Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Interactive effects of prepregnancy overweight and gestational diabetes on macrosomia and large for gestational age: A population-based prospective cohort in Tianjin, China

Wen Yang [a,1], *Jin Liu* [b,1], *Jing Li* [a], *Jinnan Liu* [a], *Hongyan Liu* [b], *Yue Wang* [b], *Junhong Leng* [b], *Shuo Wang* [c], *Huaxi Chen* [d], *Juliana C.N. Chan* [e], *Zhijie Yu* [f], *Gang Hu* [g], *Xilin Yang* [a,*]

[a] *Department of Epidemiology and Biostatistics, School of Public Health, and Tianjin Key Laboratory of Environment, Nutrition & Public Health, Tianjin Medical University, Tianjin, China*

[b] *Department of Child Health, Tianjin Women and Children's Health Center, Tianjin, China*

[c] *Project Office, Tianjin Women and Children's Health Center, Tianjin, China*

[d] *Integration in Clinical Medicine, College of Basic Medicine, Tianjin Medical University, Tianjin, China*

[e] *Department of Medicine and Therapeutics, Hong Kong Institute of Diabetes and Obesity and The Chinese University of Hong Kong-Prince of Wales Hospital-International Diabetes Federation Centre of Education, The Chinese University of Hong Kong, Hong Kong Special Administrative Region*

[f] *Population Cancer Research Program and Department of Pediatrics, Dalhousie University, Halifax, Canada*

[g] *Chronic Disease Epidemiology Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA, USA*

ARTICLE INFO

Article history:
Received 14 May 2019
Received in revised form
10 June 2019
Accepted 25 June 2019
Available online 1 July 2019

Keywords:
Gestational diabetes mellitus
Macrosomia
Large for gestational age
Overweight
Chinese

ABSTRACT

Aims: Obesity increases risk of gestational diabetes mellitus (GDM) and GDM increases risk of macrosomia but their inter-relations for increased risk of macrosomia remain uncertain. We aimed to examine associations between prepregnancy overweight and macrosomia, and synergistic effects between prepregnancy overweight and GDM on macrosomia.

Methods: From 2010 to 2012, 19,622 women in urban Tianjin, China, underwent a 50-g 1-h glucose challenge test (GCT) at 24–28 gestational weeks and followed by a 75-g 2-h oral glucose tolerance test (OGTT) if the GCT value was $\geq$ 7.8 mmol/L. GDM was defined according to International Association of Diabetes and Pregnancy Study Group's criteria. Overweight was defined as body mass index $\geq$ 24.0 kg/m^2. Logistic regression was performed to obtain odds ratios (ORs) and 95% confidence intervals (CIs). Additive interaction between prepregnancy overweight and GDM was used to test synergistic effects.

Results: In the cohort, 1791 (9.1%) and 1726 (8.8%) of the women delivered a macrosomic infant or a large-for-gestational-age (LGA) infant, respectively. Prepregnancy overweight was associated with increased risk of macrosomia and LGA with adjusted ORs being 2.29 (95%CI: 2.07–2.54) and 2.27 (2.05–2.52), respectively. Copresence of prepregnancy overweight and GDM greatly enhanced the adjusted ORs of overweight alone (ORs for macrosomia and LGA: 2.17, 1.94–2.42 & 2.21,1.98–2.47) and GDM alone (ORs for macrosomia and LGA:

* Corresponding author at: Department of Epidemiology and Biostatistics, School of Public Health, Tianjin Medical University, Tianjin 300070, China.
E-mail address: yangxilin@tmu.edu.cn (X. Yang).

[1] Equal contribution to the manuscript.

https://doi.org/10.1016/j.diabres.2019.06.014

2.01,1.48–2.72 & 2.14, 1.60–2.87) for macrosomia and LGA to 5.29 (4.07–6.87) for macrosomia and 4.72 (3.66–6.10) for LGA, with significant additive interactions.
Conclusions: Prepregnancy overweight increased the risks of macrosomia and LGA independently and synergistically with GDM.

1. Introduction

The prevalence of gestational diabetes mellitus (GDM) has been dramatically increasing worldwide including China [1], accounting for 7% of pregnant women in the world [2]. It is well established that GDM predisposes pregnant women to high risk of delivery of macrosomic infants while lifestyle intervention of GDM reduces the rate of macrosomia or large for gestational age (LGA) infants although not all trials showed that such intervention was also able to reduce the risk of perinatal morbidities [3,4]. Indeed, the current diagnostic criteria for GDM were based on their associations with macrosomia [5]. Studies suggest that macrosomia or LGA is associated with increased risk of adverse short- and long-term health outcomes in the mothers and their offspring, for the mothers, increased risk of caesarean section [6,7], postpartum hemorrhage [8], vaginal lacerations [9], uterine rupture and postpartum infection [8], and for the offspring, increased risk of shoulder dystocia [6], birth asphyxia, nerve injures, admission to the intensive-care unit, increased perinatal mortality [10,11], obesity and diabetes in early adulthood [12]. Although widespread introduction of screening and management of GDM, the prevalence of macrosomia and LGA in China was still on the rise, for example, 7.3% in 2011 [8] being increased to 8.7% in 2010–2014 [13]. These observations suggest that factors other than GDM were also contributing to the high rate of macrosomia. As a major risk factor of GDM, maternal obesity was found to be associated with increased risk of macrosomia and fetal obesity [14], probably by increased placenta transport of amino acids and other nutrients [15]. Pedersen's Hypothesis describes a plausible biological link from GDM to macrosomia that maternal hyperglycemia results in fetal hyperinsulinemia, which leads to fetal insulin resistance and then fetal over-growth [16]. It is observed that in non-GDM pregnancy, maternal overweight and high increase in fasting plasma glucose from early to late pregnancy was associated with a 4.5-fold increase in risk of newborn macrosomia as compared to those women with high body mass index (BMI) only [17]. It seems also possible that maternal prepregnancy overweight and GDM have a synergistic effect on newborn macrosomia.

Using a population-based cohort of pregnant women in urban districts of Tianjin, China, established in 2010–2012 [18], the present study aimed to examine synergistic effect between maternal overweight at the first antenatal care visit and GDM on newborn macrosomia or large for gestational age (LGA) in Chinese pregnant women.

2. Materials and methods

2.1. Study population and settings

The study settings, population and methods were published elsewhere [18]. Briefly, Tianjin is one of cities directly under the administration of the central government of China, adjacent to Beijing, and covers an area of more than 10,000 km^2. There are over 5 million residents in six central urban districts where the GDM screening and management system was established in 1998. The antenatal care system was consisted of three levels of antenatal care facilities, i.e., (1) 65 primary hospitals (1st tier); (2) six district-level Women and Children's Health Centers (WCHC) and other secondary obstetric hospitals (2nd tier); (3) a city-level Tianjin WCHC (TWCHC) and other tertiary hospitals (3rd tier). From 2010 to 2012, 22,302 pregnant women were registered at a primary care hospital where close to their residence. Of them, we sequentially excluded 1252 women who lacked the glucose challenge test (GCT) results, 891 women who had a positive GCT but did not have the standard oral glucose tolerance test (OGTT) results, 197 women with multiple pregnancy and 341 women whose key variables were missing, i.e., missing maternal BMI, children weight, sex and date of delivery. Finally, the remaining 19,622 women were included in the ultimate analysis. Ethical approval was obtained from the Ethics Committee for Clinical Research of Tianjin Women and Children's Health Centre. Informed consent was acquired from all participants before data collection.

2.2. Screening for and diagnosis of GDM

A two-step procedure was performed to identify GDM. At 24th to 28th gestational weeks, all pregnant women were offered a 50-g 1-h GCT at a primary hospital. Women who had a GCT value $\geq$7.8 mmol/L were referred to a centralized GDM clinic, established within Tianjin Women and Children's Health Care Center, where those women underwent a standard 75-g 2-h OGTT. The participants underwent the 75-g OGTT in the morning after more than 8 hours fasting. Plasma glucose levels at fasting, 1-h, 2-h were measured at the Central Laboratory of TWCHC using an automatic analyzer (Toshiba TBA-120FR, Japan) [18]. GDM was diagnosed based on the International Association of Diabetes and Pregnancy Study Group (IADPSG) cut-points: fasting plasma glucose $\geq$5.1 mmol/L or 1-h plasma glucose $\geq$10.0 mmol/L or 2-h plasma glucose $\geq$8.5 mmol/L [19].

2.3. Clinical measurements and data collection

Data were obtained from a series of questionnaires at registration for pregnancy and at GCT time or retrieved from the database of Maternal and Child Health Information System. Clinical and biochemical samples of the mothers and children were collected and recorded in electronic system from registration to delivery. At registration for pregnancy, we collected information on maternal height, weight, age, parity, ethnicity, systolic/diastolic blood pressure, diabetes history in first degree relatives, gestational age at delivery, habitual use of tobacco and alcohol. Children's weight, sex and birth date were also received from questionnaires.

Participants were asked to wear light clothing and without shoes when height and weight were measured. BMI was calculated as body weight in kilograms divided by squared body height in meters. We classified BMI into four categories according to Chinese adult's criteria: underweight (<18.5 kg/m^2), normal weight (18.5–24.0 kg/m^2), overweight (24.0–28.0 kg/m^2) and obesity (≥28.0 kg/m^2) [20]. Sitting blood pressure (BP) was determined after break at least 10 min. Family history of diabetes in first-degree relatives was defined as parents or siblings with diabetes. One or more cigarettes each day for at least 6 months before pregnancy or smoking one or more cigarettes each day during pregnancy was considered as habitual smoking before or during pregnancy. Habitual drinking before or during pregnancy was defined as drinking once or more every week before or during pregnancy.

2.4. Definition of clinical outcomes

Fetal macrosomia was defined as birth weight value being equal to or greater than 4000 g [21]. LGA was defined as birth weight value greater than the gestational week and gender specific 90th percentiles according to Tianjin local references [22].

2.5. Statistical analyses

All analyses were performed in Statistical Analysis System (SAS), release 9.4 (SAS Institute Inc., Cary, NC). Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range, IQR) where appropriate and compared using Student's *t*-test or Wilcoxon Two Sample test. Categorical variables were expressed as number (percentage) and compared using Chi-square test or Fisher exact test where appropriate. We classified prepregnancy BMI into two groups according to Chinese standard: overweight/obesity group (BMI ≥ 24.0 kg/m^2) and underweight/normal weight group (BMI < 24.0 kg/m^2) and used underweight/normal weight group as the reference. Binary logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (CIs) of prepregnancy BMI and GDM for macrosomia or LGA. In multivariable analysis, we adjusted for traditional risk factors including age, family history of diabetes in first degree relatives, height, parity, nationality, gestational age at delivery (only for macrosomia), gender (only for macrosomia), smoking before or during pregnancy and drinking before or during pregnancy to control traditional confounders (Model 2). In the cohort, 948 women diagnosed with GDM entered a randomized controlled trial of lifestyle intervention on pregnancy outcomes. The details of intervention protocol were described in a previous study [22]. In this analysis, we further adjusted for care status, i.e., intensive care, usual care and non-inclusion in the trial in Model 3 to minimize possible confounding effects from different managements. Ryan-Holm step-down Bonferroni procedure was used to adjust P-values and 95%CIs for multiple comparisons where appropriate.

Subgroup analysis among participants with or without prepregnancy overweight was performed to test the consistency of ORs of GDM for macrosomia and LGA across subgroups. Synergistic effects between prepregnancy overweight and GDM for macrosomia and LGA were examined using additive interaction. We applied three indicators to evaluate additive interaction: relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) or synergy index (S). RERI > 0, AP > 0, or S > 1 was regarded as significant additive interaction [23]. Multivariable analysis was performed to control for confounding variables.

All statistical tests were two-sided and $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Characteristics of participants

The cohort had a mean age of 28.5 (SD: 2.9) years, a mean height of 163.2 (SD: 4.7) cm, a mean BMI of 22.3 (SD: 3.4) kg/m^2 and a mean gestational age at registration of 10.4 (SD: 2.4) weeks. Among the 19,622 pregnant women, 3.8% (n = 746) had parity ≥ 1 and 8.0% (n = 1569) had a family history of diabetes in first degree relatives. Overall, 7.6% (n = 1495) pregnant women had GDM, macrosomia and large for gestational age infants accounted for 9.1% (n = 1791) and 8.8% (n = 1726), respectively. Women who delivered a macrosomia or LGA infant were taller and more likely to have drinking and smoking habits, to have GDM and family history of diabetes, and also tended to have higher systolic/diastolic BP and higher prepregnancy BMI (Table 1).

3.2. Risk associations of prepregnancy overweight and GDM with macrosomia and LGA

When prepregnancy BMI < 24.0 kg/m^2 or non-GDM was used as the reference, the ORs of overweight and GDM for macrosomia were 2.28 (95%CI: 2.06–2.52) and 2.02 (95%CI: 1.74–2.34) in univariable analysis, respectively. After adjusted for confounding variables, the risk associations between prepregnancy overweight and macrosomia and between GDM and macrosomia remained persistent in model 2 (OR of overweight for macrosomia: 2.34, 95%CI: 2.11–2.59; OR of GDM for macrosomia: 2.25, 95%CI: 1.93–2.62). Adjusting for care status for GDM did not substantially change the effect of overweight for macrosomia and slightly enhanced the association between GDM and macrosomia (Model 3). In the same manner, the associations between prepregnancy overweight and LGA, and between GDM and LGA were significant in univari-

Table 1 – Clinical characteristics of participants by delivering macrosomia or large for gestational age infant status.

Variables	Macrosomia			LGA		
	YES	NO	P value	YES	NO	P value
Registration age, year	28.5 ± 2.8	28.5 ± 3.0	0.753*	28.6 ± 2.9	28.5 ± 2.9	0.026*
Height, cm	164.8 ± 4.8	163.0 ± 4.7	<0.0001*	164.7 ± 4.9	163.1 ± 4.7	<0.0001*
Parity ≥ 1	72(4.0%)	674(3.8%)	0.612**	87(5.0%)	659(3.7%)	0.005**
Han-nationality	1721(96.1%)	17005(95.4%)	0.162**	1654(95.8%)	17072(95.4%)	0.410**
Family history of diabetes in first degree relatives	174(9.7%)	1395(7.8%)	0.005**	171(9.9%)	1398(7.8%)	0.002**
Habitual smoker before or during pregnancy	73(4.1%)	582(3.3%)	0.068**	77(4.5%)	578(3.2%)	0.007**
Habitual drinker before or during pregnancy	583(32.6%)	5397(30.3%)	0.045**	569(33.0%)	5411(30.2%)	0.019**
Gestational age at registration, weeks	10.4 ± 2.4	10.4 ± 2.4	0.664*	10.5 ± 2.5	10.4 ± 2.4	0.238*
DBP, mmHg	69.5 ± 7.7	68.2 ± 7.7	<0.0001*	69.5 ± 7.7	68.3 ± 7.7	<0.0001*
SBP, mmHg	106.9 ± 10.6	105.3 ± 10.6	<0.0001*	107.2 ± 10.5	105.4 ± 10.6	<0.0001*
GDM	238(13.3%)	1257(7.1%)	<0.0001**	240(13.9%)	1255(7.0%)	<0.0001**
Pre-pregnancy BMI, kg/m^2	23.8 ± 3.6	22.1 ± 3.3	<0.0001*	23.9 ± 3.7	22.2 ± 3.3	<0.0001*
Pre-pregnancy BMI group, kg/m^2			<0.0001**			<0.0001**
<18.5	50(2.8%)	1869(10.5%)		47(2.7%)	1872(10.5%)	
≥18.5–<24.0	980(54.7%)	11600(65.1%)		933(54.1%)	11647(65.1%)	
≥24.0 -<28.0	526(29.4%)	3318(18.6%)		503(29.1%)	3341(18.7%)	
≥28.0	235(13.1%)	1044(5.9%)		243(14.1%)	1036(5.8%)	
Gestational age at delivery, weeks	40.1 ± 1.2	39.5 ± 1.6	<0.0001*	39.6 ± 1.6	39.5 ± 1.6	0.580*

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; LGA, large for gestational age.
DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure.
* Derived from Student's t-test.
** Derived from Chi-square Test or Fisher's Exact Test.

able analysis and persisted after adjustment for confounders (Model 3) (adjusted OR of overweight for LGA: 2.27, 95%CI: 2.05–2.52; adjusted OR of GDM for LGA: 2.57, 95%CI: 2.05–3.21) (Table 2).

3.3. Subgroup analysis of GDM for macrosomia and LGA by overweight

Among overweight/obesity pregnant women, the OR of GDM for macrosomia was 1.83 (95%CI: 1.50–2.23) in univariable analysis and 2.56 (95%CI: 1.91–3.41) after adjustments for confounders (Model 3 in Table 3), both being higher than those among normal weight or underweight women at registration. Their unadjusted OR and adjusted OR were 1.55 (95%CI: 1.22–2.00) and 1.71 (95%CI: 1.14–2.57), respectively. The adjusted OR of GDM for LGA was slightly higher in the overweight group (OR: 2.28, 95%CI: 1.71–3.04) as compared with normal weight or underweight group (OR: 1.85, 95%CI:1.26–2.71) after further adjustment for care status (Model 3 in Table 3).

3.4. Additive interaction between prepregnancy overweight and GDM for macrosomia and LGA

If non-GDM and BMI <24.0 kg/m^2 were used as the reference, GDM alone and BMI≥ 24.0 kg/m^2 alone were both associated with increased risks of macrosomia and LGA. Co-presence of both factors had a greater effect than either of them alone. After adjusted for traditional risk factors and lifestyle

Table 2 – Odds ratio of prepregnant overweight and GDM for macrosomia and large for gestational age.

	Macrosomia			LGA		
	OR	95%CI	P value	OR	95%CI	P value
Prepregnant overweight						
Model 1	2.28	2.06–2.52	<0.0001	2.34	2.11–2.59	<0.0001
Model 2	2.34	2.11–2.59	<0.0001	2.32	2.10–2.57	<0.0001
Model 3	2.29	2.07–2.54	<0.0001	2.27	2.05–2.52	<0.0001
GDM						
Model 1	2.02	1.74–2.34	<0.0001	2.14	1.85–2.48	<0.0001
Model 2	2.25	1.93–2.62	<0.0001	2.17	1.87–2.53	<0.0001
Model 3	2.70	2.15–3.40	<0.0001	2.57	2.05–3.21	<0.0001

Abbreviations: GDM, gestational diabetes mellitus; LGA, large for gestational age.
Model 1: Univariable analysis.
Model 2: Multivariable analysis, adjusted for age, family history of diabetes in first degree relatives, height, parity, nationality, gestational age at delivery (only for macrosomia), gender (only for macrosomia), smoking before or during pregnancy, drinking before or during pregnancy.
Model 3: Further adjusted for lifestyle intervention for GDM, in addition to the variables listed in Model 2.

Table 3 – Odds ratio of pre-pregnancy overweight and GDM for macrosomia and large for gestational age.

	Macrosomia			Large for gestational age		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Subgroup analysis						
Among pre-pregnancy BMI ≥ 24.0 kg/m^2						
Non-GDM	1.00	1.00	1.00	1.00	1.00	1.00
GDM	1.83(1.50–2.23)	2.01(1.63–2.47)	2.56(1.91–3.41)	1.80(1.48–2.20)	1.82(1.48–2.23)	2.28(1.71–3.04)
Among pre-pregnancy BMI < 24.0 kg/m^2						
Non-GDM	1.00	1.00	1.00	1.00	1.00	1.00
GDM	1.55(1.22–2.00)	1.76(1.38–2.24)	1.71(1.14–2.57)	1.79(1.42–2.25)	1.87(1.48–2.37)	1.85(1.26–2.71)
Additive interaction models						
Non-GDM and BMI < 24.0 kg/m^2	1.00	1.00	1.00	1.00	1.00	1.00
GDM and BMI < 24.0 kg/m^2	1.55(1.22–1.96)	1.71(1.34–2.17)	2.01(1.48–2.72)	1.79(1.42–2.25)	1.84(1.46–2.33)	2.14(1.60–2.87)
Non-GDM and BMI ≥ 24.0 kg/m^2	2.13(1.91–2.37)	2.17(1.94–2.42)	2.17(1.94–2.42)	2.23(2.00–2.49)	2.21(1.98–2.47)	2.21(1.98–2.47)
GDM and BMI ≥ 24.0 kg/m^2	3.89(3.21–4.70)	4.56(3.73–5.58)	5.29(4.07–6.87)	4.02(3.31–4.87)	4.12(3.38–5.02)	4.72(3.66–6.10)

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus.
Model 1: Univariable analysis.
Model 2: Multivariable analysis, adjusted for age, family history of diabetes in first degree relatives, height, parity, nationality, gestational age at delivery (only for macrosomia), gender (only for macrosomia), smoking before or during pregnancy, drinking before or during pregnancy.
Model 3: Further adjusted for lifestyle intervention for GDM, in addition to the variables listed in Model 2.

intervention, copresence of GDM and BMI≥ 24.0 kg/m^2 markedly increased the ORs further to 5.29 (95%CI: 4.07–6.87) for macrosomia and 4.72 (95%CI: 3.66–6.10) for LGA (Table 3). The three indicators of additive interaction were all significant for macrosomia in univariable analysis. After adjusted for confounders in model 3, the three indicators for macrosomia were still statistically significant (RERI: 2.11, 95%CI, 0.88–3.34; AP: 0.40, 95%CI, 0.25–0.56; S: 2.00, 95%CI, 1.41–2.74) and they were also true for LGA (RERI: 1.37, 95%CI, 0.29–2.45; AP: 0.29, 95%CI, 0.12–0.46; S: 1.58, 95%CI, 1.14–2.19) (Table 4).

Table 4 – Additive interaction between pre-pregnancy BMI ≥ 24 kg/m^2 and GDM for macrosomia and large for gestational age.

	Estimates (95%CI)		
	Model 1	Model 2	Model 3
Macrosomia as the outcome			
RERI	1.21(0.42–2.01)	1.69(0.73–2.65)	2.11 (0.88–3.34)
AP	0.31(0.15–0.47)	0.37(0.22–0.52)	0.40 (0.25–0.56)
S	1.73(1.23–2.43)	1.90(1.36–2.67)	2.00 (1.41–2.74)
Large for gestational age as the outcome			
RERI	1.00(0.15–1.85)	1.01 (0.18–1.95)	1.37(0.29–2.45)
AP	0.25(0.07–0.42)	0.26(0.08–0.43)	0.29(0.12–0.46)
S	1.50(1.08–2.08)	1.52(1.09–2.12)	1.58(1.14–2.19)

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus. RERI, relative excess risk due to interaction (RERI); AP, attributable proportion due to interaction and S, synergy index. RERI > 0, AP > 0, or S > 1 suggest significant additive interaction.
Model 1: Univariable analysis.
Model 2: Multivariable analysis, adjusted for age, family history of diabetes in first degree relatives, height, parity, nationality, gestational age at delivery (only for macrosomia), gender (only for macrosomia), smoking before or during pregnancy, drinking before or during pregnancy.
Model 3: Further adjusted for lifestyle intervention for GDM, in addition to the variables listed in Model 2.

4. Discussion

Our study revealed that prepregnancy overweight and GDM themselves were not only associated with increased risks of macrosomia and LGA, but the two risk factors had a synergistic effect on macrosomia and LGA, and copresence of both risk factors predisposed women to a 5-fold risk of macrosomia and LGA as compared with women who had a prepregnancy BMI <24.0 kg/m^2 and did not have GDM during pregnancy.

Accumulating evidence confirms that GDM may play a causal role in development of macrosomia or LGA. Cohort studies showed that GDM increased risk of macrosomia in our [24] and other populations [25]. Randomized controlled trials consistently demonstrated that tight glycemic control via lifestyle modification was able to reduce the rates of macrosomia and/or LGA [3,4,22]. On the other hand, studies reported inconsistent findings regarding the association between prepregnancy overweight/obesity and macrosomia/LGA. For example, a prospective hospital-based cohort in Shanghai found that prepregnancy BMI was positively associated with macrosomia (OR: 2.24; 95%CI: 1.55–3.23)[26] while another prospective cohort study in China observed that prepregnancy BMI was not associated with risk of macrosomia in singleton women with GDM after adjustment for potential confounders [27]. Using a population-based prospective cohort, our study provided stronger evidence that prepregnancy overweight was associated with about 2-fold risk of macrosomia and LGA. The effect was independent of traditional risk factors of macrosomia.

The present study is the first to report a synergistic effect of prepregnancy overweight and GDM on the risk of macrosomia and LGA. In other words, copresence of maternal prepregnancy overweight and GDM greatly increased the risk of macrosomia or LGA, more than summation of the risks due to exposure to either of them. Previous studies implied that there may be a synergistic effect of pepregnancy overweight

and GDM on the risk of macrosomia. The HAPO study observed that co-existence of GDM and obesity had a higher OR on LGA compared to either one alone numerically (adjusted OR of GDM and obesity: 3.62, 95%CI: 3.04–4.32 & adjusted OR of GDM: 2.19, 95%CI: 1.93–2.47 & adjusted OR of obesity: 1.73, 95%CI: 1.50–2.00). The observation suggests that obesity and GDM may have an interactive effect on LGA although there was no formal statistical test preformed [28]. In this regard, the Kaiser Permanente Southern California (KPSC) Medical Care Program also found that the effects of GDM and maternal BMI appeared to be additive for LGA (OR of obesity and GDM: 4.08, 95%CI: 3.27–5.09; OR of obesity: 1.85, 95%CI: 1.52–2.27; OR of GDM: 2.10, 95%CI: 1.54–2.86), but formal tests were not preformed, probably due to small sample size [29]. In a population-based prospective cohort with detailed documentation of covariables throughout pregnancy, we confirmed that pregnancy overweight and GDM had a synergistic effect on the risks of macrosomia and LGA, and co-exposure to both risk factors predisposed women to 4-fold macrosomia risk of those women without either of them.

Pedersen's hypothesis states that maternal high blood glucose could cross the placenta, but insulin couldn't, thus causing glucose accumulation in the fetus. Extra glucose in the fetus stimulates pancreatic islet cells secreting insulin to uptake glucose, leading to fetal hyperinsulinemia and hyperglycemia and consequently, excessive accumulation of fat tissue and large body weight [16]. The HAPO study observed positive associations between fasting, 1-h and 2-h plasma glucose levels and macrosomia in a linear manner without clear threshold effects [5]. A prospective pregnant women cohort in England provided further evidence that maternal pregnant hyperglycemia had a long effect on offspring overnutrition and obesity [25], supporting Pedersen's hypothesis. In this regard, our group showed that increased insulin resistance rather than decreased beta cell function was a major contributor to macrosomia and LGA in Chinese women with GDM [30]. Prepregnancy obesity can also aggravate offspring obesity through genetic predisposition [31] and in utero environment [32]. On the other hand, prepregnancy obesity is a strong risk factor for occurrence of GDM during pregnancy. Thus, the synergistic effect between prepregnancy overweight and GDM is biologically plausible.

Our study has public health importance. Prepregnancy overweight, GDM and copresence of both risk factors were quite common in pregnant women, up to 26.1%, 7.6% and 3.5% in our subjects. Our study shows that women who were exposed to both risk factors had greatly increased risk of delivery of a macrosomia or LGA infant and the increased risk due to the co-exposure accounted for 40% of macrosomia and 29% of LGA in urban Tianjin. Large randomized controlled trials demonstrated that intensive lifestyle intervention of GDM was able to reduce the rate of macrosomia and LGA [3,4,22]. It is presumable that such intervention is also effective to reduce the risk of macrosomia and LGA in overweight women with GDM who were at particular high risk of macrosomia and LGA. Our findings also highlight that overweight even without GDM also predisposes women to a high risk of macrosomia and LGA. Given to the long-term risk of cardiovascular disease of macrosomic infants [33], maintaining healthy body weight well before pregnancy may benefit women in many ways, such as reduced risk of GDM and improved pregnancy outcomes even if these women are not to develop GDM during their pregnancy.

Our study has several advantages. First, our study was a prospective population-based cohort with a large sample size. Second, covariables during pregnancy were documented in details, so that adjustment for those major confounders was feasible. Our study also had limitations. First, all participants were from a single population and our findings need replications in other pregnant women populations. Second, although weight gain is an established risk factor for macrosomia and LGA [34,35], our study did not collect body weight at delivery and weight gain during whole pregnancy was not available for adjustment. Third, we adopted a two-step procedure to diagnose GDM and some cases of GDM might have missed.

In conclusion, our study confirmed that prepregnancy overweight was a risk factor for macrosomia and LGA in Chinese pregnant women, and copresence of overweight and GDM had a synergistic effect on the risk of macrosomia/LGA. Our study highlights the importance to maintain normal body weight prior to pregnancy for a reduced risk of GDM and adverse pregnancy outcomes. Nevertheless, our findings need to be further confirmed by well-designed cohorts of other pregnant women populations.

Declaration of Competing Interest

The authors have no competing interests in this article.

Acknowledgement

The authors would like to express our special thanks to obstetricians and other health professionals in the 64 primary care hospitals and 6 district women and children's health care institutes who were involved in the setting up of the cohort.

Authors' Contributions

X.Y. conceived and designed the study. W.Y. analyzed the data and wrote the first draft, J.L., H.L., Y.W., J.L. and S.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 W.Y. (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. All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

Funding

This study was supported by the National Key Research and Development Program of China (Grant number: 2018YFC1313903) and National Natural Science Foundation of China (Grant number: 81870549).

REFERENCES

[1] Liao S, Mei J, Song W, Liu Y, Tan YD, Chi S, et al. The impact of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) fasting glucose diagnostic criterion on the prevalence and outcomes of gestational diabetes mellitus in Han Chinese women. Diabet Med. 2014;31:341–51.

[2] American Diabetes A. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37:S81-90.

[3] Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–86.

[4] Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–48.

[5] Group HSCR, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991-2002, PMID: 18463375, doi: 10.1056/NEJMoa0707943.

[6] Vidarsdottir H, Geirsson RT, Hardardottir H, Valdimarsdottir U, Dagbjartsson A. Obstetric and neonatal risks among extremely macrosomic babies and their mothers. Am J Obstet Gynecol 2011;204(423):e1–6.

[7] Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. Obstet Gynecol 2011;118:29–38.

[8] Li G, Kong L, Li Z, Zhang L, Fan L, Zou L, et al. Prevalence of macrosomia and its risk factors in china: a multicentre survey based on birth data involving 101,723 singleton term infants. Paediatr Perinat Epidemiol. 2014;28:345–50.

[9] Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab 2015;66 (Suppl 2):14–20. https://doi.org/10.1159/000371628. PMID: 26045324.

[10] Kamanu CI, Onwere S, Chigbu B, Aluka C, Okoro O, Obasi M. Fetal macrosomia in African women: a study of 249 cases. Arch Gynecol Obstet 2009;279:857–61.

[11] Boulet SL, Alexander GR, Salihu HM, Pass M. Macrosomic births in the united states: determinants, outcomes, and proposed grades of risk. Am J Obstet Gynecol 2003;188:1372–8.

[12] Pan XF, Tang L, Lee AH, Binns C, Yang CX, Xu ZP, et al. Association between fetal macrosomia and risk of obesity in children under 3 years in Western China: a cohort study. World J Pediatr 2019;15:153–60.

[13] Wang D, Hong Y, Zhu L, Wang X, Lv Q, Zhou Q, et al. Risk factors and outcomes of macrosomia in China: a multicentric survey based on birth data. J Matern Fetal Neonatal Med 2017;30:623–7.

[14] Yessoufou A, Moutairou K. Maternal diabetes in pregnancy: early and long-term outcomes on the offspring and the concept of "metabolic memory". Exp Diabet Res 2011;2011:218598.

[15] Brett KE, Ferraro ZM, Yockell-Lelievre J, Gruslin A, Adamo KB. Maternal-fetal nutrient transport in pregnancy pathologies: the role of the placenta. Int J Mol Sci 2014;15:16153–85.

[16] Pedersen J. Weight and length at birth of infants of diabetic mothers. Acta Endocrinol (Copenh) 1954;16:330–42.

[17] Voldner N, Qvigstad E, Froslie KF, Godang K, Henriksen T, Bollerslev J. Increased risk of macrosomia among overweight women with high gestational rise in fasting glucose. J Matern Fetal Neonatal Med. 2010;23:74–81.

[18] Leng J, Shao P, Zhang C, Tian H, Zhang F, Zhang S, et al. Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: a prospective population-based study in Tianjin China. PLoS One 2015;10: e0121029.

[19] Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabet Care 2010;33:676–82. https://doi.org/10.2337/dc09-1848. PMID:20190296.

[20] National Health Commission of the People's Republic of China. Criteria of Weight for Adults (2013). <http://www.nhc.gov.cn/ewebeditor/uploadfile/2013/08/20130808135715967>.

[21] Li N, Liu E, Guo J, Pan L, Li B, Wang P, et al. Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes. PLoS ONE 2013;8:e82310. https://doi.org/10.1371/journal.pone.0082310.

[22] Yang X, Tian H, Zhang F, Zhang C, Li Y, Leng J, et al. A randomised translational trial of lifestyle intervention using a 3-tier shared care approach on pregnancy outcomes in Chinese women with gestational diabetes mellitus but without diabetes. J Transl Med. 2014;12:290.

[23] Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol 2005;20:575–9.

[24] Heikkinen J. Serum bile acids in the early diagnosis of intrahepatic cholestasis of pregnancy. Obstet Gynecol. 1983;61:581–7.

[25] Lawlor DA, Fraser A, Lindsay RS, Ness A, Dabelea D, Catalano P, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. Diabetologia 2010;53:89–97.

[26] Shen J, Zhang Z, Chen K, Lu M, Qian Q, Liu P, et al. Prepregnancy obesity status and risks on pregnancy outcomes in Shanghai: a prospective cohort study. Medicine (Baltimore) 2018;97:e12670.

[27] Wang N, Ding Y, Wu J. Effects of pre-pregnancy body mass index and gestational weight gain on neonatal birth weight in women with gestational diabetes mellitus. Early Hum Dev 2018;124:17–21.

[28] Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger BE, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diabet. Care 2012;35:780–6.

[29] Black MH, Sacks DA, Xiang AH, Lawrence JM. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diabet. Care 2013;36:56–62.

[30] Li J, Leng J, Li W, Zhang C, Feng L, Wang P, et al. Roles of insulin resistance and beta cell dysfunction in macrosomia among Chinese women with gestational diabetes mellitus. Prim Care Diabet 2018;12:565–73.

[31] Chagnon YC, Rankinen T, Snyder EE, Weisnagel SJ, Perusse L, Bouchard C. The human obesity gene map: the 2002 update. Obes Res 2003;11:313–67.

[32] Rhee KE, Phelan S, McCaffery J. Early determinants of obesity: genetic, epigenetic, and in utero influences. Int J Pediatr 2012;2012:463850.

[33] Briana DD, Germanou K, Boutsikou M, Boutsikou T, Athanasopoulos N, Marmarinos A, et al. Potential prognostic biomarkers of cardiovascular disease in fetal macrosomia: the impact of gestational diabetes. J Matern Fetal Neonatal Med 2018;31:895–900.

[34] Goldstein RF, Abell SK, Ranasinha S, Misso ML, Boyle JA, Harrison CL, et al. Gestational weight gain across continents and ethnicity: systematic review and meta-analysis of maternal and infant outcomes in more than one million women. BMC Med 2018;16:153.

[35] Hung TH, Hsieh TT. Pregestational body mass index, gestational weight gain, and risks for adverse pregnancy outcomes among Taiwanese women: A retrospective cohort study. Taiwan J Obstet Gynecol 2016;55:575–81.