BMJ Open

Association between maternal pregestational glucose level and adverse pregnancy outcomes: a population-based retrospective cohort study

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To cite: Zeng M, He Y, Li M, *et al*. Association between maternal pregestational glucose level and adverse pregnancy outcomes: a population-based retrospective cohort study. *BMJ Open* 2021;**11**:e048530. doi:10.1136/bmjopen-2020-048530

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-048530).

Received 29 December 2020
Accepted 20 August 2021

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ABSTRACT

Objective To investigate the association between maternal pregestational blood glucose level and adverse pregnancy outcomes.

Design Retrospective cohort study.

Setting This study was conducted in the Chongqing Municipality of China between April 2010 and December 2016.

Participants A total of 60 222 women (60 360 pregnancies) from all 39 counties of Chongqing who participated in the National Free Preconception Health Examination Project and had pregnancy outcomes were included.

Primary outcome measures Adverse pregnancy outcomes included spontaneous abortion, induced abortion or labour due to medical reasons, stillbirth, preterm birth (PTB), macrosomia, large for gestational age, low birth weight (LBW) and small for gestational age.

Results Of the 60 360 pregnancies, rates of hypoglycaemic, normoglycaemia, impaired fasting glycaemia (IFG) and diabetic hyperglycaemic before conception were 5.06%, 89.30%, 4.59% and 1.05%, respectively. Compared with women with normoglycaemia, women with pregestational glucose at the diabetic level (≥7.0 mmol/L) might have a higher rate of macrosomia (6.18% vs 4.16%), whereas pregestational IFG seemed to be associated with reduced risks of many adverse outcomes, including spontaneous abortion, induced abortion due to medical reasons, PTB and LBW. After adjusting for potential confounders, pregestational diabetic hyperglycaemic was remained to be significantly associated with an increased risk of macrosomia (adjusted risk ratio 1.49, 95% CI 1.07 to 2.09). Abnormal maternal glucose levels before pregnancy (either hypoglycaemic or hyperglycaemic) seemed to have no significant negative effect on spontaneous abortion or induced abortion due to medical reasons.

Conclusion Although without overt diabetes mellitus, women with once diabetic fasting glucose level during their preconception examinations could be associated with an increased risk for macrosomia. Uniform guidelines are needed for maternal blood glucose management during pre-pregnancy care to improve pregnancy outcomes.

Strengths and limitations of this study

- ► This is one of the few studies with large sample size addressing the impact of glucose level before pregnancy on adverse birth outcomes among the general women at childbearing age.
- ► Compared with the previous similar studies, we analysed the association of maternal pregestational glucose level with spontaneous abortion, induced abortion due to medical reasons, and stillbirth for the first time.
- ► Neonatal gender was considered when we investigated the impact of maternal pregestational glucose level on birth outcomes.
- ► Since this is a retrospective cohort study design, our database lacks some important information during the pregnancy period which cannot be collected again, so the findings of our study should be interpreted with caution.

BACKGROUND

Pregestational diabetes mellitus (PGDM) and gestational diabetes mellitus (GDM) have been proven to be positively associated with adverse pregnancy outcomes for mothers and their fetuses, including pregnancy complications, preterm birth (PTB) and congenital anomalies.[1–3] In addition, a series of large cohort studies, such as Hyperglycemia and Adverse Pregnancy Outcome (HAPO) studies, have shown that increasing maternal glucose levels during pregnancy, regardless of GDM status, are also associated with increased risks of adverse perinatal outcomes such as large for gestational age (LGA) and macrosomia.[4–6] Although there is some evidence showing that mild maternal hyperglycaemic before pregnancy might also be associated with increased risks for GDM and LGA in some specific groups such as women with polycystic ovary syndrome or those who received assisted reproductive

technology,[7 8] few studies have focused on the preconception maternal glucose level, and whether abnormal maternal glucose level before pregnancy is associated with any adverse pregnancy outcomes in the general population remains unclear.

In China, although national guidelines for the treatment and management of patients diagnosed with diabetes or GDM are available,[9 10] there are no standard guidelines for women with abnormal glucose levels when they prepare to conceive or during the early pregnancy. According to the current guidelines for diabetes screening and the management of pregnant women, for most women with no known diagnosis of diabetes, they receive their first blood glucose testing for GDM screening at 24–28 weeks of gestation. Since the diagnostic criteria for diabetes are slightly 'restrictive' for asymptomatic people, who need to repeat the testing for abnormal results on another day, a significant percentage of people with abnormal glucose levels are undiagnosed diabetics.[11 12] Therefore, whether and how to provide healthcare to these women with abnormal glucose levels but without overt diabetes mellitus before the pregnancy is unclear.

Our study aimed to examine the association between maternal pregestational glucose level and adverse pregnancy outcomes, which might provide a new insight or better criteria to manage potential high-risk women in advance and improve their pregnancy outcomes.

METHODS

Study design and participants

We conducted this population-based, retrospective cohort study in Chongqing Municipality, Western China. The participants were women recruited from the National Free Preconception Health Examination Project (NFPHEP), which was a national project launched to provide free pregestational health examinations, consultations and risk assessments for couples who prepared to conceive, aiming to improve maternal and infant health in China. More detailed information about the design and implementation of this project has been described previously.[13–15] We extracted Chongqing data from the national NFPHEP database regarding the preconception care and following pregnancy outcomes of 68 096 women (68 266 pregnancies) from April 2010 to December 2016. The eligibility criteria for inclusion were as follows: women aged 20–49 years, who accepted the preconception health examination, and without a definite diagnosis of diabetes at enrolment. Women who failed to undergo pregestational blood glucose testing were excluded. Notably, through our quality control process, we found that blood glucose levels for a portion of the pregnancies were measured inaccurately using non-fasting blood samples from Dianjiang County in Chongqing from 2012 to 2013, leading to an abnormally higher rate of hyperglycaemic compared with other counties (18.42% vs 1.36% averaged in others). Therefore, we decided to exclude the 609 pregnancies from this county in our study. A flowchart of the study population is shown in figure 1.

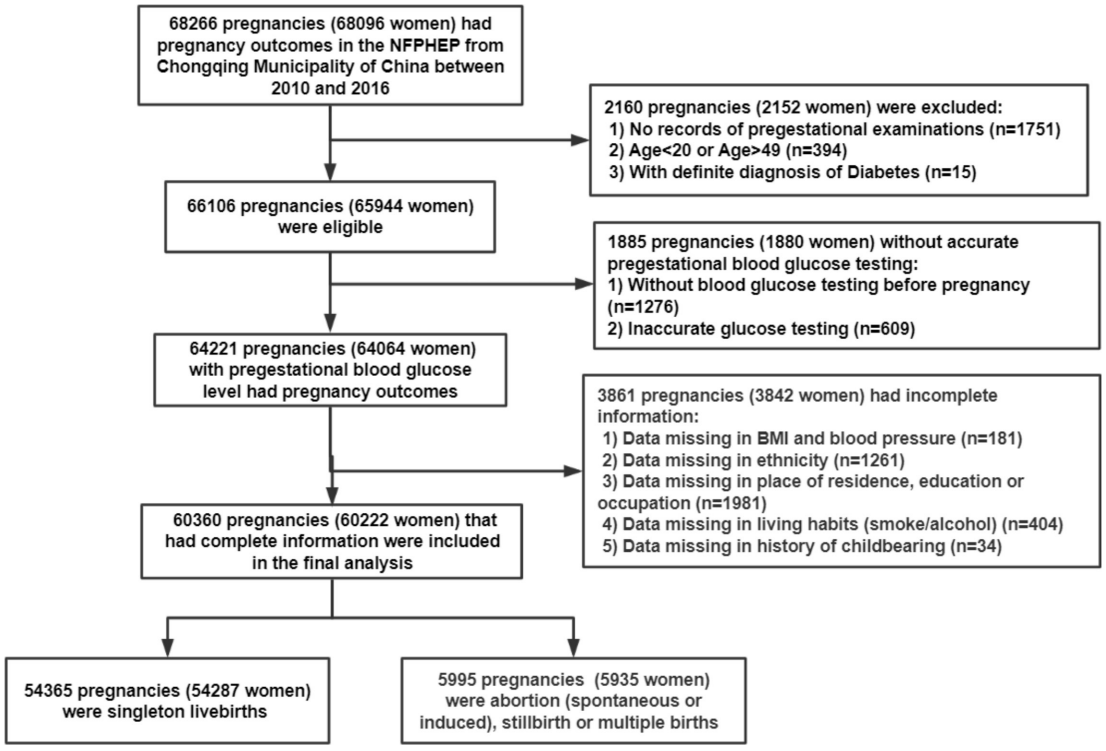


Figure 1 Flowchart for the study population. BMI, body mass index; NFPHEP, National Free Preconception Health Examination Project.

Our final analyses included 60 222 women (60 360 pregnancies) who had complete information on the basic characteristics that we were interested in, including age, body mass index (BMI), ethnicity, educational level, occupation, place of residence, lifestyle habits, history of childbearing and blood pressure. Of the included pregnancies, 54 365 had singleton live births.

Procedures

When the participants enrolled in the NFPHEP, their baseline characteristics, including demographic information (age, educational level, ethnicity, place of residence and occupation), lifestyle habits (smoking and alcohol consumption) and childbearing history information (gravidity, parity, history of preterm, history of spontaneous abortion and history of induced abortion), were collected by the locally trained health workers using a standardised questionnaire. Blood glucose concentrations of the participants were measured in the clinic laboratory based on their overnight fasting blood samples collected during the preconception health examination. Fasting blood glucose (FBG) concentrations were analysed using automatic analysers selected by the local laboratories, all of which were approved by the China Food and Drug Administration. After enrolment, the participants were followed up by telephone calls every 3 months for a year to check for the status of their conception. If pregnant, their pregnancy outcomes, including gestational days, birth weight and neonate sex, were collected from the medical records or interviews at the postpartum follow-up after delivery.

Exposure assessment

The exposure in this study was pregestational blood glucose in women who planned to conceive. We divided the participants into four subgroups by their venous blood glucose levels: hypoglycaemic (FBG <3.9 mmol/L), normoglycaemia (FBG 3.9–6.0 mmol/L), impaired fasting glucose (IFG, FBG 6.1–6.9 mmol/L) and diabetic hyperglycaemic (FBG ≥7.0 mmol/L), according to the latest guidelines of the American Diabetes Association.[16 17] It should be noted that although we used 'diabetes' here, it was not a definite diagnosis because of the absence of other information on clinical features, results of oral glucose tolerance test or multiple fasting glucose tests recorded in our data. Hypertension was defined as a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.[18] Maternal BMI was categorised into four groups according to the Working Group of China definition (<18.5, 18.5–23.9, 24.0–27.9 or ≥28.0 kg/m^2).[19 20]

Outcome definition

Regarding the outcomes in this study, spontaneous abortion was defined as the loss of pregnancy before 28 complete gestational weeks.[21] Induced abortion (or induced labour) due to medical reasons was defined as pregnancies that were terminated due to maternal serious diseases or abnormal conditions following the physicians' advice. Abortions on self-request were excluded in induced abortion. Stillbirth was defined as the death of a fetus at any time after the 28th week of pregnancy.[22] PTB was defined as delivery at ≤37 completed gestational weeks. Very PTB (VPTB) was defined as delivery earlier than 32 completed gestational weeks. Low birth weight (LBW) was defined as birth weight ≤2500 g, whereas macrosomia was characterised by neonates with birth weight ≥4000 g. Small for gestational age (SGA) or LGA was defined as birth weight <10th or >90th percentile, respectively, based on the Chinese neonatal birth weight curve for each gestational age by newborn sex established in 2015.[23] The rates or risks of PTB, VPTB, macrosomia, LBW, LGA and SGA were measured only in women with singleton live births.

Statistical analyses

The proportions of maternal baseline characteristics according to the four pregestational glucose levels were grouped and computed. Pearson χ^2 tests were used to examine the univariate associations of these categorical characteristics with glucose level. Since all of our outcomes followed the Poisson distribution, which were checked using the Kolmogorov-Smirnov test, Poisson regression models were used to estimate the effect of pregestational glucose level on the risk of adverse pregnancy outcomes. Each result was presented as a risk ratio with a 95% CI of hypoglycaemic, IFG and diabetic hyperglycaemic compared with the normoglycaemia group. Adjusted risk ratio (aRR) with its 95% CI was also calculated by adjusting for potential confounders including maternal age, BMI, ethnicity, educational level, place of residence, occupation, smoking and passive smoking, alcohol, parity, gravidity and history of PTB and abortion (both spontaneous and induced). For outcomes of women with singleton live births (PTB, VPTB, macrosomia, LGA, LBW and SGA), aRR was additionally adjusted for neonate sex. Subgroup analysis was used to examine the aRRs and their 95% CIs of macrosomia in women with the pregestational diabetic hyperglycaemic among different subgroups on the baseline characteristics. Sensitivity analyses were conducted to assess the potential bias from missing data: we set the missing data as a single group in each of the covariables in multivariate analysis. Statistical analyses were performed using the Statistical Analysis System statistical software (V.9.4). A two-tailed level of $p<0.05$ was considered statistically significant.

Patient and public involvement

Neither patients nor the public were involved in the design or implementation of our study. Additionally, there are also no specific plans to disseminate the results of the study to the study participants.

RESULTS

Of the 60 360 pregnancies that had pregnancy outcomes, rates of hypoglycaemic, normoglycaemia, IFG and

diabetic hyperglycaemic before conception were 3053 (5.06%), 53904 (89.30%), 2772 (4.59%) and 631 (1.05%), respectively (table 1). Compared with the hypoglycaemic and normoglycaemic groups, women with hyperglycaemic (both IFG and diabetic) had a higher proportion of advanced maternal age (age 35 years or more) (6.85% and 9.67% vs 3.01% and 4.06%, respectively), overweight and obesity (13.63% and 18.70% vs 9.69% and 11.88%, respectively), and agricultural residence registration (78.46% and 80.82% vs 76.61% and 73.11%, respectively), and a relatively lower educational level. In addition, women with hyperglycaemic were more likely to have hypertension compared with women in the hypoglycaemic or normal group (3.07% and 2.69% vs 1.21% and 1.44%, respectively). Moreover, the hypoglycaemic group had the highest percentage of passive smoking and alcohol consumption.

After adjusting for potential confounders, we found that pregestational IFG might be associated with decreased risks of spontaneous abortion (aRR 0.68, 95% CI 0.57 to 0.82) and induced abortion for medical reasons (aRR 0.62, 95% CI 0.47 to 0.81) (table 2). There was a higher risk of stillbirth in women with diabetic hyperglycaemic compared with women with normoglycaemia (0.48 vs 0.21%), although the wide 95% CI (aRR 2.08, 95% CI 0.66 to 6.60) showed that the difference between the two groups was not statistically significant. Of the 54365 pregnancies with singleton live births, the IFG group also seemed to have a lower risk of PTB (aRR 0.78, 95% CI 0.67 to 0.92), VPTB (aRR 0.59, 95% CI 0.37 to 0.93), LBW (aRR 0.52, 95% CI 0.31 to 0.86) and SGA (aRR 0.72, 95% CI 0.60 to 0.88) compared with the normoglycaemia group, whereas no significant effect was observed in the diabetic hyperglycaemic group on these outcomes. It is worth noting that the diabetic hyperglycaemic group had a higher rate of macrosomia than the normoglycaemia group (6.18% vs 4.16%). Compared with the normoglycaemia group, the diabetic hyperglycaemic group had a statistically significant higher risk for macrosomia (aRR 1.49, 95% CI 1.07 to 2.09) after adjusting for potential confounders. There was no difference in most of the pregnancy outcomes between pregnancies with hypoglycaemic and normoglycaemia, with the exception of spontaneous abortion (aRR 0.79, 95% CI 0.66 to 0.93).

The cumulative occurrence of macrosomia by glucose level is presented in figure 2, which reveals that women with diabetic glucose levels before pregnancy could be associated with an increased risk of macrosomia. From 39 to 42 gestational weeks, the cumulative proportion of macrosomia in the diabetic hyperglycaemic group was approximately 1.5 times higher than those in the other three groups.

In the subgroup analysis of macrosomia in the pregestational diabetic hyperglycaemic group compared with the normoglycaemia group stratified by maternal characteristics. There was an overall higher risk of macrosomia in women with diabetic hyperglycaemic, although some subgroups no longer presented a statistically significant risk (figure 3). In addition, we found that compared with the normoglycaemia group, pregestational diabetic hyperglycaemic was associated with a significantly higher risk of macrosomia in women bearing a male fetus (aRR 1.85, 95% CI 1.26 to 2.71), but there was no difference in the risk of macrosomia between different glucose groups among women bearing a female fetus (aRR 0.94, 95% CI 0.47 to 1.89). In addition, after stratifying by the period between glucose testing and pregnancy, the data suggested that among the women who underwent the pregestational health examinations within 3 months before their pregnancies, diabetic hyperglycaemic was a better predictor sign of a higher risk of macrosomia (aRR 1.64, 95% CI 1.13 to 2.39).

DISCUSSION

In our study, we aimed to evaluate the association between pregestational maternal glucose level and adverse pregnancy outcomes. We found that pregestational maternal diabetic hyperglycaemic might be associated with an increased risk for macrosomia, whereas pregestational IFG seemed to be associated with a reduced risk of adverse outcomes, including spontaneous abortion, induced abortion due to medical reasons, PTB and LBW. Moreover, pregestational diabetic hyperglycaemic might be associated with a higher risk of stillbirth.

To the best of our knowledge, the association between GDM or PGDM and pregnancy outcomes has been well studied, regardless of at a population level,[24 25] or at the molecular level.[26–28] In recent years, researchers have begun to focus on the association between IFG during pregnancy and adverse perinatal outcomes and later diabetes mellitus. Although the HAPO study has established the association between glucose levels below the diagnosis of diabetes during the pregnancy with GDM and increased birth weight,[4 29 30] the association between pre-pregnancy maternal glucose level among women without overt diabetes mellitus and later pregnancy or delivery remains unclear. In this study, we found a significant association between diabetic glucose level within 1 year before pregnancy and macrosomia, indicating that diabetic hyperglycaemic is one fasting glucose test during the preconception examination, especially for women who took the pregestational health examinations within 3 months before their pregnancies, might also be an early sign of macrosomia.

This finding is compatible with those of similar but different studies. In previous studies as we know, women with GDM, PGDM, first-trimester hyperglycaemic or mild hyperglycaemic in the late trimester, were all proven to be associated with an increased risk of macrosomia or LGA.[4 29 31–33] Moreover, our findings indicated that the existing insulin resistance before pregnancy might also have an influence on the mothers and their fetuses during the pregnancy or at the delivery, although its degree was under the current diagnostic criteria for diabetes. As a result, the current standard diagnostic criteria for

Table 1 Maternal characteristics according to pregestational glucose level (N=60 360)

Characteristics	Hypoglycaemia (<3.9 mmol/L)	Normoglycaemia (3.9–6.0 mmol/L)	Hyperglycaemia (≥6.1 mmol/L)		P value
			IFG (6.1–6.9 mmol/L)	Diabetic (≥7.0 mmol/L)	
No. of pregnancies (%)	3053 (5.06)	53 904 (89.30)	2772 (4.59)	631 (1.05)	
Age, years					<0.001
20–24	1630 (53.39)	24 630 (45.69)	1367 (49.31)	296 (46.91)	
25–29	1083 (35.47)	21 686 (40.23)	937 (33.81)	209 (33.12)	
30–34	248 (8.13)	5402 (10.02)	278 (10.03)	65 (10.30)	
35–49	92 (3.01)	2186 (4.06)	190 (6.85)	61 (9.67)	
BMI, kg/m^2					<0.001
<18.5	544 (17.82)	8142 (15.10)	388 (14.00)	70 (11.09)	
18.5–23.9	2213 (72.49)	39 360 (73.02)	2006 (72.37)	443 (70.21)	
24–27.9	251 (8.22)	5502 (10.21)	300 (10.82)	92 (14.58)	
≥28	45 (1.47)	900 (1.67)	78 (2.81)	26 (4.12)	
Ethnicity					<0.001
Han	2821 (92.4)	51 522 (95.58)	2699 (97.37)	616 (97.62)	
Others	232 (7.6)	2382 (4.42)	73 (2.63)	15 (2.38)	
Education					<0.001
Primary or below	113 (3.70)	2237 (4.15)	209 (7.54)	57 (9.03)	
Middle school	1391 (45.56)	23 524 (43.64)	1331 (48.02)	321 (50.87)	
High school	846 (27.71)	13 450 (24.95)	641 (23.12)	145 (22.98)	
College or above	703 (23.03)	14 693 (27.26)	591 (21.32)	108 (17.12)	
Place of residence					<0.001
Non-agricultural	714 (23.39)	14 495 (26.89)	597 (21.54)	121 (19.18)	
Agricultural	2339 (76.61)	39 409 (73.11)	2175 (78.46)	510 (80.82)	
Occupation					<0.001
Peasant	1414 (46.32)	23 590 (43.76)	1429 (51.55)	350 (55.47)	
Labour worker	317 (10.38)	5529 (10.26)	290 (10.46)	67 (10.62)	
Merchant	481 (15.75)	5836 (10.83)	254 (9.16)	77 (12.20)	
Service staff	111 (3.64)	1952 (3.62)	99 (3.57)	17 (2.69)	
Housewife	155 (5.08)	3300 (6.12)	95 (3.43)	28 (4.44)	
Civil servant	348 (11.40)	8598 (15.95)	301 (10.86)	50 (7.92)	
Others	227 (7.43)	5099 (9.46)	304 (10.97)	42 (6.66)	
Smoking					0.562
No	3038 (99.51)	53 542 (99.33)	2756 (99.42)	628 (99.52)	
Yes	15 (0.49)	362 (0.67)	16 (0.58)	3 (0.48)	
Passive smoking					<0.001
No	2433 (79.69)	45 247 (83.94)	2419 (87.27)	548 (86.85)	
Yes	620 (20.31)	8657 (16.06)	353 (12.73)	83 (13.15)	
Alcohol					<0.001
No	2806 (91.91)	50 799 (94.24)	2671 (96.36)	602 (95.40)	
Yes	247 (8.09)	3105 (5.76)	101 (3.64)	29 (4.60)	
Gravidity					<0.001
0	1701 (55.72)	25 330 (46.99)	1353 (48.81)	280 (44.37)	
≥1	1352 (44.28)	28 574 (53.01)	1419 (51.19)	351 (55.63)	
Parity					<0.001
0	2209 (72.36)	37 820 (70.16)	1998 (72.08)	409 (64.82)	
≥1	844 (27.64)	16 084 (29.84)	774 (27.92)	222 (35.18)	

Continued

Table 1 Continued

Characteristics	Hypoglycaemia (<3.9 mmol/L)	Normoglycaemia (3.9–6.0 mmol/L)	Hyperglycaemia (≥6.1 mmol/L)		P value
			IFG (6.1–6.9 mmol/L)	Diabetic (≥7.0 mmol/L)	
History of preterm birth					0.938
No	3047 (99.80)	53 777 (99.76)	2765 (99.75)	629 (99.68)	
Yes	6 (0.20)	127 (0.24)	7 (0.25)	2 (0.32)	
History of spontaneous abortion					0.013
No	2942 (96.36)	51 339 (95.24)	2643 (95.35)	610 (96.67)	
Yes	111 (3.64)	2565 (4.76)	129 (4.65)	21 (3.33)	
History of induced abortion					<0.001
No	2190 (71.73)	34 079 (63.22)	1808 (65.22)	421 (66.72)	
Yes	863 (28.27)	19 825 (36.78)	964 (34.78)	210 (33.28)	
Hypertension					<0.001
No	3016 (98.79)	53 129 (98.56)	2687 (96.93)	614 (97.31)	
Yes	37 (1.21)	775 (1.44)	85 (3.07)	17 (2.69)	

Data were presented as N (%) with p value from χ^2 test.
BMI is calculated as the weight in kilograms divided by height in metres squared.
BMI, body mass index; IFG, impaired fasting glycaemia.

diabetes might be stricter for women who prepare for pregnancy. Early prejudgement and proper intervention need to be taken into consideration for women with hyperglycaemic in the absence of overt diabetes during pregnancy preparation.

Interestingly, the possible effect of maternal diabetic hyperglycaemic before pregnancy on macrosomia was significantly greater in male fetuses (aRR 1.85, 95% CI 1.26 to 2.71) than in female fetuses (aRR 0.94, 95% CI 0.47 to 1.89). This difference also existed in LGA, which suggests that it cannot just be interpreted simply by sex or gestational age. A previous study in Spain has shown a similar result that GDM was only a predictor of macrosomia in male fetuses.[34] According to their interpretation, the difference in fetal sex might be due to the higher frailty of male fetuses to external influences during the pregnancy, which means male fetuses would be more affected by maternal hyperglycaemic and then to be overweight than female fetuses.

Questions have been raised regarding the possible benefits of pregestational IFG in neonatal outcomes among pregnant women. In our study, 'mild hyperglycaemic' before the pregnancy might be a harmless factor to many adverse outcomes, including PTB, LBW and even miscarriage due to physiological factors. Moreover, it seemed not to increase the risks of macrosomia and LGA as diabetic hyperglycaemic did. However, this finding was inconsistent with the finding of a similar study in Guangdong Province of China, which suggested that maternal pre-pregnancy IFG increased the risk of PTB (aRR 1.07, 95% CI 1.02 to 1.12) and LGA (aRR 1.10, 95% CI 1.06 to 1.14).[35] Another study focusing on the pre-pregnancy IFG has found that there was no significant difference in neonatal outcome in women with IFG from the normoglycaemia group, but it might be associated with increased risks for maternal outcomes including gestational diabetes and mild pre-eclampsia.[36] Based on their findings that pregestational maternal IFG was associated with GDM and the guideline of diabetes management for pregnant women in China, we hypothesised that the protective effect of IFG in our study might be influenced by the intervention such as healthy diet, exercise or insulin taking during the pregnancy, considering that there was some evidence showing that treating women with 'mild' GDM could improve birth outcome,[37] but it should be interpreted with caution due to the insufficient data. Furthermore, the analysis of associations between pregestational hyperglycaemic and maternal outcomes, such as GDM, pregnancy hypertension and mild pre-eclampsia, with information that was lacking in the NFPHEP database, should be considered in future studies.

The potential negative effect of pregestational diabetic hyperglycaemic on stillbirth was consistent with previous studies, although under different situations. Existing evidence has suggested that PGDM, GDM or hyperglycaemic during pregnancy is associated with a higher risk of stillbirth.[38–40] Our findings indicate that hyperglycaemic before pregnancy might also be associated with an increased risk of stillbirth, although the occurrence of stillbirth cases was significantly small in this study.

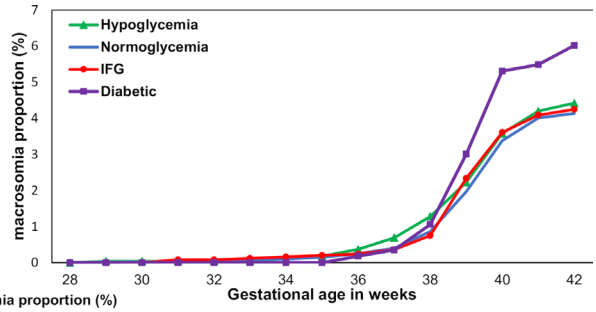
As we know, this is one of the few studies with a large sample size addressing the effect of glucose level before pregnancy on adverse birth outcomes among the general women of childbearing age. The strength of our study is the large cohort based on an unselected population covering almost the whole Chongqing Municipality of

Table 2 Associations between pregestational glucose and adverse pregnancy outcomes

			Hyperglycaemia (≥6.1 mmol/L)	
	Hypoglycaemia (<3.9 mmol/L)	Normoglycaemia (3.9–6.0 mmol/L)	IFG (6.1–6.9 mmol/L)	Diabetic (≥7.0 mmol/L)
Among 60 360 pregnancies that had pregnancy outcomes				
Spontaneous abortion				
No. (%)	133 (4.36)	3204 (5.94)	115 (4.15)	34 (5.39)
Unadjusted RR (95% CI)	0.73 (0.62 to 0.87)	1.00	0.70 (0.58 to 0.84)	0.91 (0.65 to 1.27)
Adjusted RR* (95% CI)	0.79 (0.66 to 0.93)	1.00	0.68 (0.57 to 0.82)	0.81 (0.57 to 1.13)
Induced abortion/labour due to medical reasons				
No. (%)	82 (2.69)	1703 (3.16)	54 (1.95)	18 (2.85)
Unadjusted RR (95% CI)	0.85 (0.68 to 1.06)	1.00	0.62 (0.47 to 0.81)	0.90 (0.57 to 1.44)
Adjusted RR* (95% CI)	0.92 (0.74 to 1.15)	1.00	0.62 (0.47 to 0.81)	0.82 (0.51 to 1.30)
Stillbirth				
No. (%)	6 (0.20)	115 (0.21)	4 (0.14)	3 (0.48)
Unadjusted RR (95% CI)	0.92 (0.41 to 2.09)	1.00	0.68 (0.25 to 1.83)	2.23 (0.71 to 7.01)
Adjusted RR* (95% CI)	0.88 (0.39 to 2.01)	1.00	0.68 (0.25 to 1.84)	2.08 (0.66 to 6.60)
Among 54 365 pregnancies with singleton live births				
Preterm births				
No. (%)	217 (7.73)	3565 (7.38)	149 (5.78)	44 (7.72)
Unadjusted RR (95% CI)	1.05 (0.91 to 1.20)	1.00	0.78 (0.67 to 0.92)	1.05 (0.78 to 1.41)
Adjusted RR† (95% CI)	1.03 (0.90 to 1.18)	1.00	0.78 (0.67 to 0.92)	1.04 (0.77 to 1.40)
Very preterm births				
No. (%)	33 (1.18)	602 (1.25)	19 (0.74)	6 (1.05)
Unadjusted RR (95% CI)	0.94 (0.66 to 1.34)	1.00	0.59 (0.37 to 0.93)	0.84 (0.38 to 1.89)
Adjusted RR† (95% CI)	0.94 (0.66 to 1.34)	1.00	0.59 (0.37 to 0.93)	0.79 (0.35 to 1.76)
Macrosomia				
No. (%)	128 (4.60)	1992 (4.16)	110 (4.32)	35 (6.18)
Unadjusted RR (95% CI)	1.11 (0.93 to 1.32)	1.00	1.04 (0.86 to 1.26)	1.49 (1.06 to 2.08)
Adjusted RR† (95% CI)	1.17 (0.98 to 1.40)	1.00	1.07 (0.88 to 1.29)	1.49 (1.07 to 2.09)
LGA				
No. (%)	285 (10.25)	4692 (9.81)	237 (9.33)	61 (10.80)
Unadjusted RR (95% CI)	1.04 (0.93 to 1.18)	1.00	0.95 (0.83 to 1.08)	1.10 (0.85 to 1.42)
Adjusted RR† (95% CI)	1.06 (0.94 to 1.20)	1.00	0.97 (0.85 to 1.10)	1.09 (0.84 to 1.40)
LBW				
No. (%)	40 (1.44)	564 (1.18)	15 (0.59)	7 (1.24)
Unadjusted RR (95% CI)	1.22 (0.89 to 1.68)	1.00	0.50 (0.30 to 0.84)	1.05 (0.50 to 2.21)
Adjusted RR† (95% CI)	1.22 (0.88 to 1.67)	1.00	0.52 (0.31 to 0.86)	1.10 (0.52 to 2.32)
SGA				
No. (%)	170 (6.12)	2832 (5.92)	109 (4.29)	28 (4.96)
Unadjusted RR (95% CI)	1.03 (0.89 to 1.21)	1.00	0.72 (0.60 to 0.88)	0.84 (0.58 to 1.21)
Adjusted RR† (95% CI)	1.02 (0.87 to 1.19)	1.00	0.72 (0.60 to 0.88)	0.86 (0.59 to 1.25)

*Adjusted RR were adjusted for maternal age, maternal pregestational BMI, ethnicity, education level, occupation, place of residence, smoking, passive smoking, alcohol, parity, gravidity, history of preterm birth, history of spontaneous abortion, history of induced abortion and hypertension.
†Adjusted RR were additionally adjusted for neonate sex.
IFG, impaired fasting glycaemia; LBW, low birth weight; LGA, large for gestational age; RR, risk ratio; SGA, small for gestational age.

China, which supports the good generalisability of our findings. Compared with the similar previous studies, we analysed the association between maternal pregestational glucose level and fatal loss including abortion and stillbirth first. Our study also has some limitations. First, our database lacked some important information during the pregnancy period, such as the information on pregnancy complications, including GDM and gestational hypertension. Thus, we could not adjust them in the multivariate analysis, which might have influenced our final findings. Second, whether the participants with pregestational hyperglycaemic had any treatment or intervention to fight



Macrosomia proportion (%)								
Hypoglycemia	0	0.04	0.04	0.11	0.37	1.28	3.58	4.42
Normoglycemia	0.01	0.02	0.06	0.10	0.25	0.86	3.38	4.14
IFG	0	0	0.08	0.16	0.24	0.75	3.61	4.25
Diabetic	0	0	0	0	0.18	1.06	5.31	6.02

Figure 2 Cumulative occurrence of macrosomia according to pregestational glucose. IFG, impaired fasting glycaemia.

insulin resistance after their preconception health examinations was unclear. Although this lack of information resulted in uncertainty and possible bias, we believe that the significant risk of macrosomia in women with pregestational diabetic hyperglycaemic women might be underestimated due to their higher probability of developing

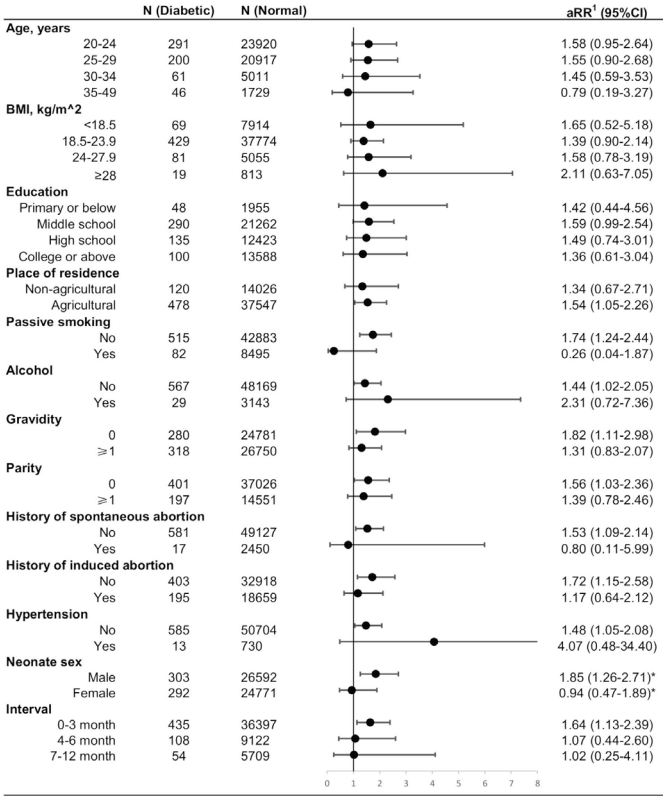


Figure 3 Subgroup analysis of macrosomia in the pregestational diabetic compared with the pregestational normoglycaemia. Interval: the period between the date of glucose testing and the date of the last menstrual period of pregnant women. [1]After adjusting maternal age, BMI, ethnicity, education level, occupation, place of residence, smoking, passive smoking, alcohol, parity, gravidity, history of preterm birth, history of abortion (spontaneous and induced), hypertension and neonate sex . *Additional adjustment for the gestational age in days. aRR, adjusted risk ratio; BMI, body mass index.

GDM and the possible subsequent intervention.[8 36] The aRR of macrosomia might be higher if there was no intervention before or during pregnancy. Third, as the number of cases, such as stillbirth, was significantly small after stratifying by glucose levels, the estimated RRs might not be reliable. Therefore, the findings of our study should be interpreted with caution since these factors might have an effect on the final associations between pregestational glucose level and pregnancy outcomes. Sensitivity analyses showed that the potential bias from missing data had few influences on the final findings (online supplemental table S1).

In this retrospective cohort from preconception to delivery, we found that once FBG testing of 7.0 mmol/L or higher within 1 year before the pregnancy might be considered as an early sign of overweight neonates. Considering that currently there are no standard guidelines for pre-pregnancy care on blood glucose management in China and many other low-income and middle-income countries, such evidence could justify the need for standard guidelines for maternal blood glucose testing and related interventions during pre-pregnancy care to improve pregnancy outcomes. Further high-quality prospective studies, which include information on mothers during the pregnancy, are needed to investigate the effect of pregestational glucose level on maternal outcomes and metabolic-related variables during pregnancy.

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Funding This study was supported by Natural Science Foundation of Shanghai (19ZR1444700); Innovation-oriented Science and Technology Grant from NHC Key Laboratory of Reproduction Regulation (No. CX2017-04); grant from Chongqing Science and Technology Bureau (cstc2017shmsA130102, cstc2017jxjl10001, 2019cstc-jbky-01701); grant from Health Commission of Chongqing province (2017ZDXM015); grant from NHC Key Laboratory of Reproduction Regulation (2017KF04); grant from Key Laboratory of Birth Defects and Reproductive Health of National Health and Family Planning Commission (2018cstc-kfkt-01718).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Institutional Review Board of the Chinese Association of Maternal and Child Health Studies. Written informed consent was obtained from all participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No additional data are available. Not applicable

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REFERENCES

1 von Kries R, Kimmerle R, Schmidt JE, *et al*. Pregnancy outcomes in mothers with pregestational diabetes: a population-based study in North Rhine (Germany) from 1988 to 1993. *Eur J Pediatr* 1997;156:963–7.
2 Vambergue A, Fajardy I. Consequences of gestational and pregestational diabetes on placental function and birth weight. *World J Diabetes* 2011;2:196–203.
3 Zheng W, Huang W, Liu C, *et al*. Weight gain after diagnosis of gestational diabetes mellitus and its association with adverse pregnancy outcomes: a cohort study. *BMC Pregnancy Childbirth* 2021;21:216.
4 , Metzger BE, Lowe LP, *et al*, HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991–2002.
5 Lowe LP, Metzger BE, Dyer AR, *et al*. Hyperglycemia and adverse pregnancy outcome (HAPO) study: associations of maternal A1C and glucose with pregnancy outcomes. *Diabetes Care* 2012;35:574–80.
6 Boriboonhirunsarn D, Sunsaneevithayakul P. Relationship between 50-g glucose challenge test and large for gestational age infants among pregnant women without gestational diabetes. *J Obstet Gynaecol* 2019;39:141–6.
7 Wei D, Zhang B, Shi Y, *et al*. Effect of preconception impaired glucose tolerance on pregnancy outcomes in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2017;102:3822–9.
8 Kouhkan A, Khamseh ME, Moini A, *et al*. Diagnostic accuracy of body mass index and fasting glucose for the prediction of gestational diabetes mellitus after assisted reproductive technology. *Int J Fertil Steril* 2019;13:32–7.
9 Chinese Diabetes S. National Offic for Primary Diabetes C. [National guidelines for the prevention and control of diabetes in primary care(2018)]. *Zhonghua Nei Ke Za Zhi* 2018;57:885–93.
10 Bao YQ. [Interpretation of blood glucose measurement in national guidelines for the prevention and control of diabetes in primary care(2018): early diagnosis and standard monitoring]. *Zhonghua Nei Ke Za Zhi* 2019;58:318–20.
11 Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. *Diabetes Res Clin Pract* 2011;93:299–309.
12 Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414:782–7.
13 Liu J, Zhang S, Liu M, *et al*. Maternal pre-pregnancy infection with hepatitis B virus and the risk of preterm birth: a population-based cohort study. *Lancet Glob Health* 2017;5:e624–32.
14 Zhou Q, Wang Q, Shen H, *et al*. Rubella virus immunization status in preconception period among Chinese women of reproductive age: a nation-wide, cross-sectional study. *Vaccine* 2017;35:3076–81.
15 Pan Y, Zhang S, Wang Q, *et al*. Investigating the association between prepregnancy body mass index and adverse pregnancy outcomes: a large cohort study of 536 098 Chinese pregnant women in rural China. *BMJ Open* 2016;6:e011227.
16 American Diabetes Association. 15. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care* 2021;44:S211–20.
17 American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care* 2021;44:S15–33.
18 Mills KT, Bundy JD, Kelly TN, *et al*. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation* 2016;134:441-50.
19 Wang T, Zhang J, Lu X, *et al*. Maternal early pregnancy body mass index and risk of preterm birth. *Arch Gynecol Obstet* 2011;284:813–9.
20 Jia W. Obesity in China: its characteristics, diagnostic criteria, and implications. *Front Med* 2015;9:129–33.
21 Zhang JP. Pregnancy complication. In: *Obstetrics and gynecology*. 9th ed. Beijing, China: People's Medical Publishing House, 2018: 140–6.
22 Blencowe H, Cousens S, Jassir FB, *et al*. National, regional, and worldwide estimates of stillbirth rates in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health* 2016;4:e98–108.
23 Zhu L, Zhang R, Zhang S, *et al*. [Chinese neonatal birth weight curve for different gestational age]. *Zhonghua Er Ke Za Zhi* 2015;53:97–103.
24 Catalano PM, McIntyre HD, Cruickshank JK, *et al*. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care* 2012;35:780–6.
25 Filardi T, Tavaglione F, Di Stasio M, *et al*. Impact of risk factors for gestational diabetes (GDM) on pregnancy outcomes in women with GDM. *J Endocrinol Invest* 2018;41:671–6.
26 Peng H-Y, Li M-Q, Li H-P. MiR-137 restricts the viability and migration of HTR-8/SVneo cells by downregulating FNDC5 in gestational diabetes mellitus. *Curr Mol Med* 2019;19:494–505.
27 Xing B, Wang L, Li Q, *et al*. Human embryonic stem cell-derived pancreatic endoderm alleviates diabetic pathology and improves reproductive outcome in C57BL/KsJ-Lep(db/+) gestational diabetes mellitus mice. *Nutr Res* 2015;35:603–9.
28 Starikov RS, Inman K, Has P, *et al*. Correlation of placental pathology and perinatal outcomes with hemoglobin A1c in early pregnancy in gravidas with pregestational diabetes mellitus. *Placenta* 2017;52:94–9.
29 Riskin-Mashiah S, Younes G, Damti A, *et al*. First-Trimester fasting hyperglycemia and adverse pregnancy outcomes. *Diabetes Care* 2009;32:1639–43.
30 Riskin-Mashiah S, Damti A, Younes G, *et al*. First trimester fasting hyperglycemia as a predictor for the development of gestational diabetes mellitus. *Eur J Obstet Gynecol Reprod Biol* 2010;152:163–7.
31 Kwik M, Seeho SKM, Smith C, *et al*. Outcomes of pregnancies affected by impaired glucose tolerance. *Diabetes Res Clin Pract* 2007;77:263–8.
32 Chan JCN, Malik V, Jia W, *et al*. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009;301:2129–40.
33 Kong L, Nilsson IAK, Gissler M, *et al*. Associations of maternal diabetes and body mass index with offspring birth weight and prematurity. *JAMA Pediatr* 2019;173:371–8.
34 Ricart W, López J, Mozas J, *et al*. Maternal glucose tolerance status influences the risk of macrosomia in male but not in female fetuses. *J Epidemiol Community Health* 2009;63:64–8.
35 Tang J, Zhu X, Li M, *et al*. The impact of maternal prepregnancy impaired fasting glucose on preterm birth and large for gestational age: a large population-based cohort study. *Am J Obstet Gynecol* 2020;222:265.e1–265.e19.
36 Salman L, Arbib N, Shmueli A, *et al*. The association between pre-pregnancy impaired fasting glucose and adverse perinatal outcome. *Diabetes Res Clin Pract* 2018;140:148–53.
37 Landon MB, Thom E, Spong CY, *et al*. The National Institute of child health and human development Maternal-Fetal medicine unit network randomized clinical trial in progress: standard therapy versus no therapy for mild gestational diabetes. *Diabetes Care* 2007;30 Suppl 2:S194–9.
38 Gui J, Li A, Su X, *et al*. Association between hyperglycemia in middle and late pregnancy and maternal-fetal outcomes: a retrospective study. *BMC Pregnancy Childbirth* 2014;14:34.
39 Mathiesen ER, Ringholm L, Damm P. Stillbirth in diabetic pregnancies. *Best Pract Res Clin Obstet Gynaecol* 2011;25:105–11.
40 Keshavarz M, Cheung NW, Babaee GR, *et al*. Gestational diabetes in Iran: incidence, risk factors and pregnancy outcomes. *Diabetes Res Clin Pract* 2005;69:279–86.