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## Genetic Risk Score of Hemoglobin A<sub>1c</sub> interact with Postpartum Weight Reduction on Glycemic Changes: Gene-Weight Interaction Analysis

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### Abstract

**Aim:** We aimed to investigate the interaction between genetic risk score of HbA<sub>1c</sub> and weight changes during and after pregnancy (postpartum weight reduction and gestational weight gain) on long-term glycemic changes in the largest cohort of women with preceding history of gestational diabetes mellitus (GDM).

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Conflict of interest

The authors have no conflicts of interest to disclose

Author Contributions

LH, DD, SZ, WL, LW, HL, JL, NL, XS, GH and LQ: designed the research, acquisition of data, analysis and interpretation of the data, drafting of the manuscript, and critical revision of the manuscript. DD: analyzed the data. GH and LQ: involved in the collection and analysis of data and funding of the initial project. GH and LQ: conducted the research, administration, material support, and study supervision. LQ: had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the final manuscript.

**Methods:** This is a retrospective cohort using the baseline data from the Tianjin Gestational Diabetes Mellitus Prevention Program. A genetic risk score was established by combining 10 HbA<sub>1c</sub> related single nucleotide polymorphisms (SNPs), which were identified by genome-wide association studies (GWAS). General linear regression models were applied to evaluate the interaction between HbA<sub>1c</sub> genetic risk score and weight changes during and after pregnancy (postpartum weight reduction and gestational weight gain) on glycemic changes.

**Results:** A total of 1156 women with preceding history of GDM were included in this respective cohort study. Statistical differences in pre-pregnancy weight, pre-delivery weight and postpartum weight were evidenced across different groups of postpartum weight reduction. After adjusted for covariates, statistical significance in changes of HbA<sub>1c</sub> % was only observed in postpartum weight reduction <5 kg/yr group (p= 0.002), and significant interaction between HbA<sub>1c</sub> genetic risk score and postpartum weight reduction on long-term changes of HbA<sub>1c</sub> was evidenced (p-interaction=0.01). In the category of postpartum weight reduction 8kg/y group, women with a lower genetic risk score of HbA<sub>1c</sub> had a greater decrease of HbA<sub>1c</sub>.

**Conclusions:** A genetic risk score of HbA<sub>1c</sub> interact with postpartum weight reduction on long-term changes of HbA<sub>1c</sub> among women with preceding history of GDM.

### Keywords

postpartum weight reduction; glycemic changes; genetic risk score; gestational diabetes mellitus

## INTRODUCTION

During pregnancy, women will gain about 20 percent or more of body weight<sup>1</sup>. Abnormal metabolism of glucose are greatly affected by weight changes during and after pregnancy<sup>2,3</sup>. Compelling evidence indicates that low postpartum weight reduction is associated with aberrant glucose metabolism and an increased risk of type 2 diabetes in later life<sup>1,4-7</sup>, women with greater postpartum weight retention and preceding history of gestational diabetes mellitus (GDM) are more likely to involve in this metabolic disease<sup>8-11</sup>.

As a common biomarker, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is regarded as a stable biomarker for hyperglycemia. Genetic susceptibility to higher HbA<sub>1c</sub> levels had been verified by genome-wide association studies (GWAS)<sup>12,13</sup>. However, the interactions between genetic variations of HbA<sub>1c</sub> and weight changes during and after pregnancy (postpartum weight reduction and gestational weight gain) on long-term changes of glycemic traits remain unclear. We hypothesized that weight changes during and after pregnancy (postpartum weight reduction and gestational weight gain) might modify the genetic variations of HbA<sub>1c</sub> on glycemic changes.

Taken together, we investigated the interaction between genetic risk score of HbA<sub>1c</sub> and weight changes during and after pregnancy (postpartum weight reduction and gestational weight gain) on long-term changes of glycemic traits in the largest cohort of women with preceding history of GDM.

## 2 MATERIALS AND METHODS

### 2.1 Study samples

Our study is a retrospective cohort using the baseline data from the Tianjin Gestational Diabetes Mellitus Prevention Program<sup>14</sup>. In accordance with the criteria of World Health Organization) at 26–30 gestational weeks (2005–2009) were recruited. Women with pregnancy, resided in the 6 central urban districts of Tianjin and with diagnosis of GDM (to engage in a postpartum survey (2009–2011)). Those with chronic diseases, diabetes after delivery, usage of medicine to change the glucose values, pregnant and going to be pregnant in the next two years were excluded. A group of 4644 women with preceding history of GDM (postpartum at 1–5 years) were recruited from the Tianjin Gestational Diabetes Mellitus Prevention Study<sup>14–17</sup>.

A total of 1263 women with preceding history of GDM finished the questionnaire. Glucose levels, the prevalence of impaired glucose tolerance and diabetes at 26–30 gestational weeks didn't differ between women who returned the questionnaire and those who did not. The 3-day 24-hour food records were obtained by a dietitian. The final analysis was restricted to a group of 1156 participants with available genotype data. The proposal of this retrospective cohort study was approved by the Human Subjects Committee of Tianjin Women's and Children's Health Center. Informed consent was acquired for all of the women with preceding history of GDM.

#### Tianjin gestational diabetes mellitus screening program

The Tianjin Gestational Diabetes Mellitus Prevention Program is ongoing and 2-arm, 4-year randomized controlled trial, which is conducted by Tianjin Women's and Children's Health Centre, Tianjin, China. Compared to the usual-care group, six face-to-face sessions with study dietitians in the first year, and two extra sessions and two telephone calls in second year were performed in the intervention group. The detailed information about the study design has been described in elsewhere<sup>14</sup>. The registered number is NCT01554358 at [ClinicalTrials.gov](http://ClinicalTrials.gov). Among the 1263 women with preceding history of GDM, who finished the questionnaire, a total of 1180 women were randomly assigned (1:1) to receive a 4-year lifestyle intervention or standard care<sup>14</sup>. Our current analysis is retrospective, the outcomes are changes in glycaemic traits from pregnancy to baseline of the intervention trial. Therefore, intervention would not affect our analyses.

#### Variable definition

All participants completed a baseline self-administered questionnaire. Pre-pregnancy weight, postpartum weight, and weight gain in pregnancy were self-reported. Baseline weight was measured by trained physicians<sup>14</sup>. Body weight and height were measured using the standardized protocol according to the WHO MONICA project<sup>18</sup>. Weight was measured to the nearest 0.1 kg and height (without shoes) to the nearest 0.1 cm.

The postpartum weight retention (weight change between pre-pregnancy and 1–5 y postpartum) was classified as gestational weight gain and postpartum weight reduction. The annual post-partum weight reduction was calculated by dividing the difference between

postpartum weight and predelivery weight (pre-pregnancy weight plus gestational weight gain) by follow-up years. Gestational weight gain was categorized as inadequate, adequate, and excessive according to 2009 Institute of Medicine guideline<sup>19</sup>. For the range of pre-pregnancy BMI of <18.5 kg/m<sup>2</sup>, 18.5–24.9 kg/m<sup>2</sup>, 25.0–29.9 kg/m<sup>2</sup>, BMI of ≥30 kg/m<sup>2</sup>, weight in the range of 12.5 to 18 kg, 11.5 to 16 kg, 7 to 11.5 kg, and 5 to 9 kg were defined as adequate gestational weight gain<sup>20</sup>. Otherwise under or higher than the cut-off values were taken as inadequate or excessive, separately<sup>20</sup>. Fasting glucose, 2-hour glucose and HbA<sub>1c</sub> were measured according to the standard protocols (with analytical machines TBA-120FR and ADAMS A<sub>1c</sub> HA-8160; Arkray, Japan, respectively). The changes in glycemic traits were computed as the corresponding values at postpartum minus the values at pre-pregnancy (GDM diagnosis).

## 2.2 Calculation of HbA<sub>1c</sub> genetic risk score

DNA was extracted from the buffy coat fraction of centrifuged blood using a QIAamp Blood Maxi Kit (Qiagen, Chatsworth, CA, USA). SNPs were genotyped by a quantitative real-time TaqMan PCR (Applied Biosystems) with a success rate of 98%. The HbA<sub>1c</sub> genetic risk score was established by aggregating the HbA<sub>1c</sub>-increasing alleles according to the HbA<sub>1c</sub> susceptibility SNPs discovered by GWAS (Table S1)<sup>12,13</sup>, and mutual independence was observed for all HbA<sub>1c</sub> SNPs. Among them, rs1800562 and rs855791 were not in accordance with Hardy-Weinberg equilibrium in our data, thus rs266717 and rs12597579 were used as proxies, respectively ( $r^2=1$ ). GWAS provided the  $\beta$ -coefficients (effect sizes) for the 10 HbA<sub>1c</sub> susceptibility SNPs<sup>12,13</sup> (Table S1). A genetic risk score was established by summing the 10 effect alleles, weighted by the  $\beta$ -coefficients. We actually transformed the  $\beta$ -coefficients to indicate a higher HbA<sub>1c</sub>. The HbA<sub>1c</sub> genetic risk score was divided into tertiles (tertile 1 for the lowest, tertile 2 in the middle, and tertile 3 for the highest).

## 2.3 Statistical analysis

We did a retrospective analysis using the baseline data from Tianjin Gestational Diabetes Mellitus Prevention Program, the final analysis was restricted to a group of 1156 participants with available genotype data. The baseline characteristics across different groups of annual postpartum weight reduction (<5, 5–8, and ≥8 kg/y) and gestational weight gain (inadequate, adequate, excessive) were estimated by chi-square tests and general linear model (GLM), as appropriate. The association of HbA<sub>1c</sub> genetic risk score and changes in glycemic traits by annual weight reduction groups was tested by GLM. An interaction between the HbA<sub>1c</sub> genetic risk score and annual postpartum weight reduction on changes in glycemic traits was tested by including an interaction term in the models. The long-term effect of weight changes on the glycemic traits stratified by tertiles of HbA<sub>1c</sub> genetic risk score were also estimated by GLM. In addition, sensitivity analyses were performed to estimate the effect of follow-up years on the observed association. SAS 9.4 was used to perform all of the analysis with two-sided significance at 0.05 (SAS Institute, Cary, NC).

## 3 RESULTS

Characteristics across different groups of postpartum weight reduction and gestational weight gain are summarized in Table 1 and Table S2, respectively. Statistical differences in

pre-pregnancy weight, pre-delivery weight and postpartum weight were evidenced across different groups of postpartum weight reduction. Others characteristics and HbA<sub>1c</sub> genetic risk score were not significant across different groups (Table 1).

The distribution of the HbA<sub>1c</sub> genetic risk score is illustrated in Figure S1. There were no statistical differences for the HbA<sub>1c</sub> genetic risk score with reference levels of glycemic traits, even adjusted for covariates. The association between HbA<sub>1c</sub> genetic risk score with changes in glycemic traits stratified by annual postpartum weight reduction and gestational weight gain are summarized in Table 2 and Table S3, respectively. After adjusted for covariates, statistical significance in changes of HbA<sub>1c</sub> was only observed in postpartum weight reduction <5 kg/yr group (p= 0.002) (Table 2). Significant interactions were evidenced for the association between HbA<sub>1c</sub> genetic risk score and postpartum weight reduction on changes of HbA<sub>1c</sub> (p-interaction=0.01). In the category of postpartum weight reduction 8 kg/y, women with a lower genetic predisposition to high HbA<sub>1c</sub> might be more susceptible to the improvement of HbA<sub>1c</sub> (P=0.036). Along with the accumulation of HbA<sub>1c</sub> genetic risk score, elevated HbA<sub>1c</sub> was evidenced in the largest postpartum weight loss group (Figure 1C). In the group of postpartum weight reduction <5 kg/yr, HbA<sub>1c</sub> levels were decreased across tertiles of HbA<sub>1c</sub> genetic risk score, whereas, HbA<sub>1c</sub> levels were increased in the group of postpartum weight reduction 8 kg/y (Figure 1C). We also estimated the tertiles of HbA<sub>1c</sub> genetic risk score divided by weight reduction (kg/yr) on changes of HbA<sub>1c</sub> (Table S5). In the category of postpartum weight reduction 8 kg/y, women with a lower genetic predisposition to high HbA<sub>1c</sub> showed more improvement of HbA<sub>1c</sub> (p=0.036) (Table S5). We didn't observe any significant interactions on variations of fasting glucose and 2-hour glucose, as well as in different groups of gestational weight gain (Table S2).

The HbA<sub>1c</sub> genetic risk score were divided into tertiles (tertile 1 for the lowest, tertile 2 in the middle, and tertile 3 for the highest). From tertile 1 to tertile 3, the  $\beta$  values for every 1-unit postpartum weight reduction with changes of fasting glucose were 0.182 (P = 0.624), -0.508 (P = 0.091), and -0.219 (P = 0.493) mmol/L, respectively (Figure 2A). The  $\beta$  values for every 1-unit postpartum weight reduction with changes of 2-hour glucose were 0.192 (P = 0.809), -0.122 (P = 0.174), and -0.364 (P = 0.613) mmol/L, respectively (Figure 2B). And the  $\beta$  values for every 1-unit postpartum weight reduction with changes of HbA<sub>1c</sub> were -0.972% (P = 0.002), -0.124% (P = 0.729) and -0.176% (P = 0.095), respectively (Figure 2C).

A sensitivity analyses by limiting the study to participants with delivery within the first 1.5 years was also performed (sample size equal 207). No statistical significant interactions between HbA<sub>1c</sub> genetic risk score and postpartum weight reduction/gestational weight gain on any glycemic changes were observed (Table 3 and Table S4, respectively).

## 4 CONCLUSION

To our knowledge, significant interaction between genetic risk score of HbA<sub>1c</sub> and postpartum weight reduction on changes of HbA<sub>1c</sub> was evidenced in currently the largest cohort of women with preceding history of GDM. Our data demonstrated that across

different categories of postpartum weight reduction, the genetic risk score of HbA<sub>1c</sub> differed significantly on changes of HbA<sub>1c</sub>. Interestingly, In the group of postpartum weight reduction <5 kg/yr, HbA<sub>1c</sub> levels were decreased across tertiles of HbA<sub>1c</sub> genetic risk score, whereas HbA<sub>1c</sub> levels were increased in the group of postpartum weight reduction ≥ 8 kg/y. Our data indicated that postpartum weight reduction might modify the genetic risk score of HbA<sub>1c</sub> on long-term HbA<sub>1c</sub> changes, the “vulnerability genes” of HbA<sub>1c</sub> may act as “plasticity genes”<sup>21</sup>, with some women more susceptible to postpartum weight reduction, others not. In the category of postpartum weight reduction ≥ 8 kg/y, women with a lower genetic predisposition to high HbA<sub>1c</sub> might be more susceptible to the improvement of HbA<sub>1c</sub> (P=0.036).

Women with greater postpartum weight retention are more susceptible to insulin resistance<sup>22</sup>. Improvement in glucose metabolism in women with GDM was observed after moderate postpartum weight loss<sup>9</sup>. Low postpartum weight reduction contributes significantly to the long-term risk of type 2 diabetes in later life, especially in groups of women with preceding history of GDM<sup>1,4-7</sup>. Therefore, postpartum weight reduction is a great concern in this population<sup>23,24</sup>.

To the best of our knowledge, our findings demonstrated that genetic predisposition to high HbA<sub>1c</sub> interacted significantly with postpartum weight reduction on postpartum changes of HbA<sub>1c</sub>. This study brings novel perspectives to understand the role of postpartum body weight management in glycemic improvement under the genetic background. Furthermore, we created the HbA<sub>1c</sub> genetic risk score using widely accepted methods to sum up the genetic variations weighted by their effect sizes<sup>25,26</sup>. Individual genetic variants explain a very small fraction of the overall variation, and a combination of a higher number of included variants with weak to moderate effect sizes into a genetic risk score can explain a larger proportion of heritability<sup>27,28</sup>.

Two large GWAS analyzed the common genetic determinants of HbA<sub>1c</sub> levels with larger sample sizes and independent replications, the identified SNPs reached genome-wide significance levels ( $p < 5 \times 10^{-8}$ ), thus providing more reliable estimates<sup>12,29</sup>. Currently, the construction of GRS use the weighted published effect size from GWAS identified SNPs that achieved genome-wide significance<sup>30,31</sup>. However, the SNPs in our study didn't reach the stringent levels, therefore, we used the weighted  $\beta$ -coefficients from the published two large GWAS<sup>12,29</sup>, and the results were similar when we used the un-weighted GRS scores. Besides, genetic architectures for HbA<sub>1c</sub> and fasting glucose were partially overlapped, GWAS of fasting glucose suggested that SNPs near three loci (G6PC2, MTNR1B, and GCK) were also associated with HbA<sub>1c</sub> levels<sup>13</sup>. Therefore, we not only investigated the interaction between HbA<sub>1c</sub> genetic risk score and postpartum weight reduction on HbA<sub>1c</sub> changes, but also on changes of fasting glucose and 2-h glucose.

The results should be mentioned cautiously, our findings may not be generalized to other populations, therefore different studies are required to verify our findings. The sample size of women in the sensitivity analysis was comparatively small, thus the interaction effect was not significant in this sub-group of analysis. The genetic susceptibility of HbA<sub>1c</sub> SNPs were

primarily originated from European ancestry<sup>12,29</sup>, which may not be representative of the genetic susceptibility of Chinese women with GDM.

Taken together, we found postpartum weight reduction interacted with genetic predisposition to HbA<sub>1c</sub> on long-term changes of HbA<sub>1c</sub>. Contradictory to women with a higher genetic risk score, women with a lower genetic risk score demonstrated a more distinct association between postpartum weight reduction and HbA<sub>1c</sub> improvement. In women genetically predisposed to high HbA<sub>1c</sub>, postpartum weight management is of great concern.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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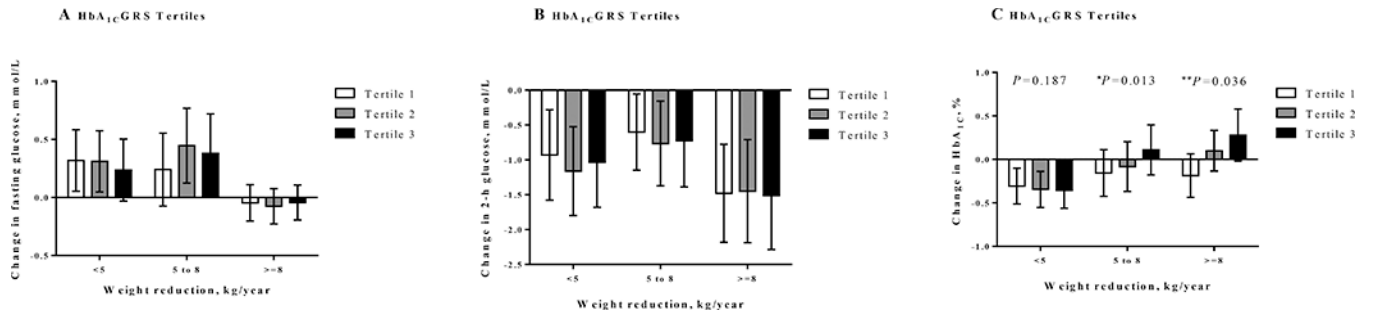
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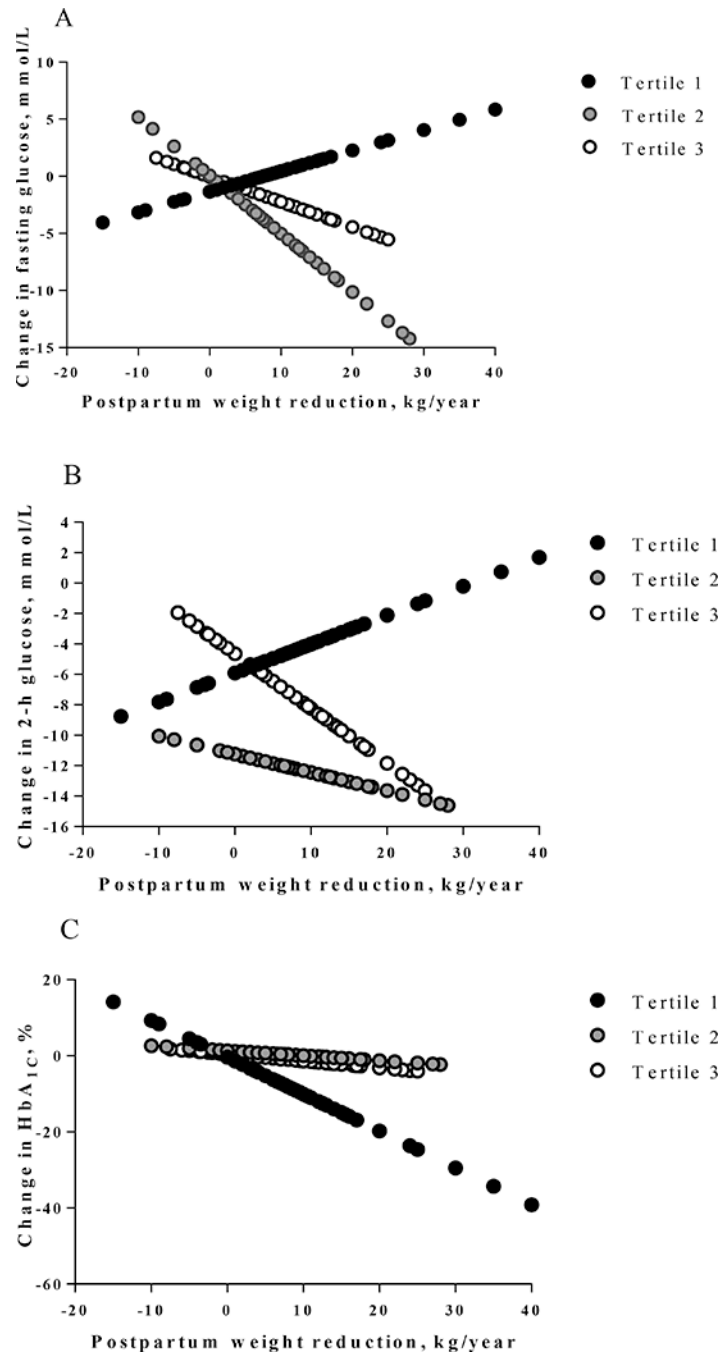
**Figure 1.** Changes in glycemic traits according to weight reduction and HbA<sub>1c</sub> genetic risk score.

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**Figure 2.** Predicted differences in glycemic traits stratified by HbA<sub>1c</sub> genetic risk score.

**Table 1.**

Characteristics of women with prior gestational diabetes mellitus by annual weight reduction

Variables	Weight reduction			P value
	<5 kg/year	5 to 8 kg/year	8 kg/year	
Number	428	396	332	
Age (years)	32.46 ± 3.45	32.79 ± 3.76	31.89 ± 3.56	0.0548
Follow-up (years)	2.71 ± 0.91	2.42 ± 0.80	1.94 ± 0.78	0.1029
Pre-pregnancy BMI (kg/m <sup>2</sup> )	23.27 ± 3.47	22.95 ± 2.83	22.61 ± 2.96	0.0051
Weight (kg)				
Pre-pregnancy	59.74 ± 9.52	58.46 ± 8.43	58.56 ± 8.00	0.0486
Pre-delivery	75.94 ± 11.18	72.83 ± 9.43	78.53 ± 10.39	0.0122
Postpartum	64.49 ± 10.50	64.16 ± 8.39	71.14 ± 9.94	<0.0001
Fasting glucose (mmol/L)				
At GDM diagnosis	5.34 ± 0.81	5.23 ± 0.71	5.31 ± 0.83	0.4442
Postpartum	5.13 ± 0.76	5.66 ± 0.58	5.36 ± 0.95	0.4144
2-h glucose (mmol/L)				
At GDM diagnosis	9.19 ± 1.27	8.99 ± 1.16	9.06 ± 1.33	0.0824
Postpartum	6.05 ± 1.03	8.30 ± 2.12	3.90 ± 1.69	0.1982
HbA <sub>1C</sub> (%)				
At GDM diagnosis	5.84 ± 0.64	5.73 ± 0.63	5.78 ± 0.59	0.1479
Postpartum	5.61 ± 0.75	5.69 ± 0.67	5.69 ± 0.78	0.1040
Family history of diabetes	140 (32.71%)	117 (29.54%)	122 (36.75%)	0.7282
Current Smokers	10 (2.33%)	0 (0.00%)	10 (3.01%)	0.2654
Alcohol drinker	99 (23.13%)	79 (19.95%)	95 (28.61%)	0.4069
Leisure time physical activity				
0 min/d	120 (28.04%)	320 (80.80%)	246 (74.10%)	0.4294
1 to 30 min/d	140 (32.71%)	68 (17.17%)	79 (23.79%)	
30 min/d	168 (39.25%)	8 (1.49%)	7 (12.11%)	
Sitting time (h/d)	3.19 ± 2.15	3.51 ± 2.26	3.19 ± 1.80	0.7509
Total energy intake (kal/d)	1679.27 ± 435.85	1713.65 ± 438.90	1638.34 ± 445.58	0.2889
HbA <sub>1C</sub> GRS	10.96 ± 2.07	11.11 ± 1.85	11.07 ± 1.97	0.3602

**Table 2.** Association between HbA<sub>1c</sub> genetic risk score and changes in glycemic traits by annual weight reduction

Changes in glycemic traits	<5 kg/year			5 to 8 kg/year			8 kg/year			P for interaction
	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value		
Fasting glucose, mmol/L										
Age-adjusted	0.163 (0.372)	0.661	-0.707 (0.778)	0.365	-0.242 (0.316)	0.445	0.371			
Multivariable-adjusted <sup>†</sup>	0.182 (0.371)	0.624	-0.508 (0.298)	0.091	-0.219 (0.320)	0.493	0.428			
2-h glucose, mmol/L										
Age-adjusted	0.274 (0.824)	0.739	0.039 (0.093)	0.966	0.094 (0.073)	0.899	0.712			
Multivariable-adjusted <sup>†</sup>	0.192 (0.795)	0.809	-0.122 (0.089)	0.174	-0.364 (0.720)	0.613	0.965			
HbA <sub>1c</sub> , %										
Age-adjusted	-0.933 (0.322)	0.003	-0.226 (0.329)	0.493	-0.141 (0.103)	0.171	0.025			
Multivariable-adjusted <sup>†</sup>	-0.972 (0.323)	0.002	-0.125 (0.363)	0.729	-0.176 (0.105)	0.095	0.019			

<sup>†</sup> Covariates included glycemic traits at GDM diagnosis, age, duration of follow-up, BMI at pre-pregnancy, kcal/d for energy intake, time for sitting, smoking, drinking, physical activity and family history of diabetes.

Table 3.

Association between HbA<sub>1c</sub> genetic risk score and changes in glycemic traits by weight reduction within 1.5 years

Changes in glycemic trait	<5 kg/year (N=129)		5 to 8 kg/year (N=44)		8 kg/year (N=34)		P for interaction
	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value	
Fasting glucose, mmol/L							
Age-adjusted	0.024 (0.489)	0.960	-0.249 (0.446)	0.585	-0.857 (0.864)	0.328	0.604
Multivariable-adjusted <sup>†</sup>	0.130 (0.498)	0.793	-0.130 (1.214)	0.915	-1.290 (1.046)	0.090	0.723
2-h glucose, mmol/L							
Age-adjusted	0.137 (1.135)	0.903	1.363 (0.611)	0.185	4.859 (1.714)	0.700	0.088
Multivariable-adjusted <sup>†</sup>	0.200 (1.102)	0.856	-1.283 (1.549)	0.454	-6.149 (1.912)	0.343	0.097
HbA <sub>1c</sub> , %							
Age-adjusted	-0.032 (0.376)	0.931	-0.656 (0.572)	0.273	-0.879 (0.625)	0.168	0.332
Multivariable-adjusted <sup>†</sup>	-0.019 (0.379)	0.958	-0.607 (1.216)	0.643	-1.191 (0.667)	0.084	0.287

<sup>†</sup> Covariates included glycemic traits at GDM diagnosis, age, duration of follow-up, BMI at pre-pregnancy, kcal/d for energy intake, time for sitting, smoking, drinking, physical activity and family history of diabetes.