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Maternal GDM Status, Genetically Determined Blood Glucose, and Offspring Obesity Risk: An Observational Study

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Abstract

Objective: The purpose of this study was to estimate the associations of genetically determined maternal blood glucose levels with obesity-related outcomes among children from pregnancies with and without gestational diabetes mellitus (GDM).

Methods: A total of 1,114 mothers with (N = 560) and without (N = 554) GDM and their children were included in the present study. A maternal genetic risk score (GRS) for blood glucose

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Author contributions: QS and LQ conceptualized and designed the study, interpreted the data, and drafted and critically revised the manuscript. QS, ZL, and YC performed the statistical analysis and interpreted the data. DS, LW, HL, WL, JL, XY, MAC, and GH were involved in the critical revision of the manuscript. GH and LQ were involved in the collection and assembly of the data and obtained funding for the study. QS and LQ have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; they are the guarantors. All authors actively contributed to the final manuscript and approved the final manuscript.

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Supporting information: Additional Supporting Information may be found in the online version of this article.

was constructed on the basis of 17 single-nucleotide polymorphisms identified from a recent genome-wide association study.

Results: It was found that maternal GRS for blood glucose showed different associations with offspring risk of overweight and obesity, as well as adiposity measures (all $P_{\text{for interaction}} < 0.05$). Among mothers without GDM, genetically determined maternal blood glucose levels were associated with an 89% higher risk of overweight in their children (95% CI: 42%−152% per SD increase in GRS, $P = 1.40 \times 10^{-5}$) and a 120% higher risk of obesity (44%−235%, $P = 2.61 \times 10^{-4}$) after adjustment for covariates. In addition, higher maternal GRS for blood glucose was associated with children's increased obesity-related traits (all $P < 0.05$). However, no significant associations were observed among children of mothers with GDM.

Conclusions: This study indicates that GDM status may modify the relation between genetically determined glucose levels and obesity risk among children.

Introduction

The prevalence of childhood obesity has increased markedly in the past decades (1,2), from 0.9% in 1975 to 7.8% in 2016 in boys and from 0.7% in 1975 to 5.6% in 2016 in girls worldwide (1). Compelling evidence has shown that maternal hyperglycemia and diabetes may affect offspring risk of obesity beginning in childhood (3–7). In particular, maternal glucose levels during pregnancy, ranging from normal to gestational diabetes mellitus (GDM), have been consistently related to childhood obesity (8–11).

In a 2016 study, it was found that genetically determined higher maternal fasting glucose concentrations were associated with higher birth weight, which is a risk factor for childhood obesity (12). Glucose-associated genes of mothers may influence the long-term growth and development of children by modulating maternal glycemia during pregnancy. However, to our knowledge, no studies hitherto have explored the associations between genetically determined maternal blood glucose levels and obesity-related outcomes among children. Moreover, whether maternal GDM status may modify such relations remains unknown.

Therefore, the present study aimed to estimate the associations of maternal genetically determined fasting glucose levels, characterized by a combined genetic risk score (GRS) for blood glucose, with obesity-related outcomes among children from pregnancies with and without GDM. We particularly tested the interaction between maternal GRS and GDM status on childhood obesity-related outcomes.

Methods

Participants

This study was approved by the Human Subjects Committee of the Tianjin Women's and Children's Health Center, and written informed consent was obtained from all participants.

Our study was conducted based on Tianjin GDM Screening, an urban universal screening of GDM using the 1999 World Health Organization (WHO) criteria in all six central districts of Tianjin, China, launched by the Tianjin Women's and Children's Health Center in 1999

(13). All pregnant women participated in a 1-hour, 50-g glucose screening test at 26 to 30 weeks' gestation, and those with a glucose level ≥7.8 mmol/L were invited to take a 75-g, 2-hour oral glucose tolerance test (OGTT) at Tianjin Women's and Children's Health Center. According to criteria from WHO, GDM is defined by confirming either of the following 75-g OGTT results: (1) diabetes (fasting glucose ≥7 mmol/L or 2-hour glucose ≥11.1 mmol/L); or (2) impaired glucose tolerance (2-hour glucose ≥7.8 and <11.1 mmol/L) (14).

From 2005 to 2009, a total of 76,325 pregnant women were screened, with a screening rate >91%, among whom 4,644 pregnant women were diagnosed with GDM (15,16). We invited all 4,644 women to join the Tianjin Gestational Diabetes Mellitus Prevention Program (TGDMPP), a 4-year randomized clinical trial among women with GDM (15,17). Ultimately, a total of 1,263 women with GDM completed the baseline survey, among whom 1,180 attended the TGDMPP and were randomly assigned to either a lifestyle intervention or a control group including four follow-up visits (15,17–20). In brief, mothers with GDM would receive intensive and individually designed diet and exercise programs, which included six face-to-face sessions with dietitians and two telephone calls in the first year and two additional sessions and four telephone calls in each subsequent year. The control group received usual care, including the provision of general information on the awareness of diabetes, dietary modification, and increased physical activity at subsequent annual visits, but no specific individualized programs were offered (15,17).

Subsequently, we randomly selected 578 mother-child pairs who finished the baseline and follow-up surveys of the TGDMPP, and we enrolled 578 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 the 578 children of mothers with GDM (16,21). Among them, 1,114 mothers had available genome-wide association study (GWAS) data (560 GDM and 554 non-GDM mother-child pairs), which formed the present transgeneration cross-sectional study (see flowchart in Supporting Information Figure S1).

Measurements and questionnaires

All mother-child pairs underwent a physical examination, according to a standard protocol as previously described (16,21). Moreover, the children's physical examination also included waist circumference, hip circumference, skinfolds (triceps, subscapular, suprailiac), and body fat percentage. More details are given in Supporting Information Appendix S1. All the measurements were conducted twice by a trained medical examiner, and the averages of both measurements were used. BMI was calculated by dividing weight in kilograms by height in meters squared. Weight-for-age *z* score and BMI-for-age *z* score were calculated based on the standards for the WHO Child Growth Standards (22).

Mothers' general information was collected by a self-administered questionnaire, including sociodemographic characteristics (age, marital status, education [<13, 13–16, and ≥16 years], family monthly income [<¥5,000, ¥5,000-¥8,000 and ≥¥8,000], and family history of diabetes), basic information during pregnancy (prepregnancy weight, gestational age at delivery, gestational weight gain, self-reported hypertensive disorders of pregnancy, treatment of GDM [no, insulin, lifestyle control]), and lifestyle questions (smoking status

[no, past, current], drinking status [no, yes]) (16,21). Of note, the proportion of mothers with GDM who received insulin treatment was limited, mainly because the traditional Chinese view is that insulin treatment would affect babies, and most mothers with GDM maintained their glucose levels well after lifestyle intervention.

Children's general information, including sex, age, birth weight, birth length, feeding patterns within the first 6 months (exclusive breast feeding, mixed breast and formula feeding, or exclusive formula feeding), dietary habits assessed using a validated food frequency questionnaire (23), routine activities (indoor and outdoor activities, screening-watching time, and sleep duration), and history of diseases and medication, was collected by another questionnaire completed by their mothers (16,21).

Genotyping and GRS calculation

DNA was extracted from the buffy coat fraction of centrifuged blood using a QIAamp DNA Blood Maxi Kit (Qiagen, Chatsworth, California). Seventeen single-nucleotide polymorphisms (SNPs; $P < 5 \times 10^{-8}$, Supporting Information Table S1) significantly associated with blood glucose and identified from a large-scale GWAS (24) conducted by BioBank Japan Project among 93,146 Japanese individuals were selected and genotyped using the Illumina HumanOmniExpress (San Diego, California) covering around 750,000 SNPs. The genotyping success rate was more than 98%. For quality control, 10% of replicated samples were genotyped, and the concordance rate was more than 99%. The allele frequencies of all SNPs in total participants or in women without GDM were in Hardy-Weinberg equilibrium (all $P > 0.05$, Supporting Information Table S1).

A weighted GRS for blood glucose was calculated based on the 17 selected SNPs. The genotypes of each SNP were coded as 0, 1, and 2 according to the number of glucose-increasing alleles. Each SNP was weighted by its relative effect size (β coefficient) obtained from the original study (24) by using the following equation: weighted GRS = (β1 × SNP1 + β2 × SNP2 + … + βn × SNPn) × (total number of SNPs/sum of the β coefficients) (25). A higher GRS indicated a higher genetic predisposition to higher levels of blood glucose.

Exposure and outcomes

In the present study, exposure was genetically determined maternal blood glucose levels, represented by a combined GRS of 17 glucose-related SNPs. The primary outcome was children's overweight and obesity status, defined based on WHO Child Growth Standards. For children under 5 years of age, overweight and obesity are weight-for-height >2 and 3 SD above the WHO Child Growth Standards median, respectively; for children aged between 5 and 19 years, overweight and obesity are BMI-for-age >1 and 2 SD above the WHO Growth Reference median (26). The secondary outcomes were obesity-related quantitative traits, including weight, weight-for-age *z* score, BMI, BMI-for-age *z* score, waist circumference, hip circumference, sum of skinfolds, and body fat percentage.

Statistical analysis

Data were expressed using mean and SD for continuous variables or number and percentage for categorical variables. An χ^2 test for categorical variables and general linear models for

continuous variables were applied to compare proportions or means of characteristics across quartiles of maternal GRS for blood glucose.

Multivariable logistic regression models were used to examine the association of maternal GRS for blood glucose with overweight and obesity status in children, and general linear models were used to examine the association of GRS with children's obesity-related quantitative traits. We performed stratified analyses by GDM status to explore the modification effect of GDM status on such associations. To test for interaction effects, we examined GRS, GDM status, and their interaction term as independent predictors of children's obesity-related outcomes, adjusted for potential confounders.

Covariates were included in the multivariate models as follows: Model 1: adjusted for children's age and sex; Model 2: Model 1 plus children's birth weight, maternal age at pregnancy, prepregnancy BMI, gestational weight gain, and gestational age at delivery; Model 3: Model 2 plus maternal lifestyle and socioeconomic and other related factors: smoking status, drinking status, marital status, education, family monthly income, hypertensive disorders of pregnancy, treatment of GDM, and any family history of diabetes; Model 4: Model 3 plus children's variables: feeding patterns, outdoor physical activity time, screen-watching time, sleeping time, vegetable intake frequency, fruit intake frequency, and illness within the last 3 months. Especially for overweight, obesity, weight-for-age *z* score, and BMI-for-age *z* score, which were defined based on sex- and age-specific standards, children's age and sex were not adjusted in all models. The missing rates for covariates in the present study were low, ranging from 0.1% to 1.6%. Therefore, our analyses were conducted using the complete data.

In addition, because some glucose SNPs or their proxy SNPs, including *KCNQ1* rs60808706 (27), *GCKR* rs1260326 (in high linkage disequilibrium [LD] with rs780094 (28)), *CDKAL1* rs9358356 (in high LD with rs2206734 (29)), and *SLC30A8* rs13266634 (in high LD with rs3802177 (27)), were also known to be associated with BMI/obesity in East Asians, we performed a sensitivity analysis excluding these SNPs and constructed a new GRS for blood glucose.

A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Maternal and child characteristics according to GRS quartiles

Descriptive characteristics of mothers and their children across quartiles of maternal GRS for blood glucose were presented in Table 1. Overall, maternal characteristics among the four GRS groups (in quartiles) were similar (all $P > 0.05$), except GDM status ($P = 0.008$). There were also no significant differences in children's characteristics across the GRS quartiles (all $P > 0.05$), except sleeping time ($P = 0.006$) and BMI ($P = 0.040$). However, we observed a tendency toward higher height ($P = 0.096$), weight ($P = 0.070$), hip circumference ($P = 0.057$), and body fat percentage ($P = 0.050$) in children in higher quartiles of maternal GRS for blood glucose compared with those in the lowest quartile.

We also provided the children's characteristics according to GDM status in Supporting Information Table S2. Children born to mothers with GDM were more likely to have higher obesity measures (all $P < 0.05$).

Association of GRS with maternal glucose/GDM

In the present study, maternal glucose levels were available only among women with GDM. the association of GRS with maternal fasting glucose among women with GDM is shown in Supporting Information Figure S2. We found that maternal GRS for blood glucose was significantly associated with maternal fasting glucose levels during pregnancy (β [SE] = 0.05 (0.02), $P = 0.015$). In addition, it was also significantly associated with GDM status (odds ratio [OR] = 1.13, 95% CI: 1.02–1.25, $P = 0.024$).

Associations with childhood obesity outcomes

As presented in Table 2, among children of mothers without GDM, per SD increase in maternal GRS for blood glucose was positively associated with a 63% higher risk of childhood overweight and an 86% higher risk of childhood obesity (model 1), and the associations became stronger after adjusting for children's birth weight, maternal age at pregnancy, prepregnancy BMI, gestational weight gain, gestational age at delivery, and other maternal lifestyle, socioeconomic factors (models 2 and 3). In model 4, after additional adjustment for children's variables, the associations became more statistically significant (overweight: OR = 1.89, 95% CI: 1.42–2.52, $P = 1.40 \times 10^{-5}$; obesity: OR = 2.20, 95% CI: 1.44–3.35, $P = 2.61 \times 10^{-4}$). No significant associations were observed among children of mothers with GDM.

The interactions between maternal GRS for blood glucose and GDM status were significant on childhood overweight ($P_{\text{for interaction}} = 5.66 \times 10^{-4} \sim 0.002$) and obesity ($P_{\text{for interaction}} = 0.007 \sim 0.015$) in all models.

Associations with obesity-related quantitative traits in children

As shown in Table 3 and Figure 1, genetically determined maternal blood glucose levels were positively associated with obesity-related quantitative traits among women without GDM (all $P < 0.05$). The results were highly consistent in all models. In model 4 (fully adjusted model), per SD increase in maternal GRS for blood glucose was significantly associated with 0.79 kg higher weight ($P = 1.05 \times 10^{-4}$), 0.19 higher weight-for-age z score ($P = 2.45 \times 10^{-4}$), 0.39 kg/m^2 higher BMI ($P = 5.53 \times 10^{-5}$), 0.20 higher BMI-for-age z score ($P = 2.60 \times 10^{-4}$), 0.72 cm higher waist circumference ($P = 0.003$), 0.76 cm higher hip circumference ($P = 0.002$), 2.34 mm higher sum of skinfolds ($P = 1.38 \times 10^{-4}$), 1.35% higher body fat percentage ($P = 3.49 \times 10^{-5}$). No such associations were observed among children of mothers with GDM.

Figure 1 shows the interaction between genetically determined maternal blood glucose levels and GDM status on children's obesity-related quantitative traits in the fully adjusted model. The interactions between maternal GRS for blood glucose and GDM status were significant on weight ($P_{\text{for interaction}} = 0.046$), weight-for-age z score ($P_{\text{for interaction}} = 0.023$), BMI ($P_{\text{for interaction}} = 0.016$), BMI-for-age z score ($P_{\text{for interaction}} = 0.012$), waist circumference ($P$

$_{\text{for interaction}}$ = 0.049), sum of skinfolds ($P_{\text{for interaction}}$ = 0.007), and body fat percentage ($P_{\text{for interaction}}$ = 0.004).

Sensitivity analyses

When we excluded SNPs associated with BMI/obesity in East Asians, the interaction between the new glucose GRS and GDM status on overweight, obesity, and most measures of childhood obesity remained significant ($P_{\text{for interaction}} < 0.05$, Supporting Information Table S3). Genetically determined maternal blood glucose levels were positively associated with all the obesity-related traits among women without GDM (all $P < 0.05$, Supporting Information Table S3).

Discussion

In this study, for the first time, we found significantly different associations of genetically determined maternal blood glucose levels with offspring overweight and obesity status according to maternal GDM status. Maternal genetically determined blood glucose levels were significantly associated with childhood overweight and obesity risk among children of mothers without GDM but not among children of mothers with GDM. We also found similarly significant interactions between genetically determined maternal blood glucose levels and GDM status on children's other obesity-related outcomes, including weight, weight-for-age *z* score, BMI, BMI-for-age *z* score, waist circumference, sum of skinfolds, and body fat percentage.

A group of previous studies has examined the relation of *in utero* exposure to higher glucose levels during pregnancy with obesity in offspring, especially during childhood (3–9,30–32). However, in these observational studies, the associations might be influenced by confounding factors. In the present study, we found positive associations of genetically determined maternal blood glucose levels, which were characterized by a weighted GRS that was calculated based on 17 SNPs genome-wide significantly associated with blood glucose, with obesity and other obesity-related outcomes among children of mothers without GDM. Because genotypes are randomly determined at conception, such associations between genetically determined maternal blood glucose levels and children's obesity outcomes are less likely to be influenced by potential confounding (12).

In a 2016 study, genetically elevated maternal blood glucose levels were found to be associated with increased birth weight, which is a risk factor for childhood obesity (12). Women with a higher GRS for blood glucose had relatively higher glucose levels during pregnancy (33,34). Maternal glucose, but not insulin, could cross the placenta, leading to increased fetal insulin secretion (12,35). Because insulin is a key intrauterine growth factor, altered fetal insulin secretion would consequently influence the development of the fetus *in utero*, leading to outcomes such as higher birth weight, and even long-term health, such as childhood obesity (35,36). In addition, it has been suggested that other metabolites related to maternal glucose, such as lipids, were important contributors to excess fetal growth and fat accretion (8,37). Jacob et al. (38) found that maternal glucose levels were associated with maternal lipids levels, including triacylglycerol, nonesterified fatty acids, β-hydroxybutyrate, and several amino acids. Therefore, the transplacental transfer of mixed nutrients from

mothers to fetus might also contribute to the link between maternal glucose and offspring obesity, which was consistent with the hypothesis proposed by Freinkel and colleagues (39).

One of our predominant findings was the modification effect of GDM status on the association between genetically determined glucose levels and offspring obesity during childhood. Significant associations of maternal GRS for blood glucose with obesity-related outcomes were observed only among children whose mothers had GDM and not among children whose mothers did not have GDM. One possible explanation for such observations might be that children of mothers with GDM have been found to generally be at an increased risk for the development of overweight and obesity, having a higher weight, BMI, and other adiposity-related measures (3–7); in this case, the variance in obesity outcomes among children of mothers with GDM was smaller than children without maternal GDM, and, therefore, the genetic associations could not be detected, as demonstrated in Figure 1. Another explanation might be partly related to treatment effects of mothers with GDM, which would modify the relationship between the genetically determined glucose levels in mothers and offspring adiposity. However, more studies are needed to elucidate the underlying mechanism of the interaction between genetically determined maternal blood glucose levels and GDM status in the future.

Our findings have great public health implications. During the past decades, the prevalence of overweight and obesity among children and adolescents has risen dramatically (1,2). It is well acknowledged that obesity during childhood is associated with higher risks of subsequent obesity and unfavorable cardiometabolic outcomes in adolescence and adulthood (40–42). Thus, in order to develop early intervention strategies for primordial obesity prevention, identifying risk factors in early prenatal and postnatal life that are related to later obesity is of great significance. Our study indicated that genetically determined maternal blood glucose levels were significantly associated with obesity-related outcomes among children without maternal GDM. In other words, among women without GDM and with normal glucose levels, their children were still at higher risk to develop obesity if the mothers were genetically predisposed to higher glycemia, highlighting the potentially causal role of maternal glucose in development of childhood obesity, which was also demonstrated by another larger study using Mendelian randomization (12). Therefore, it is necessary to optimize maternal glucose values in pregnancy for long-term benefit by reducing childhood obesity. Furthermore, we should focus more on preconception health and reduction of obesity and metabolic risk before pregnancy.

To the best of our knowledge, our study is the first to evaluate the association of genetically determined maternal blood glucose levels with obesity among children from pregnancies with and without GDM and the first to test the interaction between maternal GRS of blood glucose and GDM status. In addition, GDM was diagnosed according to the standard 1999 WHO criteria in our study (14). Moreover, a variety of potential confounding factors have been measured and controlled in our analyses. Particularly, in the present study, we adjusted for maternal prepregnancy BMI, which is usually considered as a major confounding factor in the association of maternal hyperglycemia with childhood obesity, as maternal hyperglycemia is generally accompanied by higher maternal BMI (5–7). The results were robust in differently adjusted models.

However, there were several potential limitations. First, our study participants were restricted to being of Chinese descent, and it was unknown whether our results could be generalized to other ethnic groups. Second, some covariates, such as maternal prepregnancy weight and gestational weight gain, were self-reported, which may introduce recall bias. However, several validation studies in the United States have found that maternal and infant health indicators reported by mothers were in good concordance with data abstracted from hospital records (43–45). Third, glucose values were not available for women without GDM, and thus we could not validate the association between glucose GRS and glucose values among women without GDM.

Conclusion

The present study indicates for the first time that maternal GDM status may modify the relation between genetically determined maternal glucose levels and obesity risk among children. Genetically determined maternal blood glucose levels were significantly associated with childhood obesity among children of mothers without GDM. Measures to optimize maternal nutrition and health to ensure normoglycemia during pregnancy are needed for the long-term benefits of reducing childhood obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Importance

What is already known?

- Compelling evidence has shown that maternal glucose levels during pregnancy and gestational diabetes mellitus (GDM) may affect offspring risk of obesity.
- However, no studies hitherto have explored the associations between genetically determined maternal blood glucose levels and obesity-related outcomes among children.

What does this study add?

- In the present study involving 1,114 mother-child pairs, we found that GDM status modified the associations between genetically determined glucose levels and offspring obesity during childhood.
- Maternal genetic risk score for blood glucose was associated with childhood obesity–related outcomes only among children of mothers without GDM.

How might these results change the focus of clinical practice?

- Our findings highlight the importance of maintaining healthy gestational glucose levels, even among women without GDM, in prevention of offspring obesity.

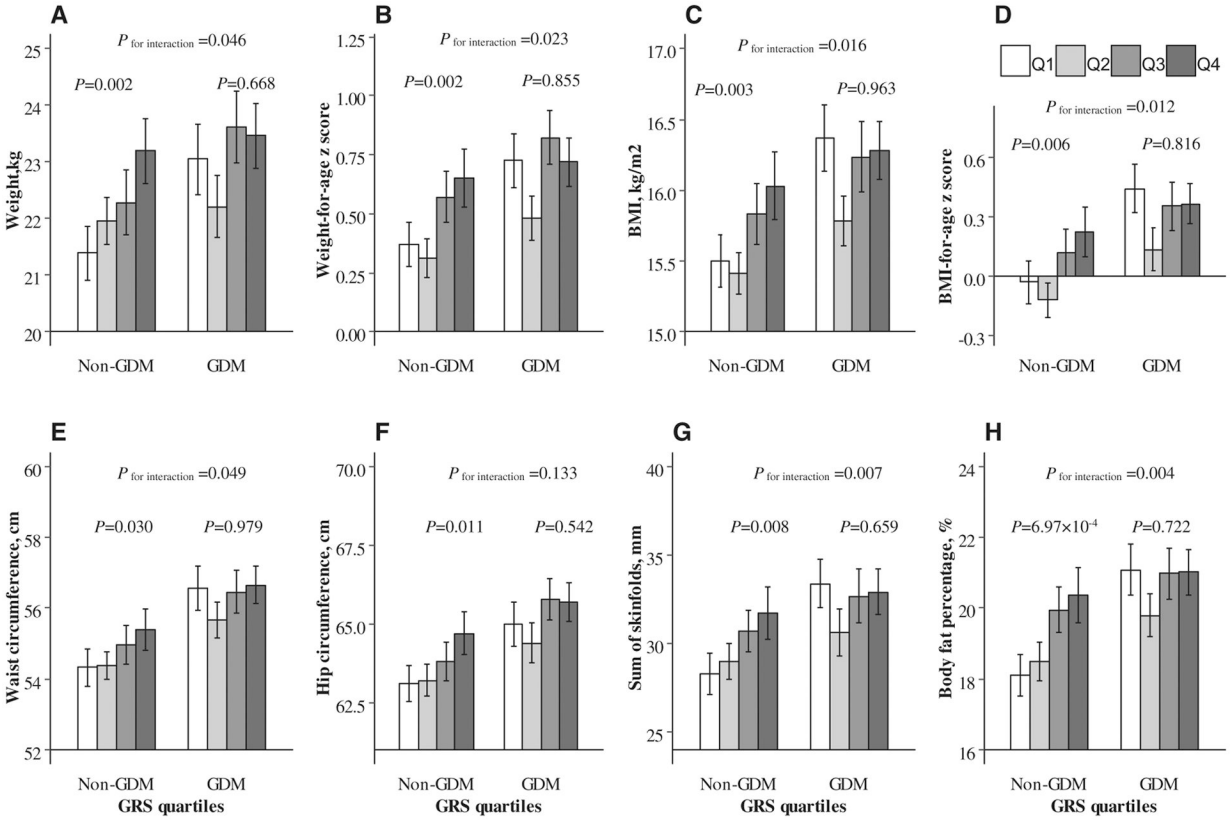

Figure 1.

Interaction between genetically determined maternal blood glucose levels and GDM status on children's obesity-related quantitative traits. General linear models were performed to explore the associations of genetically determined maternal blood glucose levels (in quartiles: Q1~Q4) with (A) weight, (B) weight-for-age *z* score, (C) BMI, (D) BMI-for-age *z* score, (E) waist circumference, (F) hip circumference, (G) sum of skinfolds, and (H) body fat percentage, respectively. Interactions were also tested, adjusted for children's age, sex, birth weight, feeding patterns, outdoor physical activity time, screen-watching time, sleeping time, vegetable intake frequency, fruit intake frequency, illness within the last 3 months, and maternal age at pregnancy, gestational weight gain, gestational age at delivery, smoking status, drinking status, marital status, education, family monthly income, hypertensive disorders of pregnancy, treatment of GDM, any family history of diabetes, and maternal prepregnancy BMI. For weight-for-age *z* score and BMI-for-age *z* score, which were calculated based on sex- and age-specific standards, children's age and sex were excluded in the adjustment. GDM, gestational diabetes mellitus; GRS, genetic risk score.

TABLE 1

Characteristics of mothers and their children, stratified by maternal glucose GRS quartiles

	Maternal glucose GRS quartiles				
	Q1 (*n* = 279)	**Q2 (*n* = 279)**	**Q3 (*n* = 275)**	**Q4 (*n* = 281)**	***P* value**
GRS	10.37~16.49	16.50~18.31	18.32~20.05	20.06~26.81	—
Maternal characteristics					
Age, y	30.3 ± 3.2	30.3 ± 3.4	30.0 ± 3.3	30.0 ± 3.3	0.466
Gestational age, wk	39.2 ± 1.5	39.0 ± 1.7	39.1 ± 1.3	39.1 ± 1.3	0.445
Prepregnancy BMI, kg/m^2	22.4 ± 3.5	21.9 ± 2.8	22.2 ± 2.9	22.1 ± 3.1	0.233
Gestational weight gain, kg	17.4 ± 6.4	17.7 ± 6.1	17.3 ± 6.2	17.1 ± 6.7	0.788
Education, *n* (%)					
<13 y	54 (19.4)	33 (11.8)	43 (15.6)	41 (14.6)	0.156
13–16 y	198 (71.0)	208 (74.6)	207 (75.3)	213 (75.8)	
≥16 y	27 (9.7)	38 (13.6)	25 (9.1)	27 (9.6)	
Income, ¥, *n* (%)					
<5,000	46 (16.9)	33 (12.0)	44 (16.1)	45 (16.2)	0.396
5,000~8,000	66 (24.2)	72 (26.3)	63 (23.1)	81 (29.1)	
≥8,000	161 (59.0)	169 (61.7)	166 (60.8)	152 (54.7)	
Current smokers, *n* (%)	3 (1.1)	9 (3.2)	11 (4.0)	8 (2.9)	0.344
Alcohol drinkers, *n* (%)	75 (26.9)	79 (28.3)	66 (24.0)	75 (26.7)	0.710
Family history of diabetes, *n* (%)	79 (28.3)	81 (29.0)	91 (33.1)	102 (36.3)	0.146
GDM, *n* (%)	138 (49.5)	119 (42.7)	143 (52.0)	160 (56.9)	**0.008**
Treatment of GDM, *n* (%)					
No	20 (14.5)	20 (16.8)	17 (11.9)	16 (10.0)	0.506
Insulin	5 (3.6)	1 (0.8)	4 (2.8)	4 (2.5)	
Lifestyle control	113 (81.9)	98 (82.4)	122 (85.3)	140 (87.5)	
Hypertensive disorders of pregnancy, *n* (%)	11 (3.9)	11 (3.9)	11 (4.0)	13 (4.6)	0.972
Children's characteristics					
Age, y	5.8 ± 1.2	6.0 ± 1.3	5.8 ± 1.2	6.0 ± 1.3	0.119
Sex, boys, *n* (%)	144 (51.6)	158 (56.6)	145 (52.7)	137 (48.8)	0.311
Feeding pattern, *n* (%)					

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	Maternal glucose GRS quartiles				
	Q1 (*n* = 279)	**Q2 (*n* = 279)**	**Q3 (*n* = 275)**	**Q4 (*n* = 281)**	***P* value**
Exclusive breast feeding	120 (43.0)	120 (43.2)	119 (43.3)	122 (43.4)	0.865
Mixed breast and formula feeding	124 (44.4)	120 (43.2)	124 (45.1)	115 (40.9)	
Exclusive formula feeding	35 (12.5)	38 (13.7)	32 (11.6)	44 (15.7)	
Vegetable intake frequency, *n* (%)					
≤1 time/d	23 (8.2)	25 (9.0)	21 (7.6)	21 (7.5)	0.801
2 times/d	247 (88.5)	238 (85.3)	239 (86.9)	248 (88.3)	
≥3 times/d	9 (3.2)	16 (5.7)	15 (5.5)	12 (4.3)	
Fruit intake frequency, *n* (%)					
<1 time/d	5 (1.8)	12 (4.3)	9 (3.3)	12 (4.3)	0.448
1 times/d	93 (33.3)	101 (36.2)	95 (34.6)	107 (38.1)	
>3 times/d	181 (64.9)	166 (59.5)	171 (62.2)	162 (57.7)	
Sleeping time, *n* (%)					
≤8 h/d	29 (10.4)	45 (16.1)	37 (13.5)	35 (12.5)	**0.006**
9–10 h/d	193 (69.2)	181 (64.9)	180 (65.7)	216 (76.9)	
≥11 h/d	57 (20.4)	53 (19.0)	57 (20.8)	30 (10.7)	
Screen-watching time, h/d	1.0 ± 0.8	1.1 ± 0.8	1.1 ± 0.8	1.0 ± 0.7	0.562
Outdoor activity, h/d	2.2 ± 0.9	2.2 ± 0.9	2.1 ± 0.8	2.1 ± 0.9	0.423
Birth length, cm	50.7 ± 1.7	50.5 ± 2.0	50.8 ± 2.0	50.8 ± 2.2	0.206
Birth weight, g	3,487.5 ± 483.2	3,425.9 ± 495.1	3,500.4 ± 490.4	3,471.8 ± 475.8	0.293
Height, cm	117.1 ± 9.4	118.3 ± 9.5	118.6 ± 9.9	119.0 ± 9.5	0.096
Weight, kg	22.2 ± 6.5	22.1 ± 5.5	22.9 ± 7.2	23.4 ± 6.8	0.070
BMI, kg/m^2	15.9 ± 2.6	15.6 ± 1.9	16.0 ± 2.7	16.2 ± 2.6	**0.040**
Waist circumference, cm	55.4 ± 7.0	55.0 ± 5.2	55.7 ± 7	56.1 ± 6.7	0.199
Hip circumference, cm	64.0 ± 7.4	63.8 ± 6.5	64.7 ± 7.6	65.3 ± 7.7	0.057
Sum of skinfolds, mm	30.8 ± 15.4	29.7 ± 13.5	31.6 ± 16.4	32.5 ± 16.3	0.189
Body fat percentage, %	19.6 ± 7.8	19.1 ± 6.8	20.4 ± 8.1	20.8 ± 8.3	0.050

Data are shown as mean ± SD or *n* (%). Significant differences in maternal and children's characteristics among the four groups are highlighted in bold.

GDM, gestational diabetes mellitus; GRS, genetic risk score.

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TABLE 2

Associations of genetically determined maternal blood glucose levels with overweight and obesity status among children with and without maternal GDM

	Non-GDM (*N* = 554)		GDM (*N* = 560)		
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	$P_{\text{for interaction}}$
Model 1 [a]					
Overweight	1.63 (1.27–2.09)	**1.42×10^{-4}**	1.00 (0.83–1.21)	0.976	**0.002**
Obesity	1.86 (1.29–2.67)	**8.20×10^{-4}**	1.07 (0.82–1.38)	0.626	**0.015**
Model 2 [b]					
Overweight	1.75 (1.34–2.28)	**3.17×10^{-5}**	1.01 (0.83–1.23)	0.924	**0.001**
Obesity	2.02 (1.38–2.94)	**2.68×10^{-4}**	1.07 (0.81–1.40)	0.646	**0.008**
Model 3 [c]					
Overweight	1.86 (1.40–2.45)	**1.38×10^{-5}**	0.98 (0.80–1.20)	0.851	**6.91×10^{-4}**
Obesity	2.18 (1.46–3.27)	**1.40×10^{-4}**	1.08 (0.81–1.42)	0.605	**0.007**
Model 4 [d]					
Overweight	1.89 (1.42–2.52)	**1.40×10^{-5}**	0.94 (0.76–1.16)	0.573	**5.66×10^{-4}**
Obesity	2.20 (1.44–3.35)	**2.61×10^{-4}**	1.04 (0.78–1.39)	0.777	**0.008**

Significant associations are highlighted in bold.

[a]Model 1: unadjusted for any covariates because the definitions of overweight and obesity were based on sex- and age-specific standards.

[b]Model 2: Model 1 + children's birth weight, maternal age at pregnancy, prepregnancy BMI, gestational weight gain, gestational age at delivery.

[c]Model 3: Model 2 + maternal lifestyle, socioeconomic and other related factors: smoking status, drinking status, marital status, education, family monthly income, hypertensive disorders of pregnancy, treatment of GDM, and any family history of diabetes.

[d]Model 4: Model 3 + children's variables: feeding patterns, outdoor physical activity time, screen-watching time, sleeping time, vegetable intake frequency, fruit intake frequency, illness within the last 3 months.

GDM, gestational diabetes mellitus; OR, odds ratio.

TABLE 3

Associations of genetically determined maternal blood glucose levels with obesity-related quantitative traits among children with and without maternal GDM

	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	β (SE)	***P***	**β (SE)**	***P***	**β (SE)**	***P***	**β (SE)**	***P***
Non-GDM (*N* = 554)								
Weight, kg	0.66 (0.21)	**0.002**	0.74 (0.19)	**1.61×10^{-4}**	0.79 (0.20)	**9.61×10^{-5}**	0.79 (0.20)	**1.05×10^{-4}**
Weight-for-age *z* score	0.16 (0.05)	**0.002**	0.19 (0.05)	**1.55×10^{-4}**	0.19 (0.05)	**1.35×10^{-4}**	0.19 (0.05)	**2.45×10^{-4}**
BMI, kg/m^2	0.32 (0.10)	**0.001**	0.36 (0.09)	**1.29×10^{-4}**	0.39 (0.10)	**7.27×10^{-5}**	0.39 (0.10)	**5.53×10^{-5}**
BMI-for-age *z* score	0.17 (0.06)	**0.003**	0.19 (0.05)	**2.88×10^{-4}**	0.20 (0.05)	**2.15×10^{-4}**	0.20 (0.05)	**2.60×10^{-4}**
Waist circumference, cm	0.56 (0.24)	**0.022**	0.66 (0.23)	**0.004**	0.69 (0.24)	**0.004**	0.72 (0.24)	**0.003**
Hip circumference, cm	0.61 (0.25)	**0.015**	0.70 (0.23)	**0.003**	0.77 (0.24)	**0.001**	0.76 (0.24)	**0.002**
Sum of skinfolds, mm	1.93 (0.61)	**0.002**	2.13 (0.59)	**3.23×10^{-4}**	2.32 (0.61)	**1.59×10^{-4}**	2.34 (0.61)	**1.38×10^{-4}**
Body fat percentage, %	1.17 (0.33)	**3.86×10^{-4}**	1.30 (0.31)	**4.09×10^{-5}**	1.36 (0.32)	**3.19×10^{-5}**	1.35 (0.32)	**3.49×10^{-5}**
GDM (*N* = 560)								
Weight, kg	0.08 (0.21)	0.720	0.12 (0.20)	0.572	0.06 (0.20)	0.767	0.08 (0.21)	0.717
Weight-for-age *z* score	0.01 (0.05)	0.853	0.01 (0.05)	0.825	−0.002 (0.05)	0.965	−0.01 (0.05)	0.844
BMI, kg/m^2	0.0004 (0.1)	0.997	0.03 (0.10)	0.763	0.01 (0.10)	0.941	0.01 (0.10)	0.948
BMI-for-age *z* score	−0.01 (0.06)	0.876	0.001 (0.05)	0.990	−0.01 (0.05)	0.844	−0.02 (0.05)	0.743
Waist circumference, cm	−0.08 (0.24)	0.740	−0.04 (0.24)	0.876	−0.09 (0.24)	0.718	−0.07 (0.24)	0.759
Hip circumference, cm	0.12 (0.24)	0.620	0.17 (0.23)	0.478	0.12 (0.23)	0.607	0.10 (0.24)	0.683
Sum of skinfolds, mm	−0.27 (0.61)	0.661	−0.14 (0.59)	0.818	−0.28 (0.59)	0.630	−0.31 (0.60)	0.600
Body fat percentage, %	−0.03 (0.32)	0.918	−0.01 (0.31)	0.964	−0.10 (0.31)	0.736	−0.16 (0.32)	0.606

Significant associations are highlighted in bold.

[a]Model 1: adjusted for children's age and sex. For weight-for-age z score and BMI-for-age z score, which were calculated based on sex- and age-specific standards, children's age and sex were excluded in the adjustment.

[b]Model 2: Model 1 + children's birth weight, maternal age at pregnancy, prepregnancy BMI, gestational weight gain, gestational age at delivery.

[c]Model 3: Model 2 + maternal lifestyle, socioeconomic and other related factors: smoking status, drinking status, marital status, education, family monthly income, hypertensive disorders of pregnancy, treatment of GDM, any family history of diabetes.

[d] Model 4: Model 3 + children's variables: feeding patterns, outdoor physical activity time, screen-watching time, sleeping time, vegetable intake frequency, fruit intake frequency, illness within the last 3 months.

GDM, gestational diabetes mellitus.