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β-Cell function or insulin resistance was associated with the risk of type 2 diabetes among women with or without obesity and a history of gestational diabetes

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ABSTRACT

Introduction To evaluate the single association of postpartum β-cell dysfunction and insulin resistance (IR), as well as different combinations of postpartum β-cell dysfunction, IR, obesity, and a history of gestational diabetes mellitus (GDM) with postpartum type 2 diabetes risk.

Research design and methods The study included 1263 women with prior GDM and 705 women without GDM. Homeostatic model assessment was used to estimate homeostatic model assessment of β-cell secretory function (HOMA-%β) and homeostatic model assessment of insulin resistance (HOMA-IR).

Results Multivariable-adjusted ORs of diabetes across quartiles of HOMA-%β and HOMA-IR were 1.00, 1.46, 2.15, and 6.25 (p_{trend} <0.001), and 1.00, 2.11, 5.59, and 9.36 (p_{trend} <0.001), respectively. Women with IR only had the same diabetes risk as women with β-cell dysfunction only. Obesity, together with IR or β-cell dysfunction, had a stronger effect on diabetes risk. This stronger effect was also found for a history of GDM with IR or β-cell dysfunction. Women with three risk factors, including obesity, a history of GDM and β-cell dysfunction/IR, showed the highest ORs of diabetes.

Conclusions β-cell dysfunction or IR was significantly associated with postpartum diabetes. IR and β-cell dysfunction, together with obesity and a history of GDM, had the highest ORs of postpartum diabetes risk.

Significance of this study

What is already known about this subject?

► Postpartum β-cell dysfunction, insulin resistance (IR) and obesity are all associated with postpartum type 2 diabetes. However, very few studies have examined the joint association of β-cell dysfunction, IR, obesity, and a history of gestational diabetes mellitus (GDM) with the risk of postpartum type 2 diabetes.

What are the new findings?

► β-cell dysfunction or IR was significantly associated with postpartum diabetes. IR and β-cell dysfunction, together with obesity and a history of GDM, had stronger effects on postpartum diabetes risk.

How might these results change the focus of research or clinical practice?

► Interventions for maintaining a healthy lifestyle and normal weight status among women with and without GDM during the early postpartum period might be the key point for reducing the risk of obesity, IR, and type 2 diabetes.

INTRODUCTION

Gestational diabetes mellitus (GDM) is paralleling the obesity epidemic and characterized by any degree of carbohydrate intolerance with onset during pregnancy and without previously known diabetes among women. Women with a history of GDM have an approximately 7.4 higher risk of developing postpartum diabetes than those who have normal glucose tolerance during pregnancy.[1 2] Epidemiological evidence suggests that the prevalence of GDM has increased in all ethnicity groups.[3] In China, some studies reported that there was a dramatic increase in the prevalence of GDM from 2.4% in 1999 to 8.2% in 2012.[4 5]

Some studies have indicated that insulin response to oral glucose among women with GDM during pregnancy is lower than that in women with normal glucose tolerance during pregnancy, while these women have significantly higher mean values of plasma glucose. Furthermore, peak plasma insulin concentrations in women with GDM occur later than those in women with normal glucose tolerance during pregnancy and a reduced first-phase insulin response to intravenous glucose can be observed in women with GDM.[6 7] Several epidemiological studies have also reported a persistent defect in β-cell function after delivery and weight gain during the first several years after delivery. A significantly

declining β-cell compensation for insulin resistance (IR) after delivery results in a higher postpartum diabetes risk among women with a history of GDM. Evidence from many large studies indicates that obesity is associated with an increased risk of type 2 diabetes.[8 9] Our recent study has found that prior GDM and prepregnancy or postpartum obesity contribute equally to postpartum diabetes.[10] Numerous findings have solidified that obesity causes peripheral tissue resistance to insulin's actions, which raises blood glucose levels and then stimulates islet β-cell insulin secretion.[11] However, very few studies examined the joint association of β-cell dysfunction, IR, obesity, and a history of GDM with the risk of postpartum type 2 diabetes. Therefore, our study aimed to evaluate single effects of postpartum β-cell dysfunction and IR, and joint effects of postpartum β-cell dysfunction, IR, obesity, and a history of GDM on diabetes risk.

DESIGN AND METHODS

Tianjin GDM screening project

The study subjects were living in Tianjin, a municipality directly adjacent to the sea. A total of 4.3 million residents were living in six central urban districts. Since 1999, the pregnant women living in the urban regions in Tianjin have been recruited into a two-step GDM screening program launched by Tianjin Women's and Children's Health Center. The screening rate was reported to be more than 91% from 1999 to 2008.[5] The center conducted a 1-hour 50 g glucose screening test at 26–30 gestational weeks, and the gestational women who had a 1-hour glucose level over 7.8 mmol/L would experience another 2-hour 75 g oral glucose tolerance test (OGTT). According to the 1999 WHO criteria, women were diagnosed with GDM when the 2-hour 75 g OGTT result confirmed either diabetes (fasting glucose of ≥7 mmol/L or 2-hour glucose of ≥11.1 mmol/L) or impaired glucose tolerance (2-hour glucose of ≥7.8 and<11.1 mmol/L).[12]

Study samples

A total of 76 325 women participated in the Tianjin GDM screening project between 2005 and 2009; 4644 women (6.1%) were screened for GDM, and 71 681 women were free from GDM. During 1–5 years after delivery, all 4644 women with GDM were invited to participate in a baseline survey for the Tianjin Gestational Diabetes Mellitus Prevention Program (TGDMPP) between August 2009 and July 2011.[13–15] Finally, 1263 women with GDM completed the baseline survey, and 83 women were newly diagnosed with type 2 diabetes after a 75 g OGTT. A total of 1180 women with GDM without baseline diabetes were randomly assigned to either a 4-year lifestyle intervention (n=586) or a control group (n=594). In year 1 or year 2 of the TGDMPP follow-up survey, we added one non-GDM normal control group. We randomly selected 580 GDM mother–child pairs who finished the year 1 or year 2 follow-up survey and 83 children of women with GDM who were newly diagnosed with diabetes at baseline as the GDM case group. In parallel, we simultaneously and randomly recruited 705 non-GDM mother–child pairs from 71 681 women without GDM who finished the GDM screening at the same period with age and sex frequency matched to 663 children of the GDM case group. The clinical examination's procedure, items and timing for non-GDM mother–child pairs were almost the same as those for the GDM mother–child pairs.[16] The flowchart was presented in online supplementary figure 1. In the present analysis, we only assessed the mothers.

Questionnaires and examinations

All participants filled in a questionnaire about their social demographics (age, education, marital status, family income, and occupation), history of GDM (values of fasting and 2-hour glucose in the OGTT and treatment of GDM during the pregnancy), family history of diabetes, medical history (hypertension, diabetes, and hypercholesterolemia), pregnancy outcomes (prepregnancy weight, gestational weight gain, and number of children), dietary habits (a self-administered Food Frequency Questionnaire (FFQ) to measure the frequency and quantity of intake of 33 major food groups and beverages during the past year),[17] alcohol intake, smoking habits, passive smoking, and physical activity (the frequency and duration of leisure time and sedentary activities) at the postpartum baseline survey. They also completed the 3-day 24-hour food records using methods for dietary record collections taught by a dietician. The performance of 3-day 24-hour food records, the FFQ[17] and the aforementioned questionnaire on assessing physical activity, were validated in the China National Nutrition and Health Survey in 2002.

Anthropometric variables such as body weight and height were measured for all women using the standardized protocol by specially trained research doctors. Postpartum baseline body mass index (BMI) was calculated by current weight in kilogram divided by the square of height in meter. According to the Chinese BMI classification standard,[18] BMI was classified into three categories: normal weight (<24 kg/m^2), overweight (24.0–27.9 kg/m^2), and obesity (≥28 kg/m^2). Body fat was measured by using the Body Composition Analyzer (SC-240, Tanita, Tokyo, Japan), and the accuracy was validated as being acceptable with dual-energy X-ray absorptiometry.[19] Fasting blood samples were collected after 8–12 hours of fasting overnight. Participants were given a standard 75 g glucose solution. The plasma glucose was measured 0 and 2 hours after administration during the OGTT on an automatic analyzer (Toshiba TBA120FR, Japan). Insulin was measured with chemiluminescence using a Siemens ADVIA Centaur CP Immunoassay System.

Definition of postpartum type 2 diabetes

Based on the WHO's criteria, diabetes is defined as fasting plasma glucose of ≥7.0 mmol/L and/or 2-hour plasma glucose of ≥11.1 mmol/L.[20]

Markers of β-cell function and IR

The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated with the following formula: [fasting plasma insulin×fasting plasma glucose (mmol/L)]/22.5.[21] The homeostatic model assessment of β-cell function (HOMA-%β) was calculated as the product of 20 and the basal insulin levels divided by the value of basal glucose concentrations minus 3.5.[21] IR and β-cell dysfunction were defined as the upper quartile of HOMA-IR and lower quartile of HOMA-%β among women without GDM, respectively.

Statistical analyses

Means and SDs or proportions were presented among women with and without GDM. We used the standard t-test and χ^2 test to compare the two groups for continuous variables and categorical variables, respectively. Logistic regression was used to estimate ORs of diabetes according to single or joint effects of HOMA-IR, HOMA-%β, obesity, and a history of GDM. HOMA-IR was categorized by quartile: <1.44 (reference group), 1.44–2.02, 2.03–2.78, and ≥2.79; HOMA-%β was categorized by quartile: ≥146.3 (reference group), 103.6–146.2, 74.7–103.5, and <74.7; BMI was assessed in three categories: normal weight (BMI<24 kg/m^2), overweight (BMI 24.0–27.9 kg/m^2) and obesity (≥28 kg/m^2) according to the Chinese obesity criteria.[22] Different levels of HOMA-IR and HOMA-%β were included in the models as dummy variables, and the significance of the trend quartiles of HOMA-IR and HOMA-%β was tested in the same models by giving an ordinal numerical value for each dummy variable. All analyses were adjusted for age (model 1) and further for education, family income, family history of diabetes, current smoking, passive smoking, current alcohol drinking, leisure-time physical activity, sleeping time, energy intake, fiber, fat, protein and carbohydrate consumption, sweetened beverage drinking, weight gain during pregnancy, postpartum time, lactation duration, lactation intensity, GDM status, BMI, and other variables for stratification (model 2). A p value of <0.05 was considered statistically significant. All analyses were performed with IBM SPSS Statistics V.25.0.

RESULTS

In total, 1263 women with a history of GDM and 705 women without GDM participated in the study. Of these women, 83 diabetes cases were identified in women with GDM and 10 diabetes cases were diagnosed in women without GDM. The baseline characteristics of the study participants are presented in table 1.

Compared with women without GDM, women with GDM were older at the delivery but slightly younger at the baseline survey, had less weight gain during pregnancy, and reported a shorter lactation duration. The postpartum BMI, waist circumference, and body fat were all significantly higher among women with a history of GDM compared with those among women without GDM. In the aspect of glucose tolerance, the present study showed significant differences between women with and without GDM in fasting glucose, 2-hour glucose, glycated hemoglobin, and HOMA-%β levels, as expected. Compared with women without GDM, women with prior GDM had lower education levels and family income.

HOMA-%β was inversely associated with postpartum diabetes and HOMA-IR was positively associated with postpartum diabetes (table 2).

The multivariable-adjusted (age, education, family income, family history of diabetes, current smoking, passive smoking, current alcohol drinking, leisure-time physical activity, sleeping time, energy consumption, fiber, fat, protein and carbohydrate consumption, sweetened beverage drinking, weight gain during pregnancy, postpartum time, lactation duration, lactation intensity, GDM status, and BMI) ORs of diabetes across quartiles of HOMA-%β (≥146.3, 103.6–146.2, 74.7–103.5, and <74.6) and HOMA-IR (<1.44, 1.44–2.02, 2.03–2.78, and ≥2.79) were 1.00, 1.46 (95% CI 0.59 to 3.66), 2.15 (95% CI 0.89 to 5.22), and 6.25 (95% CI 2.86 to 13.7) (p value for trend <0.001), and 1.00, 2.11 (95% CI 0.83 to 5.35), 5.49 (95% CI 2.35 to 12.9), and 9.36 (95% CI 4.08 to 21.5) (p for trend <0.001), respectively.

The joint effects of any two risk factors of β-cell dysfunction, IR, postpartum obesity, and a history of GDM on the risk of diabetes are presented in table 3.

Compared with normal-weight women with normal β-cell function, the multivariable-adjusted ORs of diabetes among normal-weight women with β-cell dysfunction, overweight women with normal β-cell function, overweight women with β-cell dysfunction, obese women with normal β-cell function, and obese women with β-cell dysfunction were 3.89 (95% CI 1.27 to 11.9), 3.73 (95% CI 1.17 to 11.9), 18.9 (95% CI 6.15 to 58.5), 12.8 (95% CI 4.14 to 39.4) and 62.5 (95% CI 18.4 to 212), respectively. Compared with normal-weight women with good insulin sensitivity, the multivariable-adjusted ORs of diabetes among normal-weight women with IR, overweight women with good insulin sensitivity, overweight women with IR, obese women with good insulin sensitivity, and obese women with IR were 11.5 (95% CI 4.43 to 30.0), 4.12 (95% CI 1.96 to 8.64), 7.07 (95% CI 3.10 to 16.1), 7.09 (95% CI 2.85 to 17.7) and 18.5 (95% CI 8.68 to 39.3), respectively. In comparison with women without GDM with normal β-cell function or good insulin sensitivity, the OR of diabetes among women without GDM with β-cell dysfunction or IR were 0.62 (95% CI 0.07 to 5.31) and 6.57 (95% CI 1.31 to 32.9), women with GDM with normal β-cell function or good insulin sensitivity had a 3.46-fold or 23.0-fold risk of diabetes, and women with GDM with β-cell dysfunction or IR had a 20.3-fold to 64.2-fold risk of diabetes. Multivariable-adjusted ORs

Table 1 Characteristics of women with and without GDM

	Non-GDM	GDM	P value
Number of participants	705	1263	
Age at delivery (years)	29.7±2.83	30.1±3.50	0.008
Age at baseline (years)	35.4±3.23	32.4±3.52	<0.001
Duration after delivery (years)	5.74±1.19	2.29±0.88	<0.001
Prepregnancy weight (kg)	55.8±8.21	59.4±9.14	<0.001
Weight gain during pregnancy (kg)	18.3±6.67	16.8±5.99	<0.001
Prepregnancy BMI (km/m^2)	21.4±2.97	23.1±3.32	<0.001
Postpartum BMI (kg/m^2)	22.9±3.68	24.2±3.93	<0.001
Waist circumference (cm)	75.8±8.26	80.6±9.47	<0.001
Body fat (%)	30.8±5.84	33.1±5.82	<0.001
Fasting glucose (mmol/L)	5.23±0.52	5.38±0.97	<0.001
2-hour glucose (mmol/L)	6.14±1.41	7.08±2.49	<0.001
Serum fasting insulin	8.86 (6.27–11.6)	6.91 (4.76–10.2)	<0.001
HOMA-IR	2.03 (1.44–2.79)	1.61 (1.08–2.51)	<0.001
HOMA-%β	104 (74.7–146)	81.8 (54.3–123)	<0.001
HbA1c (mmol/mol)	35±3	38±8	<0.001
HbA1c (%)	5.3±0.2	5.6±0.7	<0.001
Education (%)			<0.001
<13 years	10.4	22.5	
13–16 years	75.5	70.1	
≥16 years	14.2	7.4	
Income (%)			<0.001
¥<5000/month	5.4	27.5	
¥5000–8000/month	15.5	36.9	
¥≥8000 yuan/month	79.1	35.6	
Family history of diabetes (%)	27.1	35.7	<0.001
Current smoking (%)	4.0	2.0	0.355
Passive smoking (%)	55.2	53.8	0.572
Current alcohol drinker (%)	32.1	21.8	<0.001
Leisure-time physical activity (%)			<0.001
0 min/day	61.7	78.8	
1–29 min/day	33.8	19.1	
≥30 min/day	4.5	2.1	
Lactation intensity (%)			
Exclusive formula	13.6	14.5	
Mixed feeding	44.4	42.6	
Exclusive feeding	42.0	42.9	
Lactation duration (months)	9.88±7.06	8.70±6.23	<0.01
Sleeping time (hours/day)	7.48±0.95	7.81±1.06	<0.01
Energy consumption (kcal/day)*	1627±381	1676±436	0.01
Fiber (g/day)	11.6±4.42	12.2±4.75	0.01
Fat, % of energy	31.1±5.65	33.5±6.34	<0.001
Carbohydrate, % of energy	52.3±6.81	49.5±7.30	<0.001
Protein, % of energy	16.6±2.62	17.0±2.78	0.006
Sweetened beverage drink (%)	77.9	75.5	0.223

*Dietary intakes were assessed by 3-day 24-hour food records.
BMI, body mass index; GDM, gestational diabetes mellitus; HbA1c, glycated hemoglobin; HOMA-%β, homeostatic model assessment of β-cell secretory function; HOMA-IR, homeostatic model assessment insulin resistance.

Table 2 ORs of postpartum diabetes among women according to the different status of HOMA-%β and HOMA-IR

	Participants (n)	Cases (n)	ORs (95% CIs) Model 1	Model 2
HOMA-%β (quartiles)				
≥146.3	381	9	1	1
103.6–146.2	400	12	1.28 (0.53 to 3.07)	1.46 (0.59 to 3.66)
74.7–103.5	443	15	1.45 (0.63 to 3.36)	2.15 (0.89 to 5.22)
<74.7	744	57	3.44 (1.68 to 7.04)	6.25 (2.86 to 13.7)
P for trend			<0.001	<0.001
HOMA-IR (quartiles)				
<1.44	716	9	1	1
1.44–2.02	443	11	2.03 (0.84 to 4.95)	2.11 (0.83 to 5.35)
2.03–2.78	384	23	5.08 (2.32 to 11.1)	5.49 (2.35 to 12.9)
≥2.79	425	50	10.8 (5.22 to 22.2)	9.36 (4.08 to 21.5)
P for trend			<0.001	<0.001

Model 1 adjusted for age; model 2 adjusted for age, education, family income, family history of diabetes, current smoking, passive smoking, current alcohol drinking, leisure-time physical activity, sleeping time, energy consumption, fiber, fat, protein and carbohydrate consumption, sweetened beverage drinking, weight gain during pregnancy, postpartum time, lactation duration, lactation intensity, gestational diabetes status, and body mass index. HOMA-IR and HOMA-%β are divided by quartile among women without gestational diabetes mellitus. HOMA-%β, homeostatic model assessment of β-cell secretory function; HOMA-IR, homeostatic model assessment insulin resistance.

of diabetes among women with normal β-cell function and good insulin sensitivity, women with IR only, women with β-cell dysfunction only, and women with both β-cell dysfunction and IR were 1.00, 6.86 (95% CI 2.91 to 16.1), 4.33 (95% CI 1.78 to 10.5), and 285 (95% CI 77.9 to 1041), respectively. There was no difference in diabetes risk between women with IR only and women with β-cell dysfunction only.

The joint effects of three risk factors on the risk of diabetes are presented in table 4 (β-cell dysfunction/IR, postpartum obesity, and a history of GDM) and table 5 (β-cell dysfunction, IR, and a history of GDM).

Compared with normal-weight women without GDM and with normal β-cell function after delivery, women with any one risk factor (β-cell dysfunction, postpartum obesity, or a history of GDM) had a 0.78-fold to 7.22-fold risk of diabetes, women with any two risk factors had an 8.53-fold to 27.5-fold risk of diabetes, and women with all three risk factors had a 45.6-fold to 172-fold risk of diabetes. Similarly, women with all three risk factors of IR, postpartum obesity, and a history of GDM were associated with the highest risk of diabetes (OR 60.1–151), followed by women with any two risk factors (ORs 5.52–114) and women with any one risk factor (ORs 5.56–8.19), compared with non-obese women without GDM and with normal insulin sensitivity. In comparison with women with GDM who had normal β-cell function and good insulin sensitivity, women with GDM who had both β-cell dysfunction and IR showed the highest OR as 342 (95% CI 84.7 to 1364) of diabetes, followed by women with GDM with β-cell dysfunction only (OR 7.60, 95% CI 3.00 to 18.8) and women with IR only (OR 3.72, 95% CI 1.42 to 9.81). Women without GDM with different status of β-cell function and IR had no significant difference in diabetes risk. There were no significant interactions of HOMA-IR, HOMA- β%, BMI, and a history of GDM with the risk of diabetes (all p values for interaction >0.1).

DISCUSSION

The present study demonstrated that postpartum β-cell dysfunction and IR were independently and significantly associated with an increased risk of postpartum diabetes. Women with IR only had the same diabetes risk as women with β-cell dysfunction only. Obesity with IR or with β-cell dysfunction had stronger effects on the development of postpartum diabetes. Meanwhile, a history of GDM with β-cell dysfunction or with IR also had stronger effects on the development of postpartum diabetes. Women who had a history of GDM and β-cell dysfunction as well as IR, and women who had a history of GDM and obesity as well as β-cell dysfunction/IR showed the highest risk of diabetes.

Epidemiological studies have shown that GDM is now becoming the most common pregnancy complication with the prevalence of 7%–17% worldwide,[3 23] which makes it a public health concern. Recent studies have shown that a racial difference existed in the risk of postpartum diabetes after GDM. Black women with GDM have the highest risk of developing diabetes,[24] and Asian–Americans with GDM are more likely to develop type 2 diabetes than non-Hispanic Caucasians with GDM.[8 25] The mechanism may be illustrated by the fact that Asian women are more sensitive to metabolic derangement at a lower BMI level and that increased BMI levels are

Table 3 ORs of diabetes according to any two different levels of HOMA-%β, HOMA-IR, postpartum BMI, and gestational diabetes

Factor 1	Factor 2	Participants (n)	Cases (n)	ORs (95% CI) Model 1	ORs (95% CI) Model 2
HOMA-%β*	BMI (kg/m^2)				
≥74.7	<24	639	4	1	1
<74.7	<24	537	18	5.51 (1.85 to 16.4)	3.89 (1.27 to 11.8)
≥74.7	24–27.9	378	12	5.21 (1.67 to 16.3)	3.73 (1.17 to 11.9)
<74.7	24–27.9	159	22	25.6 (8.66 to 75.5)	18.9 (6.15 to 58.5)
≥74.7	≥28	207	20	16.9 (5.72 to 50.2)	12.8 (4.14 to 39.4)
<74.7	≥28	48	17	87.2 (27.7 to 274)	62.5 (18.4 to 212)
HOMA-IR†	BMI (kg/m^2)				
<2.79	<24	1072	13	1	1
≥2.79	<24	104	9	7.81 (3.25 to 18.8)	11.5 (4.43 to 30.0)
<2.79	24–27.9	375	20	4.54 (2.24 to 9.23)	4.12 (1.96 to 8.64)
≥2.79	24–27.9	162	14	7.74 (3.5716.8)	7.07 (3.10 to 16.1)
<2.79	≥28	96	10	9.46 (4.03 to 22.20	7.09 (2.85 to 17.7)
≥2.79	≥28	159	27	17.0 (8.55 to 33.9)	18.5 (8.68 to 39.3)
HOMA-%β	GDM				
≥74.7	No	530	9	1	1
<74.7	No	175	1	0.33 (0.04 to 2.65)	0.62 (0.07 to 5.31)
≥74.7	Yes	694	27	2.35 (1.10 to 5.04)	3.46 (1.03 to 11.6)
<74.7	Yes	569	56	6.36 (3.11 to 13.0)	20.3 (6.15 to 66.9)
HOMA-IR	GDM				
<2.79	No	531	2	1	1
≥2.79	No	174	8	12.8 (2.70 to 61.0)	6.57 (1.31 to 32.9)
<2.79	Yes	1012	41	11.1 (2.67 to 46.0)	23.0 (4.19 to 126)
≥2.79	Yes	251	42	53.3 (12.8 to 222)	64.2 (11.1 to 370)
HOMA-%β	HOMA-IR				
≥74.7	<2.79	826	7	1	1
<74.7	<2.79	717	36	6.13 (2.71 to 13.9)	6.86 (2.91 to 16.1)
≥74.7	≥2.79	398	29	9.28 (4.02 to 21.4)	4.33 (1.78 to 10.5)
<74.7	≥2.79	27	21	414 (128 to 1342)	285 (77.9 to 1041)

Model 1 adjusted for age; model 2 adjusted for age, education, family income, family history of diabetes, current smoking, passive smoking, current alcohol drinking, leisure-time physical activity, sleeping time, energy consumption, fiber, fat, protein and carbohydrate consumption, sweetened beverage drinking, weight gain during pregnancy, postpartum time, lactation duration, lactation intensity, gestational diabetes status, and body mass index, other than the variables for stratification.
*The lowest quartile of HOMA-%β (<74.7) was defined as β-cell dysfunction.
†The highest quartile of HOMA-IR (≥2.79) was defined as insulin resistance.
BMI, body mass index; GDM, gestational diabetes mellitus; HOMA-%β, homeostatic model assessment of β-cell secretory function; HOMA-IR, homeostatic model assessment insulin resistance.

correlated with elevated fasting glucose levels and diminished insulin sensitivity.[26 27]

Many studies have demonstrated that weight gain, β-cell dysfunction, and IR could contribute to gestational diabetes during pregnancy and diabetes among general people.[28 29] A recent study found that central obesity was strongly associated with IR, which was calculated by HOMA-IR, and increased the risk of gestational diabetes in early pregnancy.[30] Alptekin *et al* indicated that in women with BMI>25.95 kg/m^2 and HOMA-IR>2.08 during pregnancy, weight loss may help reduce the risk of GDM.[31] An observation has demonstrated that during the first pregnancy trimester, HOMA-IR>2.60 can predict GDM.[32] In addition, some studies have shown that during the pregnancy period, the placenta will secrete many cytokines and hormones, considered as adipokines[33 34] which could lead to a state of peripheral IR mainly located in muscle tissue and with a relative

Table 4 ORs of postpartum diabetes according to different levels of GDM, BMI, HOMA-%β and HOMA-IR

	Non-GDM			GDM		
	BMI<24	BMI 24.0–27.9	BMI≥28	BMI<24	BMI 24.0–27.9	BMI≥28
HOMA-%β						
≥74.7	1	1.44 (0.23 to 9.17)	7.22 (1.48 to 35.2)	0.78 (0.07 to 9.24)	8.53 (1.71 to 42.7)	27.5 (5.64 to 134)
<74.7	0.78 (0.08 to 7.74)	–*	–*	9.45 (2.63 to 44.0)	45.6 (9.40 to 221)	172 (34.1 to 869)
HOMA-IR						
<2.79	1	–*	–*	8.19 (1.37 to 48.8)	38.8 (6.68 to 226)	65.6 (10.6 to 407)
≥2.79	5.56 (0.74 to 41.8)	5.52 (0.69 to 44.2)	18.3 (3.06 to 109)	114 (16.9 to 772)	60.1 (9.69 to 373)	151 (25.6 to 898)

All analyses adjusted for age, education, family income, family history of diabetes, current smoking, passive smoking, current alcohol drinking, leisure-time physical activity, sleeping time, energy consumption, fiber, fat, protein and carbohydrate consumption, sweetened beverage drinking, weight gain during pregnancy, lactation duration, lactation intensity, and postpartum time. All p values for interaction are >0.1.
*No incident cases were found.
BMI, body mass index; GDM, gestational diabetes mellitus; HOMA-%β, homeostatic model assessment of β-cell secretory function; HOMA-IR, homeostatic model assessment insulin resistance.

attenuation of insulin secretion.[35 36] Moreover, obesity is correlated with some inflammation markers that also play an important role in IR. The expression of some adipokines such as ENPP1 (ectonucleotide pyrophosphate phosphodiesterase-1) in obese pregnant women was higher than that in lean women without GDM.[37] Although most of the women with a history of GDM return to normal glucose, about 20%–50% women with GDM develop type 2 diabetes within 5 years of the index pregnancy.[38] Several previous studies demonstrated that β-cell function declined in the 1–3 years of postpartum among women with a history of GDM, which contributed to a higher risk of future diabetes.[39 40] In Hispanic women, GDM represents detection of a chronic disease process characterized by falling β-cell function compensation for chronic IR, and weight gain during the first several years after delivery with significantly declining β-cell compensation for IR.[41] It is also suggested that β-cell function is the most critical factor of the progression to future diabetes.[39–41] Our previous study has concluded that β-cell dysfunction contributed more to postpartum diabetes among non-obese women with prior GDM, and IR contributed more to postpartum diabetes among obese women with GDM.[13] Moreover, a study has found that IR and β-cell dysfunction were more pronounced among lean women with prior GDM than those in obese women without GDM.[42] Another study identified that IR appeared to be the major contributor among Chinese women with a history of GDM.[43] The authors concluded that IR and obesity are very important on the etiology of type 2 diabetes after GDM.[43] Since IR and β-cell dysfunction are not separate physiological changes during the postpartum period, the mechanism for postpartum diabetes should be inadequate β-cell compensation for peripheral IR. The present study found that postpartum β-cell dysfunction and IR were independently and significantly associated with an increased risk of postpartum diabetes. There was no significant difference in diabetes risk between women with IR only and those with β-cell dysfunction only. Moreover, we found that obesity and IR or obesity and β-cell dysfunction had stronger effects on the development of postpartum diabetes; a history of GDM and β-cell dysfunction or a history of GDM and IR also had stronger effects on the development of postpartum diabetes; women who had a history of GDM, β-cell dysfunction and IR, or women who had a history of GDM and obesity and also had β-cell dysfunction/IR, showed the highest risk of diabetes. The study provided insights into future prevention methods to reduce the risk of postpartum diabetes by prevention and control of

Table 5 ORs of postpartum diabetes according to different GDM, HOMA-%β and HOMA-IR

	Non-GDM		GDM	
	HOMA-IR <2.79	HOMA-IR ≥2.79	HOMA-IR <2.79	HOMA-IR ≥2.79
HOMA-%β				
≥74.7	0.22 (0.06 to 2.20)	1.46 (0.36 to 6.37)	1	3.72 (1.42 to 9.81)
<74.7	0.52 (0.06 to 5.26)	- *	7.60 (3.00 to 18.8)	342 (85.6 to 1360)

All analyses adjusted for age, education, family income, family history of diabetes, current smoking, passive smoking, current alcohol drinking, leisure-time physical activity, sleeping time, energy consumption, fiber, fat, protein and carbohydrate consumption, sweetened beverage drinking, weight gain during pregnancy, lactation duration, lactation intensity, postpartum time, and body mass index. All p values for interaction are >0.1.
*No incident cases were found.
GDM, gestational diabetes mellitus; HOMA-%β, homeostatic model assessment of β-cell secretory function; HOMA-IR, homeostatic model assessment insulin resistance.

GDM, weight loss or weight control, improving IR, and β-cell function.

A major strength of our study is that the diagnoses of GDM at 26–30 gestational weeks were based on the whole population's GDM universal screening by using the 1999 WHO's criteria after a 2-hour 75 g OGTT, and the diagnosed postpartum diabetes was based on the WHO's criteria after a 2-hour 75 g OGTT. Furthermore, our study is a large population-based survey among women with and without GDM. Thus, the present study could provide a comprehensive and robust evaluation of the single effects of postpartum β-cell function and IR, and joint effects of postpartum β-cell function, IR, obesity, and a history of GDM on the risk of consequent diabetes among women with and without a history of GDM. Several limitations inevitably exist in the present study. First, the present study is a cross-sectional design; thus, the temporal and causal association cannot be assessed. Second, women with GDM were not screened immediately postpartum (1–3 months); thus, the time to diabetes after GDM was not systematic but encompassed a wide variation in testing rather than natural progression. This may be the explanation of why the baseline HOMA-IR of women without GDM was higher than that in women with GDM. Third, diabetes cases were only 10 among women without GDM; the limited cases may reduce statistical power in joint analyses. Fourth, we used homeostatic model assessment (HOMA) models to assess the IR and β-cell function. HOMA model was used to describe steady-state insulin secretion that is a late marker of β-cell dysfunction, which may influence the final results. However, HOMA models are very cost-effective and have been widely used in clinical and epidemiological studies. Finally, the postpartum diabetes cases of women without prior GDM were not enough, which may influence the final results.

In conclusion, the present study found that β-cell dysfunction and IR were all significantly associated with an increased risk of postpartum type 2 diabetes. Obesity and IR, obesity and β-cell dysfunction, as well as a history of GDM and IR, a history of GDM and β-cell dysfunction, had stronger effects on the development of postpartum diabetes. Interventions such as maintaining a healthy lifestyle and normal weight status among women with and without GDM during the early postpartum period might be the key point for reducing the risk of obesity, IR, and type 2 diabetes.

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