BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

DOI: 10.1111/1471-0528.16906
www.bjog.org

Research Article
General obstetrics

Fasting plasma glucose, diagnosis of gestational diabetes and the risk of large for gestational age: a regression discontinuity analysis of routine data

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Accepted 4 August 2021. Published Online 26 September 2021.

Objective To estimate the causal effects of fasting plasma glucose (FPG) and diagnosis of gestational diabetes (GDM) on birthweight and the risks of large for gestational age (LGA).

Design Regression discontinuity analysis of routine data.

Setting Two district general hospitals in West Yorkshire, UK.

Population A cohort of 7062 women with singleton pregnancies who were screened for GDM and gave birth to a baby at ≥24 weeks of gestation in 2017–2019, inclusive.

Methods The causal effects of FPG and GDM diagnosis were estimated using the two-stage least-squares approach, around the diagnostic threshold of FPG ≥ 5.6 mmol/l recommended by the UK's National Institute for Health and Care Excellent (NICE), controlling for ethnicity, maternal age, parity, height and weight.

Main outcome measures Birthweight (standardised for sex and gestational age) and large for gestational age (standardised as birthweight above the 90th centile).

Results For each 1 mmol/l increase in FPG the observed birthweight increased by Z-score = 0.48 standard deviations (95% CI 0.39 to 0.57) and the odds of LGA increased by OR = 2.61 (95% CI 1.86 to 3.66). Conversely, GDM diagnosis reduced the observed birthweight by Z = −0.61 (95% CI −0.94 to −0.29) and lowered the odds of LGA by OR = 0.33 (95% CI 0.15 to 0.74). Similar, but less certain, patterns were observed for caesarean section, shoulder dystocia and perinatal death.

Conclusions The relationship between FPG and LGA is potent but is dramatically reduced by GDM diagnosis (and all the consequences thereof). Women with mild hyperglycaemia (with an FPG of 5.1–5.5 mmol/l) who fall below the current NICE threshold for GDM diagnosis have the highest risks of adverse outcomes, suggesting a need to reconsider their current care.

Keywords Birthweight, diabetes, large for gestational age, natural experiment, regression discontinuity design.

Tweetable abstract Regression discontinuity analysis shows that untreated mild hyperglycaemia increases the odds of large for gestational age, but that a diagnosis of gestational #diabetes lowers the odds by three times.

Linked article This article is commented on by S John and KS Joseph, p. 90 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16939.

Please cite this paper as: Tennant PWG, Doxford-Hook E, Flynn L, Kershaw K, Goddard J, Stacey T. Fasting plasma glucose, diagnosis of gestational diabetes and the risk of large for gestational age: a regression discontinuity analysis of routine data. BJOG 2022;129:82–89.

Introduction

Around one-in-six births worldwide are affected by hyperglycaemia in pregnancy through pre-existing diabetes, such as type-1 or type-2 diabetes, or gestational diabetes mellitus (GDM), where the hyperglycaemia arises in pregnancy.[1] Hyperglycaemia is becoming more common in pregnancy because an increasing proportion of pregnancies occur in women who are obese and older than 30 years of age.[2,3] Without treatment, hyperglycaemia in pregnancy brings an increased risk of several adverse pregnancy outcomes, including: large for gestational age (LGA), birth injury, caesarean delivery and stillbirth.[4] These risks can be reduced, however, with proactive screening and diagnosis of GDM and the provision of enhanced care and management with diet, metformin and/or insulin.[5,6]

Exactly what level of hyperglycaemia in pregnancy is sufficient to prompt a diagnosis of GDM has not been agreed entirely, resulting in several different diagnostic thresholds.[7–9] Both the World Health Organization (WHO) and the American Diabetes Association (ADA) recommend the criteria set by the International Association of Diabetes Pregnancy Study Group (IADPSG), which advises that a diagnosis be made for pregnant women with a fasting plasma glucose (FPG) level of ≥5.1 mmol/l (91.8 mg/dl) or, following a 75-g oral glucose tolerance test (OGTT), a plasma glucose concentration of ≥10 mmol/l (180 mg/dl) after 1 hour or ≥8.5 mmol/l (153 mg/dl) after 2 hours.[9,10] Alternatively, in the UK the National Institute for Health and Care Excellence (NICE) recommend thresholds of FPG ≥ 5.6 mmol/l (100.8 mg/dl) or 2-hour OGTT ≥ 7.8 mmol/l (140.4 mg/dl), reportedly based on a theoretical analysis of the costs, benefits and capacity limits of providing enhanced care provision.[7]

These different thresholds represent different attempts to balance the competing risks and costs – to the mother, her child, the health system and society – of adopting a more, or less, intensive approach to the management of mild hyperglycaemia. These judgements are, however, strongly informed by observational studies in populations that are not treatment naive, which may greatly underestimate the true risks of untreated hyperglycaemia. Our previous causal mediation analysis of the effect of GDM on the risk of stillbirth, for example, found that a significant harmful effect of hyperglycaemia was largely obscured in routine data as a result of the provision of effective screening and management.[11] Unfortunately, there is limited information on whether the same is true for other adverse pregnancy outcomes. The current study therefore aimed to estimate the distinct effects of hyperglycaemia and receipt of GDM diagnosis on the risks of large for gestational age (LGA), and other adverse pregnancy outcomes, by conducting a regression discontinuity analysis of routine data from two hospitals in West Yorkshire, UK.

Methods

Population and sample

All women with singleton pregnancies who gave birth to a baby after 24 weeks of gestation, in either the Huddersfield Royal Infirmary (Huddersfield, UK) or the Calderdale Royal Hospital (Halifax, UK), and had a 75-g OGTT between January 2017 and December 2019 were included in the study. Information on the health of the mother and her offspring were obtained from electronic clinical records. Women with a previous history of GDM were offered an OGTT as soon as possible after booking, all women who fulfilled the NICE screening criteria were offered an OGTT at 26–28 weeks of gestation and some OGTTs were also performed later in pregnancy if symptoms were present.[11] Fasting and 2-hour glucose levels were recorded and women were clinically diagnosed if they met either of the NICE criteria.[11] Women with pre-existing diabetes (diagnosed prior to the onset of pregnancy) were excluded from the analysis.

Birthweight was standardized for sex and gestational age against the expected healthy weight for gestational age. Expected weights for gestational age were calculated by applying the Hadlock–Gardosi proportionality formula, which models the expected (healthy) fetal size as a proportion of the observed size on the 280th day,[12] to recent UK 40-week live-birth reference values for boys (mean = 3573 g, SD = 432 g) and girls (mean = 3437 g, SD = 416 g).[13] LGA was defined as a standardised birthweight that lies above Z = 1.282 (the 90th centile) and small for gestational age (SGA) was defined as a standardised birthweight that lies below Z = −1.282 (the 10th centile). Perinatal death constitutes a stillbirth occurring at or after 24 weeks of gestational age or an infant death during the first 28 days after live birth. There was no overt involvement of patients in the analysis or interpretation of these data and a core outcomes set was not used.

Exposures and outcomes

The primary exposure was clinical diagnosis of GDM (and all consequences thereof, including receipt of enhanced care and management with diet, metformin and/or insulin); the secondary exposure was FPG concentration. The primary outcomes were (standardised) birthweight and LGA; the secondary outcomes are SGA, delivery by caesarean section (CS) (compared with spontaneous vaginal delivery), shoulder dystocia and perinatal death.

Analyses

The controlled direct effects of FPG concentration and the complier average causal effects of clinical diagnosis of GDM on birthweight and the risks of LGA, SGA, CS, shoulder dystocia and perinatal death were examined by regression discontinuity analysis: a quasi-experimental approach to estimating the effects of an intervention by comparing outcomes either side of a threshold for the intervention, such as that created by a diagnostic and/or treatment cut-off. During the period of study, the NICE guidelines for the management of women with diabetes in pregnancy recommended diagnosing GDM for all women with an FPG of ≥5.6 mmol/l, whereas women with an FPG of <5.6 mmol/l were not recommended for diagnosis, unless they had a 2-hour OGTT test result of ≥7.8 mmol/l. This creates a fuzzy discontinuity between FPG (as the running variable) and diagnosis of GDM around the threshold of FPG = 5.6 mmol/l.

The effects of GDM diagnosis and FPG were estimated using the two-stage least-squares approach over a window of FPG values between 4.1 and 7.1 mmol/l, inclusive. First, the relationship between FPG and probability of GDM diagnosis was estimated by logistic regression, conditioning on self-reported ethnicity (categorised into white, south Asian, Black and any other ethnicity), maternal age at booking, parity at booking, maternal height and maternal weight. Next, the relationship between FPG, the modelled probability of GDM diagnosis and each outcome was estimated by either linear regression (for birthweight) or logistic regression (for all other outcomes), again controlling for ethnicity, maternal age at booking, parity at booking, maternal height and maternal weight. Height was modelled with two terms (height and height^{-2} to reflect the contribution of height to the body mass index, BMI). Cross-term interactions were examined in all models, and interactions between weight and maternal age, ethnicity and FPG, and between maternal age and FPG, were included, based on superior Bayesian information criteria. There was notably little benefit of including interaction terms between ethnicity and FPG ($P = 0.52$ and $P = 0.24$ for birthweight and LGA models, respectively) and between ethnicity and GDM diagnosis ($P = 0.52$ and $P = 0.78$ for birthweight and LGA models, respectively). The relationships between FPG and birthweight and between FPG and the logit of all other outcomes were approximately linear when inspected with locally weighted scatter-plot smoothing, and there was limited evidence of interaction between FPG and diagnosis of GDM ($P = 0.75$ and $P = 0.84$ for birthweight and LGA models, respectively). The controlled direct effects of FPG and complier average causal effects of GDM diagnosis were therefore modelled as uniform across the observed window and are equal to the model average coefficients and odds ratios (ORs). To describe the effects in absolute terms, model predicted birthweights and probabilities of LGA were evaluated for FPG values (X) between 4.1 and 7.1 mmol/l in the presence of GDM diagnosis (M), i.e. $E(Y_x\mathrm{M}_1)$, in the absence of GDM diagnosis, i.e. $E(Y_x\mathrm{M}_0)$, and under the observed (factual) probability of GDM diagnosis, i.e. $E(Y_x\mathrm{M}_{m|X=x})$. In response to peer review, we also explored the potential mediating contribution of induction of labour (N) towards the total (complier average) causal effect of GDM diagnosis on standardised birthweight and LGA by additionally adjusting for induction of labour to estimate the effect acting through induction: natural indirect effect, $E(Y_x\mathrm{M}_1\mathrm{N}_1 - Y_x\mathrm{M}_0\mathrm{N}_0)$; effect independent of induction, i.e. controlled direct effect, $\mathrm{E}(Y_x\mathrm{M}_1\mathrm{N}_0 - Y_x\mathrm{M}_0\mathrm{N}_0)$. The manipulation of FPG values around the diagnosis threshold was examined by visually inspecting the FPG distribution and by performing local polynomial manipulation tests. No evidence of discontinuities in FPG were observed. Analyses were also repeated with alternative FPG windows of 3.1–8.1, 3.6–7.6, 4.6–6.6 and 5.1–6.1 mmol/l (Table S1). Except for the smallest window, where the estimates became very uncertain, none of the effect estimates were materially changed. We therefore focus on reporting the results from the primary analytic window (4.1–7.1 mmol/l, inclusive).

Analyses were conducted using R 4.0.2 (www.R-project.org) and the analytical code is provided in Method S1. The 95% confidence intervals (95% CIs) were estimated using the Clopper–Pearson (exact) method (for proportions) or the delta method (for model predictions). Following guidance from the American Statistical Association and current practice in leading epidemiology journals, no null-hypothesis significance tests were performed.[14] With the high levels of data completeness, missing data were managed by case-wise deletion.

Results

During the study period, a total of 15 651 births beyond 24 weeks of gestation were registered in the two hospitals, 747 (4.8%) of which were diagnosed with GDM. From these, 7062 women were screened for GDM, 6433 (91%) had a 'normal' FPG (<5.1 mmol/l), 426 (6%) had a 'raised' FPG (5.1–5.5 mmol/l) and 203 (2.9%) had a 'diagnostic' FPG (≥5.6 mmol/l). In total, 747 (11.1%) of the cohort were clinically diagnosed with GDM, based on either their FPG or 2-hour OGTT result. The demographic profile of the women screened for GDM is summarised in Tables 1 and 2.

The probability of GDM diagnosis in women with a 'normal', 'raised' and 'diagnostic' FPG were 7.4% (95% CI 6.8–8.1%), 24.2% (20.2–28.6%) and 95.6% (91.8–98.0%), respectively. The modelled relationship between FPG and the probability of being clinically diagnosed with GDM is shown in Figure S1.

Effects of FPG and diagnosis of GDM on birthweight and LGA

Both the observed birthweight and probability of LGA increased steadily with increasing FPG, except for a large localised drop at the NICE threshold for GDM diagnosis (Figures 1 and 2).

The controlled direct effect of FPG on (standardised) birthweight was Z = 0.48 (95% CI 0.39 to 0.57) (Table 3), meaning that, independent of GDM diagnosis, each additional 1 mmol/l of FPG was associated with the equivalent of a 207 or 200 g increase in birthweight for a 40-week boy or girl, respectively. The complier average causal effect of GDM diagnosis was Z = −0.61 (95% CI −0.94 to −0.29), meaning that for the same FPG, the receipt of diagnosis was associated with the equivalent of a 264 or 254 g decrease in birthweight for a 40-week boy or girl, respectively (Table S1). Table S2 presents the expected

Table 1. Profile of participants (categorical variables), overall and by FPG level

Variable	Category	All (*n* = 7062)		Normal FPG (*n* = 6433)			Raised FPG (*n* = 426)			Diagnostic FPG (*n* = 203)		
		n	Col %	*n*	Col %	Row %	*n*	Col %	Row %	*n*	Col %	Row %
Maternal characteristics												
Ethnicity	White	3680	57	3404	58	93	200	52	5	76	41	2
	Asian	2050	32	1805	31	88	153	40	7	92	40	5
	Black	218	3	202	4	93	9	2	4	7	4	3
	Other	466	7	434	7	93	21	6	5	11	6	2
	Missing	648		588			43			17		
Parity at booking	Nulli/primiparous	4941	70	4575	71	93	260	61	5	106	52	2
	Multiparous	2120	30	1857	29	86	166	39	8	97	48	5
	Missing	1		1			0			0		
Body mass index	Underweight	138	2	136	2	99	1	0	1	1	1	1
	Recommended	2189	31	2098	33	96	67	16	3	24	12	1
	Overweight	1673	24	1528	24	91	103	24	6	42	21	3
	Obese I–II	2607	37	2314	3	89	191	45	7	102	50	4
	Obese III	424	6	327	5	77	63	15	15	34	17	8
	Missing	31		30			1			0		
GDM diagnosis	No	5978	89	5653	93	95	316	76	5	9	4	0
	Yes	747	11	452	7	61	101	24	14	194	96	26
	Missing	337		328			9			0		
Induction of labour	No	4932	70	4564	71	93	277	65	6	91	55	2
	Yes	2130	30	1869	29	88	149	35	7	112	45	5
	Missing	0		0			0			0		
Infant characteristics and outcomes												
Pregnancy outcome	Live birth	7034	99.6	6410	99.6	91	422	99.1	6	202	99.5	3
	Antepartum stillbirth	19	0.3	14	0.2	74	4	0.9	21	1	0.5	5
	Early neonatal death	9	0.1	9	0.1	100	0	0.0	0	0	0.0	0
	Missing	0		0			0			0		
Mode of delivery	Spontaneous vaginal	4245	60	3928	61	93	217	51	5	100	49	2
	Caesarean section	2045	29	1793	28	88	166	39	8	86	42	4
	Assisted or breech	772	11	712	11	92	43	10	6	17	8	2
	Missing	0		0			0			0		
LGA	No	5951	86	5484	87	92	314	75	5	153	76	3
	Yes	1006	15	852	13	85	105	25	10	49	24	5
	Missing	105		97			7			1		
SGA	No	6175	89	5602	88	91	383	91	6	190	94	3
	Yes	782	11	734	12	94	36	9	5	12	6	1
	Missing	105		97			7			1		
Shoulder dystocia	No	6728	99	6133	99	91	398	97	6	197	99	3
	Yes	82	1	68	1	83	11	3	13	3	2	4
	Missing	252		232			17			3		

(standardised) birthweight for various values of FPG, with a GDM diagnosis, without a GDM diagnosis and at the observed probability of diagnosis. In absolute terms, a woman with an FPG concentration of 5.5 mmol/l – just below the threshold for GDM diagnosis – who is *not* diagnosed is expected to have a baby of weight Z = 0.77 (95% CI 0.60 to 0.93; equivalent to 3905 or 3757 g for a 40-week boy or girl, respectively), whereas a women with an FPG concentration of 5.6 mmol/l – just above the threshold for diagnosis – who *is* diagnosed is expected to have a baby of weight Z = 0.21 (95% CI 0.02 to 0.40; equivalent to 3664 or 3524 g for a 40-week boy or girl, respectively). Only 5% of the effect of GDM on (standardised) birthweight was mediated by differences in induction

Table 2. Profile of participants (outcome variables), overall and by FPG level

Variable	All (*n* = 7062)		Normal FPG (*N* = 6433)		Raised FPG (*N* = 426)		Diabetic FPG (*N* = 203)	
	n	Median (IQR) [Range]	*n*	Median (IQR) [Range]	*n*	Median (IQR) [Range]	*n*	Median (IQR) [Range]
Maternal characteristics								
Maternal age (years)	7061	29 (26,33) [15,53]	6432	29 (25,33) [15,53]	426	31 (27,35) [19,46]	203	32 (28,36) [17,45]
Maternal height (cm)	7031	163 (159,168) [138,188]	6403	163 (159,168) [138,188]	425	163 (158,168) [147,184]	203	164 (159,168) [145,178]
Maternal weight (kg)	7031	75 (63,90) [36,165]	6403	74 (62,89) [36,160]	425	83 (70,100) [45,152]	203	86 (74,100) [51,165]
Maternal BMI (kg/m^2)	7031	28.3 (23.7,33.3) [14.8,57.8]	6403	27.9 (23.5,32.9) [14.8,57.8]	425	31.6 (27.2,37.3) [18.3,52.1]	203	32.4 (28.3,38.3) [18.2,57.8]
FPG at booking (mmol/l)	7062	4.3 (4.1,4.6) [2.0,11.5]	6433	4.3 (4.1,4.5) [2.0,5.0]	426	5.2 (5.1,5.3) [5.1,5.5]	203	5.9 (5.7,6.2) [5.6,11.5]
Infant characteristics and outcomes								
Birthweight (g)	6959	3395 (3030,3735) [270,5525]	6338	3390 (3030,3725) [270,5525]	419	3520 (3090,3870) [1605,5400]	202	3330 (2920,3688) [1250,4610]
Gestational age (weeks)	7062	39.6 (38.6,40.4) [24.0,43.9]	6433	39.6 (38.7,40.4) [24.0,43.9]	426	39.1 (38.3,40.1) [29.7,42.1]	203	38.3 (37.7,38.7) [27.7,41.7]
Standardised birthweight (Z)	6957	0.01 (−0.70,0.80) [−5.96,5.42]	6336	−0.02 (−0.72,0.74) [−5.96,4.91]	419	0.52 (−0.43,1.28) [−2.69,5.42]	202	0.31 (−0.47,1.26) [−3.03,4.70]

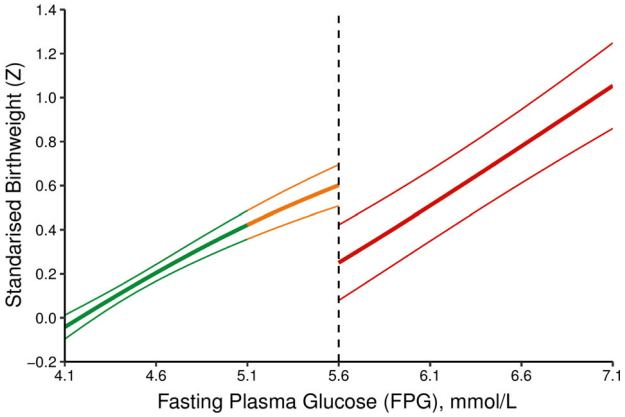

Figure 1. Modelled (observed) relationship between FPG and birthweight, standardised by sex and gestational age.

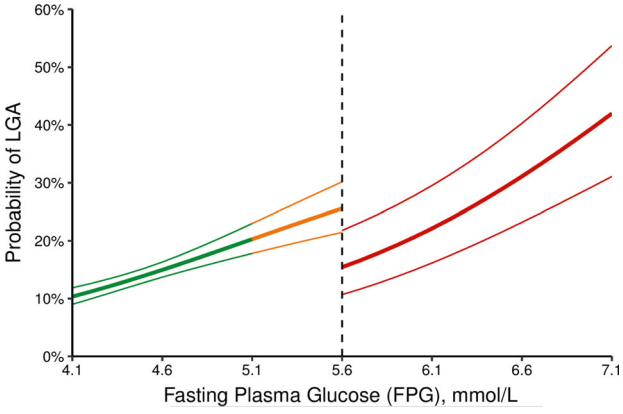

Figure 2. Modelled (observed) relationship between FPG and probability of LGA.

of labour: controlled direct effect, Z = −0.58 (95% CI −0.26 to −0.91); natural indirect effect, Z = −0.03 (95% CI −0.01 to −0.05).

The controlled direct effect of FPG on risk of LGA was OR = 2.61 (95% CI 1.86–3.66) (Table 3), meaning, independent of GDM diagnosis, each additional 1 mmol/l of FPG was associated with more than double the odds of LGA. The complier average causal effect of GDM diagnosis was OR = 0.33 (95% CI 0.15–0.74), meaning that for the same FPG, diagnosis was associated with a three times reduction in the odds of LGA. Table S3 presents risk of LGA for various values of FPG, with a GDM diagnosis, without a GDM diagnosis and under the observed probability of diagnosis. In absolute terms, a woman with an

Table 3. Estimated controlled direct effects of FPG and complier average causal effects of GDM diagnosis on fetal, infant and pregnancy outcome

Outcome	FPG (Controlled direct effect)	GDM diagnosis (Complier average) causal effect)
Coefficient (95% CI)		
Standardised birthweight (Z)	0.48 (0.39, 0.57)	−0.61 (−0.94, −0.29)
Odds ratio (95% CI)		
LGA	2.61 (1.86, 3.66)	0.33 (0.15, 0.74)
SGA	0.51 (0.32, 0.79)	1.49 (0.43, 4.67)
Caesarean section	1.53 (1.15, 2.02)	0.83 (0.42, 1.63)
Shoulder dystocia	3.19 (1.11, 9.35)	0.25 (0.01, 2.70)
Perinatal death	3.11 (0.40, 24.46)	0.33 (<0.01, 22.74)

FPG concentration of 5.5 mmol/l – just below the threshold for GDM diagnosis – who is *not* diagnosed has an estimated LGA risk of 32% (95% CI 24–41%), whereas a woman with an FPG concentration of 5.6 mmol/l – just above the threshold for diagnosis – who *is* diagnosed has an estimated LGA risk of 15% (95% CI 10–21%). None of the effect of GDM on LGA was mediated by differences in induction of labour: controlled direct effect, OR = 0.33 (95% CI 0.15–0.75); natural indirect effect, OR = 1.00 (95% CI 0.96–1.05).

Effects of FPG and diagnosis of GDM on SGA, delivery by CS, shoulder dystocia and perinatal death

The controlled direct effect of FPG on risk of SGA was OR = 0.51 (95% CI 0.32–0.79) (Table 3), meaning that, unlike for LGA, an increasing FPG was associated with a *reduced* risk of SGA. The observed effect of GDM diagnosis on the risk of SGA implied a small increase although this may be explained by sampling variation (complier average causal effect: OR = 1.49; 95% CI 0.43–4.67).

For all other outcomes a similar pattern was observed to the one seen with LGA, with increasing FPG associated with an observed increase in odds and with GDM diagnosis associated with an observed (if modest) decrease (Table 3). For example, the observed odds of shoulder dystocia tripled with each 1 mmol/l increase in FPG (controlled directed effect: OR = 3.19; 95% CI 1.11–9.35) and were four times smaller for those who received a diagnosis of GDM, although this estimate is somewhat uncertain (complier average causal effect: OR = 0.25; 95% CI 0.01–2.70) (Table 3). The same pattern was observed for perinatal death, with the odds increasing by three times for each 1 mmol/l of FPG (controlled directed effect: OR = 3.11; 95% CI 0.40–24.46) and decreasing by three times for those who received a diagnosis (complier average causal effect: OR = 0.33; 95% CI <0.01–22.74), although both these estimates are extremely uncertain (Table 3). Although less pronounced, increasing FPG was associated with an increased risk of delivery by CS (controlled directed effect: OR = 1.53; 95% CI 1.15–2.02), but any reduction as a result of a diagnosis of GDM was modest (complier average causal effect: OR = 0.83; 95% CI 0.42–1.63) (Table 3).

Discussion

Main findings

This study examined the distinct effects of hyperglycaemia and GDM diagnosis on birthweight, the risks of LGA and several other adverse pregnancy outcomes by conducting a novel regression discontinuity analysis in routinely collected data. The study observed a large and (generally) harmful effect of increasing FPG with each additional 1 mmol/l (18 mg/dl), leading to an increase of around 200 g in birthweight, a doubling in the odds of LGA and a tripling in the odds of shoulder dystocia, although an increase in FPG was also associated with a reduction in the odds of SGA. A similarly large but positive effect was observed for receipt of GDM diagnosis, however, which led to a decrease of over 200 g in birthweight, reducing the odds of LGA and shoulder dystocia by two-thirds or more. Women with 'raised' FPG levels (5.1–5.5 mmol/l) below the current threshold in England and Wales for GDM diagnosis experienced the highest risks overall because they did not benefit from either naturally lower FPG levels or receiving enhanced care or management following GDM diagnosis.

Strengths and limitations

This study benefitted from using data that were prospectively collected by health professionals undertaking the routine care provided to all women with a singleton pregnancy undergoing screening for GDM. The sample was ethnically diverse and there was notably little suggestion of interaction between either FPG or GDM diagnosis with ethnicity, suggesting consistent effects between groups. The results are therefore likely to be generalisable to women at risk of GDM in settings with similar screening and care programmes. That said, because our sample only included women who were selected from screening, the results should not be extrapolated to the wider population of women at lower risk of GDM.

We used a novel regression continuity analysis to explore the distinct effects of hyperglycaemia and GDM diagnosis. This causal inference approach remains underused in applied health research but is not without limitations.[15] A narrow analytical window is needed to minimise confounding and selection biases, but this in turn requires a large sample size. As our sample was derived from just two

hospitals over 3 years, a wider analytical window was necessary to maximise the analytical power. Nevertheless, the estimates are most valid around the 5.6 mmol/l threshold for diagnosis. Although there was no apparent interaction between FPG and GDM diagnosis, the results should be viewed with increasing uncertainty at increasing distance from the threshold. Thus, although a beneficial effect of GDM diagnosis is likely to exist across the 5.1–5.5 mmol/l range of 'raised' FPG, it may be smaller for women at the lower end of this range, and we caution against interpreting any benefit for women with 'normal' FPG (<5.1 mmol/l). We therefore controlled for ethnicity, maternal age, parity, height and weight at booking to ensure comparable groups, but unobserved and residual confounding are possible. No material differences were, however, observed when the analyses were repeated over alternative analytical windows. The sample was also too small to provide precise effect estimates for rarer outcomes such as shoulder dystocia and perinatal mortality and, in particular, perinatal mortality should not be interpreted in isolation.

Interpretation and implications

This study adds to the developing evidence in favour of the IADPSG criteria for the diagnosis of GDM at lower levels of FPG.[16–18] Our results suggest that the use of the NICE criteria leaves many women with a 'raised' FPG of between 5.1 and 5.5 mmol/l at significantly increased risks of LGA, as well as other adverse pregnancy outcomes. Meek et al. similarly found that women with a 'raised' FPG (5.1–5.5 mmol/l) had more than three times the risk of LGA (aOR = 3.64, compared with women who did not receive an OGTT). As in our sample, this was higher than the risk observed among women with more severe 'diagnostic' hyperglycaemia (aOR = 2.76), who are assumed to have received a GDM diagnosis. Djelmis et al. also found that women with FPG values in the interval 5.1–5.5 mmol/l had the highest risks of LGA (OR = 3.7, versus FPG < 5.6 mmol/l), again higher than those with more severe hyperglycaemia (OR = 1.5 for FPG ≥ 5.6 mmol/l).[17] This is somewhat surprising given that the diagnosis of GDM in this Croatian sample was supposed to be following the IADSPG guidelines. However, actual GDM diagnoses were not known or reported, so there may have been some divergence in diagnostic practice, or women with milder hyperglycaemia may have received different care to those with more severe hyperglycaemia.

In our sample of 7062 women screened for GDM from 15651 registered births, an additional 316 would have been diagnosed with GDM if the IADSPG criteria had been applied, resulting in a 40% increase in GDM diagnosis from 747 (4.8%) to 1063 (6.8%). This clearly has substantial resource implications, although it may recoup savings in the prevention of adverse events. An economic comparison of the cost-effectiveness of the NICE criteria and the IADSPG criteria suggests that the stricter NICE approach is more cost effective, although the modelled treatment effects appear conservative and several perinatal outcomes, including LGA and perinatal mortality, were not considered.[19] Economic evaluations need to accurately enumerate *all* the consequences of untreated hyperglycaemia and consider *all* the effects of enhanced antenatal care (both positive and negative) to provide an accurate assessment of the relative merits of different approaches.[20]

Like the hyperglycaemia and pregnancy outcome (HAPO) study,[5] our study observed a continuous relationship between FPG concentration and the risk of adverse pregnancy outcomes, which was perturbed only by the diagnosis of GDM at FPG ≥ 5.6 mmol/l. There is hence no obvious cut-off point for diagnosis where the risks of increasing hyperglycaemia suddenly accelerate, making it impossible to recommend a particular threshold for diagnosis based on biology alone.[5] This suggests that a graded approach may be more pragmatic than a single diagnostic cut-off, in which women with mild hyperglycaemia receive closer monitoring and additional dietary/lifestyle advice but less intense (and less costly) care than those with more severe hyperglycaemia.[11,18] Both this current study and our previous study of stillbirth suggest that the management of women with GDM is extremely effective at reducing the risks of adverse pregnancy outcomes. For birthweight and LGA this does not appear to be explained by higher rates of induction. Future research is needed to confirm these findings, especially for the rarer outcomes. Clearly, any insight into which parts of the overall package of care are so effective at reducing adverse outcomes would be extremely useful for managing the growing numbers of women with mild hyperglycaemia.

Conclusion

There is a strong relationship between FPG and the risk of adverse pregnancy outcomes, with each additional 1 mmol/l leading to an increase of around 200 g in birthweight, double the odds of LGA and triple the odds of shoulder dystocia. The receipt of a GDM diagnosis goes a long way to eliminating these risks, leading to a 200-g reduction in birthweight, two-thirds lower odds of LGA and three-quarters lower odds of shoulder dystocia. Women with mild hyperglycaemia that falls below the NICE threshold for GDM diagnosis therefore experience some of the worse pregnancy outcomes, suggesting a need to reconsider the deviation from international guidelines in England and Wales.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

EDH, TS and PWGT conceived the study. EDH assisted in data collection and contributed to writing the article. TS assisted with data collection, interpretation and contributed to writing and editing the article. PWGT performed data analysis, interpretation and contributed to writing and editing the article and is the guarantor for the accuracy and robustness of the analysis and results. KK contributed to data collection and reviewed the article. LF contributed to writing and reviewing the article. JG reviewed and revised the final version for publication. All authors gave approval of the final article prior to publication.

Details of ethics approval

This study was reviewed by the National Research Ethics Service (NRES) and ethical approval was gained on 27 July 2020: Integrated Research Application System, IRAS 285954.

Funding

PWGT is supported by The Alan Turing Institute (EP/N510129/1). The funding sources had no role in: (i) the design or conduct of the study; (ii) the collection, analysis or interpretation of the data; or (iii) the preparation of the manuscript and the decision to submit for publication.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Modelled (observed) relationship between FPG and probability of being diagnosed with GDM.

Table S1. Estimated controlled direct effects of FPG and complier average causal effects of GDM diagnosis on birthweight and LGA for a range of FPG windows of analysis.

Table S2. Predicted birthweight, standardised for sex and gestational age (Z), by FPG concentration and receipt of GDM diagnosis.

Table S3. Predicted probability of LGA, by FPG concentration and receipt of GDM diagnosis.

Method S1. ■

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