCT data	Low (but subset of trial)	Low	Low	Low	Unclear	Unclear	Low	Low
HAPO	2008	P	Low	Low	Low	Low	Low	Low	Low	Low
HAPO	2010	P	Low	Low	Low	Low	Low	Low	Low	Low
Hillier	2008	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Low
Jensen[1]	2001	R	High (higher risk group)	Low	Low	Low	High	High	Low	High
Kerenyi	2009	Unclear	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low
Landon	2011	Secondary analyses of RCT data	Low (subset of trial)	Low	Low	Low	Unclear	Low	Low	Low
Lao	2003	R	Low (Chinese)	Low	Low	Low	High	High	Low	High
Little	1990	P	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	High
Lurie	1998	P	Low	Low	Low	Low	Unclear	Low	Low	High
Metzger	2010	P	Low	Low	Low	Low	Low	Low	Low	Low
Moses	1995	P	Low	Unclear	Low	Low	Unclear	Unclear	Low	High
Ong	2008	R	Low	Low	Low	Unclear	High	High	Unclear	High
Pettitt	1980	P	High (Pima Indian)	Low	Low	Low	Unclear	Unclear	Unclear	High
Riskin-Mashia	2009	R	Low	Low	Low	Low	High	High	Low	Limited adjustment
Savona-Ventura	2010	R	Low	Low	Low	Unclear	High	High	Unclear	High
Scholl	2001	P	Low	Low	Low	Low	Unclear	Unclear	Low	Low
Sermer	1995	P	Low	Low	Low	Low	Low	Low	Low	High
~~Subramaniam~~	~~2014~~	~~R~~	~~Low~~	~~Low~~	~~Low~~	~~Unclear~~	~~High~~	~~High~~	~~Unclear~~	~~Low~~
Tallarigo	1986	Unclear	Low	Low	Low	Low	Unclear	Unclear	Low	High
Witter	1988	R	Low, but young age group	Low	Low	Low	High	High	Low	High
Yee	2011	R	Low	Low	Low	Low	High	High	Low	Low

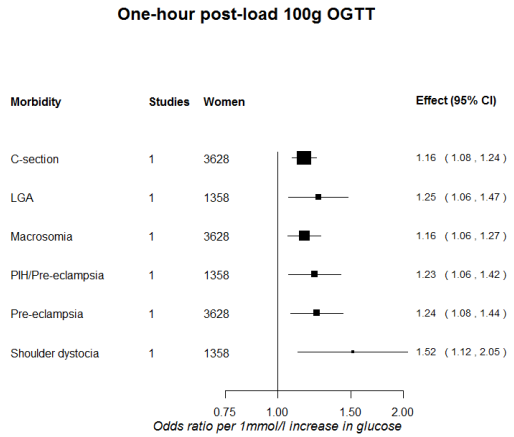
R=retrospective, P=prospective,

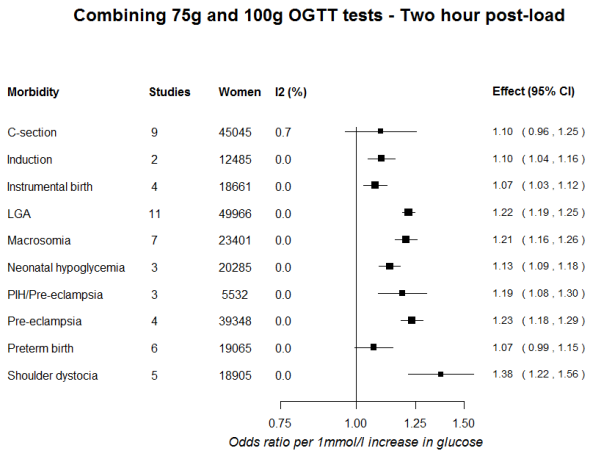
Supplementary Table 2. Analysis testing for linearity of association between glucose levels and outcomes

Outcome	Number of studies	Log odds ratio of glucose squared	95% CI	P-value
Fasting 75g OGTT				
C-section	6	-0.115	(-0.25 - 0.02)	0.1
Induction	3	-0.197	(-0.52 - 0.13)	0.23
Instrumental birth	3	0.107	(-0.21 - 0.42)	0.5
LGA	7	-0.02	(-0.16 - 0.12)	0.77
Macrosomia	6	-0.18	(-0.39 - 0.03)	0.09
Neonatal hypoglycemia	2	0.29	(0.05 - 0.53)	0.02
PIH/Pre-eclampsia	3	0.461	(0.03 - 0.9)	0.04
Pre-eclampsia	4	-0.005	(-0.28 - 0.27)	0.97
Preterm birth	3	0.577	(0.09 - 1.07)	0.02
Shoulder dystocia	4	-0.142	(-1.06 - 0.78)	0.76
50g OGCT				
C-section	7	-0.029	(-0.07 - 0.01)	0.18
Instrumental birth	2	-0.008	(-0.08 - 0.07)	0.84
LGA	4	-0.044	(-0.1 - 0.01)	0.11
Macrosomia	7	-0.004	(-0.02 - 0.02)	0.69
Neonatal hypoglycemia	3	0.047	(-0.18 - 0.27)	0.68
Pre-eclampsia	6	-0.082	(-0.15 - -0.02)	0.01
Preterm birth	2	0.021	(-0.05 - 0.09)	0.55
Shoulder dystocia	2	-0.113	(-0.25 - 0.03)	0.12
2 hour 75g OGTT				
C-section	9	-0.016	(-0.03 – 0.00)	0.06
Induction	3	0.006	(-0.04 - 0.05)	0.81
Instrumental birth	4	-0.01	(-0.05 - 0.03)	0.65
LGA	11	0.004	(-0.01 - 0.02)	0.67
Macrosomia	7	0.006	(-0.03 - 0.05)	0.77
Neonatal hypoglycemia	3	0.002	(-0.02 - 0.03)	0.91
PIH/Pre-eclampsia	3	0.02	(-0.07 - 0.11)	0.67
Pre-eclampsia	4	-0.026	(-0.05 – 0.00)	0.05
Preterm birth	6	0.009	(-0.05 - 0.07)	0.78
Shoulder dystocia	5	-0.067	(-0.19 - 0.06)	0.29

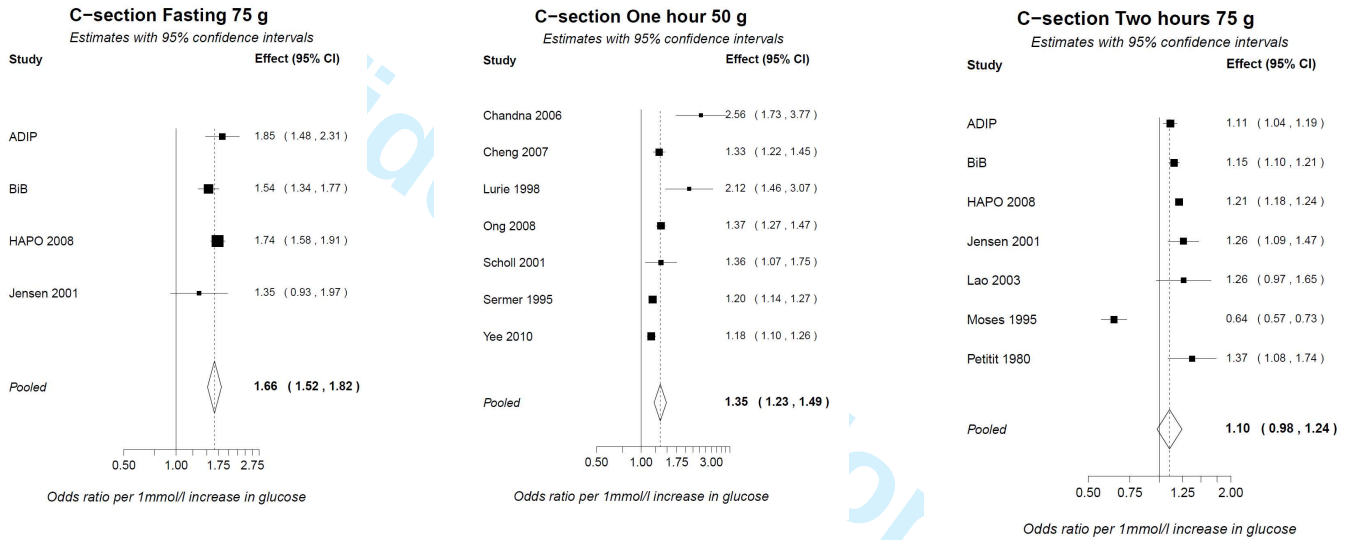
Supplementary Figure 1. Odd ratios for outcomes at one and two-hour and combined for the 75g and 100g post-load OGTT



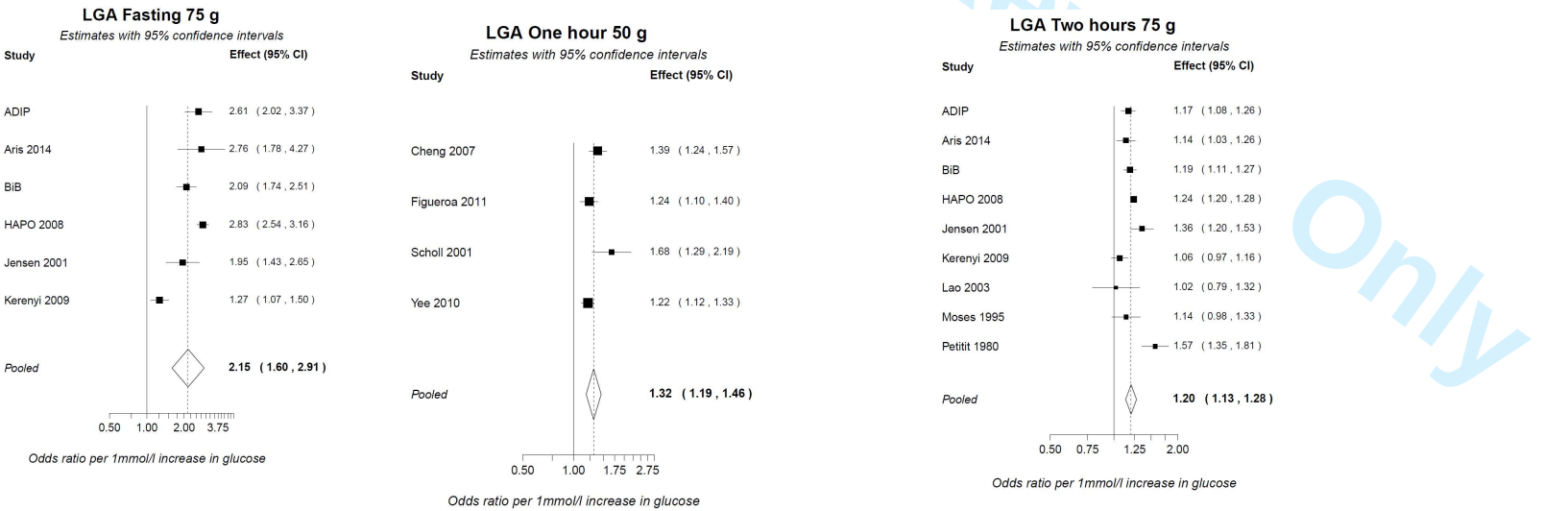




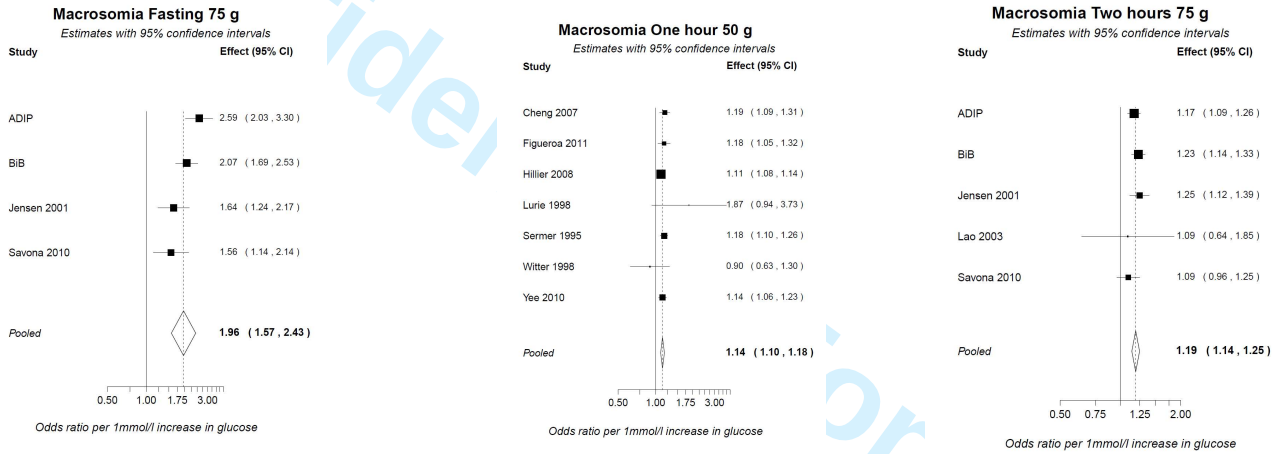
Supplementary Figure 2. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and Caesarean section



Supplementary Figure 3. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and Large for gestational age

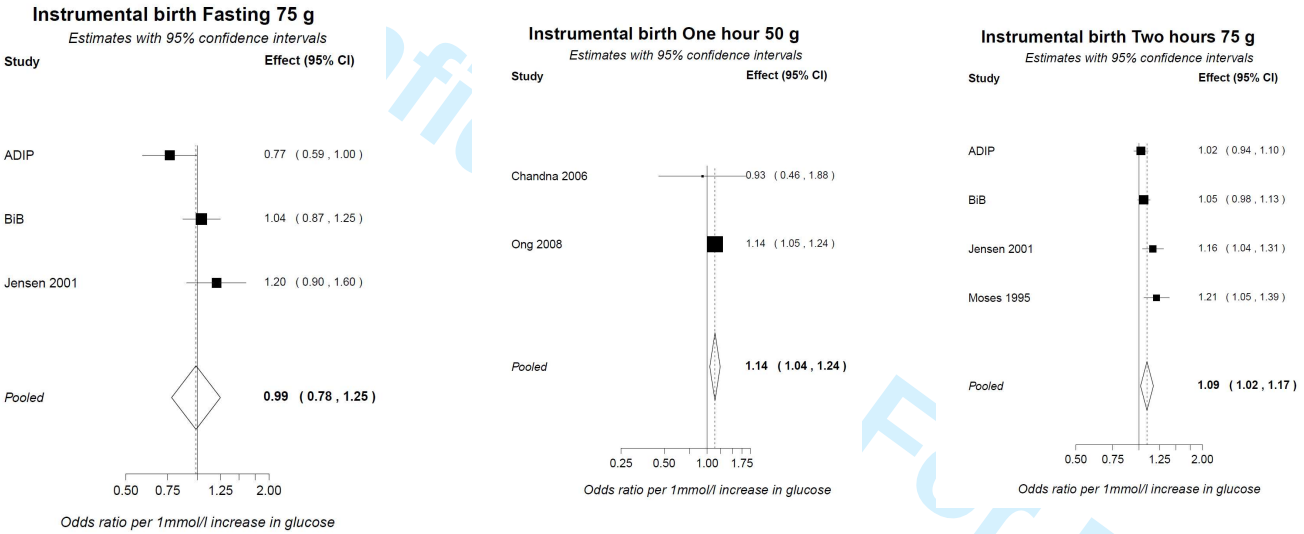


Supplementary Figure 4. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and macrosomia

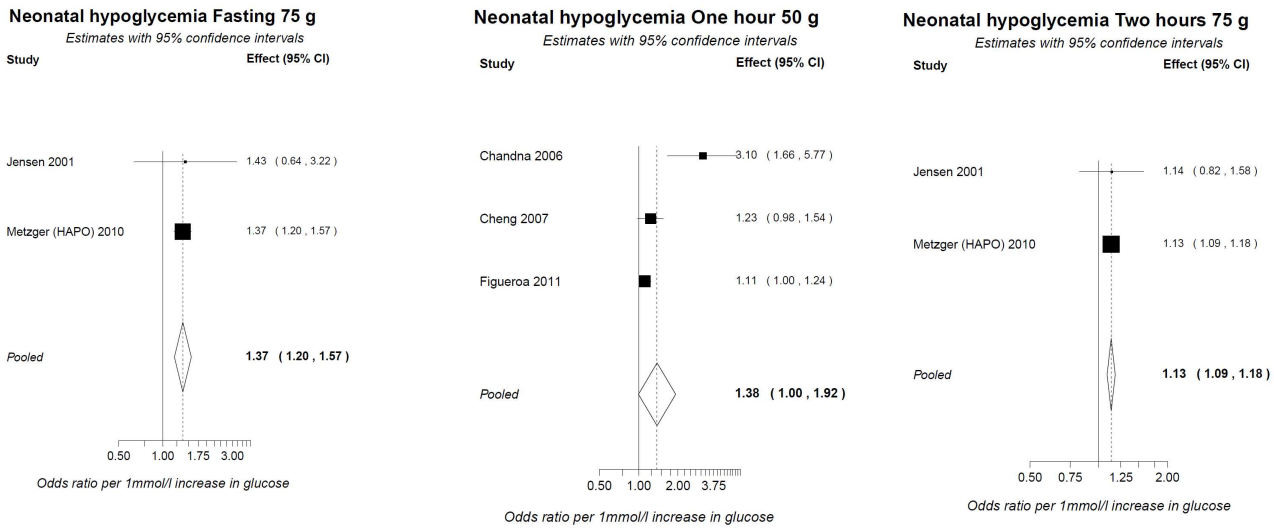


Supplementary Figure 5. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and induction of labour

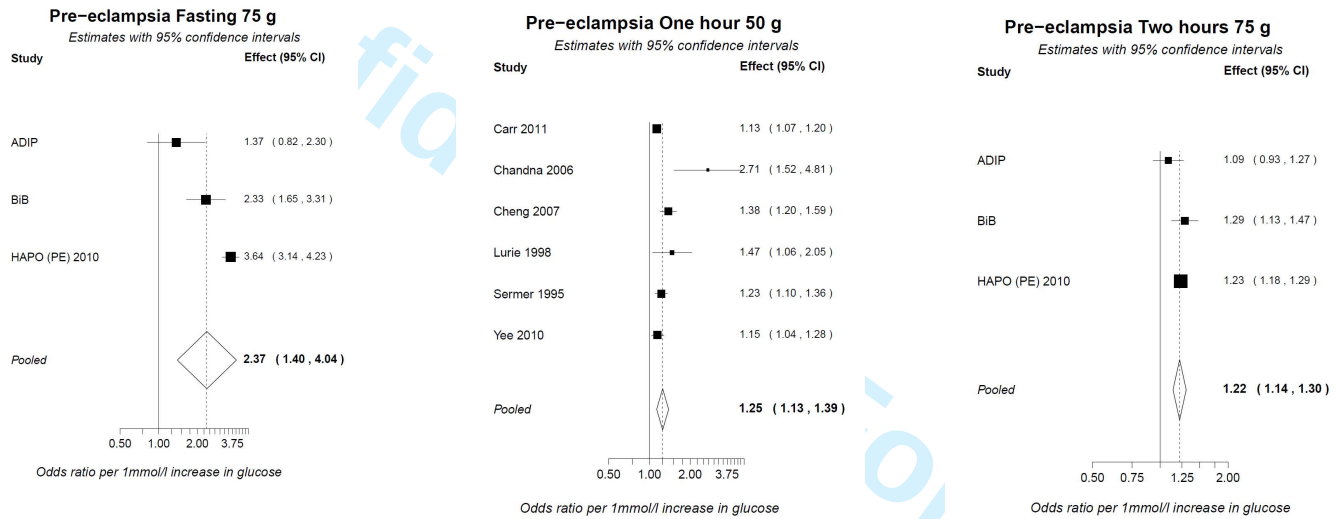
Supplementary Figure 6. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and instrumental birth



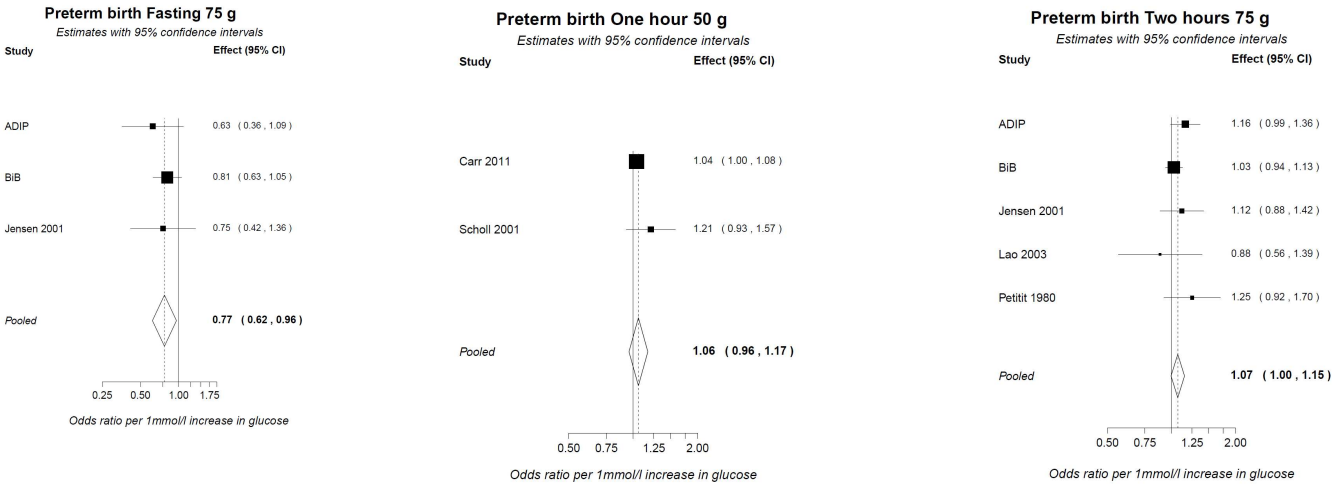
Supplementary Figure 7. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and macrosomia



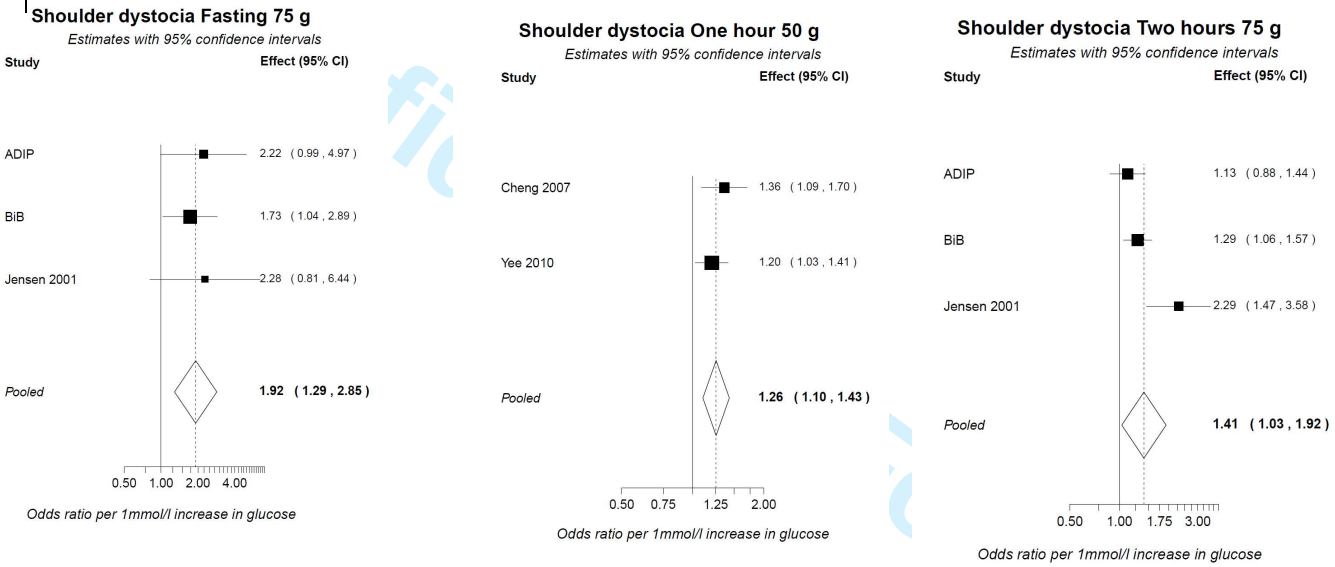
Supplementary Figure 8. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and pre-eclampsia



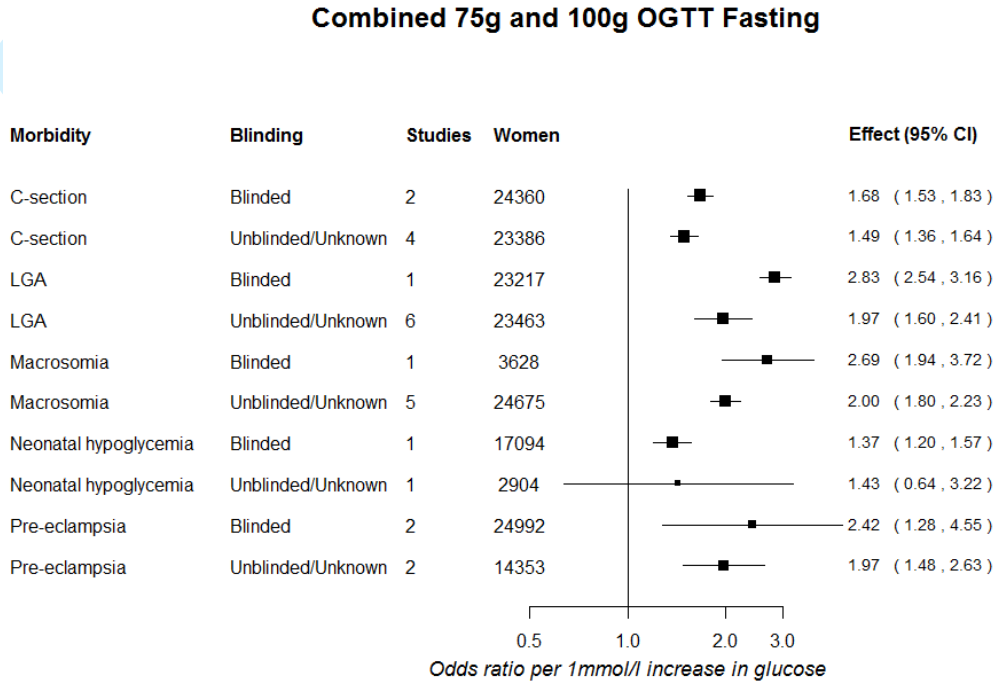
Supplementary Figure 9. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and preterm birth



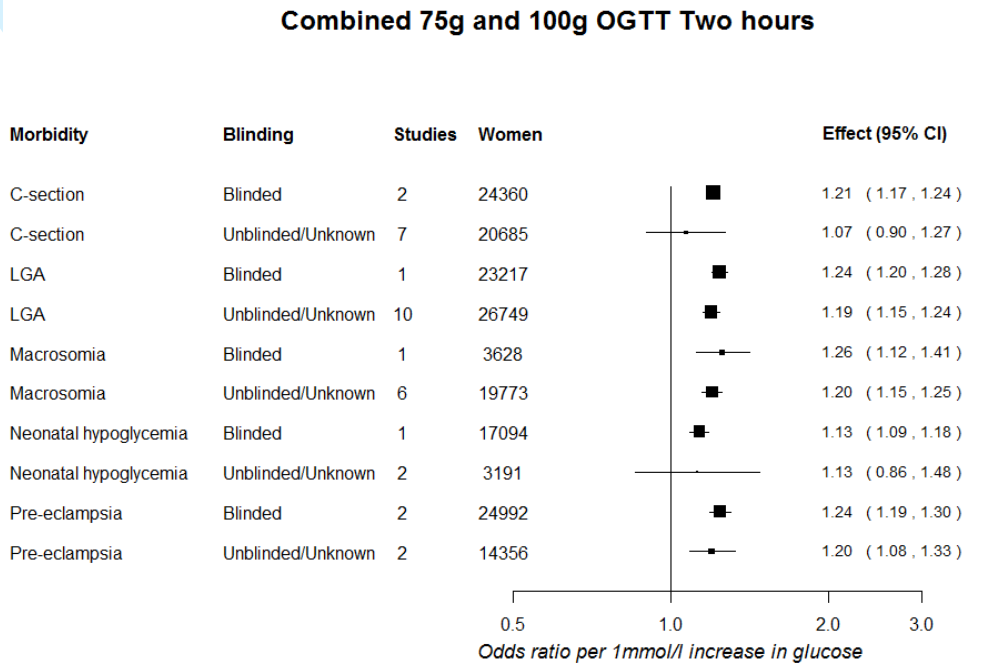
Supplementary Figure 10. Associations for fasting, one-hour post-load 50g OGCT and two-hour post-load 75g OGTT and shoulder dystocia



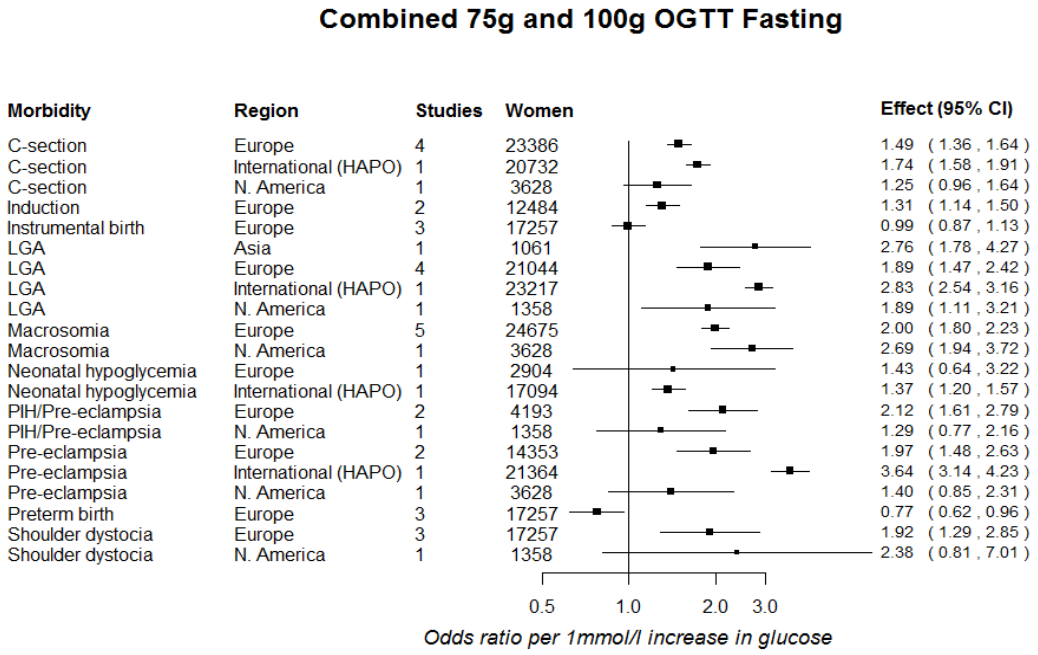
Supplementary Figure 11. Odd ratios for outcomes at fasting 75g and 100g OGTT combined and grouped by whether blinded or unblinded/unclear



Supplementary Figure 12. Odd ratios for outcomes at two-hour post-load 75g and 100g OGTT combined and grouped by whether blinded or unblinded/unclear

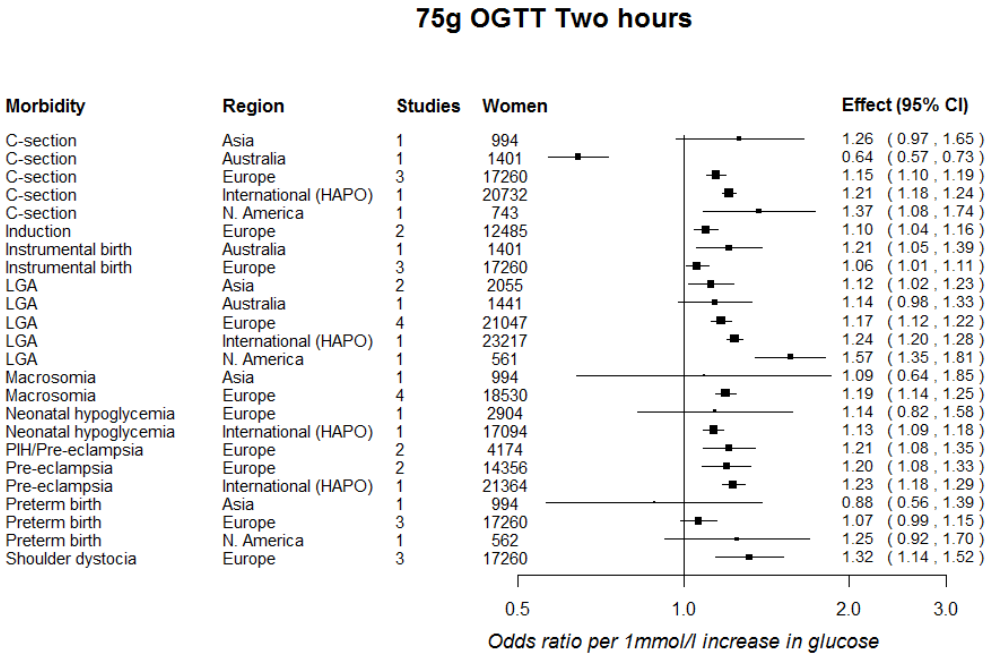


Supplementary Figure 13. Odd ratios for outcomes at fasting 75g and 100g OGTT combined and grouped by region



N. America (North America= Canada and USA),[2] Multinational,[3-5] Asia (Singapore, China),[6,7] Europe (Denmark, Hungry, Malta UK),[1,8-11] Australia[12]

Supplementary Figure 14. Odd ratios for outcomes at two-hour post-load 75g OGTT grouped by region



N. America (North America= Canada and USA),[2] Multinational,[3-5] Asia (Singapore, China),[6,7] Europe (Denmark, Hungry, Malta UK),[1,8-11] Australia[12]

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Hyperglycaemia and risk of adverse perinatal outcomes: A systematic review and meta-analysis

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Abstract

Objectives: Assess the association between maternal l glucose levels and adverse perinatal outcomes in women without gestational or existing diabetes, to determine whether clear thresholds for identifying women at risk of perinatal outcomes can be identified.

Design: Systematic review and meta-analysis of prospective cohort studies and control arms of randomised trials

Data sources: Databases including MEDLINE and Embase were searched up to October 2014 and combined with individual participant data (IPD) from two additional birth cohorts.

Eligibility criteria for selecting studies: Studies including pregnant women with oral glucose tolerance (OGTT) or challenge test (OGCT) results, with data on at least one adverse perinatal outcome.

Appraisal and Data extraction: Glucose test results were extracted for OGCT (50g) and OGTT (75g and 100g) at fasting, one and two-hour post-load timings. Data were extracted on: induction of labour (IOL); Caesarean; instrumental; pregnancy-induced hypertension; pre-eclampsia; macrosomia ; large for gestational age (LGA); preterm birth; birth injury and neonatal hypoglycaemia. Risk of bias was assessed using a modified version of the critical appraisal skills programme and quality in prognostic studies tools.

Results: We included 23 reports from 25 published studies and two IPD cohorts, with up to 207,172 women (numbers varied by the test and outcome analysed in the meta-analyses). Overall most studies were judged as having a low risk of bias. There were positive linear associations for all glucose exposures with Caesarean-section, IOL, LGA, macrosomia and shoulder dystocia, across the distribution of glucose. There was no clear evidence of a threshold effect. In general, associations were stronger for fasting compared with post-load glucose. For example, the odds ratios for LGA per 1mmol/L of fasting and two-hour post-load glucose (following a 75g OGTT) were 2.15 (95% CI 1.60 to 2.91,), and 1.20 (95% CI 1.13 to 1.28), respectively. Heterogeneity was very low between studies in all analyses.

Conclusions: This review and meta-analysis identified a large number of studies, in a variety of countries. We have demonstrated a graded linear association between fasting and post-load glucose, across the whole glucose distribution, and the majority of adverse perinatal outcomes in women without pre-existing or gestational diabetes. The lack of a clear glucose threshold at which risk increases means that decisions regarding thresholds for diagnosing gestational diabetes are somewhat arbitrary. We suggest that research should now investigate the clinical and cost-effectiveness of applying different glucose thresholds for gestational diabetes diagnosis on perinatal and longer-term outcomes.

Systematic Review Registration: PROSPERO CRD42013004608

Lay Plain English summary

Study question: We examined the association between blood glucose (sugar) levels in pregnant women without diabetes and birth outcomes, such as whether they needed a Caesarean section.

Methods: We searched for all studies that had looked at the association between pregnancy blood glucose and outcomes for mother and her baby.

Study answer and limitations: We found 27 reports from 25 studies with information on up to 207,172 women and their infants. Most of the studies were well conducted, but for some the doctors and midwives looking after the women knew their blood glucose levels and that could have affected how they treated the women and as a result the outcomes. When we combined results from all studies there was a straight line association between glucose levels and Caesarean-section, induction of labour, a heavy baby and shoulder dystocia (the baby getting stuck as their mother gives birth). This means, for each blood glucose increase, the risk of these problems increased by a similar amount, for example Figure 3 shows how the risk of Caesarean section increases with each increase in maternal glucose across all included studies. This straight line pattern was similar when we looked at studies separately by different geographical area across the world and when we looked between those studies where only researchers knew the blood glucose levels and those where the person looking after the women knew them.

What this study adds: These results show that there is no obvious level to diagnose gestational diabetes. What we now need to work out is what the best threshold is for balancing the benefit of preventing pregnancy and birth problems by treating women with high blood glucose levels against the problems of overtreating some women and causing problems.

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Background

Gestational diabetes (GDM), defined as hyperglycaemia that is first identified during pregnancy, increases the risk of a range of adverse perinatal outcomes including macrosomia and Caesarean section.[1] There is also growing evidence that the longer-term health of the mother and infant may be adversely affected.[2-4] The primary aim of diagnosing GDM is to identify those at risk of maternal or offspring short- or longer-term adverse outcomes. Whilst traditionally the primary aim was to identify women at risk of type 2 diabetes, the recent Independent Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed glucose thresholds were calculated to identify adverse perinatal outcomes with the ultimate aim of preventing future offspring obesity.[5] Although treatment of GDM can reduce the risk of perinatal outcomes,[6, 7] there is uncertainty regarding the optimal glucose threshold (at oral glucose tolerance testing (OGTT)) that should define GDM. Findings from the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study showed graded linear increases in large for gestational age (LGA), large skinfold thicknesses, high cord-blood C-peptide and several other important perinatal outcomes, across the whole distribution of fasting and post-load glucose in women without existing diabetes or GDM.[8] Given the lack of any clear threshold for increased risk, the IADPSG calculated thresholds using the HAPO data as the glucose values at which odds for birthweight, cord C-peptide, and percent body fat above the 90th percentile reached 1.75 times the estimated odds of these outcomes above mean glucose values.[5] The IADPSG criteria for diagnosing GDM have been endorsed by the World Health Organization (WHO),[9] and more recently by the International Federation of Gynecology and Obstetrics (FIGO),[10] but not by all countries or institutions, for example UK National Institute of Health and Care Excellence (NICE)[11] and American College of Obstetrics and Gynaecology[12] have not endorsed these criteria. Whilst HAPO is large, multi-centred and well conducted, results were not presented for each country or by ethnicity and new diagnostic criteria would benefit from being based on all available knowledge rather than from just one study.

The question of whether the shape and magnitude of association would be seen in all populations remains unanswered. We recently analysed a cohort of white British and south Asian women[13] and found that the HAPO/IADPSG findings were replicated in the white British women, but in the south Asian women our results suggested lower fasting and post-load glucose levels to achieve the same odds of identifying adverse perinatal outcomes were required. We also noted that the IADPSG thresholds for post-load glucose were importantly influenced by the fact that the post-load threshold used by HAPO to exclude women with GDM, was much higher than that used in clinical practice currently and also at the time of starting that study. A further issue is whether different thresholds to those selected by the IADPSG would be implied for a different set of perinatal outcomes to those that were the focus of the IADPSG criteria. In particular the IADPSG did not consider important clinical

outcomes such as hypertensive disorders of pregnancy, the requirement for induction of labour, Caesarean-section, whether the infant suffered from shoulder dystocia, neonatal hypoglycaemia and/or required admission to neonatal intensive care, which are the key clinical criteria that clinicians and pregnant women are concerned about. To address these issues we conducted a systematic search of the literature to fully appreciate the available evidence and the degree to which these questions had been examined in different populations. Wherever possible we pooled data and conducted appropriate sensitivity analyses to investigate any potential study and population effects.

Methods

We conducted this systematic review and meta-analysis in accordance with Cochrane Systematic Reviews[14] and the Centre for Reviews and Dissemination recommendations,[15] we have reported our findings following the PRISMA reporting guidelines.[16]

Patient involvement

As this is a systematic review and meta-analyses using conventional methods we did not seek the views of women in the design or conduct of our study. The outcomes we included in this review were those identified by the Cochrane Pregnancy and Childbirth Group (CPCG) as being essential for reviews of diabetes in pregnancy. The CPCG includes relevant patients/service users (in this case women of reproductive age and/or who have experience gestational diabetes) who contribute to decisions about which outcomes are included in the standard list

Search strategy

Searches were undertaken and three reviewers (DF, MS and SG) independently assessed the literature for inclusion. Data from eligible studies were combined with data from two additional birth cohort studies; one of which was the Born in Bradford cohort that we have recently published results from[13] and the Atlantic Diabetes in Pregnancy cohort[17] for which we also had access to individual participant data.

Search: identification of studies from the Systematic Review

We searched the literature in September 2013, and again in October 2014, using MEDLINE and MEDLINE in-Process, Embase, CINAHL Plus, The Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews (CDSR), The Database of Abstracts of Reviews of Effects (DARE), The Health Technology Assessment database (HTA), NHS Economic Evaluation Database (NHS EED), and The Cochrane Methodology Register (CMR). The full MEDLINE search strategy is shown in supplementary File 1 and was appropriately translated for the other databases.

Search: identification of studies from unpublished individual participant data

We had access to three cohort studies with individual participant data (IPD): (1) Born in Bradford (BiB);[18] (2) Atlantic Diabetes in Pregnancy (Atlantic-DIP);[17] (3) the Warwick / Coventry cohort.[19] Warwick / Coventry had insufficient complete case data and were not included.

Born in Bradford is a prospective birth cohort, the study methods have been previously described.[20] All women booked for delivery in Bradford are offered a 75g oral glucose tolerance test (OGTT) at around 26–28 weeks' gestation, and women were recruited mainly at their OGTT appointment.[13] Ethics approval was obtained (07/H1302/112). All participants provided informed written consent. The Atlantic DIP is a multi-centre cohort study comprising of a partnership of five hospitals at the Irish Atlantic seaboard. It was set up in 2006 with a focus on research, audit, clinical care, and professional and patient education for diabetes in pregnancy.[21] As with the BiB cohort, women were offered a 75g OGTT at 24-28 weeks gestation from September 2006 to April 2012. Research ethics committee approval was obtained from participating centres,[22] and data on women with singleton pregnancies were collected from study entry until 12 weeks postpartum.

Study selection: Inclusion and exclusion criteria

To be eligible, studies had to include pregnant women who had undergone an OGTT (comprising of fasted , one, two, three-hour post-load samples) or oral glucose challenge test (OGCT) (comprising a non-fasted one-hour post-load sample) with measures of fasting and/or post-load glucose. Women were excluded from the analyses if they had pre-existing diabetes or were diagnosed with GDM, using various criteria thresholds set by each included study (see Table 1 for criteria and Tables 2 to 4 for glucose thresholds). Women with pre-existing diabetes or GDM were excluded from this study because they would have received treatment and this would have influenced the natural association between glucose and outcome. Studies had to provide data on at least one perinatal adverse outcome in a form that could be included in the meta-analyses (number of women and events in each glucose category).

Data extraction and quality assessment

Data were extracted by two reviewers (MS and SG) who also conducted the quality assessments. Any disagreements between reviewers were resolved through discussion, including with other authors as necessary. Risk of bias in the included studies was assessed using a modified version of the Critical Appraisal Skills Programme (CASP) and Quality in Prognostic Studies (QUIPS) assessment tools, designed for observational studies of association and prediction.[23] When undertaking quality assessment of the studies, we considered the: representative nature of the included population; loss to follow-up; consistency of glucose measurement and outcome assessment; blinding of participants and

medical practitioners to glucose level; blinding of outcome assessors to glucose level and selective reporting of outcomes. We also extracted information on any adjustment for covariates, though our interest here is on a diagnostic threshold of glucose and in clinical practice this would not be adjusted for, our aim was therefore to primarily use unadjusted associations. Each criterion was classified as being at low, high or unclear risk of bias.

All of the studies reported numbers of women and numbers of adverse outcomes in a range of glucose categories. Data on these glucose categories (e.g. range and/or median glucose for each category, numbers of women and of outcomes in each category) were extracted for OGTT (75g and 100g test (fasting, one-hour and two-hour post-load)) and one-hour 50g OGCT. Data were extracted for the following perinatal outcomes: induction of labour; Caesarean section (elective or emergency); instrumental delivery (ventouse or forceps); pregnancy-induced hypertension (PIH) (pre-eclampsia; macrosomia (birth weight $\geq$4kg); large for gestational age (LGA) ($\geq 90^{th}$ birth weight percentile); preterm birth (<37 weeks gestation); birth injury/trauma (shoulder dystocia, Erbs palsy, fractured clavicle) and neonatal hypoglycaemia. Socio-demographic and clinical data, such as age range of participants, how those with diabetes were excluded and parity, were also extracted.

For the two studies with IPD we created seven glucose categories for both fasting and two-hour post-load glucose levels, designed to include approximately equal numbers of women in each category. The numbers of women and numbers of adverse outcomes, in each glucose category, were then calculated for each outcome, to generate summary data similar to that extracted from publications.

Statistical analysis

Analyses were based on the number of women and number of adverse perinatal outcomes in each glucose category in each study. Using these raw numbers means that our results are not adjusted for any covariates. However, our aim was to determine whether there were clear glucose thresholds for diagnosing GDM across a range of pregnancy and perinatal outcomes and not to assess causality. Thus, confounding is not a concern and reflects clinical practice (where glucose thresholds without adjustment are used) the lack of any adjustment for covariates is therefore appropriate here. We explored whether results were heterogeneous (differ statistically between studies) and if so, whether this related to characteristics that differ between participants in the different studies, which was relevant to our aim of determining whether the HAPO/IADPSG results were generalisable.

One study[24] presented only adjusted odds ratios (adjusted for maternal age, gestational age at enrolment and at delivery, parity, BMI, and race or ethnicity). With the exception of that one study all other results from all other studies were the unadjusted associations, that we wanted to address our question.

In order to determine whether any glucose threshold exists above which women or infants are at significantly greater risk of adverse perinatal outcomes, the validity of the assumption of a log-linear association between outcome and glucose was tested both by visual assessment (based on plotting the results from each study (Figures 3 to 11) and by using a model with an additional glucose-squared term. A statistically significant association with glucose squared would suggest a quadratic-curvilinear relationship.

Following our initial visual assessment of glucose and perinatal outcome plots, we modelled associations across studies in a "one-stage" hierarchical logistic regression analysis.[25] The numbers of women with an outcome event in each glucose category was regressed against the average glucose level in each category. Independent intercepts and random effects on the slopes across studies were included, to allow the baseline risk and the association between glucose level and outcome to vary between studies, thus accounting for any potential heterogeneity. Mixed effects logistical regression routines in R software were used for the modelling. We assessed the percentage of variance between study findings not due to chance by determining the I^2 statistic.[14] Where an outcome was reported in only one study we fitted the same logistic regression model, but without the meta-analysis component, to estimate the association between outcome and glucose level as for outcomes reported by several studies.

Associations were modelled separately for each outcome, glucose test (75g OGTT, 100g OGTT, 50g OCGT) and timing of the glucose measure (fasting, one-hour or two-hour post-load). These models produced a summary estimate across studies for the association between glucose and outcome in terms of the odds ratio (OR) of outcome per 1mmol/L increase in glucose. Full details of the statistical methods and models are provided in the Supplementary File 2.

To increase the number of studies and participants we combined the fasting glucose results from the 75g OGTT and 100g OGTT in meta-analyses using the logistic regression models described above because fasting glucose should not be affected by the subsequent glucose test load (75g or 100g). We also combined the 75g and 100g one-hour post-load results and the 75g and 100g two-hour post-load results, assuming the associations between glucose and outcomes were the same for both tests.

We conducted two sensitivity analyses: one excluding studies which had a high or unclear risk of surveillance and detection bias (lacked blinding) from analyses (leaving four published reports related to two studies.[8, 26-28] We also examined the influence of study population/region of residence on estimates using the 75g and 100g OGTT, by dividing studies into five categories (International, North

America, Europe, Asia, Australasia), and repeating the meta-analyses within each region. These regions were chosen once we had completed our search and are based on identified relevant studies.

Results

Details of included and excluded studies

Figure 1 shows the number of reports and studies identified and numbers included and excluded. After title and abstract screening, 125 study reports were obtained for full text review. After full text review 25 published reports detailing associations between perinatal outcomes and maternal glucose levels were included. At title and abstract screening, studies were excluded mainly because they were not answering the question we were examining. At full text screening, studies were mostly excluded because they did not present data (conference abstracts), did not report on any of our included outcomes, did not report outcomes by glucose levels or did not report data in a form that could be included or converted for inclusion in the meta-analyses. Published studies were combined with the two IPD cohorts; BiB and Atlantic DIP. Tables 2, 3 and 4 summarise the characteristics of the included publications and IPD cohorts.

Quality assessment

Generally, studies demonstrated a low risk of bias (Supplementary Table 1), with the exception of surveillance and detection bias which was high or unclear for all but four published reports related to two studies. Most studies recruited any pregnant women, without pre-existing diabetes or newly diagnosed GDM, often at the study hospital's GDM screening clinic. Few studies applied any further inclusion/exclusion criteria; so the study populations' are likely to be representative of the general obstetric population at the study site. Studies generally did not report comprehensive participant demographic details and did not report results by subgroups, including by ethnic groups. In studies that included a proportion of women with GDM and reported outcome separately, only data for those without GDM were extracted. The majority of studies were in Western populations from high income countries, with a small number from other populations, for example the Pima Indian population of Arizona. There was minimal loss to follow up in most studies. Studies diagnosed GDM (and excluded women) using both the one and two-step approach with either the 75g or 100g OGTT and a variety of glucose thresholds (Tables 3 and 4).

The main potential risk of bias was due to lack of blinding of glucose levels following OGTT. This could have resulted in surveillance or detection bias (and potentially to a self-fulfilling prophesy). For example, pregnancy surveillance may have been increased in women with higher glucose levels, which may have increased the likelihood of interventions including induction of labour or Caesarean section or the scrutiny with which other outcomes are determined, in comparison to those with lower glucose levels.

Linear associations of glucose with perinatal outcomes

Figure 2 shows the pooled results for the association of fasting glucose, one-hour post-load 50g OGCT, two-hour 75g OGTT and two-hour 100g OGTT with each perinatal outcome.

There were positive associations for all glucose exposures with Caesarean-section, induction of labour, LGA, macrosomia, and shoulder dystocia. In general for these outcomes, the magnitudes of association were stronger for fasting, compared with any of the post-load glucose measurements. Fasting glucose was also clearly inversely associated with preterm delivery, whereas the association of post-load glucose with this outcome was more inconsistent: weakly positive for 50g one-hour OGCT, weakly positive for the 75g two-hour OGTT and inverse with 100g two-hour OGTT; but for some of these, particularly the latter, the confidence intervals are wide and include the null. 50g one-hour post-load OGCT and 75g two-hour OGTT were positively associated with instrumental delivery. Whereas fasting glucose was not clearly associated with this outcome (no studies using a 100g OGTT reported this outcome). All glucose measurments, except the two-hour 100g post-load glucose from the OGTT, were positively associated with neonatal hypoglycaemia. The 75g two-hour post-load OGTT was positively associated with combined PIH/pre-eclampsia, but there was no consistent association of the 50g OGCT or 100g two-hour post-load OGTT with this outcome.

When we pooled two-hour post-load glucose associations with outcomes for studies that used either a 75g or a 100g OGTT, the pattern of associations were broadly similar to those when the two sets of studies were considered separately (Supplementary Figure 1).

Associations between glucose levels and outcomes were generally monotonic, suggesting linear associations across the distribution with no clear threshold at which risk substantially increases (Figures 3 to 11). The quadratic statistical tests largely supported the linear association, with some possible flattening of the positive association with PIH combined with pre-eclampsia or pre-eclampsia alone at the upper end of the post-load glucose distribution (Supplementary Table 2). Very few studies assessed one-hour post-load glucose for either 75g or 100g OGTT and only a subset of the outcomes were examined in those studies for this exposure. In general results for the one-hour post-load were broadly similar to those for the two-hour post-load, but given the limited amount of data for these associations, estimates were less precise with wider confidence intervals.

Sensititvity and Subgroup analyses

Supplementary Figures 11 and 12 show the pooled results for the association of fasting and two-hour post-load glucose (75g OGTT) with each perinatal outcome excluding all results from the two studies (four published reports) that were least likely to suffer from bias due to lack of blinding

Our analyses were limited by the fact that there were only two studies for which we could ascertain clinical staff were definitely blinded, one of which was the largest study included in the whole meta-analyses.[8] Broadly, results for fasting glucose and two-hour post-load were similar between studies with definite blinding and those without blinding or where we were unsure (Supplementary Figures 11 and 12). The association of fasting glucose, but not two-hour post-load glucose, with birth size (both LGA and macrosomia), but not other outcomes, appears stronger for the blinded studies (LGA[8] and macrosomia[28]) than all other studies pooled together.

Excluding studies with blinding, left only data from one study examining the fasting glucose association with neonatal hypoglycaemia. This study[29] included 2904 women and demonstrated a positive association, with point estimates that were higher than those in the main meta-analysis without these exclusions (OR 1.43, 95% CI 0.64 to 3.22 and OR 1.37 95% CI 1.20 to 1.57 respectively). However, because of the small sample size of this one study the confidence intervals were wide and included the null result. The only other study with this outcome at fasting was HAPO and the results from HAPO (based on the point estimate) suggested a possible weaker association, but the results from the two studies are consistent with each other (Results for HAPO alone: OR 1.37 95% CI 1.20 to 1.57. Similarly following exclusions, only two studies with 3191 women remained for the two-hour post-load association with neonatal hyperglycaemia, the point estimates were the same as the main analyses, however again because of the reduced sample size, the confidence intervals were wide and included the null result.

We examined the effect of region on the association of fasting and two-hour post-load glucose (75g OGTT) with each perinatal outcome (Supplementary Figures 13 and 14). These results suggest that the positive linear associations seen when all studies are combined are seen across each of the regions we were were able to examine. There is some suggestion that the magnitude of the associations varies by region for some outcomes where these were assessed in several regions. Specifically, the associations with LGA appeared weakest in studies from Asian regions and strongest in studies that were international or from North America, with those from Australasia and Europe between these two regions. But, given the reduced sample sizes within these stratified analyses it is not possible to determine whether these differences are due to chance.

Heterogeneity between studies

The individual forest plots for each association of fasting, one-hour 50g OGCT post-load and two-hour 75g OGTT are shown in Supplementary Figures 2 to 11. The I^2 statistic for heterogeneity between the studies for the majority of the associations was very low or 0 (Figure 2 and Supplementary Figure 1).

Discussion

We have shown positive linear associations of fasting and post-load glucose (50g, 75g and 100g loads) with most adverse perinatal outcomes, including: Caesarean section, induction of labour, LGA, macrosomia, and shoulder dystocia, across the distribution of glucose, in women without existing diabetes or GDM. In general, associations of fasting glucose with these outcomes were stronger than those of post-load glucose. Fasting glucose was inversely associated with preterm delivery, but there was no strong evidence of a clear association of post-load glucose with this outcome. In a majority of studies the clinican caring for the woman was likely to have known the woman's glucose levels and so the findings could have been biased by surveillance/detection bias. However, when we exclucde two studies with four reports in which there was blinding (including the largest, and potentially most influential study) the results were similar to those with all studies included. When we explored associations by geographical region (Asia, Australasia, Europe, International and North-America) they showed the same similar linear pattern of association. The 50g OGCT is not administered following an overnight fast which invariably introduces a greater degree of variability, however we found that the same linear associations are seen with this test as with the more controlled 75g and 100g OGTT (that is administered following an overnight fast). Thus, our results are robust to different sensitivity analyses based on study quality, population and type of glucose test. The similarity of results from an OGCT to those from the OGTT suggest that in populations that find fasting difficult, this test may provide some indication of a woman's glucose response and degree of associated risk, though it is important to note that for this test, there were relatively few studies and no data available on some of our outcomes.

This detailed systematic review and large-scale meta-analysis provides no clear glucose threshold to define GDM above which, risk increases notably across a wide range of clinically relevant pregnancy and perinatal outcomes. The recent IADPSG criteria acknowledged the need to arbitrarily define a threshold for diagnosis. They based this on the point (for fasting, one-hour and two-hour post-load) at which glucose levels resulted in an odds ratio of at least 1.75 above mean glucose levels, but only considered three outcomes- LGA, large skinfold thickness at birth and cord-blood C-peptide. These do not include key clinical outcomes, including the need for induction, Caesarean-section, neonatal hypoglycaemia, shoulder dystocia and admission to neonatal intensive care, that obstetricians, midwives and pregnant women consider important.[30] Thus, our results show linear associations without thresholds across a range of different populations, with different glucose tests and for clinically relevant outcomes.

We found no strong evidence of heterogeneity, with low to negligible I^2 results for all tests. This further supports the robustness of our findings across a wide-range of populations, though we

acknowledge that our findings would not necessarily generalise to populations in low and middle income (LMIC) countries for which there is little relevant information.

We have not applied the IADPSG odds ratio of 1.75 to define glucose thresholds for GDM across the wider range of perinatal outcomes explored here for several reasons. First, 1.75 is arbitrary and we feel a range of thresholds ought to be considered. Second, applying one odds ratio to all of our outcomes would assume that they are all equally clinically important. For example, that clinicians and parents would consider labour induction to be as important as shoulder dystocia or an infant requiring neonatal intensive care. The three outcomes that IADPSG used to define GDM thresholds (LGA, large birth skinfolds and cord-blood c-peptide) were all concerned with the same broad concept of infant adiposity and markers of future risk of offspring obesity and so applying the same odds ratio to each of these may be appropriate, but we do not believe it is, for the range of outcomes we have examined here. Third, we believe that the results from this review should be combined with relevant evidence of treatment effects and economic evaluations, as well as consideration of whether different risk levels should be applied to different outcomes, in order to define the optimal clinical and cost-effective thresholds.

Strengths and limitations

This systematic review and meta-analysis includes a large number of studies with varied populations, and provides the largest sample of women in whom these associations have been examined. We intentionally had broad Inclusion criteria so that we could explore any heterogeneity between study populations and make conclusions relevant to most pregnant women. We found no evidence of heterogeneity overall, but it should be noted that the majority of the women came from high-income countries. Thus our findings are not necessarily generalisable to lower-income settings. We wanted to examine the influence of ethnicity on associations, however most studies did not provide the detail to allow this. Whilst we found similar patterns of association by geographical region we cannot assume that this reflects ethnicity. For example the UK Born in Bradford cohort, includes approximately 50% white British and 50% south Asian women.

One of the main limitations of the individual studies was the lack of definite blinding of those who were looking after the pregnant women, to their OGTT fasting and post-load glucose levels. This could bias the magnitudes of the association towards the null if carers provided advice (for example about diet) or even treatment with oral hypoglycaemics, to those women who had borderline high glucose levels that did not quite reach the diagnostic criteria for excluding women with GDM. We tried to explore this in sensitivity analyses comparing pooled results in those studies that had definitely blinded clinical staff to those that had not blinded staff or for which it was unclear whether or not they had blinded them. In general results looked similar in the two groups. However, only two

studies had definitely blinded staff and one of these was the largest study HAPO. The strong associations of fasting glucose with LGA and macrosomia in the blinded studies compared to other studies could reflect blinding, but it could also be a chance finding considering the number of comparisons undertaken in this sensitivity analysis. Given this analysis is comparing just one or two studies with all others it could also be driven by other differences. Importantly the difference is small and does not alter our overall conclusion regarding the linear dose-response nature of the associations of glucose with a wide-range of clinically important perinatal outcomes

The inclusion of women with diagnosed GDM would have affected the estimates of the association of glucose with outcomes, since these women would be treated to reduce their glucose they were therefore excluded. Although we found no evidence of a curvilinear association between glucose and outcomes at levels below current treatment thresholds, the possibility exists that risks may increase substantially at glucose levels exceeding them.

The increased identification of women, resulting from lowering glucose thresholds to diagnose GDM, has resource implications for maternity services in terms of antenatal care (OGTTs, treatments, induction of labour), intrapartum care (Caesarean section) and short and longer-term postnatal care (infant care, screening for type 2 diabetes). Costs are likely to be greater for identification and treatment strategies that use lower glucose thresholds if care packages are unchanged. Because there is a graded linear association between maternal glucose and risk of perinatal outcomes, risk of these outcomes may be reduced if glucose thresholds are lowered; however there are no trials using these new thresholds and no robust evidence that longer-term obesity risk would be improved.[31]

Recommendations for research

Considering all eligible evidence, it is clear that the association between glucose and a wide range of clinically relevant adverse perinatal outcomes is linear and there is no glucose threshold above which odds increases substantially in high-income countries. With the exception of large well-conducted studies in low and middle income countries we recommend that further studies of the nature of the association of gestational glucose with perinatal outcomes are not required. We do believe that studies in low and middle income countries are important and this might be particularly the case for sub-Saharan Africa, were there seem to have been no studies to date, but where diabetes prevalence is increasing and possibly has a different phenotype to that seen in Western high-income countries and were perinatal outcomes also have different presentations.[32, 33] Also there are few studies in South Asia, but again diabetes is an increasing problem and may influence perinatal outcomes in a different way to that seen in European origin populations, as suggested by our earlier results in Born in Bradford.[13]

As noted above rather than apply an arbitrary level of risk such as am odds ratio of 1.75 to all of the clinically relevant outcomes we have examined here, we believe that future research needs to combine our results with robust evidence from well conducted randomised trials (and meta-analyses of those) of treatment effects on GDM related adverse outcomes, economic evaluations and research to determine what relative importance women, their partners and care-givers would give to the different outcomes in order to determine the level at which clinical and cost- effectiveness is maximised.

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What is already known on this subject

• Gestational diabetes (GDM) is associated with increased risk of a range of perinatal outcomes and may impact on the longer-term health of mother and offspring.

• Treatment seems to reduce the risk of adverse perinatal outcomes, but it is unclear what the optimal glucose threshold to define GDM is.

• The Independent Association of Diabetes and Pregnancy Study Groups (IADPSG) fasting and post-load glucose thresholds for diagnosing GDM are based on results from just one study and considered just three outcomes (large for gestational age, large skinfold thickness at birth and cord-blood C-peptide) and did not take account of outcomes that pregnant women and their carers would consider to be more clinically important (including labour induction, Caesarean-section, neonatal hypoglycaemia, shoulder dystocia and the need for neonatal intensive care).

What this study adds

• By combining high quality evidence from a large number of studies and exploring a range of clinically important outcomes we have demonstrated consistent graded linear associations between glucose and clinically relevant perinatal outcomes (Caesarean section, induction of labour, LGA, macrosomia, and shoulder dystocia), with no clear threshold.

• These patterns were robust to sensitivity analyses exploring the impact of study quality and type of glucose exposure and within the evidence available we were able to demonstrate similar linear associations across geographical regions (studies from Asia, Australasia, Europe, North America and International (multicentre) studies).

• There is currently no evidence from sub-Saharan Africa regarding the relation of gestational glucose to perinatal outcomes and very little from other low and middle income countries.

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Declaration of competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation 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.

Details of contributors

DF, DAL and TAS designed the study and secured funding. DF monitored the review process. DF, MS, MB, DAL, TAS, DT and FD interpreted the data, DF wrote the draft paper and all authors contributed. MS wrote the statistical analysis plan with contribution from DAL. DF, MS and SG assessed studies for inclusion. MS cleaned and analysed the data, DF is guarantor.

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X I am one author signing on behalf of all co-owners of the Contribution.

Transparency declaration

I Dr Diane Farrar affirm 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.

Data sharing

Extracted data are available upon request to the corresponding author

Ethical approval

Ethics approval was obtained from the Bradford Research Ethics Committee (07/H1302/112). All participants provided informed written consent.

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Table 1 Recommended criteria for the diagnosis of gestational diabetes

	Fasting	One-hour post-load	Two-hour post-load	Three-hour post-load
75g OGTT (plasma glucose)				
*IADPSG[5] (2010) ADIPS (2013) WHO[9] (2013)	≥5.1	≥10.0	≥8.5	-
*WHO[34] (1999)	≥6.1	-	≥7.8	-
*ADA[35] (2006)	≥5.3	≥10.0	≥8.6	
*ADIPS[36] (1998)	≥5.5	-	≥8.0	-
100g OGTT (plasma or serum glucose)				
**ACOG[12]/C&C	≥5.3	≥10.0	≥8.6	≥7.8
**NDDG[37]	≥5.8	≥10.6	≥9.2	≥8.0
**O'Sullivan[38]	≥5.0	≥9.2	≥8.1	≥6.9

IADPSG = International Association of Diabetes and Pregnancy Study Groups
ACOG = American College of Obstetricians and Gynecologists
ADIPS= Australasian Diabetes in Pregnancy Society
ADA= American Diabetes Association
C&C= Carpenter and Coustan
NDDG= National Diabetes Data Group
WHO= World Health Organization

*one threshold should be equalled or exceeded for GDM to be diagnosed

** two thresholds should be equalled or exceeded for GDM to be diagnosed

Table 2: Characteristics of included studies using the 50g oral glucose challenge test

First author	Year	Location	Women (N)	Glucose test	Test timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	S. Dystocia	Neonatal hypoglyc.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
Carr[39]	2011	USA (Seattle)	25969	50g OGCT		X		100g OGTT two or more values fasting ≥5.3, 1 hour ≥ 10.0, 2 hour ≥8.6 and 3 hour ≥7.8					X	X			
Chandna[40]	2006	Pakistan (Karachi)	633	50g OGCT		X		Not reported				X	X		X		X
Cheng[41]	2007	USA (California)	13901	50g OGCT		X		Not reported	X	X	X	X				X	
Figueroa[42]	2013	USA (multicentre)	1839	50g OGCT		X		100g OGTT fasting <5.3 plus two or more values: 1 hour ≥10.0, 2 hour ≥8.6 and 3 hour ≥7.8	X	X		X					

First author	Year	Location	Women (N)	Glucose test	Test timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	S. Dystocia	Neonatal hypoglyc.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
Hillier[43]	2008	USA (Hawaii and Portland)	41450	50g OGCT		X		100g OGTT Two criteria used: (i) 2 or more values: fasting ≥5.8 or 1 hour ≥10.5 or 2 hour ≥9.2 or 3 hour ≥8.0 (ii) 2 or more values: fasting ≥5.3 or 1 hour ≥10.0 or 2 hour ≥8.6 or 3 hour ≥7.8		X							
Ong[44]	2008	UK (Cambridge)	3826	50g OGCT		X		50g OGCT 1-hr >7.8 and 75g OGTT levels not reported Fasting >6.1 2 hour level not reported							X		X
Scholl[45]	2001	USA (New Jersey)	1157	50g OGCT		X		Not reported	X				X	X	X		

First author	Year	Location	Women (N)	Glucose test	Test timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	S. Dystocia	Neonatal hypoglyc.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
Sermer[28]	1995	Canada (Toronto)	3637	50g OGCT / 100g OGTT	X	X	X	100g OGTT 2 or more values: fasting >5.8 or 1 hour >10.5 or 2 hour >9.1 or 3 hour >8.0		X			X		X		
Witter[46]	1988	USA (Baltimore)	3897	50g OGCT		X		100g OGTT 2 or more values: fasting ≥5.8 or or 1 hour ≥10.5 or 2 hour ≥9.1 or 3 hour ≥8.0		X							
Yee[47]	2011	USA (California)	13789	50g OGCT		X		100g OGTT 2 or more values: fasting ≥5.8 or or 1 hour ≥10.5 or	X	X	X		X		X		

First author	Year	Location	Women (N)	Glucose test	Test timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	S. Dystocia	Neonatal hypoglyc.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
								2 hour ≥9.1 or 3 hour ≥8.0									

Table 3: Characteristics of included studies using the 75g oral glucose tolerance test

First author	Year	Location	Women (N)	Glucose test	Test Timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	Sh. Dystocia	Neonatal hypogly.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
Aris[48]	2014	Singapore	1081	75g OGTT	X		X	75g OGTT fasting ≥7.0 or 2 hour ≥7.8	X								
Atlantic Dip[17]	2015	Ireland (west coast)	4869	75g OGTT	X		X	75g OGTT fasting ≥6.1 or 2 hour ≥7.8	X	X	X		X	X	X		X
BIB[18]	2015	UK (Bradford)	9645	75g OGTT	X		X	75g OGTT fasting ≥6.1 or 2 hour ≥7.8	X	X	X		X	X	X	X	X
HAPO group[8]	2008	International multicentre	23316	75g OGTT	X	X	X	75g OGTT fasting > 5.8 or 2 hour >11.1 or RPG >8.9]	X			X			X		
HAPO group[27]	2010	International multicentre	21364	75g OGTT	X	X	X	75g OGTT fasting > 5.8					X				

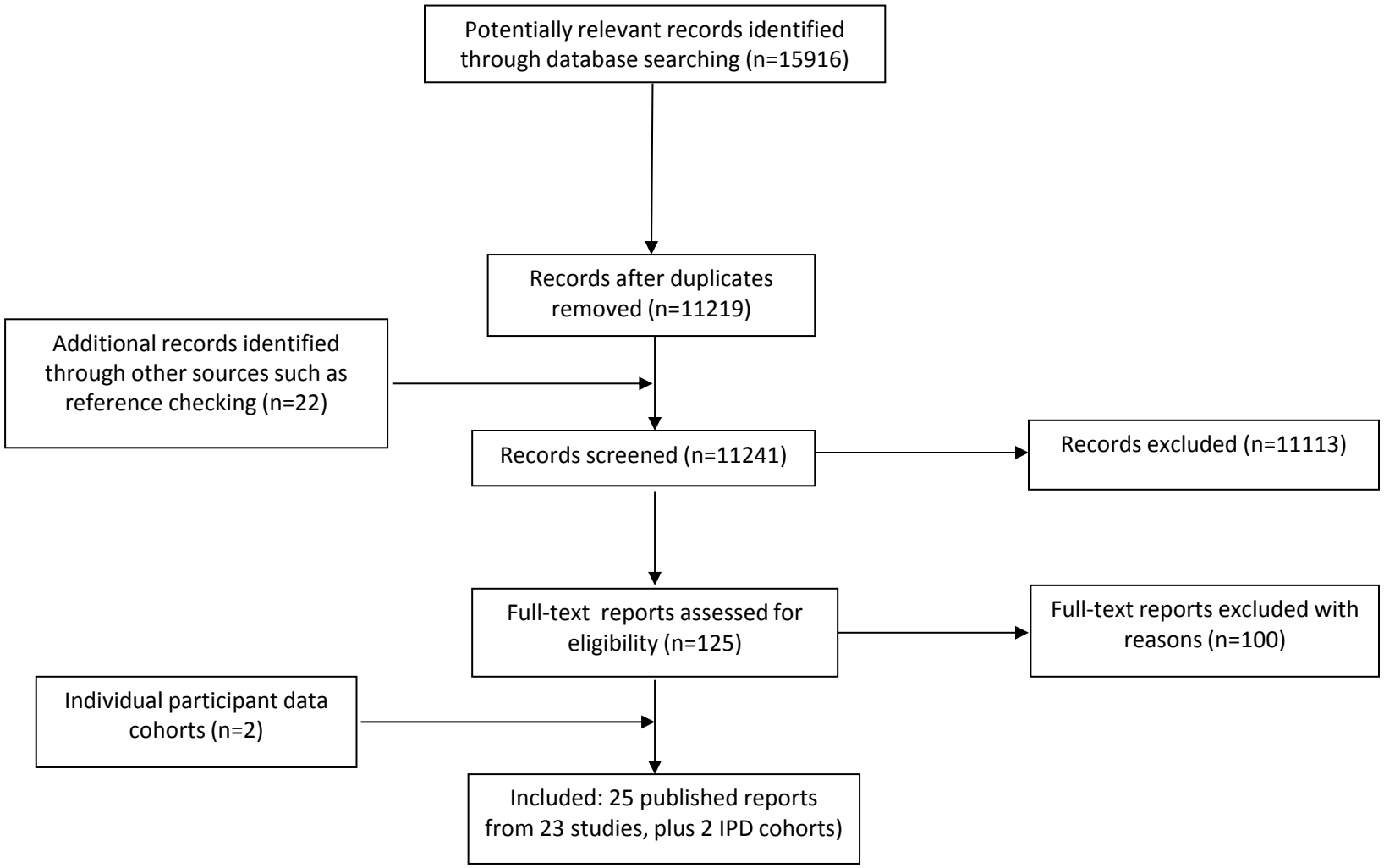
First author	Year	Location	Women (N)	Glucose test	Test Timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	Sh. Dystocia	Neonatal hypogly.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
								or 2 hour >11.1 or RPG >8.9									
Jensen[29]	2001	Denmark (multicentre)	2904	75g OGTT	X		X	75g OGTT 2 or more values: fasting >5.7 or 30mins >11.9 or 1 hour 12.0 or 90mins >9.7 or 2 hour >8.9 or 180mins >7.4	X	X	X	X	X	X	X	X	X
Kerenyi[49]	2009	Hungary (Budapest)	3787	75g OGTT	X		X	75g OGTT fasting ≥7.0 or 2 hour ≥7.8	X								
Lao[50]	2003	China (Hong Kong)	2168	75g OGTT			X	75g OGTT 2 hour ≥8.0	X	X				X	X		
Metzger[51] [HAPO]	2010	International multicentre	17094	75g OGTT	X	X	X	75g OGTT fasting >5.8 or 2 hour				X					

First author	Year	Location	Women (N)	Glucose test	Test Timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	Sh. Dystocia	Neonatal hypogly.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
								>11.1or RPG >8.9									
Moses[52]	1995	Australia (Illawarra, NSW)	1441	75g OGTT			X	75g OGTT 2 hour ≥8.0	X						X		X
Pettitt[53]	1980	USA (Arizona)	811	75g OGTT			X	75g OGTT 2 hour ≥11.1	X					X	X		
Savona-Ventura[54]	2010	Malta	1289	75g OGTT	X		X	Not reported		X			X				

Table 4: Characteristics of included studies using the 100g oral glucose tolerance test

First author	Year	Location	Women (N)	Glucose test	Test timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	Sh. Dystocia	Neonatal hypogly.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
Landon[24]	2011	USA (multicentre)	1368	100g OGTT	X	X	X	fasting ≥ 5.3	X		X		X				
Little[55]	1990	USA (Missouri)	287	100g OGTT			X	75g OGTT fasting ≥5.7 or 2 hour ≥9.2	X		X	X			X		
Riskin-Mashiah[56]	2009	Israel (Haifa)	6129	100g OGTT	X			100g OGTT first trimester fasting >5.8		X					X		
Sermer[28]	1995	Canada (Toronto)	3637	50g OGCT / 100g OGTT	X	X	X	100g OGTT 2 or more values: fasting >5.8 or 1 hour >10.5		X			X		X		

First author	Year	Location	Women (N)	Glucose test	Test timing			GDM diagnosis exclusion criteria (mmol/L)	Outcomes								
					F	1	2		LGA	Macrosomia	Sh. Dystocia	Neonatal hypogly.	Pre-eclampsia/PIH	Preterm birth	C-section	In. labour	In. delivery
								or 2 hour >9.1 or 3 hour >8.0									
Tallarigo[57]	1986	Italy (Pisa)	249	100g OGTT			X	100g OGTT 2 or more values: fasting ≥5.8 or or 1 hour ≥10.5 or 2 hour ≥9.1 or 3 hour ≥8.0		X				X	X		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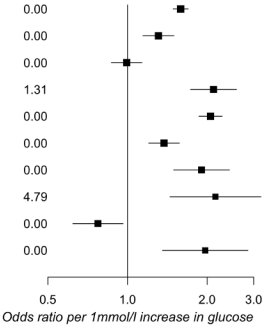
Records after duplicates removed (n=11219)
Additional records identified through other sources such as reference checking (n=22)
Records screened (n=11241)
Records excluded (n=11113)
Full-text reports assessed for eligibility (n=125)
Full-text reports excluded with reasons (n=100)
Individual participant data cohorts (n=2)
Included: 25 published reports from 23 studies, plus 2 IPD cohorts)

Combining 75g and 100g OGTT tests − Fasting

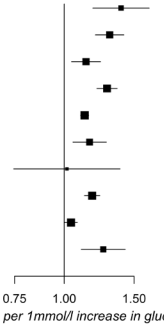
Morbidity	Studies	Women	I2 (%)	Effect (95% CI)
C−section	6	47746	0.00	1.59 (1.49 , 1.70)
Induction	2	12484	0.00	1.31 (1.14 , 1.50)
Instrumental birth	3	17257	0.00	0.99 (0.87 , 1.13)
LGA	7	46680	1.31	2.11 (1.73 , 2.58)
Macrosomia	6	28303	0.00	2.06 (1.86 , 2.28)
Neonatal hypoglycemia	2	19998	0.00	1.37 (1.20 , 1.57)
PIH/Pre−eclampsia	3	5551	0.00	1.91 (1.49 , 2.43)
Pre−eclampsia	4	39345	4.79	2.15 (1.45 , 3.19)
Preterm birth	3	17257	0.00	0.77 (0.62 , 0.96)
Shoulder dystocia	4	18615	0.00	1.97 (1.36 , 2.85)



Odds ratio per 1mmol/l increase in glucose

50g OGCT

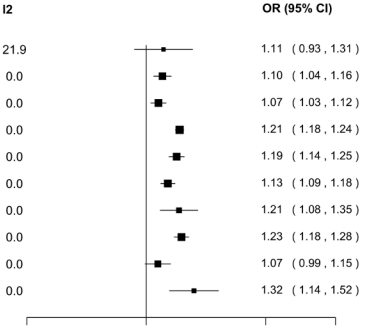
Morbidity	Studies	Women	I2	OR (95% CI)
C−section	7	36616	5.6	1.39 (1.18 , 1.64)
Induction	1	13902	0.0	1.30 (1.20 , 1.41)
Instrumental birth	2	3791	0.0	1.14 (1.04 , 1.23)
LGA	4	30626	0.0	1.28 (1.21 , 1.36)
Macrosomia	7	64851	0.0	1.13 (1.10 , 1.15)
Neonatal hypoglycemia	3	15619	0.0	1.16 (1.05 , 1.28)
PIH/Pre−eclampsia	1	1157	0.0	1.02 (0.75 , 1.38)
Pre−eclampsia	6	58270	0.0	1.18 (1.13 , 1.23)
Preterm birth	2	27126	0.0	1.04 (1.00 , 1.08)
Shoulder dystocia	2	27688	0.0	1.25 (1.10 , 1.43)



Odds ratio per 1mmol/l increase in glucose

Two−hour postload 75g OGTT

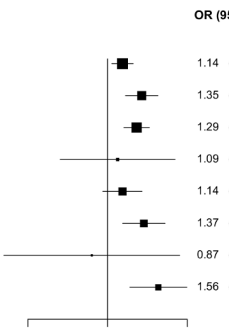
Morbidity	Studies	Women	I2	OR (95% CI)
C−section	7	41130	21.9	1.11 (0.93 , 1.31)
Induction	2	12485	0.0	1.10 (1.04 , 1.16)
Instrumental birth	4	18661	0.0	1.07 (1.03 , 1.12)
LGA	9	48321	0.0	1.21 (1.18 , 1.24)
Macrosomia	5	19524	0.0	1.19 (1.14 , 1.25)
Neonatal hypoglycemia	2	19998	0.0	1.13 (1.09 , 1.18)
PIH/Pre−eclampsia	2	4174	0.0	1.21 (1.08 , 1.35)
Pre−eclampsia	3	35720	0.0	1.23 (1.18 , 1.28)
Preterm birth	5	18816	0.0	1.07 (0.99 , 1.15)
Shoulder dystocia	3	17260	0.0	1.32 (1.14 , 1.52)



Odds ratio per 1mmol/l increase in glucose

Two−hour postload 100g OGTT

Morbidity	Studies	Women	OR (95% CI)
C−section	2	3915	1.14 (1.04 , 1.25)
LGA	2	1645	1.35 (1.17 , 1.55)
Macrosomia	2	3877	1.29 (1.15 , 1.44)
Neonatal hypoglycemia	1	287	1.09 (0.66 , 1.80)
PIH/Pre−eclampsia	1	1358	1.14 (0.96 , 1.35)
Pre−eclampsia	1	3628	1.37 (1.14 , 1.65)
Preterm birth	1	249	0.87 (0.41 , 1.87)
Shoulder dystocia	2	1645	1.56 (1.21 , 1.99)



Odds ratio per 1mmol/l increase in glucose