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## Roles of Insulin Resistance and Beta Cell Dysfunction in Macrosomia among Chinese Women with Gestational Diabetes Mellitus

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### Abstract

**Aims**—The aim was to examine associations of insulin resistance and beta cell dysfunction with macrosomia in Chinese women with gestational diabetes mellitus (GDM).

**Methods**—We performed a secondary analysis of 923 women with GDM enrolled in a randomized controlled trial in 2010–2012 in Tianjin, China. Insulin resistance and beta-cell function were estimated using Homeostasis model assessment. Binary logistic regression was used

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#### Authors' Contributions

X.Y. conceived and designed the study. J.L. analyzed the data and wrote the first draft, J.H.L., W.L., C.Z., L.F. and P.W. provided the study material and patients, collected and assembly the data; All other authors gave critical comments on the manuscript; X.Y. (the corresponding authors) and J.L. (the first author) take full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

#### Competing interests

The authors report no conflicts of interest to this manuscript.

#### Availability of data and materials

Data used in this study are not currently publicly available. Requests for access to this dataset should be made to the corresponding author, and it will require all necessary ethical approvals and data sharing agreements to be in place.

#### Ethics approval and consent to participate

The approval of the ethics was granted by Tianjin Women and Children's Health Center Ethics Committee and written informed consent was obtained before data collection.

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to obtain adjusted odds ratios (ORs) and 95% confidence intervals (CIs). A two-step adjustment scheme was used to control for effects of potential confounders.

**Results**—A total of 138 women (16.5%) had excessive weight gain, 127 (7.3%) had macrosomia and 150 (16.3%) had a large for gestational age (LGA) infant. Compared to women in bottom tertile of insulin resistance, women in upper tertile had increased risk of excessive weight gain (OR: 4.32, 95%CI: 1.95–9.62), macrosomia and LGA (OR: 2.61, 95%CI: 1.20–5.69; 2.75, 95%CI: 1.35–5.62, respectively). The observed overall effects were mainly due to their large effect sizes among women with normal pre-pregnancy body weight. However, beta cell function was not found to be associated with either of them.

**Conclusions**—Increased insulin resistance during pregnancy was associated with excessive weight gain, macrosomia and LGA in Chinese women with GDM.

### Keywords

Beta Cell Function; Chinese; Gestational Diabetes Mellitus; Insulin Resistance

### Introduction

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorders of pregnancy[1]. More and more pregnant women are being affected, especially in developing countries such as China[1]. In Tianjin, the prevalence of GDM increased by 3.5-fold from 2.3%[2] in 1999 to 8.1%[3] in 2010–2012. It is well established that hyperglycemia in GDM is associated with increased risk of adverse pregnancy outcomes, including maternal excessive weight gain during pregnancy, macrosomia or large for gestational age (LGA), and neonatal morbidity[4], and long-term increased risk of diabetes in the mother and childhood obesity and hypertension in the offspring[5]. Two major randomized controlled trials demonstrated that tight glycaemia control during pregnancy was able to reduce the risk of macrosomia and LGA although its effect on neonatal morbidity was inconsistent [6, 7].

The mechanism underlying fetal overgrowth in mothers complicated by GDM is only partially understood. Maternal hyperglycemia can pass across the placental barrier and stimulate fetal pancreas to secrete excessive insulin while fetal hyperinsulinemia leads to accumulation of adipose tissues and protein in the fetus and thus, macrosomia[8]. It is known that pre-pregnancy obesity is associated with increased risk of macrosomia and LGA in normal pregnancy[9], suggesting that maternal insulin resistance might play a role in fetal overgrowth. GDM is characterized by increased insulin resistance and decreased beta cell function[10, 11], and the former may consist of pregnancy-induced insulin resistance and pre-existing insulin resistance before pregnancy that continues in pregnancy. It remains unknown whether insulin resistance or beta cell dysfunction plays a more important role in fetal over-growth in GDM-complicated pregnancy.

Our group conducted a randomized translational trial in a 3-tier antenatal care system in Tianjin, China, which designed to address the effectiveness of lifestyle intervention on pregnancy outcomes. We performed a secondary analysis of the trial data to test whether

insulin resistance and beta cell function were associated with excessive weight, macrosomia and LGA in Chinese women with GDM.

## Methods

### The participants and Settings

Tianjin is a large metropolitan city located in the North of China, with 13 million people, and directly under administration of the central government of China. There are 16 country-level administrative districts or counties and approximately 4.3 million inhabitants live in the six central urban districts.

We established a universal screening and management system for GDM in Tianjin 20 years ago[2]. As a quality improvement effort, we conducted a randomized translational trial to test the effectiveness and cost-effectiveness of a lifestyle intervention on pregnancy outcomes of women with GDM. The trial was implemented in the 3-tier's antenatal care system of the six central urban districts of Tianjin. The study design, participants and methods were described in details previously[12]. Briefly, a total of 19 847 pregnant women underwent a 50-g 1-h glucose challenge test (GCT) at 24–28 gestational weeks from December 2010 to October 2012. Of them, 2921 women with GCT  $\geq 7.8$ mmol/L were offered a 75-gram 2-h oral glucose tolerance test (OGTT) at central GDM clinic of Tianjin Women and Children's Health Center (TWCHC). During the trial period, 1440 women were diagnosed to have GDM using the cutoff points by the International Association of Diabetes and Pregnancy Study Groups (IADPSG)[13]. Among these women, 948 women met the criteria and were enrolled in the trial (Figure 1). After exclusion of 12 women with missing birth weight and 13 women with missing fasting insulin, 923 women with GDM were included in the current analysis. The exclusion criteria of the trial were 1). With diabetes defined by fasting plasma glucose (PG)  $\geq 7.0$  mmol/L, 2-hour PG  $\geq 11.1$  mmol/L or HbA<sub>1c</sub>  $\geq 6.5\%$  (48 mmol/mol)[14]; 2). Younger than 18 years of age; 3). Non-singleton pregnancy; 4). Maternal-fetal ABO blood type incompatibility; and 5). Maternal diseases such as chronic hypertension, thyrotoxicosis, pre-pregnancy diabetes and use of long-term medications. The approval of the ethics was granted by Tianjin Women and Children's Health Center Ethics Committee and written informed consent was obtained before data collection.

### Clinical measurement and definitions

Maternal pre-pregnancy weight was recorded as body weight at the first antenatal care visit. Pre-pregnancy body mass index (BMI) was calculated as pre-pregnancy weight in kilogram divided by the square of height in meters and categorized according to Chinese adults' criteria for overweight and obesity[15]. Gestational weight gain was measured as the maternal weight at delivery minus pre-pregnancy. Because the Homeostasis model assessment (HOMA) was validated for estimation of insulin resistance and beta cell function during pregnancy[16], our study estimated insulin resistance and insulin beta-cell functions at OGTT using the HOMA insulin resistance (HOMA-IR) and beta-cell function (HOMA-B) formula:

$$\text{HOMA-IR} = \text{fasting insulin (mU/L)} \times \text{fasting glucose (mmol/L)} \div 22.5;$$

$$\text{HOMA-B} = 20 \times \text{fasting insulin (mU/L)} \div (\text{fasting glucose (mmol/L)} - 3.5).$$

### Clinical outcomes

Excessive gestational weight gain was defined by gestational weight gain more than or equal to the 85<sup>th</sup> percentile range. Macrosomia was defined as birth weight  $\geq$  4000 grams and LGA was defined as birth weight greater than the gestational week and gender specific 90<sup>th</sup> percentile on the standard growth chart in Tianjin local reference.

### Treatment of GDM in the shared care and in the usual care groups

The trial subjects were randomly allocated to receiving either the usual care (UC) or shared care (SC, lifestyle intervention). The details of the SC and UC contents were described previously[12]. Briefly, women who received the SC were offered three individualized counseling sessions and three group diabetes education sessions. Different low total energy intakes by pre-pregnancy BMI were recommended. Meals were evenly spaced during the day. Women in the SC group were asked to walk at least 30 minutes per day, 7 days a week. These women were asked to perform self-monitoring of blood glucose (SMBG). The targets of hyperglycemia control were 3.5- 5.1 mmol/l for fasting capillary blood glucose and 7.0 mmol/L for 2-hour postprandial capillary blood glucose up to 36<sup>th</sup> gestational week and 8.0 mmol/L from 36<sup>th</sup> week onwards. If the targets of glycemia control were exceeded two times or more during a 2-week interval, insulin therapy was recommended. Women who received the UC were offered a group education session at diagnosis of GDM and were also offered a follow-up review of hyperglycemia control one week after the group diabetes education. However, they were not specifically taught to perform SMBG. From Nov 2010 to July 2011, the building of TWCHC was in renovation and separate areas were unavailable, so that the 242 women entering the trial during this period received either the SC or the UC in a same consulting room and contamination was hard to avoid[12]. Although this group of women was excluded in the primary analysis of the trial data, we included them in this secondary analysis of the trial data. To control for the potential contamination, a new variable for women enrolled during this period was created for use in the multivariable analysis in this study.

### Statistical Analysis

IBM SPSS Statistics 19.0 (IBM SPSS, Chicago, IL, USA) was used to analyze all data. Data was expressed as mean  $\pm$  standard deviation (SD) or median (interquartile range, IQR). Student's *t* test was used to compare means of continuous variables while Chi-squared test (or Fisher's exact test where appropriate) was used to compare categorical variables between two groups. Wilcoxon two-sample test was used to compare ordinal variables or continuous variables if they were not normally distributed. Binary logistic regression was used to obtain odds ratios (OR) and 95% confidence intervals of insulin resistance and beta-cell dysfunction for excessive weight gain, macrosomia and LGA. A two-step adjustment

scheme was used to control for effects of potential confounders. Model 1 was adjusted for age, pre-pregnancy BMI, gestational age at delivery (only for macrosomia and excessive gestational weight gain), gestational age at OGTT, 2-hour plasma glucose, 2-hour insulin (continuous variables for above all variables), infant gender (only for macrosomia and excessive gestational weight gain), family history of diabetes (first degree relatives), and smoking and drinking status; Model 2 was further adjusted for SC and whether they were enrolled Nov 2010 to 31 Jul 2011 to remove possible confounding effects from potential contamination.  $P < 0.05$  was considered to be statistically significant.

Additional subgroup analyses by pre-pregnancy body mass (i.e., by BMI  $\geq 24$  kg/m<sup>2</sup>) and SC status were performed to explore possible subgroup effects of HOMA-IR on outcomes in GDM women.

## Results

### Clinical and biochemical characteristics

The cohort of 923 women with GDM had a mean age of 29.8 (SD: 3.1) years and a mean gestation age of 10.7 (SD: 2.3) weeks at their first antenatal care visit. Of them, 92 women (10.0%) were obese and 215 (23.3%) were overweight before pregnancy while 66.7% had normal weight (n=616). Primiparas accounted for 95.6% and 97.3% had a Han-ethnicity. Women with excessive weight gain had higher body weight, higher fasting insulin and higher insulin resistance and better beta-cell function but lower pre-pregnancy BMI and relatively low postprandial 2-hour glycemic in OGTT than those women who gained less body weight. Women who delivered a macrosomia or LGA infant were taller and had higher pre-pregnancy BMI. They were also more likely to be smokers and alcohol drinkers, gained more body weight during pregnancy, and had longer gestational age at term. HOMA-B was similar between the two groups, but HOMA-IR was only marginally higher in women who delivery a LGA infant than in those who did not (Table 1).

### Associations of insulin resistance with macrosomia and LGA

HOMA-IR at OGTT was associated with excessive weight gain, macrosomia and LGA. HOMA-IR increase per SD was associated with a 1.72-fold increase in the risk of excessive weight gain (95%CI: 1.32–2.23) and 1.32-fold increase in the risk of macrosomia (95%CI: 1.02–1.70) and a 1.33-fold increase in the risk of LGA (95%CI: 1.05–1.68) after adjusting for confounders including pre-pregnancy BMI and weight gain during pregnancy (Table 2). Further adjusting for SC and potential contamination did not change the effect sizes (OR for excessive weight gain: 1.69, 1.29–2.21 and OR for macrosomia: 1.35, 1.04–1.75 and OR for LGA: 1.34, 1.05–1.71, respectively).

If HOMA-IR was stratified into tertiles, the adjusted ORs of the upper versus bottom tertile in Model 1 were 4.57(2.07–10.08) for excessive weight gain, 2.46 (1.15–5.30) for macrosomia and 2.70 (1.34–5.46) for LGA. Again, further adjustment in Model 2 did not lead to large changes in the effect sizes (OR for excessive weight gain: 4.32, 1.95–9.62, OR for macrosomia: 2.61, 1.20–5.69 and OR for LGA: 2.75, 1.35–5.62), with a significant linear

trend ( $p$  for trend =0.001 for excessive weight gain, 0.019 for macrosomia and 0.006 for LGA).

### Associations of beta-cell function with macrosomia and LGA

Differently from HOMA-IR, HOMA-B was not associated with the risks of excessive weight gain (0.95, 0.73–1.23), macrosomia (1.20, 0.97–1.48) and LGA (1.14, 0.94–1.38) after adjusting for confounders. After further adjustment for treatment, i.e., the SC and potential contamination, the associations with excessive weight gain, macrosomia and LGA remained non-significant (All P values >0.09). In the same way, ORs of the bottom tertiles versus the upper tertiles of HOMA-B for excessive weight gain, macrosomia and LGA were non-significant before and after adjustment for the treatment (Table 2).

### 3.4 Subgroup analysis

The subgroup analysis by pre-pregnancy overweight or obesity status showed that HOMA-IR was associated with the risk of excessive weight gain before and after further adjusting for the treatment (adjusted OR of HOMA-IR per SD: 1.76, 95%CI: 1.27–2.46) and also associated with increased risks of macrosomia but LGA (macrosomia: 1.45, 95%CI: 1.01–2.08 and LGA: 1.39, 1.00–1.93) among women with normal body weight prior to pregnancy. If tertiles of HOMA-IR used, ORs of the upper versus bottom tertiles for excessive weight gain, macrosomia and LGA were 4.32 (95%CI: 1.75–10.63), 3.33 (1.22–9.08) and 3.36 (1.37–8.26), respectively. In addition, HOMA-IR was not associated with increased risks of macrosomia and LGA and had a weaker association with excessive weight gain (adjusted ORs of HOMA-IR per SD for excessive weight gain: 1.70, 1.02–2.82; macrosomia: 1.15, 0.77–1.72 and LGA: 1.20, 0.83–1.74) among women with pre-pregnancy overweight or obesity (Table 3).

We also performed subgroup analysis by intervention assignment (Appendix Table 1). The associations of HOMA-IR with excessive weight gain were numerically larger in the UC group than in the SC group but the differences were quite small. However, the associations of HOMA-IR with macrosomia and LGA were significantly larger in SC group.

HOMA-B was not significantly associated with the excessive weight gain, macrosomia and LGA among all GDM women or in subgroup analyses by pre-pregnancy overweight or obesity status and SC status.

## Discussion

Our study found that increased HOMA-IR was associated with occurrence of excessive weight gain during pregnancy, macrosomia and LGA. The associations were highly significant in women with normal body weight prior to pregnancy, which highlights the importance of maintaining normal weight gain during pregnancy and the role of undue insulin resistance induced by GDM-implicated pregnancy in fetal overgrowth, and consequently, macrosomia and LGA.

Maternal hyperglycemia can pass through the placenta and stimulate fetal pancreas to secrete excessively insulin, which in turn promotes the storage of fetal adipose tissues and

growth[8]. Indeed, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study observed linear associations between fasting and 2-h PG levels during pregnancy and macrosomia[4]. It is further supported by randomized controlled trials showing that intervention (diet plus insulin if necessary) aiming to maintain normal glycaemia was effective to reduce the risk of macrosomia and LGA[6, 7]. Of note, current intervention measures such as diet, physical activity and use of insulin if needed are all targeting hyperglycemia. It is undeniably that most of these measures, if not all, also tend to alleviate insulin resistance. Indeed, levels of hyperglycemia can only account for a small part of variations in birth weight, e.g., 3.4% in Chinese population of pregnant women[17]. Therefore, it remains debatable whether insulin resistance or beta cell dysfunction during pregnancy plays a more important role in overgrowth of the fetus. In this regard, several epidemiological studies observed associations between insulin resistance and birth weight or macrosomia [18–20] although a study failed to find a significant association between insulin resistance in pregnancy and macrosomia in women with GDM [21]. Ong et al [18] analyzed a cohort of 668 pregnant women and reported that maternal insulin resistance was associated with infant's adiposity at birth. Another study of 804 maternal-neonate pairs observed a strong positive correlation between HOMA-IR and neonatal birth weight, with one unit increase in HOMA-IR increasing birth weight by 25.5 grams and fat mass by 15.4 grams[22].

Insulin resistance before pregnancy may play a causal role in the development of GDM[3]. Of note, normal pregnancy is a state of insulin resistance, commencing from 12<sup>th</sup>–14<sup>th</sup> gestational week throughout pregnancy[23]. Besides pre-pregnancy insulin resistance, both insulin resistance induced by pregnancy and beta cell dysfunction due to genetic factors may also contribute to the development of GDM[10, 11]. In this connection, our study found that associations between HOMA-IR and excessive weight gain, macrosomia and LGA were highly significant and stronger in GDM women with normal body weight before pregnancy. The findings are consistent with recent findings that use of metformin, an insulin sensitizer, in obese women with GDM, did not have effects on fetal growth[24]. The findings from our subgroup analysis support the notion that existing insulin resistance before pregnancy and increased insulin resistance during pregnancy have different roles in fetal growth and the latter may play a more important role in macrosomia or LGA.

Our study has clinical and mechanistic implications. The prevalence of GDM has been increasing worldwide[25]. GDM is associated with increased risks of adverse pregnancy outcomes including macrosomia and LGA[4] and increased risk of childhood obesity at the age of 8–10 years[26] and impaired glucose tolerance at the age of 10–16 years in the offspring, irrespective of whether the hyperglycemic status of the mother was gestational or pre-gestational in nature[27]. The offspring born to mothers with GDM also exhibit early features of metabolic syndrome with high blood pressure and low high-density lipoprotein cholesterol[27]. Therefore, pregnancy is a window period and GDM may be a manifestation of short-term and long-term adverse health outcomes for the offspring. Besides, it remains inconclusive whether lifestyle intervention of GDM during pregnancy has long-term benefits on the offspring born to the GDM-implicated pregnancy[28].

Our study had limitations. First, adjustment for pre-pregnancy BMI may not completely remove confounding effects of pre-pregnancy insulin resistance. Second, we only used the HOMA models to estimate insulin resistance and beta cell function because the fasting and 2-h insulin levels were measured in the OGTT. Third, the subjects of our analysis participated in a randomized controlled trial and half of them received intensive lifestyle intervention. The 242 women entering the trial from Nov 2010 to July 2011 received the care in a same consulting room and the UC women were also likely to receive the intervention designed only for the SC group. Although we carefully adjusted for the treatment effect and the possible contamination, the residual confounding effects were unavoidable. Finally, HOMA-IR was measured at the OGTT while maternal weight gain was calculated from the maternal body weight at the first antenatal care visit to the time of being hospitalized for delivery. It is unknown which of pregnancy-induced insulin resistance or excessive maternal weight gain happened first. Therefore, we cannot exclude the possibility of the insulin resistance was a consequence of maternal weight gain.

In conclusion, our study found that insulin resistance during pregnancy was associated with excessive maternal weight gain, macrosomia and LGA. Our findings suggest that more research is warranted to investigate the mechanism of pregnancy induced insulin resistance and its interplays with pre-pregnancy insulin resistance and beta cell function for short-term and long-term effects on the health of mothers and their offspring.

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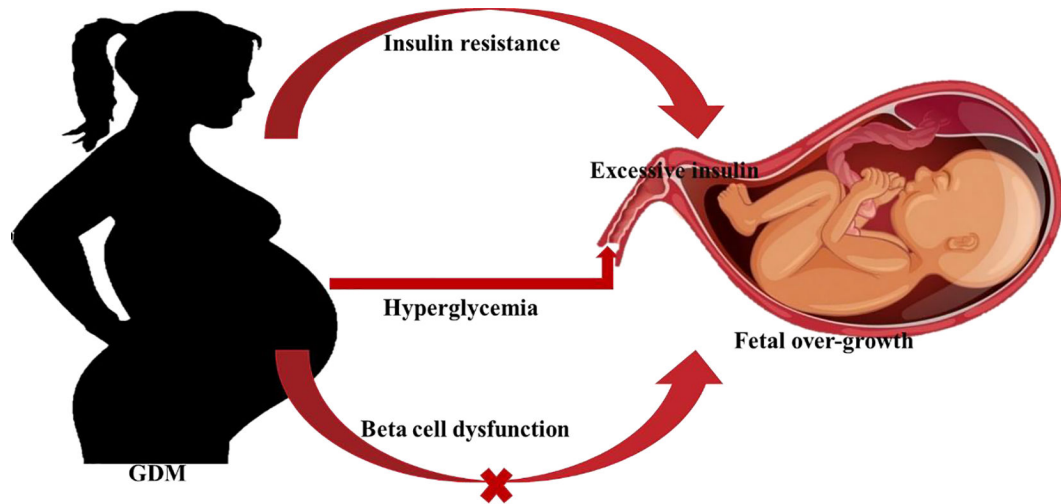
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## Appendix





**Appendix figure 1.**  
Conceptual Diagram

Insulin resistance, rather than beta cell dysfunction, was related to macrosomia and large for gestational age infant.

**Appendix Table 1:**

Subgroup analysis of odds ratio of HOMA insulin resistance for macrosomia and large for gestational age by lifestyle intervention

	Excessive weight gain <sup>†</sup>		Macrosomia		Large for gestational age	
	OR (95%CI)	P <sup>§</sup>	OR (95%CI)	P <sup>§</sup>	OR(95%CI)	P <sup>§</sup>
Usual care						
Model 1						
IR per SD	2.30(1.50–3.54)	<0.001	1.19(0.83–1.17)	0.342	1.23(0.89–1.70)	0.212
IR in tertiles		0.008		0.216		0.102
Bottom	Reference		Reference		Reference	
Middle	3.20(1.35–7.58)		1.17(0.54–2.52)		1.50(0.75–3.02)	
Upper	4.88(1.54–14.45)		1.95(0.70–5.43)		2.17(0.86–5.49)	
Model 2						
IR, per SD	2.28(1.47–3.52)	<0.001	1.25(0.86–1.81)	0.235	1.25(0.90–1.74)	0.183
IR in tertiles		0.011		0.142		0.084
Bottom	Reference		Reference		Reference	
Middle	3.15(1.33–7.46)		1.22(0.56–2.63)		1.54(0.76–3.10)	
Upper	4.62(1.45–14.75)		2.26(0.79–6.45)		2.30(0.89–5.89)	
Shared care						
Model 1						
IR per SD	1.37(0.94–1.98)	0.101	1.66(1.13–2.46)	0.011	1.44(0.99–2.10)	0.056
IR in tertiles		0.007		0.008		0.030
Bottom	Reference		Reference		Reference	

	Excessive weight gain <sup>‡</sup>		Macrosomia		Large for gestational age	
	OR (95%CI)	P <sup>§</sup>	OR (95%CI)	P <sup>§</sup>	OR(95%CI)	P <sup>§</sup>
Middle	2.68(1.13–6.41)		2.09(0.77–5.67)		1.48(0.63–3.52)	
Upper	4.81(1.61–14.40)		5.53(1.63–18.85)		3.42(1.17–10.02)	
Model 2						
IR per SD	1.34(0.92–1.96)	0.127	1.64(1.11–2.44)	0.014	1.43(0.98–2.09)	0.063
IR in tertiles		0.011		0.012		0.038
Bottom	Reference		Reference		Reference	
Middle	2.58(1.07–6.21)		1.99(0.73–5.45)		1.44(0.60–3.44)	
Upper	4.52(1.49–13.76)		5.14(1.48–17.77)		3.27(1.10–9.69)	

Model 1: adjusted for age, smoking and drinking, 2-h PG, 2-h insulin; gestational age at OGTT, gestational age at delivery and baby gender (for macrosomia and excessive gestational weight gain), family history of diabetes; Model 2: adjusted for variables in Model 1 and for unintentional intervention

<sup>‡</sup>Excessive weight gain was 85<sup>th</sup> percentile in gestational weight gain (22.0 kg)

<sup>§</sup>P values for trend

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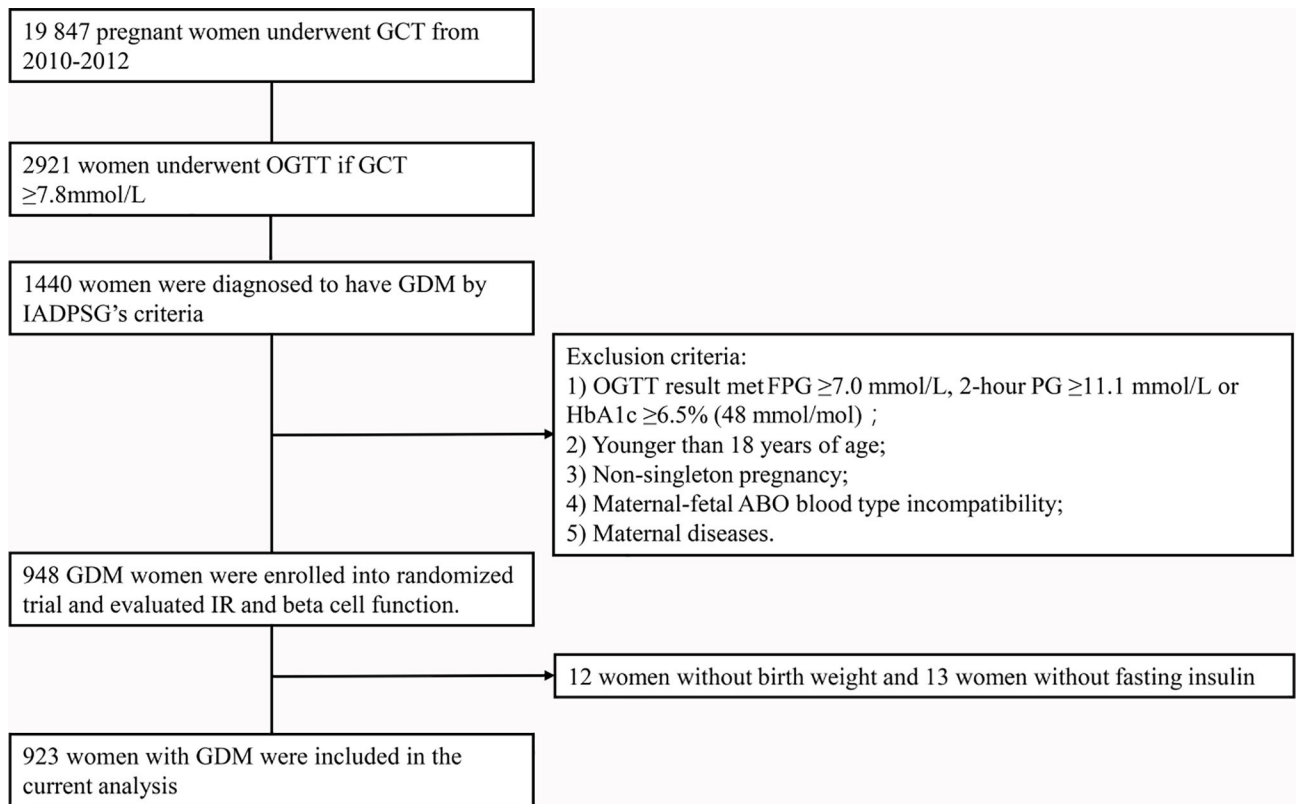
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### Highlights

- Insulin resistance was related to macrosomia and large for gestational age infant.
- It was also related to weight gain in women with gestational diabetes mellitus.
- The links were mainly due to the large effect sizes among women with BMI < 24 kg/m<sup>2</sup>.



**Fig. 1.**  
Participant Flow Diagram

**Table 1:**

Clinical and biochemical characteristics of women who delivered macrosomia or large for gestational age infants

Variables	Excessive weight gain			Macrosomia			Large for gestational age		
	Yes	No	P	Yes	No	P	Yes	No	P
n	138	699		127	796		150	773	
Age, year	29.3(3.0)	29.8(3.1)	0.073	29.2(2.7)	29.8(3.2)	0.035	29.7(3.3)	29.8(3.1)	0.932
Smoker	10(7.2%)	29(4.1%)	0.115	15(11.8%)	28(3.5%)	<0.001	17(11.3%)	26(3.4%)	<0.001
Drinker	40(9.0%)	204(29.2)	0.962	46(36.2%)	229(28.8%)	0.088	57(38.0%)	218(28.2%)	0.016
Han-ethnicity	132(95.7%)	681(97.4%)	0.389	124(97.6%)	774(97.2%)	1	146(97.3%)	752(97.3%)	1
Height, cm	163.9(4.7)	162.4(4.8)	0.001	164(4.9)	162(4.8)	<0.001	164(5.0)	162(4.7)	<0.001
Weight, kg	59.7(8.5)	61.3(10.8)	0.057	65.3(11.6)	60.5(10.5)	<0.001	64.8(11.6)	60.4(10.6)	<0.001
Pre-pregnancy BMI, kg/m <sup>2</sup>	22.2(2.8)	23.2(3.8)	0.001	24.1(3.8)	22.9(3.7)	0.001	23.9(3.8)	22.9(3.7)	0.004
BMI 24 to <28	27(19.6%)	170(24.3%)	0.001	39(30.7%)	176(22.1%)	0.006	42(28.0%)	173(22.4%)	0.021
BMI 28	4(2.9%)	76(10.9%)		17(13.4%)	75(9.4%)		21(14.0%)	71(9.2%)	
Gestational age at 1 <sup>st</sup> visit, weeks	10.8(2.2)	10.7(2.3)	0.573	10.8(2.4)	10.7(2.2)	0.608	10.9(2.4)	10.7(2.2)	0.305
Gestational age at OGTT, weeks	26.6	26.1	0.022	26	26.3	0.062	26.1	26.3	0.168
	(25.9–27.3)	(25.6–27.4)		(25.3–27.1)	(25.6–27.3)		(25.4–27.0)	(25.6–27.3)	
GCT, mmol/L	8.9	9.0	0.073	9.1	9.0	0.19	9.1	8.9	0.219
	(8.3–9.5)	(8.4–9.9)		(8.4–10.1)	(8.4–9.8)		(8.4–10.1)	(8.4–9.8)	
Fasting PG, mmol/L	5.2(0.5)	5.0(0.5)	0.007	5.1(0.6)	5.1(0.5)	0.238	5.1(0.6)	5.1(0.5)	0.063
1-h PG, mmol/L	9.9(1.5)	10.1(1.3)	0.064	10.2(1.3)	10.1(1.4)	0.429	10.2(1.3)	10.1(1.4)	0.257
2-h PG, mmol/L	8.1(1.3)	8.4(1.3)	0.011	8.4(1.4)	8.4(1.3)	0.705	8.4(1.3)	8.4(1.3)	0.868
Fasting insulin, mIU/L	11.7 (8.0–16.4)	9.4 (5.9–13.6)	<0.001	10.5 (6.7–15.3)	9.6 (6.1–13.6)	0.121	10.7 (6.8–15.0)	9.6 (6.0–13.7)	0.099
2-h insulin, mU/L	89.7 (57.3–134.8)	87.9 (55.1–131.0)	0.588	84.3 (55.0–128.3)	89.3 (56.2–133.1)	0.342	84.3 (56.1–125.7)	89.5 (55.7–133.7)	0.207
HOMA-IR, m U/L*mmol/l	2.7 (1.7–3.6)	2.0 (1.3–3.1)	<0.001	2.4 (1.4–3.6)	2.2 (1.3–3.2)	0.109	2.5 (1.4–3.5)	2.1 (1.3–3.2)	0.073
HOMA-B, m U/L*(mmol/l) <sup>-1</sup>	148.7 (92.9–211.2)	127.9 (85.1–185.4)	0.022	137.8 (94.7–207.1)	129.5 (86.4–188.8)	0.263	135.7 (93.0–196.8)	129.8 (86.5–190.0)	0.448

Variables	Excessive weight gain			Macrosomia			Large for gestational age		
	Yes	No	P	Yes	No	P	Yes	No	P
Gestational weight gain, kg	25.8(4.4)	13.9(5.2)	<0.001	19.0(6.9)	15.3(6.6)	<0.001	18.8(7.4)	15.3(6.5)	<0.001
Parity			0.178			0.447			0.884
0	135(97.8%)	666(95.3%)		123(96.9%)	759(95.4%)		143(95.3%)	739(95.6%)	
1	3(2.2%)	33(4.7%)		4(3.1%)	37(4.6%)		7(4.7%)	34(4.4%)	
Gestational week at delivery, week	39.4(1.4)	39.3(1.6)	0.537	40.0(1.2)	39.1(1.8)	<0.001	39.3(1.6)	39.2(1.8)	0.386
Infant male gender	67(48.6%)	314(44.9%)	0.434	48(37.8%)	367(46.1%)	0.08	68(45.3%)	347(44.9%)	0.92
Birth weight, g	3595(576.6)	3408(511.4)	<0.001	4252(261)	3295(467)	<0.001	4136(382)	3289(470)	<0.001
Infant stature, cm	50.5(1.9)	50.2(1.8)	0.071	52.1(1.3)	49.9(1.8)	<0.001	51.6(1.5)	49.9(1.8)	<0.001

Abbreviations: BMI, body mass index; BP, blood pressure; GDM, gestational diabetes mellitus; GCT, glucose challenge test; HbA1c, haemoglobin A1c; OGTT, oral glucose tolerance test; PG, plasma glucose; IR, insulin resistance; B, beta cell function

<sup>†</sup> P values were derived from Chi-square Test, Fisher's Exact Test, or Student T Test unless specified

<sup>‡</sup> Data were reported as median (interquartile range) and P values were derived from Wilcoxon Two-Sample Test.



**Table 2:**

Odds ratio of insulin resistance and beta cell function for macrosomia and large for gestational age among Chinese women with gestational diabetes mellitus

	Excessive weight gain <sup>†</sup>		Macrosomia		LGA	
	OR (95%CI)	P§	OR (95%CI)	P§	OR(95%CI)	P§
HOMA insulin resistance (IR)						
Model 1						
IR per SD	1.72(1.32–2.23)	<0.001	1.32(1.02–1.70)	0.037	1.33(1.05–1.68)	0.020
IR in tertiles		<0.001		0.026		0.007
Bottom	Reference		Reference		Reference	
Middle	2.75(1.49–5.07)		1.27(0.70–2.30)		1.48(0.86–2.54)	
Upper	4.57(2.07–10.08)		2.46(1.15–5.30)		2.70(1.34–5.46)	
Model 2						
IR per SD	1.69(1.29–2.21)	<0.001	1.35(1.04–1.75)	0.026	1.34(1.05–1.71)	0.018
IR in tertiles		0.001		0.019		0.006
Bottom	Reference		Reference		Reference	
Middle	2.67(1.45–4.95)		1.32(0.72–2.40)		1.49(0.87–2.57)	
Upper	4.32(1.95–9.62)		2.61(1.20–5.69)		2.75(1.35–5.62)	
HOMA beta cell function (B)						
Model 1						
B per SD	0.95(0.73–1.23)	0.703	1.20(0.97–1.48)	0.091	1.14(0.94–1.38)	0.178
B in tertiles		0.778		0.315		0.541
Bottom	1.16(0.59–2.31)		0.70(0.34–1.44)		0.83(0.43–1.58)	
Middle	0.76(0.46–1.26)		0.67(0.39–1.15)		0.79 (0.49–1.27)	
Upper	Reference		Reference		Reference	
Model 2						
B per SD	0.95(0.73–1.24)	0.691	1.19(0.97–1.47)	0.102	1.13(0.93–1.36)	0.214
B in tertiles		0.739		0.301		0.539
Bottom	1.19(0.60–2.37)		0.69(0.34–1.43)		0.82(0.43–1.58)	
Middle	0.76(0.45–1.26)		0.68(0.40–1.16)		0.80(0.49–1.29)	
Upper	Reference		Reference		Reference	

Abbreviations: OR, odds ratio; CI: confidence interval; HOMA: homeostasis model assessment; IR: HOMA insulin resistance; B: HOMA beta cell function.

Macrosomia was defined as birth weight  $\geq$ 4000 gram; Large for gestational age (LGA) was defined as birth weight greater than the gestational week and gender specific 90th percentile on the standard growth chart in Tianjin local reference.

Model 1: adjusted for age, pre-pregnancy BMI, 2-h PG, 2-h insulin, gestational age at OGTT, gestational age at delivery (only for macrosomia and excessive gestational weight gain), gender (only for macrosomia and excessive gestational weight gain), family history of diabetes, drinking and smoking

Model 2: adjusted variables in model 1 and for shared care status and unintentional intervention.

<sup>†</sup>Excessive weight gain was  $\geq$ 85<sup>th</sup> percentile in gestational weight gain (22.0 kg)

<sup>§</sup>P values for trend.

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**Table 3:**

Subgroup analysis of odds ratio of HOMA insulin resistance for macrosomia and large for gestational age by pre-pregnancy overweight or obesity (BMI  $\geq 24\text{kg/m}^2$ )

	Excessive weight gain <sup>†</sup>		Macrosomia		Large for gestational age	
	OR (95%CI)	P <sup>§</sup>	OR (95%CI)	P <sup>§</sup>	OR(95%CI)	P <sup>§</sup>
Among women with pre-pregnancy overweight or obesity*						
Model 1						
IR per SD	1.66(1.02–2.72)	0.043	1.11(0.75–1.63)	0.611	1.17(0.82–1.67)	0.392
IR in tertiles		0.266		0.474		0.357
Bottom	Reference		Reference		Reference	
Middle	2.48(0.54–11.53)		0.65(0.21–2.04)		0.76(0.26–2.19)	
Upper	3.99(0.63–25.19)		1.29(0.34–4.85)		1.23(0.36–4.22)	
Model 2						
IR, per SD	1.70(1.02–2.82)	0.041	1.15(0.77–1.72)	0.486	1.20(0.83–1.74)	0.335
IR in tertiles		0.215		0.406		0.319
Bottom	Reference		Reference		Reference	
Middle	2.71(0.58–12.57)		0.66(0.21–2.11)		0.76(0.26–2.23)	
Upper	4.55(0.71–29.09)		1.36(0.35–5.29)		1.29(0.37–4.48)	
Among women with normal pre-pregnancy weight*						
Model 1						
IR per SD	1.82(1.31–2.52)	<0.001	1.43(1.00–2.05)	0.050	1.39(1.00–1.93)	0.047
IR in tertiles		0.001		0.028		0.012
Bottom	Reference		Reference		Reference	
Middle	2.61(1.34–5.10)		1.59(0.78–3.24)		1.69(0.89–3.20)	
Upper	4.65(1.91–11.30)		3.13(1.17–8.35)		3.27(1.35–7.92)	
Model 2						
IR per SD	1.76(1.27–2.46)	0.001	1.45(1.01–2.08)	0.046	1.39(1.00–1.93)	0.053
IR in tertiles		0.002		0.021		0.011
Bottom	Reference		Reference		Reference	
Middle	2.53(1.29–4.97)		1.68(0.82–3.45)		1.72(0.90–3.27)	
Upper	4.32(1.75–10.63)		3.33(1.22–9.08)		3.36(1.37–8.26)	

Abbreviations: OR, odds ratio; CI: confidence interval; HOMA: homeostasis model assessment; IR: HOMA insulin resistance.

Model 1: adjusted for age, pre-pregnancy body mass, 2-h PG, 2-h insulin; gestational age at OGTT, gestational age at delivery and baby gender (for macrosomia and excessive gestational weight gain), family history of diabetes, smoking and drinking

Model 2: adjusted for variables in Model 1 and for shared care status and unintentional intervention

<sup>†</sup>Excessive weight gain was  $\geq 85^{\text{th}}$  percentile in gestational weight gain (22.0 kg)

<sup>§</sup>P values for trend.