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Risk Factors and Glycemic Control in Small for Gestational Age Infants Born to Mothers with Gestational Diabetes Mellitus: A Case-Control Study Utilizing Propensity Score Matching Based on a Large Population

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TITLE PAGE

Title

Risk Factors and Glycemic Control in Small for Gestational Age Infants Born to Mothers with Gestational Diabetes Mellitus: A Case-Control Study Utilizing Propensity Score Matching Based on a Large Population

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Risk Factors and Glycemic Control in Small for Gestational Age Infants Born to Mothers with Gestational Diabetes Mellitus: A Case-Control Study Utilizing Propensity Score Matching Based on a Large Population

Abstract

Background: Small for gestational age (SGA) poses a significant concern for newborns, being linked to neonatal complications and potential metabolic disorders in adulthood, especially when born to mothers with gestational diabetes, elevating their risk of complications and mortality. However, the pregnancy risk factors and glycemic control associated with SGA infants born to mothers with gestational diabetes mellitus (GDM) remain unclear.

Aims: To identify the pregnancy risk factors and glycemic control associated with SGA infants born to mothers with GDM.

Method: This case-control study was conducted in Fujian among 1910 women with GDM. Data were collected by the integrated electronic medical record system. Using 1:4 propensity scores matching analysis to adjust gestational age as confounder. Univariate and multivariate analyses were performed to identify risk factors.

Results: Risk factors for SGA born to mothers with GDM included a history of low birth weight, gestational hypertension, oligohydramnios, short maternal height, underweight pre-pregnancy BMI, and inadequate weight growth. While SGA was protected by weakly positive ketonuria levels in the first trimester, multiparous, anemia, and previous uterine scar were protective factors for SGA. Moreover, 2h postprandial glucose in the third trimester, as well as the 0 h and 2 h 75g Oral Glucose Tolerance Test (OGTT) were linked to a decreased risk of SGA.

Conclusions: SGA infants are the result of multifactorial interactions among GDM pregnant women. Notably, OGTT and glycemic control levels were associated with SGA. There is a need for enhanced perinatal monitoring and antenatal care to reduce SGA.

Strengths and limitations of this study

- Propensity score matching effectively controlled for confounding variables and reduced bias, enhancing the study's result validity. This approach provided credible insights into risk factors and glycemic control for SGA infants born to mothers with GDM.
- A large population size increases statistical power, enabling the detection of subtle associations and providing more generalizable findings.
- As a case-control study relying on retrospective data from medical records, there might be incomplete or missing information that could influence the study outcomes.
- The findings may primarily apply to the specific population from which the data was collected, limiting their generalizability to other regions or diverse populations.

Keywords: Gestational diabetes mellitus; Small for gestational age; Pregnancy risk factors; Glycemic control

Background

Gestational diabetes mellitus (GDM) is a glucose intolerance that develops or first becomes detectable during pregnancy [1], which has the most common metabolic disease and affected up to 25% of pregnant women [2]. GDM is becoming more common in China, with 14.8% of pregnant women suffering from the disease [3]. It causes a slew of short-term and long-term maternal and fetal health issues, particularly associated with accelerated growth

velocity. Fetuses receive increased amounts of glucose through maternal hyperglycemia, which promotes insulin secretion and increases fetal growth [4]. Furthermore, hyperglycemia causes placental vascular dysfunction, reducing the supply of oxygen and nutrients to the fetus [5]. There is still 2.7% GDM pregnant women deliver children that have fetal growth restrictions (FGR) [6]. The incidence of small for gestational age (SGA) infants whose mothers had GDM was 6.45% in China [7], but it is little research is known about SGA infants born to Chinese women with GDM.

SGA infants are commonly defined as having birth weight below the 10th percentile for a given gestational age and sex [8], including constitutionally small infants without pathological growth restriction. In China, the total number of SGA births is the fifth highest in the world [9], which imposes a tremendous medical and socioeconomic burden. SGA infants have an increased risk of adverse perinatal outcomes: stillbirth, asphyxia, or birth defects. Additionally, compared to infants of appropriate for gestational age (AGA), SGA infants are prone to have poor cognitive or psychological outcomes as well as metabolic diseases, such as type 2 diabetes, insulin resistance, and arterial hypertension in adulthood [10], [11]. In addition, GDM has been linked to delayed development and stunted fetal growth [12], which may exacerbate the adverse health outcomes of SGA. Epidemiological studies have shown that SGA infants born to mothers with GDM have higher rates of neonatal complications or death [13], [14]. They are also at higher risk of developing long-term cardiovascular offspring hospitalization [15]. Given the seriousness of the consequences, identifying its potential influencing factors is of great significance for the screening and prevention of SGA births among GDM pregnant women.

Maternal glycemia is well known to be associated with perinatal outcomes, including

influencing offspring' birthweight [16]. According to Hyperglycemia and Adverse Pregnancy outcomes (HAPO), women with higher glucose levels are considered to be at greater risk. Currently, the goals of prenatal treatment are still tight glucose monitoring and strict glucose control [17], [18]. As a result, the portion of women who experience hypoglycemia is generally deemed to be at low risk for antenatal care. Several investigations have reported an association between maternal hypoglycemia and FGR or SGA [19]–[22]. Particularly, Asian women with low glucose levels are vulnerable to delivering infants with FGR [6]. Whereas other researchers haven't reached a similar conclusion [23]. Presently, the related pregnancy factors for SGA born to women with GDM remain unclear. Moreover, few studies have examined the maternal glycemic level associated with SGA infants born to mothers with GDM. After the diagnosis of GDM, timely recognition of glycemic abnormalities is critical for normal fetal growth and development. Consequently, the purpose of this study was to explore the influencing factors during pregnancy associated with SGA infants born to mothers with GDM in China.

Method

Study design and population

This case-control study included pregnancies affected by GDM who delivered between January 2019 and December 2020 from a tertiary Maternal and Child Health Hospital in Fuzhou City, Fujian Province. All pregnant women followed a routine prenatal care protocol and scheduled frequent visits to the health system to identify risk factors and initiate preventive care measures [24].

Eligible participants were pregnant women diagnosed with GDM based on 75 grams oral glucose tolerance test (OGTT) between 24–32 weeks' gestation according to the modified

International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [25], when one or more of the following glucose levels were elevated: fasting plasma glucose level ≥5.1 mmol/L, 1 h plasma glucose level ≥10.0 mmol/L, and 2 h plasma glucose level ≥8.5 mmol/L [25]. The pregnant women with multiple gestations, a clinical diagnosis of pregestational diabetes mellitus (PGDM), or overt diabetes (fasting plasma glucose (FBG) ≥ 7.0 mmol/L or 2-h ≥ 11.0 mmol/L) were excluded. A total of 6,839 participants were enrolled, all of whom had complete demographic and clinical data.

All participants included in this study were divided into the SGA group (case group, <10th percentile), AGA group (controlling group, between 10 and 90th percentile), and LGA group (>90th percentile) according to the association between gestational age and birth weight. Finally, for each SGA infant, four gestation age-matched AGA infants were randomly selected using PSM analysis with gestation age-matched (Figure 1).

Data collection and study outcomes

Maternal demographic characteristics, pregnancy characteristics and pregnancy complications, and outcomes were collected retrospectively by one researcher from the electronic medical record database of the one hospital in our study. In addition, we collected glycemic levels including 75g OGTT glycemia, FPG in the 3rd trimester, and 2-h postprandial glucose in the 3rd trimester. Based on the number of abnormal OGTT values, women with GDM were stratified into 1, 2, or 3 items of abnormal OGTT values, respectively (Supplementary material 1).

The primary outcome of this study was SGA babies born to women with GDM. Gestational age was determined by subtracting the date of last menstrual period (LMP) reported

by the mother or by the first ultrasound scan (USS) from the date of birth. SGA was defined as birth weight below the 10th percentile for gestational age and sex, based on birth weight curves in Chinese [26], [27].

Statistical analysis

All statistical analyses were performed using IBM SPSS, version 27.0, and R, version 4.1.3. We applied a 1:4 nearest-neighbor matching with a caliper of 0.01, a preset value for propensity score matching (PSM), to lessen the potential selection bias and obtain matched data. The outcomes were compared between the SGA group and the AGA group among GDM pregnant women. Continuous variables were presented as mean ± standard deviation (SD) or as medians (interquartile range [IQR] 25th percentile–75th percentile), compared by using independent *t*-test or the Mann–Whitney test Categorical variables were presented as the frequency with percentages and analyzed by the Chi-square test or Fisher's exact test.

We examined the risk factors associated with SGA infants born to mothers with GDM using the Binary logistic regression model. Variables were carefully chosen to ensure parsimony of the final model (forward LR, entry 0.05, removal 0.10). Further, to explore the association between maternal glycemic levels and SGA, adjusted for parity, previous uterine scar, history of low birth weight, gestational hypertensive disorder, oligohydramnios, anemia, pre-pregnancy BMI, height, GWG rate, and ketonuria in 1st trimester. A two-sided p-value of <0.05 was considered statistically significant in all analyses.

Ethics approval

This study was approved by the Ethics Committee (No.2019-161). Given all maternal and neonatal data were extracted from the hospital EMR system by a unique identifier with no

participant involved in the design, the written informed consent was waived.

3 Results

3.1 Selection of GDM pregnant women

A total of 6,839 GDM pregnant women were enrolled in the study according to eligible and exclusion criteria, including 382 SGA infants, 964 LGA infants, and 5,493 AGA infants. After the 1:4 PSM analysis, 382 SGA infants were selected and 1,528 AGA infants were randomly matched with the SGA group according to the gestational age at birth (Figure 1). After propensity analysis, the mean (*SD*) gestational age at birth was 38.6 (*SD* = 1.61) weeks in the AGA group and 38.59 (*SD* = 1.62) weeks in the SGA group, there was no evidence of differences in the gestational age between the two groups ($P = 0.983$).

3.2 Characteristics and univariate analysis of AGA and SGA

The average age of the participants was 31.67 (*SD* = 4.36) years old. Among all women, Han Chinese accounts for 97.91%. Approximately 50% of the participants in both groups had a college or university education. More than 50% of the women in the SGA group were nulliparous, which was slightly more than the percentage of women in the AGA group (35.3%) who were nulliparous ($P < 0.001$). The previous uterine scar was shown statistically significant ($P < 0.05$).

Regarding the pregnancy history, there was no statistically significant evidence of differences in the history of abortion or miscarriage, history of preterm delivery, history of fetal distress, and history of GDM. While statistically significant evidence of differences in history of macrosomia ($P = 0.012$) and history of low birth weight ($P = 0.04$).differences in oligohydramnios ($P < 0.001$) and anemia ($P = 0.034$) were statistically significant in terms of the

pregnancy complications.

In addition, height, pre-pregnancy BMI, and GWG rate were shown statistically significant (all $P<0.05$). Regarding the glycemic level, 75g OGTT 0 h and 2 h glycemia, ketonuria in 1st trimester, fasting glucose, and 2-h postprandial glucose in the 3rd trimester were shown statistically significant ($P<0.05$). The characteristics of the SGA group and AGA group are presented in Table 1.

3.3 Multivariable logistic regression analysis for the factors of SGA

The multivariable analysis indicated that history of low birth weight (OR=5.01, 95%CI 1.21-20.72, P=0.026) was an independent risk factor for SGA. Mothers with gestational hypertensive disorder were more likely to have SGA (Gestational hypertension: OR=2.78, 95%CI 1.68-4.59, $P<0.001$; preeclampsia and eclampsia: OR=6.31, 95%CI 3.35-11.91, $P<0.001$). The risk of SGA was fourfold greater in pregnant women with oligohydramnios than in women with normal amniotic fluid (OR=4.22, 95%CI 2.5-7.12, $P<0.001$). Mothers with lower height had a higher risk of SGA (150–154.9 cm: OR=2.02,95% CI1.46-2.79, $P<0.001$; 145–149.9 cm: OR=1.95, 95%CI 1.21-3.14, P=0.006; ＜145 cm: OR =7.42, 95%CI 1.76-31.25, P=0.006) compared with >155cm height. Underweight pre-pregnancy had a 64% more chance of SGA (OR = 1.64, 95%CI 1.17-2.3, P = 0.004) than normal. Also, mothers who had inadequate weight gain during pregnancy had a 37% more chance of SGA than appropriate gain (OR=1.37, 95%CI 1.05-1.8, P = 0.023).

However, the multivariate analysis also revealed that multiparous was a protective factor (OR=0.55, 95%CI 0.43-0.71, $P<0.001$) compared to nulliparity. The SGA risk was reduced by previous uterine scar experience (OR=0.57, 95%CI 0.39-0.83, P=0.004). Anemia was

associated with a decreased incidence of SGA (OR=0.71, 95%CI 0.53-0.96, *P*=0.027). Two or three items with elevated blood glucose values on OGTT showed a lower probability of SGA (OR=0.67,95%CI 0.52-0.86, *P*=0.002; OR=0.32, 95%CI 0.18-0.55, *P* ＜0.001) than one elevated item. Ketonuria levels ranging from 0.5 to 3.9 mmol/l in the 1st trimester had a lower risk of SGA than＜0.5 mmol/l. (OR=0.59, 95%CI 0.42-0.81, *P*=0.001). The forest map of multivariate logistic regression analysis is shown in Figure 2.

3.4 Association between Blood glucose level and the risk of SGA

We further explored the relationship between OGTT, glycemic control level in 3rd trimester and SGA. Specifically, multivariate analysis revealed that when adjusted for parity, previous uterine scar, history of low birth weight, gestational hypertensive disorder, oligohydramnios, anemia, pre-pregnancy BMI, height, GWG rate, and ketonuria in 1st trimester. 75g OGTT 0 h glycemia, 75g OGTT 2 h glycemia, and 2-h postprandial glucose in 3rd trimester were associated with a decreased risk for SGA (OR=0.44, 95% CI 0.32-0.6, *P* ＜0.001; OR=0.89, 95% CI 0.82-0.96, *P*=0.003; OR ＝0.84, 95% CI 0.76-0.93, *P*＜0.001). Nevertheless, 75g OGTT 0 h glycemia had a stronger association with SGA outcomes than 2-h OGTT and 2-h postprandial glucose in 3rd trimester did. While there were no significant associations between 75g OGTT 1 h glycemia, FPG in 3rd trimester and SGA (Table 2).

4 Discussion

In this retrospective study, some key maternal demographic characteristics (height, BMI, and GWG rate), pregnancy characteristics (parity, previous uterine scar, and history of LBW), pregnancy complications (hypertensive disorders, oligohydramnios, and anemia), OGTT (0h,

2h) and glycemic control level (2-h postprandial glucose in the 3rd trimester) were identified as risk factors for SGA in GDM.

Maternal height exerts the most significant effect. Our results also confirmed maternal stature ＜145cm is a strong indicator for SGA, which was similar to previous studies [28]. This may contribute to inadequate self-nutrition in GDM pregnant women who were short stature, while the shift to a sugar-controlled diet may have a significant impact on the adequate supply of nutrients for fetal growth. Further, GWG and BMI both reflect maternal nutritional status. This study found that inadequate weight gain and underweight BMI were associated with an increased risk of SGA in women with GDM, similar to previous findings. [29]. This may be due to pregnant women who were inadequate weight gain or were underweight may have chronic malnutrition, which is harmful to fetal growth and development. Thus, health education, pregnancy nutrition monitoring, and personalized nutrition therapy should be provided to women diagnosed with GDM by the hospital.

Nulliparous pregnant women with GDM were associated with an increased risk of SGA birth outcomes in this study. A retrospective study in Chinese suggested that nulliparity was associated with an increased risk of SGA [30]. This could be explained by multiparous women having higher uteroplacental blood flow, allowing the fetus to access more energy, and a larger uterine cavity creating favorable conditions for fetal growth [30]. While nulliparous women with a higher pulsatility index of uterine artery (UtA-PI) and higher blood impedance than multiparous women, resulting in less uteroplacental perfusion, blood flow and SGA [31], [32]. Apart from physiological reasons, first-time mothers with GDM have even less experience in managing the demands of dietary change and glycemic control. Cesarean sections are preferred

by Chinese women. In 2018, the rate of Chinese maternal cesarean section was 36.7%, the highest in Asia [33]. In this research, having a history of previous uterine scar reduced the risk of giving birth to SGA among GDM pregnant women. The reason could be concluded that the previous uterine scar may be the established association between the multiparous and high rate of cesarean section in China.

Women with GDM are also at an increased risk for Hypertensive disorders (HD) due to insulin resistance and underlying pathology of the metabolic syndrome [34]. HD is closely associated with birth weight [35], and GDM combined with HD increases the risk of adverse outcomes. This corresponds with our findings that gestational hypertension as well as preeclampsia and eclampsia are risk factors for delivering SGA in pregnant women with GDM. HD can cause maternal umbilical blood vessel spasms and systemic small arterial spasms, which affect maternal-fetal circulation and insufficient oxygen supply, thus affecting the intrauterine growth and development of the fetus [36]. With hypertensive disorders, the decrease of serum vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) levels and the increase of soluble fms-like tyrosine kinase-1 (sFLT-1) levels may reflect underlying placental dysfunction and are related to fetal growth and development inhibition [37], [38]. Oligohydramnios may be accompanied by complicated pregnancy, such as hypertensive disorders [39]. This could be a sign of chronic suboptimal placental function [40], which might reduce fetal resources and are associated with SGA. Thus, maternal blood pressure should be closely monitored and regular ultrasound examinations should be performed to assess changes in her condition.

Contrary to earlier research, this study discovered that maternal anemia during pregnancy

reduces the incidence of SGA [41]. The reason could be that women with GDM pay close attention to their diet, including supplementation recommended by their obstetrician to correct anemia. As a result, they may be able to reduce the risk of SGA with appropriate nutritional supplementation. Besides, the effect of anemia on pregnancy outcomes varies between gestational periods. Therefore, further research is needed to investigate the effect of hemoglobin concentration on SGA at different gestational ages.

There is no doubt that maternal glycemic parameter levels influence fetal growth [42]. Compared with GDM women having only one hyperglycemic value in OGTT, those with 2 or 3 elevated glucose values may decrease the risk of SGA. This may contribute to a more severe disturbance in glucose metabolism and insulin sensitivity. Blood glucose passes through the placental circulation to the fetus, and extra glucose in the fetus is stored as body fat [43]. Besides, OGTT-0h and OGTT-2h were found to be significant predictors of SGA when the glucose values were analyzed as continuous variables. Therefore, for GDM women with high fasting glucose and 2h OGTT are less likely to deliver SGA infants and therefore need to be aware of their potential to deliver high birth weight newborns. In addition, GDM women with low 0h and 2h OGTT do not need for excessively rigorous strict glucose control throughout pregnancy, but should be concerned about the occurrence of FGR. It is therefore important to adjust their dietary, exercise and insulin management strategies according to their glycaemic status. As a result, their nutritional measures, exercise, and insulin administration must be tailored to their glycemic condition.

The results of the multifactorial analysis showed that 2-h postprandial glucose in the 3rd trimester was associated with delivering SGA in pregnant women with GDM. 2-h postprandial

glucose after GDM diagnosis can reflect the appropriateness of a diet modification plan [44]. In clinical practice, pregnant women are advised to control their glycemic levels when diagnosed with GDM. However, due to fear of insulin and lack of knowledge about GDM treatment options, some women may follow an overly strict diet. Consequently, maternal glucose regulation is inadequate, which can lead to fetal undergrowth [20]. Hence, pregnant women diagnosed with GDM should be warned of the potential risk of SGA if they are found to have low glucose values. Besides, more attention should be paid to glucose status in the practice of maternal and child health care. Understanding the glycemic status is an important step in adjusting the diet and exercise plan, ideally to ensure normal fetal development and avoid SGA.

Limitation

There are a few limitations to our analysis. Firstly, data regarding women's history of smoking and drinking was not recorded. Although the incidence of smoking and drinking among pregnant women is low due to Chinese customs, smoking and drinking experience may be potential contributors to SGA. Secondly, data was collected from a single hospital and may not be representative of other areas. Thirdly, this study is a case-control study even though a PSM analysis was conducted to minimize the bias.

Conclusion

SGA infants born to women with GDM are the result of a multifactorial interaction, including maternal demographic characteristics, pregnancy characteristics, pregnancy complications and clinical and laboratory parameters. Notably, SGA was correlated with OGTT and glycemic control levels. It is difficult to reverse once SGA has occurred, perinatal

monitoring and antenatal care are crucial for identifying risk factors that can help predict and prevent SGA.

DECLARATION

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. The study was approved by the Ethical Committee of Fujian Maternal and Child Health Hospital, affiliated hospital of Fujian Medical University, China (No: 2019-161). As this was a retrospective case-control study involving review of medical records, informed consent from individual participants was not obtained. However, all data collected were treated confidentially and used solely for the purpose of this study. Measures were taken to ensure the privacy and anonymity of the patients' information.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions is available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest has been declared by the authors.

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Author contributions

Jianing Li and Yuqing Pan: Writing- Original draft preparation, Writing- Reviewing and Editing, Visualization. Xiumin Jiang: Supervision, Conceptualization. Qingxiang Zheng and Xiaoqian Chen: Methodology, Validation. Yu Zhu, Rulin Liu and Ling Huang: Investigation, Data curation.

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Figure 1 Flow diagram of selection of GDM pregnant women in this study

Abv: GDM: gestational diabetes mellitus; PSM: propensity score matching; AGA: appropriate for gestational age; LGA: Large for gestational age; SGA: small for gestational age.

Figure 2 Forest plot of the risk factors of SGA (Binary logistic regression analysis).

Table1 Characteristics of AGA group and SGA group matched according to 1:4 PSM analysis.

Variables	AGA group (n=1528)	SGA group (n=382)	x^2/t/Z	*P*
Maternal Age				
18~35	1220(79.8)	305(79.8)	0.063[a]	0.969
36~45	305(20)	76(19.9)		
≥46	3(0.2)	1(0.3)		
Nationality				
The Han	1498(98)	372(97.4)	0.638[a]	0.424
Minority nationality	30(2)	10(2.6)		
Residence				
Urban	825(54)	196(51.3)	0.884[a]	0.347
Rural	703(46)	186(48.7)		
Education				
Elementary and below	528(34.6)	126(33)	3.476[a]	0.324
Secondary / Highschool	223(14.6)	45(11.8)		
College / University	770(50.4)	210(55)		
Postgraduate or above	7(0.5)	1(0.3)		
Occupation				
Manual worker	284(18.6)	69(18.1)	2.074[a]	0.557
Mental worker	708(46.3)	192(50.3)		
Unemployed	381(24.9)	86(22.5)		
Freelance	155(10.1)	35(9.2)		
Marital status				
Unmarried	27(1.8)	8(2.1)	1.179[a]	0.555
Married	1497(98)	374(97.9)		
Divorced or widowed	4(0.3)	0(0)		
Parity				
Nulliparous	539(35.3)	195(51)	32.130[a]	**＜0.001**
Multiparous	989(64.7)	187(49)		
Assisted reproductive technology (ART)				
No	1446(94.6)	362(94.8)	.010[a]	0.919
Yes	82(5.4)	20(5.2)		
Previous uterine scar				
No	1196(78.3)	337(88.2)	19.089[a]	**＜0.001**
Yes	332(21.7)	45(11.8)		
Family history				
No	1367(89.5)	336(88)	2.809[a]	0.422
Hypertension	76(5)	26(6.8)		
Diabetes	46(3)	13(3.4)		

Both	39(2.6)	7(1.8)		
History of abortion or miscarriage				
No	896(58.6)	251(65.7)	6.393[a]	**0.041**
Spontaneous miscarriage	348(22.8)	71(18.6)		
Induced abortions	284(18.6)	60(15.7)		
History of preterm delivery				
No	1467(96)	368(96.3)	.087[a]	0.768
Yes	61(4)	14(3.7)		
History of macrosomia				
No	1481(96.9)	379(99.2)	6.290[a]	**0.012**
Yes	47(3.1)	3(0.8)		
History of GDM				
No	1523(99.7)	382(100)	1.253[a]	0.263
Yes	5(0.3)	0(0)		
History of fetal distress				
No	1512(99)	380(99.5)	.897[a]	0.343
Yes	16(1)	2(0.5)		
History of low birth weight				
No	1523(99.7)	376(98.4)	8.252[a]	**0.004**
Yes	5(0.3)	6(1.6)		
Intrahepatic cholestasis of pregnancy (ICP)				
No	1508(98.7)	377(98.7)	.000[a]	1.000
Yes	20(1.3)	5(1.3)		
Gestational hypertensive disorder				
No	1431(93.7)	324(84.8)	34.867[a]	**＜0.001**
Gestational hypertension	62(4.1)	31(8.1)		
Preeclampsia and eclampsia	27(1.8)	22(5.8)		
Chronic hypertension with superimposed preeclampsia	4(0.3)	3(0.8)		
Chronic hypertension (of any cause)	4(0.3)	2(0.5)		
Hyperthyroid				
No	1487(97.3)	376(98.4)	1.576[a]	0.209
Yes	41(2.7)	6(1.6)		
Hypothyroid				
No	1434(93.8)	349(91.4)	3.045[a]	0.081
Yes	94(6.2)	33(8.6)		
Anemia				
No	1149(75.2)	307(80.4)	4.508[a]	**0.034**
Yes	379(24.8)	75(19.6)		
Polyhydramnios				

No	1517(99.3)	381(99.7)	1.027[a]	0.311
Yes	11(0.7)	1(0.3)		
Oligohydramnios				
No	1490(97.5)	349(91.4)	32.314a	**<0.001**
Yes	38(2.5)	33(8.6)		
Height (cm)				
≥155	1248(81.7)	275(72)	22.232[a]	**<0.001**
150–154.9	197(12.9)	73(19.1)		
145–149.9	79(5.2)	29(7.6)		
< 145	4(0.3)	5(1.3)		
Pre-pregnancy BMI (kg/m²)				
Normal	1130(74)	271(70.9)	9.175[a]	**0.01**
Underweight	172(11.3)	64(16.8)		
Overweight / Obese	226(14.8)	47(12.3)		
GWG rate				
Inadequate gain	690(45.2)	199(52.1)	6.107[a]	**0.047**
Appropriate gain	539(35.3)	121(31.7)		
Excessive gain	299(19.6)	62(16.2)		
Ketonuria in 1st trimester(mmol/l)				
< 0.5	1049(68.7)	275(72)	9.963[a]	**0.007**
0.5-3.9	336(22)	59(15.4)		
≥4	143(9.4)	48(12.6)		
Ketonuria in 2nd trimester (mmol/l)				
< 0.5	1090(71.3)	293(76.7)	4.903[a]	0.086
0.5-3.9	308(20.2)	59(15.4)		
≥4	130(8.5)	30(7.9)		
Elevated blood glucose in OGTT				
One item	482(31.5)	161(42.1)	24.605[a]	**<0.001**
Two items	878(57.5)	204(53.4)		
Three items	168(11.0)	17(4.5)		
75g OGTT 0 h glycemia (mmol/l)	4.83±0.48	4.64±0.44	7.187	**<0.001**
75g OGTT 1 h glycemia (mmol/l)	9.84±1.41	9.89±1.36	-0.585	0.559
75g OGTT 2 h glycemia (mmol/l)	8.06±1.59	7.83±1.58	2.586	**0.01**
FPG in the 3rd trimester (mmol/l)	4.48(5.52-5.15)	4.69(4.40-5.01)	-4.7	**<0.001**
2-h postprandial glucose in 3rd trimester (mmol/l)	5.09±1.30	5.7±1.14	5.825	**<0.001**

494 **Abv:** SGA: small-for-gestational-age; AGA: appropriate-weight-for-gestational-age; OGTT:
495 Oral Glucose Tolerance Test; FPG: fasting plasma glucose; the first trimester of pregnancy:7–
496 10 gestational weeks; the second trimester of pregnancy: 21–24 gestational weeks; the third

trimester of pregnancy: 33–37 gestational weeks.

Bold values indicate statistically significant ($P < 0.05$)

Data are presented as n (%), mean ± SD, or median (interquartile range) as appropriate.

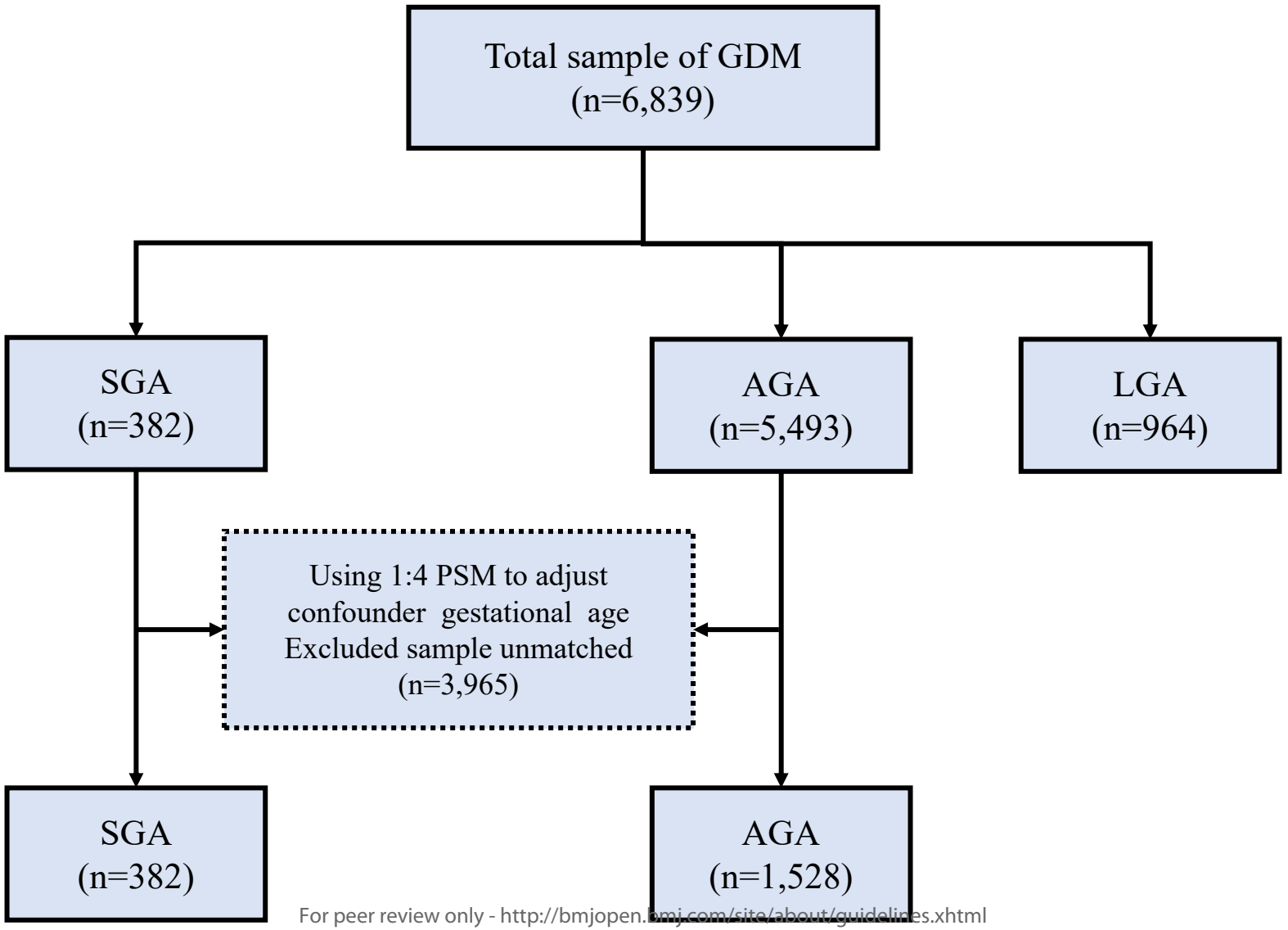
Table 2 Logistic regression analysis for SGA based on maternal glycemic parameters

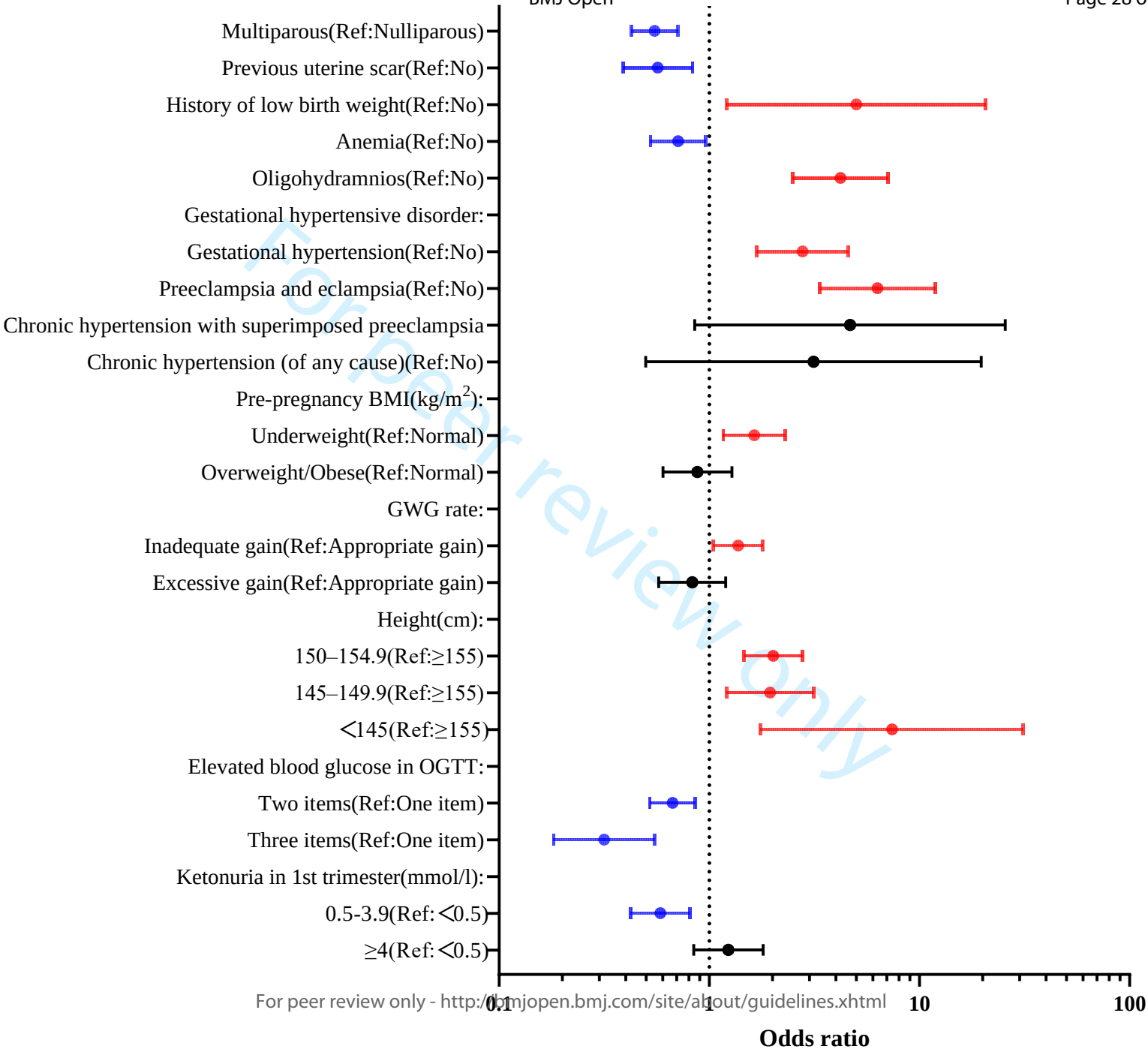
Variables	Crude OR (95% CI)	*P*	Adjusted† OR (95% CI)	*P*
75g OGTT 0 h glycemia	0.40(0.31-0.52)	**＜0.001**	0.44(0.32-0.6)	**＜0.001**
75g OGTT 1 h glycemia	1.02(0.95-1.11)	0.558	1.04(0.95-1.14)	0.378
75g OGTT 2 h glycemia	0.91(0.85-0.98)	**0.010**	0.89(0.82-0.96)	**0.003**
FPG in 3rd trimester	0.59(0.46-0.75)	**＜0.001**	0.89(0.68-1.15)	0.370
2-h postprandial glucose in 3rd trimester	0.76(0.68-0.84)	**＜0.001**	0.84(0.76-0.93)	**0.001**

† Adjusted for parity, previous uterine scar, history of low birth weight, gestational hypertensive disorder, oligohydramnios, anemia, pre-pregnancy BMI, height, GWG rate, and ketonuria in 1st trimester.

Abv: OGTT: Oral Glucose Tolerance Test; FPG: fasting plasma glucose; the third trimester of pregnancy: 33–37 gestational weeks.

OR: odd ratios, CI: confidence interval.





Supplementary material 1

1 Maternal demographic characteristic

Maternal characteristics collected included maternal age, ethnicity, educational level, occupation, marital status, place of residence, stature, pre-pregnancy Body mass index, and GWG rate.

Height: women were classified into four categories based on height < 145 cm, 145-149.9 cm, 150-154.9 cm, and ⩾155 cm. Body mass index (BMI): BMI was calculated as weight (kg)/ [height (m)]^2. Using BMI, women were classified as underweight (BMI<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (⩾ 30 kg/m^2). Gestational weight gain rate (GWG rate): To assess the adequacy of GWG among the study population, the GWG rate of each participant, which was calculated by dividing the total GWG by gestational age in weeks, was compared with the minimum recommended GWG rate. According to the IOM 2009 guidelines, The GWG of all included participants was categorized as inadequate weight gain, normal weight gain, and excessive weight gain.

2 Pregnancy characteristics

Pregnancy characteristics collected included parity, assisted reproductive technology-conceived pregnancy (ART), previous uterine scar (previous cesarean section or myomectomy), family history of hypertension or diabetes, pregnancy history (history of miscarriage, history of GDM, history of preterm labor, history of fetal distress, history of LBW).

3 Pregnancy complications

Pregnancy complications collected included intrahepatic cholestasis of pregnancy (ICP), pregnancy-associated hypertensive disorders, hyperthyroid, hypothyroid, anemia (defined by

hemoglobin < 11 g/dL before delivery) (Goonewardene, Shehata, and Hamad 2012), and pathology of amniotic fluid (oligohydramnios and polyhydramnios)

The gestational hypertensive disorder was classified into four categories: gestational hypertension, preeclampsia, and eclampsia, chronic hypertension with superimposed preeclampsia, preeclampsia and eclampsia chronic hypertension (of any cause), which was diagnosed using standard criteria (Anon 2013).

Reference

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Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary	2-3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	5-6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	5-6
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	8

		group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	7
Study size	#10	Explain how the study size was arrived at	n/a
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a
Statistical methods	#12c	Explain how missing data were addressed	
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	8
Participants	#13b	Give reasons for non-participation at each stage	8

Participants	#13c	Consider use of a flow diagram	Figure1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
Main results	#16b	Report category boundaries when continuous variables were categorized	8-9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10-11

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11-14
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

BMJ Open

Risk Factors and Glycemic Control in Small for Gestational Age Infants Born to Mothers with Gestational Diabetes Mellitus: A Case-Control Study Utilizing Propensity Score Matching Based on a Large Population

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Risk Factors, Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, Child protection < PAEDIATRICS

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TITLE PAGE

Title

Risk Factors and Glycemic Control in Small for Gestational Age Infants Born to Mothers with Gestational Diabetes Mellitus: A Case-Control Study Utilizing Propensity Score Matching Based on a Large Population

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Risk Factors and Glycemic Control in Small for Gestational Age Infants Born to Mothers with Gestational Diabetes Mellitus: A Case-Control Study Utilizing Propensity Score Matching Based on a Large Population

Abstract

Background: Small for gestational age (SGA) poses a significant concern for newborns, being linked to neonatal complications and potential metabolic disorders in adulthood, especially when born to mothers with gestational diabetes mellitus (GDM), elevating their risk of complications and mortality. However, the pregnancy risk factors and glycemic control associated with SGA infants born to mothers with GDM remain unclear.

Aims: To identify the pregnancy risk factors and glycemic control associated with SGA infants born to mothers with GDM.

Method: This case-control study was conducted among 1910 women with GDM in China. Data were collected by the integrated electronic medical record system. Using 1:4 propensity scores matching analysis to adjust gestational age as confounder. Univariate and multivariate analyses were performed to identify risk factors.

Results: Risk factors for SGA born to mothers with GDM included a history of low birth weight, gestational hypertension, oligohydramnios, short maternal height, underweight pre-pregnancy BMI, and inadequate weight growth. While SGA was protected by weakly positive ketonuria levels in the first trimester, multiparous, anemia, and previous uterine scar were protective factors for SGA. Moreover, 2-h postprandial glucose and hemoglobin A1c (HbA1c) in the 2nd trimester, as well as the 0-h and 2-h 75g Oral Glucose Tolerance Test (OGTT) were linked to

risk of SGA.

Conclusions: SGA infants are the result of multifactorial interactions among GDM pregnant women. Notably, OGTT and glycemic control levels were associated with SGA. There is a need for enhanced perinatal monitoring and antenatal care to reduce SGA.

Strengths and limitations of this study

- Propensity score matching effectively controlled for confounding variables and reduced bias, enhancing the study's result validity. This approach provided credible insights into risk factors and glycemic control for SGA infants born to mothers with GDM.
- A large population size increases statistical power, enabling the detection of subtle associations and providing more generalizable findings.
- As a case-control study relying on retrospective data from medical records, there might be incomplete or missing information that could influence the study outcomes.
- The findings may primarily apply to the specific population from which the data was collected, limiting their generalizability to other regions or diverse populations.

Keywords: Gestational diabetes mellitus; Glycemic control; Pregnancy risk factors; Small for gestational age

Background

Gestational diabetes mellitus (GDM) is a glucose intolerance that develops or first becomes detectable during pregnancy [1], which has the most common metabolic disease and affected up to 25% of pregnant women [2]. In China, the prevalence of GDM has been

increasing, with 14.8% of pregnant women now affected [3]. This condition gives rise to a range of short-term and long-term maternal and fetal health issues, particularly associated with increased pace of fetal growth. Fetuses receive increased amounts of glucose through maternal hyperglycemia, which promotes insulin secretion and increases fetal growth [4]. Furthermore, hyperglycemia causes placental vascular dysfunction, reducing the supply of oxygen and nutrients to the fetus [5]. There is still 2.7% GDM pregnant women deliver children that have fetal growth restrictions (FGR) [6]. Additionally, the incidence of small for gestational age (SGA) infants born to mothers with GDM was 6.45% in China [7]. However, limited research is available on SGA infants born to Chinese women with GDM.

SGA infants are commonly defined as having birth weight below the 10th percentile for a given gestational age and sex [8], including infants who are naturally small without pathological growth restriction. In China, the total number of SGA births is the fifth highest in the world [9], imposing a tremendous medical and socioeconomic burden. SGA infants have an increased risk of adverse perinatal outcomes, such as stillbirth, asphyxia, or birth defects. Additionally, compared to appropriate for gestational age (AGA) infants, SGA infants are prone to have poor cognitive or psychological outcomes as well as metabolic diseases, such as type 2 diabetes, insulin resistance, and arterial hypertension in adulthood [10], [11]. In addition, GDM has been linked to delayed development and stunted fetal growth [12]. This linkage may exacerbate the adverse health outcomes of SGA. Epidemiological studies show that SGA infants born to mothers with GDM have higher rates of neonatal complications or death [13], [14]. They are also at higher risk of developing long-term cardiovascular offspring hospitalization [15]. Given

the seriousness of the consequences, identifying its potential influencing factors is of great significance for the screening and prevention of SGA births among GDM pregnant women.

Maternal glycemia is widely recognized for its association with perinatal outcomes, including its impact on offspring' birthweight [16]. According to Hyperglycemia and Adverse Pregnancy outcomes (HAPO), women with higher glucose levels are considered to be at greater risk [17]. Current prenatal treatment goals emphasize tight glucose monitoring and strict glucose control [18], [19]. Consequently, women experiencing hypoglycemia are generally deemed to be at low risk for antenatal care. Several investigations have reported an association between maternal hypoglycemia and FGR or SGA [20]–[23]. Presently, the pregnancy factors related to SGA infants born to women with GDM remain unclear. Moreover, few studies have examined the association between maternal glycemic level associated with SGA infants born to mothers with GDM. After the diagnosis of GDM, timely recognition of glycemic abnormalities is critical for normal fetal growth and development. Therefore, the purpose of this study was to explore the influencing factors during pregnancy associated with SGA infants born to mothers with GDM in China.

Methods

Study design and population

This case-control study included pregnancies affected by GDM who delivered between January 2019 and December 2020 from a tertiary Maternal and Child Health Hospital in Fuzhou City, Fujian Province. All pregnant women followed a routine prenatal care protocol, scheduling frequent visits to the health system to identification of risk factors and initiation of

preventive care measures [24].

Eligible participants were pregnant women diagnosed with GDM based on 75-gram oral glucose tolerance test (OGTT) conducted between 24 and 32 weeks of gestation, following the modified International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria [25]. Diagnosis criteria included one or more elevated glucose levels: fasting plasma glucose level ≥5.1 mmol/L, 1-h plasma glucose level ≥10.0 mmol/L, and 2-h plasma glucose level ≥8.5 mmol/L [25]. Pregnant women with multiple gestations, a clinical diagnosis of pregestational diabetes mellitus (PGDM), or overt diabetes (fasting plasma glucose (FPG) ≥ 7.0 mmol/L or 2-h ≥ 11.0 mmol/L) were excluded. A total of 6,839 participants were enrolled, all of whom had complete demographic and clinical data.

All participants in this study were categorized into the SGA group (case group, <10th percentile), AGA group (controlling group, between 10 and 90th percentile), and LGA group (>90th percentile) according to the association between gestational age and birth weight. Finally, for each SGA infant, four gestation age-matched AGA infants were randomly selected using PSM analysis with gestation age-matched (Figure 1).

Patient and public involvement

No patients involved.

Data collection and study outcomes

Maternal demographic characteristics, pregnancy characteristics and pregnancy complications, and outcomes were collected retrospectively by one researcher from the electronic medical record database of the one hospital in our study. In addition, we collected

glycemic levels including 75g OGTT glycemia, FPG, 2-h postprandial glucose, and HbA1c in the 2nd trimester. Based on the number of abnormal OGTT values, women with GDM were stratified into 1, 2, or 3 items of abnormal OGTT values, respectively (Supplementary material 1).

The primary outcome of this study was SGA babies born to women with GDM. Gestational age was determined by subtracting the date of last menstrual period (LMP) reported by the mother or by the first ultrasound scan (USS) from the date of birth. SGA was defined as birth weight below the 10th percentile for gestational age and sex, based on birth weight curves in Chinese [26], [27].

Statistical analysis

All statistical analyses were performed using IBM SPSS, version 27.0, and R, version 4.1.3. We applied a 1:4 nearest-neighbor matching with a caliper of 0.01, a preset value for propensity score matching (PSM), to lessen the potential selection bias and obtain matched data. The outcomes were compared between the SGA group and the AGA group among GDM pregnant women. Continuous variables were presented as mean ± standard deviation (SD) or as medians (interquartile range [IQR] 25th percentile–75th percentile), compared by using independent *t*-test or the Mann–Whitney test Categorical variables were presented as the frequency with percentages and analyzed by the Chi-square test or Fisher's exact test.

We examined the risk factors associated with SGA infants born to mothers with GDM using the Binary logistic regression model. Variables were carefully chosen to ensure parsimony of the final model (forward LR, entry 0.05, removal 0.10). Further, to explore the

association between maternal glycemic levels and SGA, adjusted for parity, previous uterine scar, history of low birth weight, history of macrosomia, gestational hypertensive disorder, oligohydramnios, anemia, pre-pregnancy BMI, height, Gestational weight gain (GWG) rate, and ketonuria in 1st trimester. A two-sided p-value of <0.05 was considered statistically significant in all analyses.

Ethics approval

This study was approved by the Ethics Committee (No.2019-161). Given all maternal and neonatal data were extracted from the hospital electronic medical record system by a unique identifier with no participant involved in the design, the written informed consent was waived.

3 Results

3.1 Selection of GDM pregnant women

A total of 6,839 GDM pregnant women were enrolled in the study according to eligible and exclusion criteria, including 382 SGA infants, 964 LGA infants, and 5,493 AGA infants. After the 1:4 PSM analysis, 382 SGA infants were selected and 1,528 AGA infants were randomly matched with the SGA group according to the gestational age at birth (Figure 1). After propensity analysis, the mean (*SD*) gestational age at birth was 38.6 (*SD* = 1.61) weeks in the AGA group and 38.59 (*SD* = 1.62) weeks in the SGA group, there was no evidence of differences in the gestational age between the two groups ($P = 0.983$).

3.2 Characteristics and univariate analysis of AGA and SGA

The average age of the participants was 31.67 (*SD* = 4.36) years old. Among all women, Han Chinese accounts for 97.91%. Approximately 50% of the participants in both groups had

a college or university education. More than 50% of the women in the SGA group were nulliparous, which was slightly more than the percentage of women in the AGA group (35.3%) who were nulliparous ($P < 0.001$). The previous uterine scar was shown statistically significant ($P < 0.05$).

In terms of pregnancy history, there were no statistically significant differences observed in the occurrence of abortion or miscarriage, preterm delivery, fetal distress, or GDM. However, a statistically significant association was found between a history of macrosomia ($P = 0.012$) and low birth weight ($P = 0.04$). Regarding pregnancy complications, statistically significant differences were identified in the occurrence of oligohydramnios ($P < 0.001$) and anemia ($P = 0.034$). In addition, height, pre-pregnancy BMI, and GWG rate were shown statistically significant (all $P < 0.05$). Regarding the glycemic level, 75g OGTT 0 h and 2 h glycemia, as well as ketonuria in 1st trimester, fasting glucose, and 2-h postprandial glucose in the 2nd trimester, showed statistically significant ($P < 0.05$). However, 75g OGTT 1 h and HbA1c in the 2nd trimester did not exhibit significant differences ($P > 0.05$). The characteristics of the SGA group and AGA group are presented in Table 1 and Table 2.

3.3 Multivariable logistic regression analysis for the factors of SGA

The multivariable analysis indicated that history of low birth weight (OR=5.01, 95%CI 1.21-20.72, P=0.026) was an independent risk factor for SGA. Mothers with gestational hypertensive disorder were more likely to have SGA (Gestational hypertension: OR=2.78, 95%CI 1.68-4.59, $P < 0.001$; preeclampsia and eclampsia: OR=6.31, 95%CI 3.35-11.91, $P < 0.001$). The risk of SGA was fourfold greater in pregnant women with oligohydramnios than in

women with normal amniotic fluid (OR=4.22, 95%CI 2.5-7.12, P ＜0.001). Mothers with lower height had a higher risk of SGA (150–154.9 cm: OR=2.02,95% CI1.46-2.79, P ＜ 0.001; 145–149.9 cm: OR=1.95, 95%CI 1.21-3.14, P=0.006; ＜145 cm: OR =7.42, 95%CI 1.76-31.25, P=0.006) compared with >155cm height. Underweight pre-pregnancy had a 64% more chance of SGA (OR = 1.64, 95%CI 1.17-2.3, P = 0.004) than normal. Also, mothers who had inadequate weight gain during pregnancy had a 37% more chance of SGA than appropriate gain (OR=1.37, 95%CI 1.05-1.8, P = 0.023).

However, the multivariate analysis also revealed that multiparous was a protective factor (OR=0.55, 95%CI 0.43-0.71, P＜0.001) compared to nulliparity. The SGA risk was reduced by previous uterine scar experience (OR=0.57, 95%CI 0.39-0.83, P=0.004). Anemia was associated with a decreased incidence of SGA (OR=0.71, 95%CI 0.53-0.96, P=0.027). Two or three items with elevated blood glucose values on OGTT showed a lower probability of SGA (OR=0.67,95%CI 0.52-0.86, P=0.002; OR=0.32, 95%CI 0.18-0.55, P ＜ 0.001) than one elevated item. Ketonuria levels ranging from 0.5 to 3.9 mmol/l in the 1st trimester had a lower risk of SGA than＜0.5 mmol/l. (OR=0.59, 95%CI 0.42-0.81, P=0.001). The forest map of multivariate logistic regression analysis is shown in Figure 2.

3.4 Association between Blood glucose level and the risk of SGA

We further explored the relationship between OGTT, glycemic control level in the 2nd trimester and SGA. Specifically, multivariate analysis revealed that when adjusted for parity, previous uterine scar, history of macrosomia, history of low birth weight, gestational hypertensive disorder, oligohydramnios, anemia, pre-pregnancy BMI, height, GWG rate, and

ketonuria in 1st trimester. 75g OGTT 0 h, 75g OGTT 2 h, and 2-h postprandial glucose in 2nd trimester were associated with a decreased risk for SGA (OR=0.4, 95% CI 0.29-0.55, $P<0.001$; OR=0.88, 95% CI 0.81-0.95, $P=0.002$; OR = 0.81, 95% CI 0.73-0.9, $P<0.001$). However, 75g OGTT 0 h glycemia exhibited a stronger association with SGA outcomes than 2-h OGTT and 2-h postprandial glucose in the 2nd trimester. In contrast, HbA1c in the 2nd trimester was associated with an increased risk of SGA (OR=2.4, 95% CI 1.64-3.52, $P < 0.001$) (Table 3).

4 Discussion

In this Case-Control study, several key maternal demographic characteristics (height, BMI, and GWG rate), pregnancy characteristics (parity, previous uterine scar, and history of LBW), pregnancy complications (hypertensive disorders, oligohydramnios, and anemia), OGTT (0h, 2h) and glycemic control level (2-h postprandial glucose and HbA1c in the 2nd trimester) were identified as risk factors for SGA in women with GDM.

Maternal height exerts the most significant influence. Our results confirmed maternal stature below145cm is a strong indicator for SGA, aligning with previous studies [28]. This may contribute to inadequate self-nutrition in GDM pregnant women who are of short stature. The transition to a sugar-controlled diet may have a significant impact on the adequate supply of nutrients for fetal growth. Further, both GWG and BMI serve as reflections of maternal nutritional status. Our study reveals that inadequate weight gain and underweight BMI were associated with an increased risk of SGA in women with GDM, consistent with prior research [29]. This heightened risk may be attributed to pregnant women experiencing inadequate weight gain or being underweight, potentially indicating chronic malnutrition, which can be

detrimental to fetal growth and development. Therefore, it is imperative that hospitals offer comprehensive health education, monitor pregnancy nutrition, and implement personalized nutrition therapy for women diagnosed with GDM.

Nulliparous pregnant women with gestational diabetes mellitus (GDM) exhibited an increased susceptibility to small for gestational age (SGA) births in our study, corroborating findings from a prior retrospective Chinese study [30]. This heightened risk can be attributed to physiological disparities between nulliparous and multiparous women. Multiparous women showcased superior uteroplacental circulation, optimizing oxygen and nutrient delivery to the fetus and creating a conducive environment for fetal growth [30]. Conversely, nulliparous women displayed potential hemodynamic differences, including a higher pulsatility index of the uterine artery (UtA-PI) and elevated blood impedance, contributing to an elevated risk of SGA [31], [32]. Moreover, multiparous women were likely to possess a higher degree of maternal adaptation to gestational changes, encompassing improved blood volume expansion and hormonal regulation, thus fostering a favorable environment for fetal growth and diminishing the likelihood of SGA. Notably, differences in risk perception and prenatal care practices were apparent. Multiparous women, drawing on their experience, demonstrated proactive management skills for dietary changes and glycemic control, resulting in more effective prenatal care and potentially reducing the risk of SGA. Conversely, nulliparous women's relative inexperience might contribute to delayed or suboptimal prenatal care, impacting fetal growth outcomes.

Our research findings revealed an intriguing association wherein a history of a previous

uterine scar appeared to reduce the risk of SGA births among pregnant women with GDM. Remarkably, cesarean sections are widely preferred by Chinese women, with a national rate reaching 36.7% in 2018, the highest in Asia [33]. In the context of Chinese obstetric practices, where multiparity is linked with a higher likelihood of opting for cesarean sections, it raises the possibility that the protective influence on SGA outcomes could be influenced by the prevalence of cesarean deliveries. It is important to emphasize that while a history of cesarean section may be associated with a lower risk of SGA, it does not imply that cesarean section itself is a recommended method for preventing SGA. The choice of delivery method should still be based on medical evaluations, taking into account the specific circumstances of the current pregnancy and medical indications.

Women with GDM face an increased risk for Hypertensive disorders (HD) due to insulin resistance and the underlying pathology of the metabolic syndrome [34]. HD is closely associated with birth weight [35], and when combined with GDM, it elevates the risk of adverse outcomes. This corresponds with our findings that gestational hypertension as well as preeclampsia and eclampsia are risk factors for delivering SGA in pregnant women with GDM. HD can induce spasms in maternal umbilical blood vessels and systemic small arteries, impacting maternal-fetal circulation and insufficient oxygen supply. Consequently, this affects the intrauterine growth and development of the fetus [36]. The presence of hypertensive disorders with a decrease in serum vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) levels, alongside an increase in soluble fms-like tyrosine kinase-1 (sFLT-1) levels. These changes may reflect underlying placental dysfunction and are related to

inhibition in fetal growth and development [37], [38]. Oligohydramnios, often seen in conjunction with hypertensive disorders [39], may indicate complicated pregnancies, signifying chronic suboptimal placental function [40]. Such conditions could reduce fetal resources and are associated with SGA. Thus, maternal blood pressure should be closely monitored and regular ultrasound examinations should be performed to assess changes in pregnancy status.

Contrary to earlier research, this study discovered that maternal anemia during pregnancy reduces the incidence of SGA [41]. One possible explanation is that women with GDM are particularly attentive to their diet, incorporating supplementation recommended by their obstetricians to address anemia. Consequently, they may effectively mitigate the risk of SGA through appropriate nutritional support. Besides, the effect of anemia on pregnancy outcomes varies between gestational periods. Therefore, further research is needed to investigate the effect of hemoglobin concentration on SGA at different gestational ages.

Maternal glycemic parameters significantly influence fetal growth, as highlighted by findings from the HAPO study. Pregnant women with elevated glucose levels face a higher risk of adverse pregnancy outcomes. This association is driven by various mechanisms. Firstly, heightened glucose levels can stimulate increased fetal insulin production, promoting excessive fetal growth and contributing to macrosomia [17]. Conversely, elevated glucose levels may, in some instances, impair placental function, leading to reduced nutrient and oxygen supply to the fetus, ultimately resulting in growth restriction and the birth of SGA infants [42]. Our study found that GDM women with 2 or 3 elevated glucose values, as opposed to just one, may experience a decreased risk of SGA. Besides, higher OGTT-0h and OGTT-2h were found to be

significant predictors of SGA when the glucose values were analyzed as continuous variables. This may contribute to within the mild elevation range of blood glucose levels, blood glucose passes through the placental circulation to the fetus, and extra glucose in the fetus is stored as body fat [43]. There may be a protective mechanism ensuring that the fetus receives adequate nutrients within the normal range. However, this does not imply that higher blood glucose levels are better. When blood glucose rises to a certain extent, adaptive responses may be triggered, leading to the occurrence of SGA. Therefore, GDM women with elevated OGTT-0h and OGTT-2h levels are less likely to deliver SGA infants. However, they should be aware of more severe disturbance in glucose metabolism and insulin sensitivity and the potential for delivering high birth weight newborns. In addition, GDM women with low OGTT-0h and OGTT-2h do not need for excessively strict glucose control throughout pregnancy, but should be concerned about the occurrence of FGR. Therefore, personalized monitoring is crucial for assessing maternal blood glucose levels, allowing for the adjustment of dietary, exercise, and insulin management strategies based on their glycemic status.

Our study identified an association between delivering SGA in pregnant women with GDM and 2-h postprandial glucose in the 2nd trimester. Measuring 2-h postprandial glucose helps evaluate the effectiveness of dietary modifications and glycemic control strategies [44]. In clinical practice, pregnant women are advised to control their glycemic levels through dietary adjustments when diagnosed with GDM. However, due to fear of insulin and lack of knowledge about GDM treatment options, some women may follow an overly strict diet. Consequently, maternal glucose regulation is inadequate, which can lead to fetal undergrowth [21].Hence,

pregnant women diagnosed with GDM should be warned of the potential risk of SGA if they are found to have low glucose values. Besides, compared to the late pregnancy period, timely blood glucose testing in the second trimester provides a longer time window. More attention should be paid to glucose status during this period. Understanding the glycemic status is a crucial step in adjusting the diet and exercise plan to achieve stable blood glucose levels, ensuring normal fetal development, and avoiding SGA.

The multifactorial analysis revealed the association between elevated HbA1c levels in the second trimester and an increased risk of SGA, suggesting a potential impact of long-term glucose control on fetal outcomes. However, this finding different with a previous study [45], and contradicts the results of instantaneous glycemic measures (OGTT and 2-h postprandial glucose) in our study. This discrepancy may be attributed to the curvilinear relationship between HbA1c and fetal weight. Specifically, normal fetal weight may occur at low HbA1c levels, while moderately raised levels may result in macrosomia, and very high HbA1c levels may be associated with severe intrauterine growth restriction [46]. Future research could explore the relationship between glycemic control and birth weight using unrestricted cubic splines or subgroup analyses to evaluate their correlation. This approach would contribute to a more comprehensive understanding of the intricate relationship between maternal glycemic and fetal outcomes.

Limitation

There are a few limitations to our analysis. Firstly, data regarding women's history of smoking and drinking was not recorded. Although the incidence of smoking and drinking

among pregnant women is low due to Chinese customs, smoking and drinking experience may be potential contributors to SGA. Secondly, data was collected from a single hospital and may not be representative of other areas. Thirdly, this study is a case-control study even though a PSM analysis was conducted to minimize the bias. Lastly, this study lies in the inability to accurately differentiate FGR from overall SGA during the grouping process, aligning with the specific objectives of the study. Future research endeavors could consider employing more specific diagnostic criteria and focusing explicitly on FGR, offering a more comprehensive understanding of these distinct fetal growth conditions.

Conclusion

SGA infants born to women with GDM are the result of a multifactorial interaction, including maternal demographic characteristics, pregnancy characteristics, pregnancy complications and clinical and laboratory parameters. Notably, SGA was correlated with OGTT and glycemic control levels. It is difficult to reverse once SGA has occurred, perinatal monitoring and antenatal care are crucial for identifying risk factors that can help predict and prevent SGA.

DECLARATION

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. The study was approved by the Ethical Committee of Fujian Maternal and Child Health Hospital, affiliated hospital of Fujian Medical University, China (No: 2019-161). As this was a retrospective case-

control study involving review of medical records, informed consent from individual participants was not obtained. However, all data collected were treated confidentially and used solely for the purpose of this study. Measures were taken to ensure the privacy and anonymity of the patients' information.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions is available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest has been declared by the authors.

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Author contributions

Jianing Li and Yuqing Pan: Writing- Original draft preparation, Writing- Reviewing and Editing, Visualization. Xiumin Jiang: Supervision, Conceptualization. Qingxiang Zheng and Xiaoqian Chen: Methodology, Validation. Yu Zhu, Rulin Liu and Ling Huang: Investigation, Data curation.

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Figure 1 Flow diagram of selection of GDM pregnant women in this study

Abv: GDM: gestational diabetes mellitus; PSM: propensity score matching; AGA: appropriate for gestational age; LGA: Large for gestational age; SGA: small for gestational age.

Figure 2 Forest plot of the risk factors of SGA (Binary logistic regression analysis).

Table1 Maternal demographic characteristic of AGA group and SGA group matched according to 1:4 PSM analysis.

Variables	Items	AGA group (n=1528)	SGA group (n=382)	x^2/t	*P*
Maternal Age	18~35	1220(79.8)	305(79.8)	0.395	1.000[a]
	36~45	305(20)	76(19.9)		
	≥46	3(0.2)	1(0.3)		
Nationality	The Han	1498(98)	372(97.4)	0.638	0.424
	Minority nationality	30(2)	10(2.6)		
Residence	Urban	825(54)	196(51.3)	0.884	0.347
	Rural	703(46)	186(48.7)		
Education	Elementary and below	528(34.6)	126(33)	3.476	0.324
	Secondary / Highschool	223(14.6)	45(11.8)		
	College / University	770(50.4)	210(55)		
	Postgraduate or above	7(0.5)	1(0.3)		
Occupation	Manual worker	284(18.6)	69(18.1)	2.074	0.557
	Mental worker	708(46.3)	192(50.3)		
	Unemployed	381(24.9)	86(22.5)		
	Freelance	155(10.1)	35(9.2)		
Marital status	Unmarried	27(1.8)	8(2.1)	0.685	0.730[a]
	Married	1497(98)	374(97.9)		
	Divorced or widowed	4(0.3)	0(0)		
Height (cm)	≥155	1248(81.7)	275(72)	22.232	**<0.001**
	150–154.9	197(12.9)	73(19.1)		
	145–149.9	79(5.2)	29(7.6)		
	< 145	4(0.3)	5(1.3)		
Pre-pregnancy BMI (kg/m^2)	Normal	1130(74)	271(70.9)	9.175	**0.01**
	Underweight	172(11.3)	64(16.8)		
	Overweight / Obese	226(14.8)	47(12.3)		
GWG rate	Inadequate gain	690(45.2)	199(52.1)	6.107	**0.047**
	Appropriate gain	539(35.3)	121(31.7)		
	Excessive gain	299(19.6)	62(16.2)		

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Table 2 Pregnancy characteristics of AGA group and SGA group matched according to 1:4 PSM analysis.

Variables	Items	AGA group (n=1528)	SGA group (n=382)	x^2	*P*
Parity	Nulliparous	539(35.3)	195(51)	32.13	**< 0.001**
	Multiparous	989(64.7)	187(49)		
Assisted reproductive technology (ART)	No	1446(94.6)	362(94.8)	0.01	0.919
	Yes	82(5.4)	20(5.2)		
Previous uterine scar	No	1196(78.3)	337(88.2)	19.089	**< 0.001**
	Yes	332(21.7)	45(11.8)		
Family history	No	1367(89.5)	336(88)	2.809	0.422
	Hypertension	76(5)	26(6.8)		
	Diabetes	46(3)	13(3.4)		
	Both	39(2.6)	7(1.8)		
History of abortion or miscarriage	No	896(58.6)	251(65.7)	6.393	**0.041**
	Spontaneous miscarriage	348(22.8)	71(18.6)		
	Induced abortions	284(18.6)	60(15.7)		
History of preterm delivery	No	1467(96)	368(96.3)	0.087	0.768
	Yes	61(4)	14(3.7)		
History of macrosomia	No	1481(96.9)	379(99.2)	6.29	**0.012**
	Yes	47(3.1)	3(0.8)		
History of GDM	No	1523(99.7)	382(100)	/	0.590[b]
	Yes	5(0.3)	0(0)		
History of fetal distress	No	1512(99)	380(99.5)	0.897	0.343
	Yes	16(1)	2(0.5)		
History of low birth weight	No	1523(99.7)	376(98.4)	/	**0.011**[b]
	Yes	5(0.3)	6(1.6)		
Intrahepatic cholestasis of pregnancy (ICP)	No	1508(98.7)	377(98.7)	0	1
	Yes	20(1.3)	5(1.3)		

Gestational hypertensive disorder	No	1431(93.7)	324(84.8)	31.269	**< 0.001**[a]
	Gestational hypertension	62(4.1)	31(8.1)		
	Preeclampsia and eclampsia	27(1.8)	22(5.8)		
	Chronic hypertension with superimposed preeclampsia	4(0.3)	3(0.8)		
	Chronic hypertension (of any cause)	4(0.3)	2(0.5)		
Hyperthyroid	No	1487(97.3)	376(98.4)	1.576	0.209
	Yes	41(2.7)	6(1.6)		
Hypothyroid	No	1434(93.8)	349(91.4)	3.045	0.081
	Yes	94(6.2)	33(8.6)		
Anemia	No	1149(75.2)	307(80.4)	4.508	**0.034**
	Yes	379(24.8)	75(19.6)		
Polyhydramnios	No	1517(99.3)	381(99.7)	/	0.479[b]
	Yes	11(0.7)	1(0.3)		
Oligohydramnios	No	1490(97.5)	349(91.4)	32.314	**< 0.001**
	Yes	38(2.5)	33(8.6)		
Ketonuria in 1st trimester(mmol/l)	< 0.5	1049(68.7)	275(72)	9.963	**0.007**
	0.5-3.9	336(22)	59(15.4)		
	≥4	143(9.4)	48(12.6)		
Ketonuria in 2nd trimester (mmol/l)	< 0.5	1090(71.3)	293(76.7)	4.903	0.086
	0.5-3.9	308(20.2)	59(15.4)		
	≥4	130(8.5)	30(7.9)		
Elevated blood glucose in OGTT	One item	482(31.5)	161(42.1)	24.605	**< 0.001**
	Two items	878(57.5)	204(53.4)		
	Three items	168(11.0)	17(4.5)		
75g OGTT 0 h glycemia (mmol/l)		4.83±0.48	4.64±0.44	7.187	**< 0.001**
75g OGTT 1 h glycemia (mmol/l)		9.84±1.41	9.89±1.36	-0.585	0.559
75g OGTT 2 h glycemia (mmol/l)		8.06±1.59	7.83±1.58	2.586	**0.01**

FPG in the 2nd trimester (mmol/l)	4.87±0.559	4.73±0.488	4.372	**< 0.001**
2-h postprandial glucose in 2nd trimester (mmol/l)	6.09±1.30	5.7±1.14	5.825	**< 0.001**
HbA1c in the 2nd trimester (mmol/l)	5.26±0.356	5.28±0.349	-1.008	0.314

Abv: SGA: small-for-gestational-age; AGA: appropriate-weight-for-gestational-age; OGTT: *Oral Glucose Tolerance Test;* FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; the first trimester of pregnancy:7–10 gestational weeks; the second trimester of pregnancy: 21–24 gestational weeks; the third trimester of pregnancy: 33–37 gestational weeks.

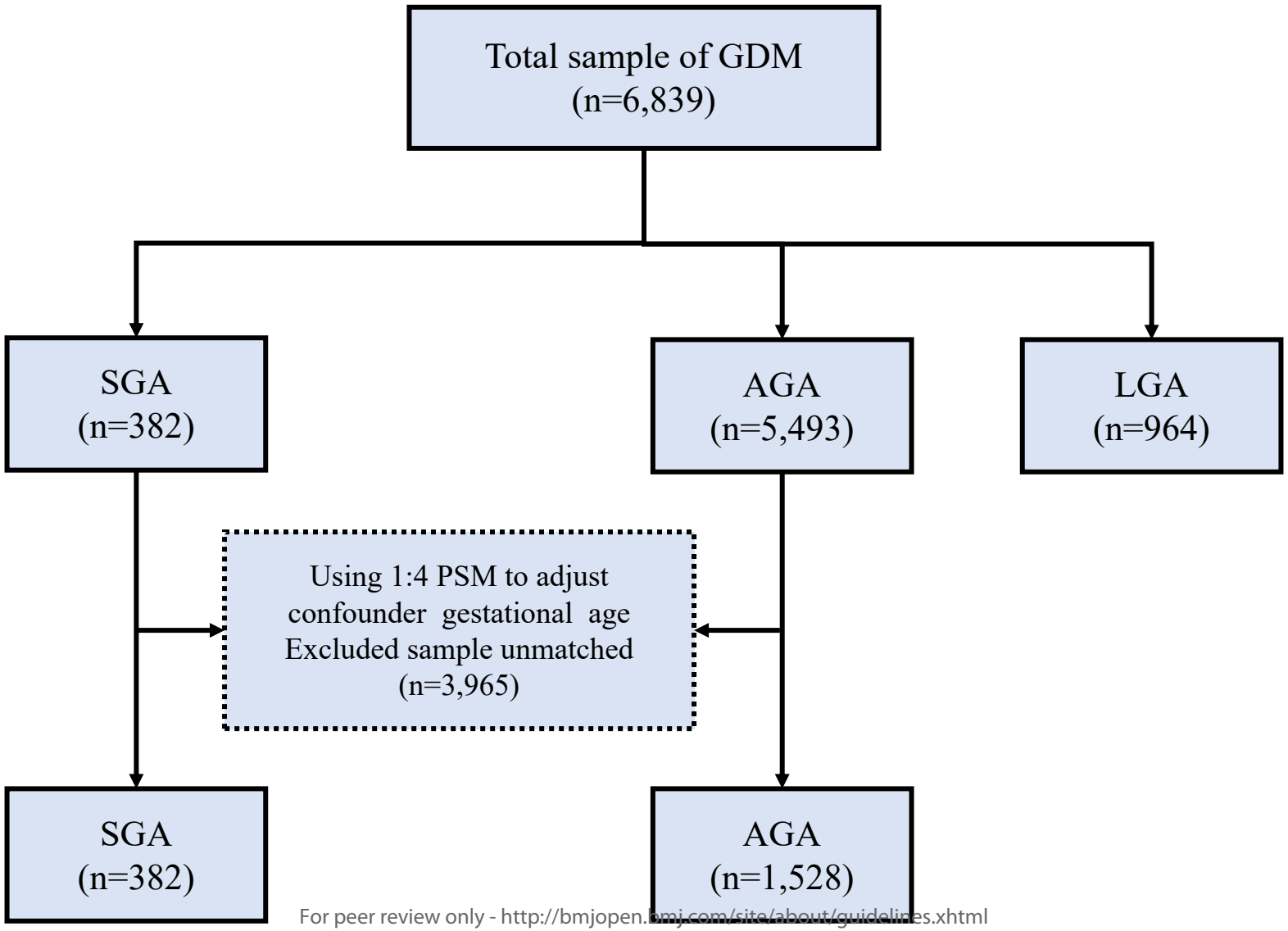
Table 3 Logistic regression analysis for SGA based on maternal glycemic parameters

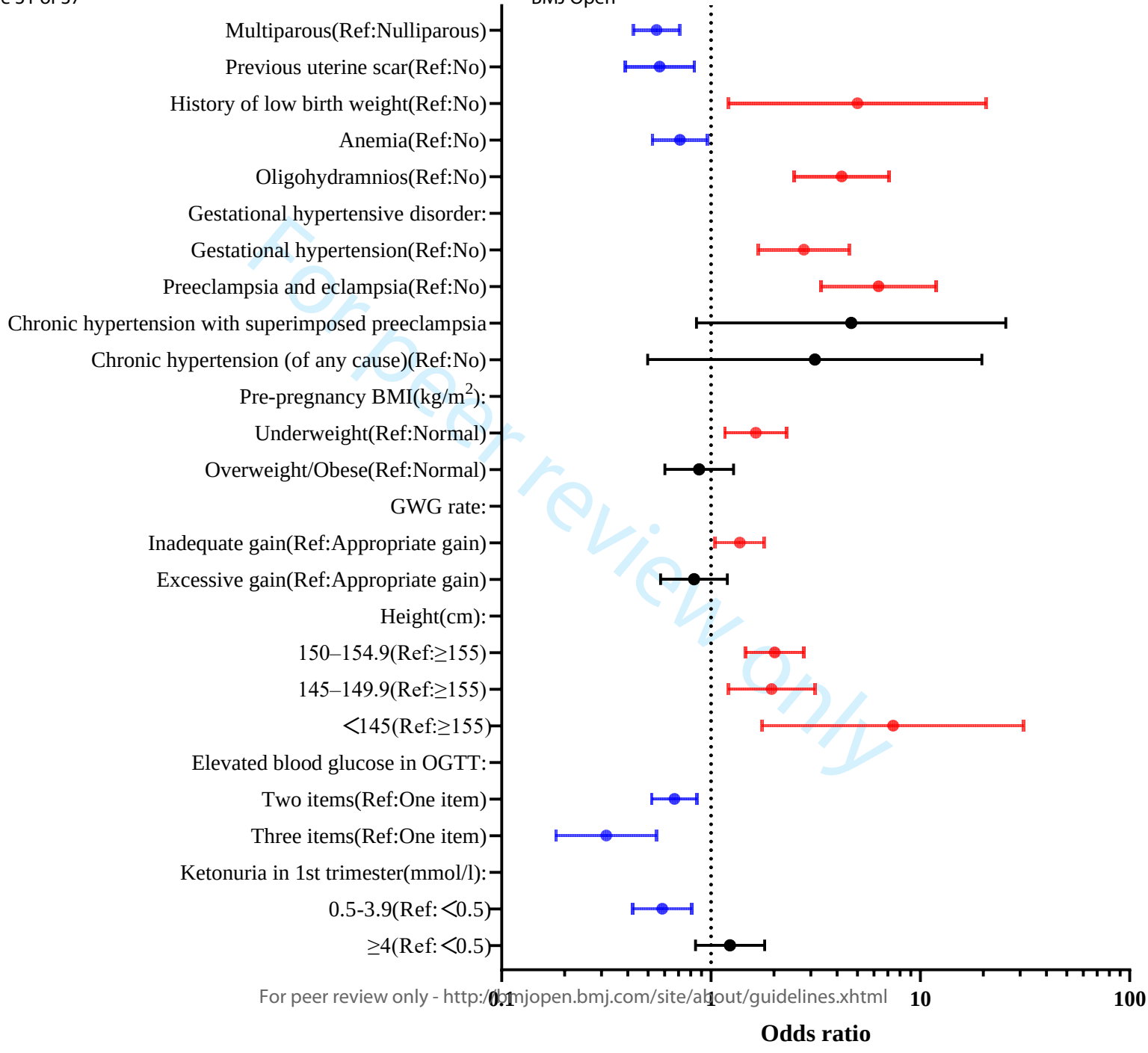
Variables	Crude OR (95% CI)	*P*	Adjusted† OR (95% CI)	*P*
75g OGTT 0 h glycemia	0.39(0.29-0.53)	**<0.001**	0.4(0.29-0.55)	**<0.001**
75g OGTT 1 h glycemia	1.06(0.97-1.15)	0.217	1.04(0.95-1.14)	0.365
75g OGTT 2 h glycemia	0.88(0.82-0.95)	**0.001**	0.88(0.81-0.95)	**0.002**
FPG in 2nd trimester	0.74(0.57-0.97)	0.026	0.77(0.59-1.01)	0.063
2-h postprandial glucose in 2nd trimester	0.79(0.71-0.88)	**<0.001**	0.81(0.73-0.9)	**<0.001**
HbA1c in the 2nd trimester	2.28(1.6-3.25)	**<0.001**	2.4(1.64-3.52)	**<0.001**

† Adjusted for parity, previous uterine scar, history of low birth weight, macrosomia, gestational hypertensive disorder, oligohydramnios, anemia, pre-pregnancy BMI, height, GWG rate, and ketonuria in 1st trimester.

Abv: OGTT: Oral Glucose Tolerance Test*;* FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; the third trimester of pregnancy: 33–37 gestational weeks.

OR: odd ratios, CI: confidence interval.





Supplementary material 1

1 Maternal demographic characteristic

Maternal characteristics collected included maternal age, ethnicity, educational level, occupation, marital status, place of residence, stature, pre-pregnancy Body mass index, and GWG rate.

Height: women were classified into four categories based on height < 145 cm, 145-149.9 cm, 150-154.9 cm, and ⩾155 cm. Body mass index (BMI): BMI was calculated as weight (kg)/ [height (m)]^2. Using BMI, women were classified as underweight (BMI<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (⩾ 30 kg/m^2). Gestational weight gain rate (GWG rate): To assess the adequacy of GWG among the study population, the GWG rate of each participant, which was calculated by dividing the total GWG by gestational age in weeks, was compared with the minimum recommended GWG rate. According to the IOM 2009 guidelines, The GWG of all included participants was categorized as inadequate weight gain, normal weight gain, and excessive weight gain.

2 Pregnancy characteristics

Pregnancy characteristics collected included parity, assisted reproductive technology-conceived pregnancy (ART), previous uterine scar (previous cesarean section or myomectomy), family history of hypertension or diabetes, pregnancy history (history of miscarriage, history of GDM, history of macrosomia, history of preterm labor, history of fetal distress, history of LBW).

3 Pregnancy complications

Pregnancy complications collected included intrahepatic cholestasis of pregnancy (ICP),

pregnancy-associated hypertensive disorders, hyperthyroid, hypothyroid, anemia (defined by hemoglobin < 11 g/dL before delivery) (Goonewardene, Shehata, and Hamad 2012), and pathology of amniotic fluid (oligohydramnios and polyhydramnios)

The gestational hypertensive disorder was classified into four categories: gestational hypertension, preeclampsia, and eclampsia, chronic hypertension with superimposed preeclampsia, preeclampsia and eclampsia chronic hypertension (of any cause), which was diagnosed using standard criteria (Anon 2013).

Reference

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Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary	2-3

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	5-6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	5-6
Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one	8

		group. Give information separately for cases and controls.	
Bias	#9	Describe any efforts to address potential sources of bias	7
Study size	#10	Explain how the study size was arrived at	n/a
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a
Statistical methods	#12c	Explain how missing data were addressed	
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	7
Statistical methods	#12e	Describe any sensitivity analyses	n/a
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	8
Participants	#13b	Give reasons for non-participation at each stage	8

Participants	#13c	Consider use of a flow diagram	Figure1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
Main results	#16b	Report category boundaries when continuous variables were categorized	8-9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10-11

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11-14
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15