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## Zinc-Associated Variant in *SLC30A8* Gene Interacts With Gestational Weight Gain on Postpartum Glycemic Changes: A Longitudinal Study in Women With Prior Gestational Diabetes Mellitus

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Zinc transporter 8 genetic variant *SLC30A8* has been associated with postpartum risk of type 2 diabetes among women with gestational diabetes mellitus (GDM). Gestational weight gain is one of the strongest risk factors for postpartum hyperglycemia. We assessed the interaction between type 2 diabetes-associated *SLC30A8* rs13266634 and gestational weight gain on 1–5 years of postpartum glycemic changes in 1,071 women with prior GDM in a longitudinal study. Compared with gestation of 26–30 weeks, postpartum levels of fasting glucose, oral glucose tolerance test 2-h glucose, and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) increased across rs13266634 TT, CT, and CC genotypes in women with excessive gestational weight gain, whereas opposite genetic associations were found in women with inadequate or adequate gestational weight gain. Postpartum changes in fasting glucose per additional copy of the C allele were  $-0.18$ ,  $-0.04$ , and  $0.12$  mmol/L in women with inadequate, adequate, and excessive gestational weight gain, respectively ( $P$  for interaction = 0.002). We also found similar interactions for changes in 2-h glucose and HbA<sub>1c</sub> ( $P$  for interaction = 0.003 and 0.005, respectively). Our data indicate that gestational weight gain may modify *SLC30A8* variant on long-term glycemic

changes, highlighting the importance of gestational weight control in the prevention of postpartum hyperglycemia in women with GDM.

Women with prior gestational diabetes mellitus (GDM) are at substantially increased risk of developing type 2 diabetes (1). Gestational weight gain has been considered as one of the strongest risk factors for GDM and has a long-term effect on postpartum development of hyperglycemia and type 2 diabetes (2,3).

Zinc is an essential micronutrient that is necessary in the human  $\beta$ -cell for insulin homeostasis. Both dietary zinc intake and serum levels of zinc have been inversely associated with gestational hyperglycemia, especially among women with GDM (4,5). Zinc homeostasis in the pancreatic  $\beta$ -cell is mainly mediated by zinc transporter 8 (ZnT8), the product of zinc transporter 8 gene *SLC30A8* (6). The genetic variant rs13266634 in *SLC30A8* has been associated with fasting glucose levels, type 2 diabetes, and GDM in genome-wide association studies and genetic association studies (7–9). Management of gestational weight gain prevents hyperglycemia (2,3,10).

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In addition, our previous study suggested that weight change might interact with the genetic factors in relation to glycemic control in women with a history of GDM (11). On the basis of the evidence above, we hypothesized that gestational weight gain might modify the genetic association of the *SLC30A8* variant with postpartum glycemic changes.

In one of the largest cohorts of women with prior GDM, we took advantage of the longitudinally collected data on changes in body weight and glycemic traits during and after pregnancy and aimed to examine the association of *SLC30A8* rs13266634 with postpartum changes in measures of glucose metabolism and particularly assessed the interactions of gestational weight gain with the *SLC30A8* genotype on glycemic changes.

## RESEARCH DESIGN AND METHODS

### Study Population

The study population included a retrospective cohort from the Tianjin Gestational Diabetes Mellitus Prevention Program (12–15). The details of the program have been described previously (12). All pregnant women living in the six central urban districts in Tianjin have participated in a GDM screening since 1999; the average proportion of screened pregnancies was >91% between 1999 and 2008 (15). All pregnant women at 26–30 weeks' gestation participated in a 1-h 50-g glucose screening test, and those who had a glucose  $\geq 7.8$  mmol/L were invited to undergo a 75-g glucose 2-h oral glucose tolerance test (OGTT) at Tianjin Women and Children's Health Center (15). In accordance with the World Health Organization (WHO) criteria (16), women with a 75-g glucose 2-h OGTT result confirming either diabetes (fasting glucose  $\geq 7$  mmol/L or 2-h glucose  $\geq 11.1$  mmol/L) or impaired glucose tolerance (2-h glucose  $\geq 7.8$  and  $< 11.1$  mmol/L) were diagnosed as having GDM. All pregnant women who were diagnosed with GDM between 2005 and 2009 ( $N = 4,644$ ) were recruited 1–5 years after delivery from 2009 to 2011. Participants who met any of the following criteria were excluded: 1) diagnosed postpartum diabetes, 2) taking medicines known to alter OGTT, 3) presence of any chronic diseases that could seriously reduce the life expectancy or the ability to participate in the study, and 4) currently pregnant or planning to become pregnant in the next 2 years. Finally, 1,263 women with GDM returned and completed the survey. Between the returned and unreturned women, there were no differences with regard to age (28.9 vs. 28.7 years), fasting glucose (5.34 vs. 5.34 mmol/L), 2-h glucose (9.23 vs. 9.16 mmol/L), and prevalence of impaired glucose tolerance (90.9% vs. 91.8%) and diabetes (9.1% vs. 8.2%) at the 26–30 gestational weeks (13). The final analysis included 1,071 women with available data of genotyping, weight, and glycemic traits. The study was approved by the Human Subjects Committee of the Tianjin Women and Children's Health Center, and informed consent was obtained from each participant.

### Assessment of Weight Change, Glycemic Traits, and Covariates

At the postpartum survey, a questionnaire was used to collect information on socio-demographics, family history of diabetes, history of GDM (values of fasting and 2-h glucose in the 26–30 gestational weeks' OGTT were copied from Central Lab and the treatment of GDM during the pregnancy), pregnancy outcomes (prepregnancy weight and gestational weight gain), diets, current alcohol drinking, current smoking, and physical activity (the frequency and duration of leisure time and sedentary activities). All participants completed a 3-day 24-h food record using dietary record collection method taught by a dietitian. The performance of the questionnaire and 3-day 24-h food record has been validated in the China National Nutrition and Health Survey (17,18).

Body weight and height were measured by trained researchers according to a standardized protocol at the postpartum survey. BMI was calculated by dividing weight in kilograms by the square of height in meters. Gestational weight gain was categorized as inadequate, adequate, and excessive according to the 2009 Institute of Medicine guideline (19). Adequate gestational weight gain was defined according to prepregnancy BMI as 12.5–18.0 kg (pregnancy BMI  $< 18.5$  kg/m<sup>2</sup>), 11.5–16.0 kg (pregnancy BMI 18.5–24.9 kg/m<sup>2</sup>), 7.0–11.5 kg (pregnancy BMI 25.0–29.9 kg/m<sup>2</sup>), and 5.0–9.0 kg (pregnancy BMI  $\geq 30$  kg/m<sup>2</sup>). We also defined adequate gestational weight gain according to the Chinese maternal prepregnancy BMI classification (20) and the 2009 Institute of Medicine guideline as 12.5–18.0 kg (pregnancy BMI  $< 18.5$  kg/m<sup>2</sup>), 11.5–16.0 kg (pregnancy BMI 18.5–23.9 kg/m<sup>2</sup>), 7.0–11.5 kg (pregnancy BMI 24.0–27.9 kg/m<sup>2</sup>), and 5.0–9.0 kg (pregnancy BMI  $\geq 28$  kg/m<sup>2</sup>). Gestational weight gain below or above the recommendation was defined as inadequate or excessive, respectively. Annual postpartum weight change was calculated by dividing the difference between postpartum weight and predelivery weight (pregnancy weight plus gestational weight gain) by follow-up years.

Postpartum blood samples were collected in all participants after an overnight fast of at least 12 h. Participants were given a 2-h 75-g OGTT, and fasting and 2-h glucose were measured on an automatic analyzer (Toshiba TBA 120FR, Japan). Glycemic hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was measured using an automatic glycohemoglobin analyzer (ADAMS A1c, HA-8160; ARKRAY, Japan). Changes in fasting glucose, 2-h glucose, and HbA<sub>1c</sub> were calculated as differences in glucose and HbA<sub>1c</sub> levels between postpartum survey and pregnancy (at GDM diagnosis).

### Genotyping

DNA was extracted from the buffy coat fraction of centrifuged blood using a QIAamp DNA Blood Maxi Kit (Qiagen, Chatsworth, CA). Single nucleotide polymorphism rs13266634 in the *SLC30A8* gene was genotyped by quantitative real-time TaqMan PCR (Applied Biosystems, Foster City, CA). The genotyping success rate was over 98%. For quality control, 10% of

the samples were genotyped, and the concordance rate was more than 99%.

### Statistical Analysis

Statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC). We applied  $\chi^2$  test for categorical variables or general linear models for continuous variables to compare proportions or means of characteristics across categories of gestational weight gain (inadequate, adequate, and excessive). Changes in glycemic traits associated with each additional copy of the *SLC30A8* rs13266634 C allele according to gestational weight gain categories were estimated using general linear models. To test for interactions, we examined the genotype, gestational weight gain (inadequate, adequate, and excessive), and genotype by gestational weight gain interactions as independent predictors of postpartum changes in glycemic traits, adjusted for age, follow-up

time, prepregnancy BMI, total energy intake, zinc intake, sitting time, postpartum weight change, and the previous value for the respective glucose trait (continuous variables for above variables) and family history of diabetes, current smoking, current alcohol drinking, leisure time physical activity, and GDM therapy (categorical variables for above variables). We also calculated the multivariable-adjusted mean values of changes in glycemic traits according to gestational weight gain and rs13266634 genotype by using general linear models. We further performed two sensitivity analyses to examine the interaction effect: the first analysis was conducted in women within 1.5 years after delivery to control for potential bias dependent on follow-up period, and the second analysis was performed using gestational weight gain defined by the Chinese maternal prepregnancy BMI classification and the 2009 Institute of Medicine guideline. *P* values are two-sided and a *P* < 0.05 was considered statistically significant.

**Table 1—Characteristics of women with prior GDM by gestational weight gain**

	Gestational weight gain			<i>P</i>
	Inadequate	Adequate	Excessive	
<i>N</i>	150	372	549	
Age (years)	33.0 ± 3.6	32.4 ± 3.5	31.9 ± 3.4	<0.001
Follow-up time (years)	2.0 ± 0.6	2.0 ± 0.6	2.1 ± 0.7	0.007
Prepregnancy BMI (kg/m <sup>2</sup> )	22.1 ± 2.9	22.4 ± 3.0	24.0 ± 3.4	<0.001
Weight (kg)				
Prepregnancy	56.6 ± 8.2	57.1 ± 8.3	62.0 ± 9.4	<0.001
Predelivery	65.4 ± 7.4	70.6 ± 7.3	82.9 ± 9.3	<0.001
Postpartum	57.9 ± 8.9	58.7 ± 8.7	65.9 ± 11.4	<0.001
Fasting glucose (mmol/L)				
At GDM diagnosis	5.3 ± 0.8	5.3 ± 0.8	5.4 ± 0.7	0.05
Postpartum	5.6 ± 1.3	5.3 ± 0.8	5.4 ± 0.9	0.06
2-h glucose (mmol/L)				
At GDM diagnosis	9.3 ± 1.4	9.2 ± 1.3	9.0 ± 1.1	0.004
Postpartum	7.5 ± 3.1	7.0 ± 2.3	6.9 ± 2.2	0.04
HbA <sub>1c</sub> (%)				
At GDM diagnosis	5.8 ± 0.6	5.8 ± 0.6	5.8 ± 0.6	0.37
Postpartum	5.7 ± 0.9	5.6 ± 0.6	5.6 ± 0.8	0.66
HbA <sub>1c</sub> (mmol/mol)				
At GDM diagnosis	40 ± 4	40 ± 4	40 ± 4	0.37
Postpartum	39 ± 5	38 ± 4	38 ± 5	0.66
Family history of diabetes (%)	32.7	32.5	30.8	0.82
Current smoking (%)	4.0	0.8	2.4	0.05
Current alcohol drinking (%)	21.3	19.4	21.5	0.72
Leisure time physical activity (%)				
0 min/day	76.7	80.7	80.5	0.27
1 to <30 min/day	23.3	17.7	17.7	
≥30 min/day	0.0	1.6	1.8	
Sitting time (h/day)	2.9 ± 2.0	3.1 ± 2.0	3.5 ± 2.3	0.002
Total energy intake (kcal/day)	1,712 ± 465	1,670 ± 424	1,679 ± 447	0.59
Dietary zinc intake (mg)	10.5 ± 3.4	10.1 ± 3.1	10.2 ± 3.3	0.66
rs13266634 CC genotype (%)	38.7	37.9	38.6	0.89

Data are mean ± SD for continuous variables or percentage for categorical variables. *P* values were calculated by general linear models for continuous variables or  $\chi^2$  test for categorical variables.

## RESULTS

Table 1 presents the characteristics of women with prior GDM according to categories of gestational weight gain. Compared with women with inadequate gestational weight gain, women with greater gestational weight gain were younger and had a higher predelivery BMI; higher weight at prepregnancy, predelivery, and postpartum; lower 2-h glucose levels at both GDM diagnosis and postpartum; and a longer sitting time (all  $P < 0.05$ ). The frequency of *SLC30A8* rs13266634 CC genotype was not different among the three categories of gestational weight gain.

Overall, there were no statistically significant associations between the rs13266634 genotype and postpartum glycemic changes (all  $P \geq 0.48$ ). We then tested the associations of each additional copy of the rs13266634 C allele with postpartum changes in glycemic traits according to gestational weight gain categories (Table 2). Gestational weight gain significantly interacted with the rs13266634 genotype on postpartum fasting glucose change. After full adjustment, changes in fasting glucose associated with each additional copy of the C allele were  $-0.18$  (SE 0.15),  $-0.04$  (0.05), and  $0.12$  mmol/L (0.05) in women with inadequate, adequate, and excessive gestational weight, respectively ( $P$  for interaction = 0.002). Similar interactions were observed for changes in 2-h glucose and HbA<sub>1c</sub>. Each additional copy of the C allele was associated with changes in 2-h glucose of  $-0.68$  (0.31),  $-0.04$  (0.16), and  $0.13$  mmol/L (0.12) across categories of inadequate, adequate, and excessive gestational weight gain, respectively ( $P$  for interaction = 0.003). Corresponding changes in HbA<sub>1c</sub> were  $-0.23$  (0.11),  $-0.08$  (0.05), and  $0.05\%$  (0.05) across these three categories of gestational weight gain, respectively ( $P$  for interaction = 0.005). We also performed similar analyses using gestational weight gain defined by the Chinese maternal prepregnancy BMI classification and the 2009 Institute of

Medicine guideline (Supplementary Table 1), and the findings were not substantially changed.

Figure 1 shows multivariable-adjusted postpartum changes of fasting glucose, 2-h glucose and HbA<sub>1c</sub> according to joint categories of gestational weight gain and the rs13266634 genotype. In all participants, mean values of postpartum changes in fasting glucose, 2-h glucose, and HbA<sub>1c</sub> were 0.05 mmol/L,  $-2.13$  mmol/L, and  $-0.18\%$ , respectively. In category of inadequate gestational weight gain, women carrying the TT, CT, and CC genotypes showed change in fasting glucose of 0.49, 0.46, and 0.13 mmol/L, respectively; change in 2-h glucose of  $-1.11$ ,  $-1.58$ , and  $-2.50$  mmol/L, respectively; and change in HbA<sub>1c</sub> of 0.08,  $-0.01$ , and  $-0.31\%$ , respectively. However, in category of excessive gestational weight gain, women carrying the TT, CT, and CC genotypes showed change in fasting glucose of  $-0.16$ ,  $-0.05$ , and  $0.09$  mmol/L, respectively; change in 2-h glucose of  $-2.39$ ,  $-2.05$ , and  $-2.04$  mmol/L, respectively; and change in HbA<sub>1c</sub> of  $-0.25$ ,  $-0.20$ , and  $-0.15\%$ , respectively.

We observed similar interactions between the rs13266634 genotype and gestational weight gain on changes in fasting glucose ( $P$  for interaction  $< 0.001$ ), 2-h glucose ( $P$  for interaction  $< 0.001$ ), and HbA<sub>1c</sub> ( $P$  for interaction = 0.059) in women with a postpartum follow-up  $< 1.5$  years (Fig. 2).

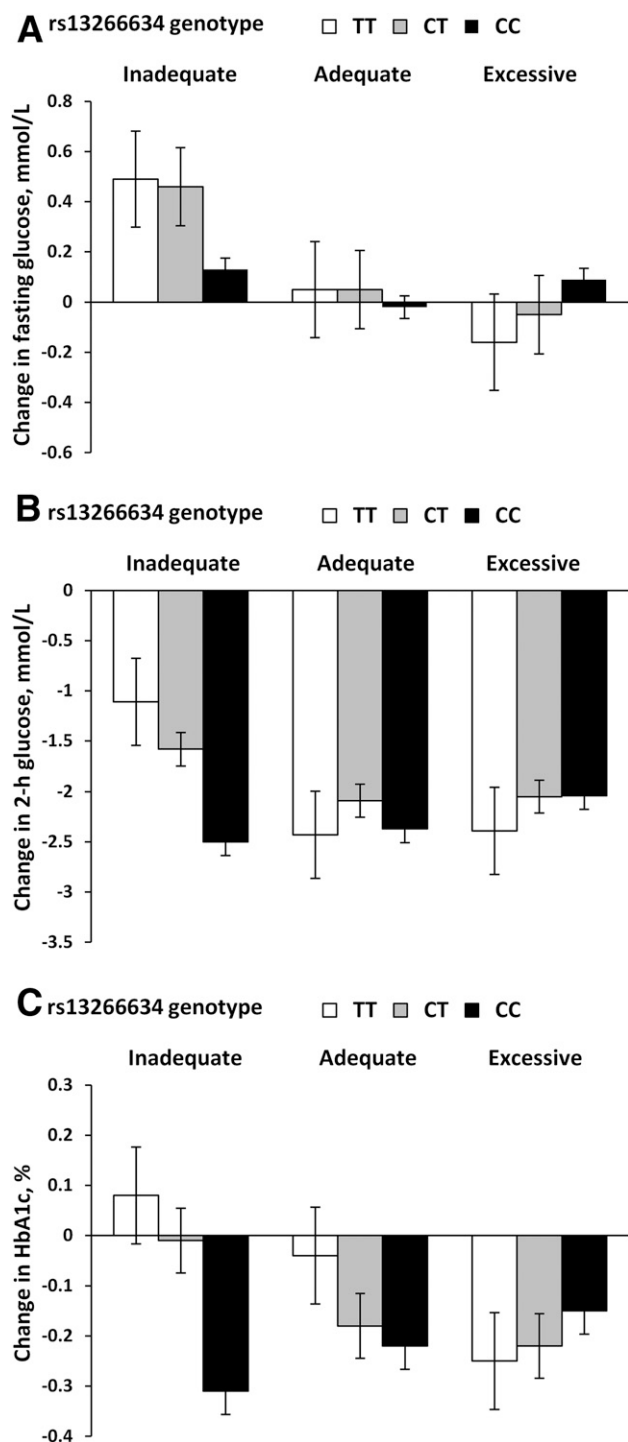
## DISCUSSION

In this cohort of Chinese women with prior GDM, we showed bidirectional interactions between the *SLC30A8* rs13266634 genotype and gestational weight gain on postpartum glycemic changes. Fasting glucose, 2-h glucose, and HbA<sub>1c</sub> levels increased across the rs13266634 TT, CT, and CC genotypes in women with excessive gestational weight gain, whereas opposite genetic associations were found in women with inadequate or adequate gestational weight gain. These results suggest that in women with a

**Table 2—Changes in glycemic traits associated with each additional copy of the *SLC30A8* rs13266634 C allele by gestational weight gain**

	Inadequate		Adequate		Excessive		<i>P</i> for interaction
	$\beta$ (SE)	<i>P</i>	$\beta$ (SE)	<i>P</i>	$\beta$ (SE)	<i>P</i>	
<b>Fasting glucose (mmol/L)</b>							
Age-adjusted	$-0.25$ (0.16)	0.12	$-0.10$ (0.07)	0.16	$0.12$ (0.06)	0.04	0.003
Multivariable-adjusted*	$-0.18$ (0.16)	0.25	$-0.04$ (0.05)	0.46	$0.13$ (0.05)	0.01	0.002
+ Zinc intake	$-0.18$ (0.15)	0.25	$-0.04$ (0.05)	0.44	$0.12$ (0.05)	0.01	0.002
<b>2-h glucose (mmol/L)</b>							
Age-adjusted	$-0.93$ (0.33)	0.01	$-0.05$ (0.18)	0.79	$0.11$ (0.13)	0.41	0.005
Multivariable-adjusted*	$-0.68$ (0.31)	0.03	$-0.03$ (0.15)	0.85	$0.13$ (0.12)	0.26	0.003
+ Zinc intake	$-0.68$ (0.31)	0.03	$-0.04$ (0.16)	0.82	$0.13$ (0.12)	0.27	0.003
<b>HbA<sub>1c</sub> (%)</b>							
Age-adjusted	$-0.29$ (0.12)	0.02	$-0.10$ (0.06)	0.11	$0.08$ (0.06)	0.16	0.002
Multivariable-adjusted*	$-0.23$ (0.11)	0.04	$-0.08$ (0.05)	0.08	$0.06$ (0.05)	0.21	0.004
+ Zinc intake	$-0.23$ (0.11)	0.05	$-0.08$ (0.05)	0.08	$0.05$ (0.05)	0.28	0.005

$\beta$ -Coefficients (SE) represent changes in each glycemic trait per additional copy of the rs13266634 C allele. \*Results were adjusted for age, follow-up time, prepregnancy BMI, total energy intake, sitting time, postpartum weight change, and the previous value for the respective glucose trait (continuous variables for above variables) and family history of diabetes, current smoking, current alcohol drinking, leisure time physical activity, and GDM therapy (categorical variables for above variables).



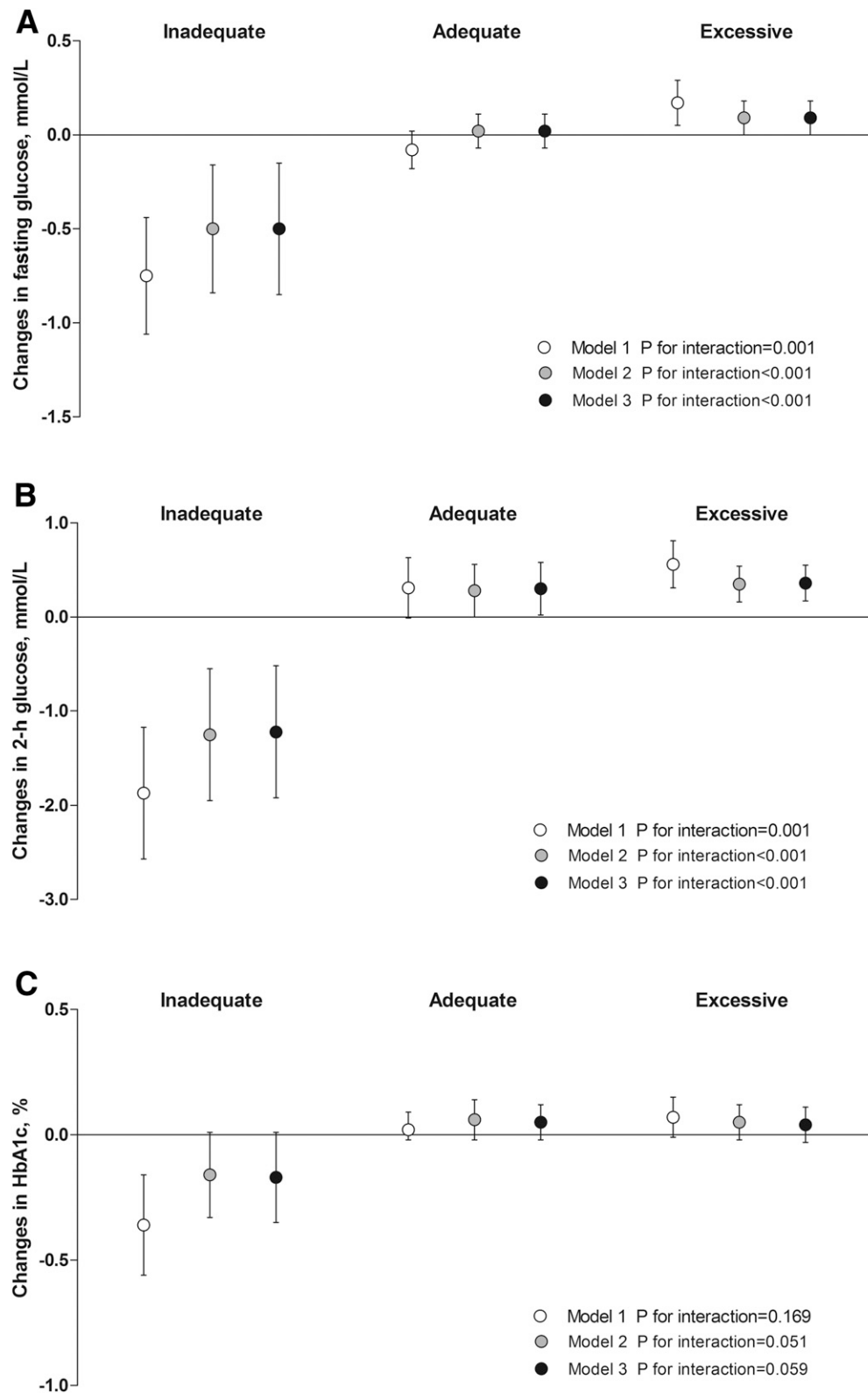
**Figure 1**—Changes in glycemic traits according to gestational weight gain and *SLC30A8* rs13266634 genotype. Fasting glucose (A), 2-h glucose (B), and HbA<sub>1c</sub> (C). Data are mean (SE), adjusted for age, follow-up time, prepregnancy BMI, total energy intake, zinc intake, sitting time, postpartum weight change, and the previous value for the respective glucose trait (continuous variables for above variables) and family history of diabetes, current smoking, current alcohol drinking, leisure time physical activity, and GDM therapy (categorical variables for above variables).

history of GDM gestational weight gain could modify the effect of *SLC30A8* rs13266634 on long-term glycemic changes and women carrying the rs13266634 C

allele might particularly benefit by controlling gestational weight gain to avoid postpartum hyperglycemia.

A history of GDM is one of the strongest risk factors for subsequent type 2 diabetes. According to a large meta-analysis, women with GDM had a relative risk of 7.45 (95% CI 4.79–11.51) for type 2 diabetes compared with women who had a normoglycemic pregnancy (1). In addition, gestational weight gain has been suggested to considerably affect women's long-term weight trajectory and predisposition to postpartum hyperglycemia and type 2 diabetes, especially in those with prior GDM (21,22). Emerging evidence has shown that in women with impaired glucose regulation or GDM, type 2 diabetes is preventable through effective lifestyle interventions on weight management (10,23,24). One feasibility randomized controlled trial particularly showed that lifestyle intervention was more effective among women who did not exceed the recommended gestational weight gain (10). In the current study, we found that the genetic effect of *SLC30A8* variant on postpartum glycemic changes varied among women with different categories of gestational weight gain. Interestingly, the *SLC30A8* rs13266634 C allele, which was associated with susceptibility to impaired glucose regulation in genome-wide association studies (7,8), was related to increased fasting glucose, 2-h glucose, and HbA<sub>1c</sub> levels among women with excessive gestational weight gain but also was related to decreased levels of these glycemic markers among women with inadequate or adequate gestational weight gain. When we restricted the analysis in women who had shorter follow-up years, the interaction patterns were not substantially changed. Moreover, the interaction was similar for gestational weight gain defined by the Chinese maternal prepregnancy BMI classification and the 2009 Institute of Medicine guideline, suggesting that the observed interaction was robust regardless of follow-up years and definitions of gestational weight gain.

The *SLC30A8* gene encodes ZnT8, which is a zinc efflux transporter that is primarily expressed in  $\beta$ -cells and is essential for the homeostasis of zinc in  $\beta$ -cell granules. ZnT8 expression strongly modulates insulin secretion and storage and the formation of insulin crystals in  $\beta$ -cells (25,26). Intriguingly, it has been suggested that the rs13266634 genotype might interact with total zinc intake and plasma zinc levels in relation to fasting glucose levels and type 2 diabetes (27,28). Although *SLC30A8* rs13266634 has also been related to GDM and body weight (9,25), no study has examined whether the association between this genetic variant and glycemia in women with GDM may be modified by weight change. Our findings are in line with the previous observations that the effect of type 2 diabetes-susceptible genes on hyperglycemia and type 2 diabetes was more prominent in obese individuals (29,30), suggesting that avoiding excessive gestational weight gain might protect women with GDM from a genetic susceptibility to hyperglycemia.



**Figure 2**—Changes in glycemic traits associated with each additional copy of the *SLC30A8* rs13266634 C allele by gestational weight gain in women within 1.5-year postpartum. Plots (error bars) are  $\beta$ -coefficients (SE) for changes in each glycemic trait per additional copy of the C allele. There were 217 women with follow-up years less than 1.5 years, including 37 with inadequate gestational weight gain, 78 with adequate gestational weight gain, and 102 with excessive gestational weight gain. Fasting glucose (A), 2-h glucose (B), and HbA<sub>1c</sub> (C). Model 1: adjusted for age; model 2: adjusted for age, follow-up time, prepregnancy BMI, total energy intake, sitting time, postpartum weight change, and the previous value for the respective glucose trait (continuous variables for above variables) and family history of diabetes, current smoking, current alcohol drinking, leisure time physical activity, and GDM therapy (categorical variables for above variables); model 3: further adjusted for zinc intake based on model 2.



The current study provides a novel perspective to understand the association between gestational weight management and postpartum glycemia on a genetic background. The strength of this study is that the findings are based on longitudinal measures of weight and glycemic traits from one of the largest cohorts of women with a history of GDM. However, several limitations need to be acknowledged. First, although it has been reported that the *SLC30A8* rs13266634 variant might interact with zinc intake on fasting glucose levels (27), we did not observe an apparent interaction between the genetic variant and zinc intake on postpartum glycemic changes in our study. The information of zinc intake was collected at postpartum survey in this study, which might not represent the exact intake during pregnancy, and the differences in health status (general vs. GDM), sex compositions (mixed vs. women), and ethnicities (Europeans vs. Chinese) among the studied populations may also partly explain the discrepant results. Second, we did not collect sufficient reproductive data, such as postpartum depression, which may influence weight change and glucose metabolism. Third, the study participants were restricted to Chinese women, and further studies in other demographic or ethnic populations are warranted to verify our findings.

In conclusion, we found that gestational weight gain significantly interacted with the *SLC30A8* rs13266634 variant on postpartum glycemic changes in Chinese women with a history of GDM. Our findings suggest that among women with a history of GDM, the glucose-rising effect of the rs13266634 variant could be prevented by a better weight control during pregnancy, highlighting the importance of gestational weight management particularly in women genetically predisposed to impaired glucose regulation.

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**Author Contributions.** T.W. produced a draft of the manuscript. T.W. and L.Q. contributed to the conception and design, analyses, and interpretation of the data. T.W., H.L., L.W., T.H., W.L., Y.Z., Y.H., D.S., J.L., S.Z., N.L., G.H., and L.Q. were involved in the critical revision of the manuscript for important intellectual content. G.H. and L.Q. were involved in the collection and assembly of data and obtained funding for the study. All of the authors approved the final manuscript. L.Q. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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