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Genetic risk of type 2 diabetes modifies the association between lifestyle and glycemic health at 5 years postpartum among high-risk women

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ABSTRACT

Introduction Lifestyle interventions are effective in preventing type 2 diabetes, but genetic background may influence the individual response. In the Finnish gestational diabetes prevention study, RADIEL, lifestyle intervention during pregnancy and first postpartum year was effective in preventing gestational diabetes (GDM) and postpartum glycemic abnormalities only among women at highest genetic risk of type 2 diabetes. This study aimed to assess whether still 5 years postpartum the genetic risk modifies the association between lifestyle and glycemic health.

Research design and methods The RADIEL study (randomized controlled trial) aimed to prevent GDM with a lifestyle intervention among high-risk women (body mass index ≥30 kg/m^2 and/or prior GDM). The follow-up study 5 years postpartum included anthropometric measurements, laboratory assessments, device-measured physical activity (PA), and questionnaires. A Healthy Lifestyle Score (HLS) indicated adherence to lifestyle goals (PA, diet, smoking) and a polygenic risk score (PRS) based on 50 type 2 diabetes risk alleles depicted the genetic risk.

Results Altogether 314 women provided genetic and glycemic data 5 years postpartum. The PRS for type 2 diabetes was not associated with glycemic abnormalities, nor was HLS in the total study sample. There was, however, an interaction between HLS and type 2 diabetes PRS on glycemic abnormalities (p=0.03). When assessing the association between HLS and glycemic abnormalities in PRS tertiles, HLS was associated with reduced risk of glycemic abnormalities only among women at the highest genetic risk (p=0.008).

Conclusions These results extend our previous findings from pregnancy and first postpartum year demonstrating that still at 5 years postpartum, healthy lifestyle is associated with a lower risk of prediabetes/diabetes only among women at the highest genetic risk of type 2 diabetes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Women with gestational diabetes are at a 10-fold risk of developing type 2 diabetes.
⇒ Healthy lifestyle is associated with lower risk of type 2 diabetes, but genetic background may modify this association.
⇒ In the RADIEL study, genetic risk of type 2 diabetes measured with a polygenic risk score (PRS) modified the effect of a lifestyle intervention during pregnancy and first postpartum year.

WHAT THIS STUDY ADDS

⇒ In this high-risk group of women, type 2 diabetes PRS modified the association between lifestyle and glycemic abnormalities 5 years postpartum.
⇒ Healthy lifestyle was associated with reduced risk of glycemic abnormalities only among women at highest genetic risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinical characteristics are insufficient for identifying those at the highest risk of type 2 diabetes after pregnancy.
⇒ Assessing the genetic background could offer one means for selecting candidates for individualized and more intensive preventive interventions.

INTRODUCTION

Gestational diabetes (GDM), currently the most common pregnancy disorder, affects both the mother and her child by increasing the risk of both short-term and long-term complications.[1 2] In Finland, GDM occurs in one out of five pregnant women and globally the incidence of GDM is around 14%, which seems to be still growing.[3–5] GDM doubles the risk for cardiovascular disease (CVD) after delivery[6] and 10-folds the risk of type 2 diabetes when compared with women without GDM.[7] Therefore, women with prior GDM are a high-risk group needing immediate attention.

The importance of type 2 diabetes prevention becomes more apparent when we look at its consequences: type 2 diabetes is linked with an increased risk of CVD and higher mortality rate.[8] The interventions combining physical activity (PA) and diet have shown effective results in lowering the risk for type 2 diabetes

complications and in preventing type 2 diabetes,[9 10] even among high-risk groups.[11 12] A recent meta-analysis confirmed that a lifestyle intervention for women with prior GDM, initiated within 3 years after delivery, reduces the risk of type 2 diabetes by 43%.[13] This was evident also in our RADIEL study: at 1 year postpartum, lifestyle intervention markedly reduced the occurrence of glycemic abnormalities.[14]

Type 2 diabetes and GDM are, however, heterogeneous diseases, and prior studies have demonstrated differences in response to lifestyle interventions in distinct groups.[15 16] One important contributing factor is the genetic background: it can modify, for example, weight gain sensitivity and the effect of lifestyle on glycemic health.[17] We discovered these interactions also in the RADIEL study. After assessing the genetic risk of type 2 diabetes with a polygenic risk score (PRS),[18] we detected an interaction both during pregnancy and the first postpartum year. The RADIEL lifestyle intervention was efficient in reducing the occurrence of GDM and glycemic abnormalities 1 year postpartum but only among the women at highest genetic risk.[19]

Whether there are differences in the response to lifestyle in later years after delivery remains still unknown. At the RADIEL 5-year follow-up, diet and PA were associated with glycemic health among women with obesity but not among women with normal weight and prior GDM.[20] To our knowledge, none of the prior postpartum intervention studies have investigated, if genetic background modifies the effects of lifestyle interventions in long term.[13] Identification of individuals benefitting the most from lifestyle changes could enable focusing the limited resources.

Therefore, the aim of this study was first to assess the association between a type 2 diabetes PRS and glycemic health 5 years postpartum and thereafter to evaluate, whether genetic risk modifies the association between lifestyle and glycemic health among these high-risk women.

METHODS

Study design and participants

This study stems from the randomized controlled intervention trial (RCT) RADIEL (Finnish GDM prevention study), and it focuses on participants of the 5-year follow-up. The original RADIEL study aimed at prevention of GDM with lifestyle modification among high-risk women with body mass index (BMI) ≥30 kg/m^2 and/or history of GDM. The study was conducted during years 2008–2014 in all maternity hospitals of the Helsinki metropolitan area (Helsinki University Hospital (HUH), Kätilöopisto Maternity Hospital, and Jorvi Hospital) and South Karelia Central Hospital (SKCH) in Lappeenranta. Previous publications have described the details of the original study.[14 21]

The original RADIEL study recruited in total 724 women with obesity and/or prior GDM, with 18 years of age or older. Exclusion criteria were current diabetes, multiple pregnancy, medications, and diagnoses that affect glucose metabolism, physical disabilities, and communication problems based on incompetent language skills.

At 5 years after delivery, all participants with a live birth and their offspring were invited to a follow-up study visit. Altogether 348 women attended the follow-up study 5 years postpartum.

Outcomes and data collection

The main outcome of this study is the presence of glycemic abnormalities at 5 years postpartum. All participants, except those who had undergone bariatric surgery for obesity or had physician-diagnosed type 2 diabetes, went through a 75 g 2-hour oral glucose tolerance test (OGTT). Type 2 diabetes was diagnosed if fasting plasma glucose was ≥7.0 mmol/L or 2-hour glucose was ≥11.1 mmol/L. The diagnosis of impaired glucose tolerance (IGT) followed if 2-hour glucose was 7.8–11.0 mmol/L and impaired fasting glucose (IFG) was defined as fasting plasma glucose 6.1–6.9 mmol/L. Meeting any of these definitions (type 2 diabetes, IGT, or IFG) resulted in the composite outcome of glycemic abnormality.

The 5-year follow-up study consisted of measurements of metabolic health and lifestyle. Anthropometric measurements included body weight, height, and waist and hip circumference. We used sphygmomanometer (Omron, M6W BP monitor device, Omron HealthCare Europe, Hoofdorp, The Netherlands) to measure blood pressure in a seated position from right arm. Every visit also included venous blood samples taken after a 10–12 hours fast for analysis of glucose metabolism (75 g 2-hour OGTT, insulin), lipids (cholesterol, low-density lipoprotein, high-density lipoprotein, and triacylglycerol), inflammatory markers (C reactive protein), and liver enzymes (alanine aminotransferase, ALAT).

All participants also filled questionnaires regarding chronic diseases, medication, lifestyle (eg, smoking and alcohol), socioeconomic status (years of education), and family history of diabetes.

Lifestyle

PA was measured for seven consecutive days by SenseWear ArmBand Pro 3, an accelerometer for objectively measuring the duration of moderate-to-vigorous physical activity (MVPA) (min/week). The same device also recorded sedentary and sleep time, and was always worn except during showers, sauna, and watersports. The monitored results were included only if wear-time was 85% of the day, for a minimum of 4 days and included at least 1 weekend day to ensure accuracy, sufficiency, and coverage of data.

Food frequency questionnaires (FFQ) provided the data on current diet for calculating a Healthy Food Intake Index (HFII). Our previous study has described the development of HFII thoroughly.[22] Different food

groups contributed points as follows: lower consumption of high-energy/low-nutrient snacks (0–2 points), sugar-sweetened beverages (0–1 points), fast food (0–1 points), and red and processed meat (0–2 points) resulted in points as indicated and higher consumption of high-fiber grains (0–2 points), quality of bread fat spread (0–2 points), low-fat cheese (0–1 points), low-fat milk (0–2 points), fish (0–2 points), fruits and berries (0–1 points), and vegetables (0–2 points) added to the score. The maximum score for HFII was 18 and a higher score suggested a healthier diet. In case of any missing component, the HFII score was not counted.

For representing the adherence to beneficial lifestyle goals, we used HFII, device-measured PA, and questionnaire-data on smoking to create a Healthy Lifestyle Score (HLS). Distinct components provided points as follows: MVPA ≥150 min/week (0–1 points), HFII score in the upper two quintiles, that is, 11–18 points (0–1 points), and being a non-smoker (0–1 points).[23] The scoring ranged from 0 to 3 and a higher score indicated a healthier lifestyle.

For measuring the adherence to healthy lifestyle habits, we calculated an HLS emphasizing lifestyle as an entity instead of focusing solely on individual lifestyle factors. We followed the example of Zhang *et al*[23] by combining three lifestyle factors: PA, diet, and smoking status. As 40%–70% of obesity has a genetic background, we decided to exclude BMI from the score and concentrate on the simple modifiable lifestyle habits.

Type 2 diabetes polygenic risk score

DNA was extracted from blood samples of 537 participants with a Maxiprep kit (Qiagen, Valencia, California, USA) and our prior publication provides detailed information on the genetic methods.[19] In 2014, we genotyped 336 single nucleotide polymorphisms (SNPs) associated with type 2 diabetes, obesity, and hyperlipidemia. For genotype quality control and clumping, we used PLINK V.1.9 software (http://pngu.mgh.harvard.edu/ ~purcell/plink/),[18] using following parameters for clumping of the genotype data: p-value threshold 1, linkage disequilibrium threshold (r2) 0.5, clumping window width 250 kb. Exclusion criteria for SNPs before clumping were a genotyping rate <0.9, Hardy-Weinberg equilibrium p-value $<1 \times 10^{-4}$ and a minor allele frequency <0.05. Missing data on >10% of SNPs led also to exclusion. After quality control, there were 537 samples with genotype data on 195 SNPs. PRSice V.2.1 was used for the calculation of PRS[24 25] and the effect-size estimates for the SNP weights were derived from Xue *et al*.[18] A p-value threshold of 5×10^{-8} was chosen for including type 2 diabetes-associated SNPs in the PRS, and this resulted in 50 SNPs in the final PRS. This PRS is exactly the same as the one we used in our previous study.

Statistical analyses

The descriptive data are presented as mean values with SD, frequencies with percentages, or as medians with IQR when appropriate. For examining the normal distribution of the variables, we used the Shapiro-Wilk test. Between-group comparisons were performed by using the χ^2 test, Fisher's exact test, Mann-Whitney U test, Kruskal-Wallis test, analysis of variance, or the independent samples t-test, depending on the variables.

We used linear regression to test associations between the PRS or HLS and glycemic markers, body fat percentage, and BMI, and logistic regression when analyzing the association with categorical outcomes such as glycemic diagnoses. All these analyses were adjusted for age. Additionally, we assessed the interaction between type 2 diabetes PRS and lifestyle score on the occurrence of glycemic abnormalities by including an interaction term (PRS×HLS) in the regression models.

To further assess the effects of lifestyle according to genetic risk, we then divided the participants into tertiles based on their genetic risk of type 2 diabetes, that is, type 2 diabetes PRS: low risk, medium risk, and high risk.

Due to some missingness in the lifestyle variables (HFII 40 participants and MVPA 128 participants), we performed multiple imputation. After carrying out linear regression analysis indicating variables associated with MVPA, we used the statistically significant variables (systolic and diastolic blood pressure, age, years of education, body fat percentage, abnormal glucose metabolism, smoking during pregnancy) in the multiple imputation with 5 imputations and 50 iterations. For sensitivity analyses, we performed the multiple imputation also with 25 random variables as well as by replacing the missing value with the mean/median. All analyses were performed with the SPSS V.24.0 software program (IBM SPSS, Chicago, Illinois, USA) and we considered a p-value ≤0.05 as statistically significant.

RESULTS

Altogether 348 women attended the follow-up, with 314 providing data on genetics and glycemic health. Medication use was quite rare among the participants, for example, type 2 diabetes medication was reported by 8 women (7 used oral medication, 1 insulin), thyroid hormones by 24, psychiatric medications by 29, and statins by 4. Data for HFII was available for 274 women and 186 provided acceptable data on device-measured PA. At the follow-up visit 5 years postpartum, mean BMI was 31.6 kg/m^2 (SD 6.82) and mean age was 38.7 years (SD 4.56). When compared with the similarity in participants to the original study, most of who reattended the 5-year follow-up were older with the mean age of 32.6 years (SD 4.53) and with lower mean BMI 30.7 kg/m^2 (SD 30.75). There was no difference in the glycemic abnormalities during pregnancy or first-year postpartum. Among these high-risk women, 45 (14.3%) had glycemic abnormalities: 11 (3.5%) were diagnosed with type 2 diabetes, 21 (6.7%) with IGT, and 22 (7%) with IFG. Altogether 41 women (13.1%) were smokers and 209 (66.6%) had a

Table 1 Associations between the type 2 diabetes PRS and markers of glycemic health at 5 years postpartum

Variable	N	OR/Beta	95% CI	P-value
fP-glucose	314	0.045	−0.021 to 0.110	0.182
30 min glucose in OGTT	194	0.166	−0.021 to 0.354	0.082
2-hour glucose in OGTT	294	0.005	−0.167 to 0.177	0.954
GHbA1c	314	0.010	−0.035 to 0.054	0.668
Insulin	314	−0.686	−1.535 to 0.164	0.113
HOMA-IR	314	−0.148	−0.374 to 0.079	0.200
HOMA-beta	314	−10.545	−19.591 to 1.499	0.022
Glycemic abnormalities	314	1.213	0.879 to 1.675	0.240
Type 2 diabetes	314	1.147	0.628 to 2.096	0.655
IGT	314	1.255	0.805 to 1.957	0.317
IFG	314	1.252	0.806 to 1.946	0.317
Metabolic syndrome	313	0.881	0.684 to 1.135	0.328
Body fat percentage	284	−0.747	−1.818 to 0.324	0.171
BMI	314	−0.483	−1.239 to 0.273	0.210

BMI, body mass index; fP-glucose, fasting plasma glucose; GHbA1c, glucose metabolism; HOMA-beta, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment for insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

history of GDM, with 146 (46.5%) having GDM in the RADIEL pregnancy.

Table 1 presents associations between the PRS and markers of glycemic health and metabolic diagnoses. After adjusting for age, the type 2 diabetes PRS was associated with lower homeostasis model assessment of β-cell function (HOMA-beta) at 5 years after delivery (p=0.02), but not with any other glycemic health outcomes (p>0.08).

Of the 163 participants with lifestyle data, 9.2% (n=15), 36.8% (n=60), 50.3% (n=82), and 3.7% (n=6) scored 0, 1, 2, and 3 in the HLS, respectively. HLS did not associate with glycemic abnormalities or metabolic syndrome when analyzed in the total study sample (p>0.18). It was, however, associated with lower body fat percentage (OR −5.87, 95% CI −7.32 to −4.42) and lower BMI (OR −2.649, 95% CI −3.74 to −1.56). The association of HLS with body fat percentage remained significant also when adjusting with BMI (OR −2.68, 95% CI −3.45 to −1.92).

There was a statistically significant interaction between the HLS and type 2 diabetes PRS on glycemic abnormalities (p-value for interaction=0.025). To illustrate the association between HLS and glycemic abnormalities according to type 2 diabetes PRS, we divided the participants into tertiles based on their genetic risk (low, medium, and high) and table 2 provides the characteristics of these groups. After adjusting for age, HLS was associated with glycemic abnormalities only among the women at highest genetic risk for type 2 diabetes (figure 1) (low risk OR 1.91 (95% CI 0.61 to 5.96), medium risk OR 1.13 (95% CI 0.48 to 2.67), and high risk OR 0.24 (95% CI 0.10 to 0.62).

DISCUSSION

Our results indicate that in this high-risk group of women, a type 2 diabetes PRS modifies the association between an HLS and glycemic abnormalities still 5 years after delivery. After adjusting for age, HLS was associated with reduced risk of glycemic abnormalities only among women at highest genetic risk of type 2 diabetes. This is well in line with our previous findings from pregnancy and the first postpartum year.[19] In the total study sample, however, the HLS associated with health benefits such as a lower BMI and body fat percentage, highlighting the importance of supporting healthy lifestyle among all postpartum women.

The PRS for type 2 diabetes was associated with HOMA-beta in our study. Although there also was a higher occurrence of IFG and other glycemic abnormalities among the women at the highest genetic risk, these associations did not reach statistical significance. Women who develop postpartum diabetes have shown lower HOMA-beta cell indexes.[26–28] It reflects the insulin secretion capacity of beta-cells and may act as an important sign of future diabetes risk.

Contrary to our results, many studies,[29–32] including our own during pregnancy and first postpartum year,[19] have shown an association between a type 2 diabetes PRS and glycemic outcomes. Similar to our study, many studies have also addressed women with a history of GDM.[30–32] In a recent population-based study, women with prior GDM who developed type 2 diabetes in 10 years of follow-up had a higher diabetes PRS compared with those remaining normoglycemic. Also, women with GDM but no later diagnosis of type 2 diabetes had a higher PRS than

Table 2 Characteristics of the participants based on their genetic risk for type 2 diabetes (PRS tertile low, medium, or high)

	N	Low risk	Medium risk	High risk	P-value
Age (years)	314	38.2 (4.67)	38.6 (4.67)	39.1 (4.35)	0.393
Education (years)	313	14.9 (1.86)	14.4 (2.15)	14.7 (2.08)	0.184
GDM history, n (%)	314	56 (56.0)	67 (64.4)	86 (78.2)	0.003
IFG, n (%)	314	6 (6.0)	3 (2.9)	13 (11.8)	0.034
IGT, n (%)	314	3 (3.0)	9 (8.7)	9 (8.2)	0.200
Type 2 diabetes, n (%)	314	2 (2.0)	4 (3.8)	5 (4.5)	0.589
Glycemic abnormalities, n (%)	314	9 (9.0)	14 (13.5)	22 (20.0)	0.072
Metabolic syndrome, n (%)	313	29 (29.3)	25 (24.0)	28 (25.5)	0.680
BMI (kg/m^2)	314	32.0 (7.06)	32.2 (7.13)	30.6 (6.22)	0.180
BP systolic (mmHg)	314	126 (13)	126 (15)	124 (14)	0.418
BP diastolic (mmHg)	314	80 (10)	79 (11)	78 (10)	0.334
Waist (cm)	314	104.8 (18.1)	106.2 (16.9)	102.4 (14.9)	0.240
fP-glucose (mmol/L)	314	5.15 (0.51)	5.21 (0.67)	5.32 (0.59)	0.107
2-hour glucose (mmol/L)	294	5.74 (1.60)	5.88 (1.46)	5.81 (1.53)	0.819
Insulin (mU/L)	314	10.0 (6.50 to 15.65)	9.35 (6.00 to 14.45)	8.45 (5.70 to 14.10)	0.473
GHbA1c (%)	314	5.40 (0.31)	5.39 (0.50)	5.45 (0.38)	0.522
HOMA-IR	314	2.40 (1.43 to 3.29)	2.14 (1.40 to 3.47)	1.97 (1.32 to 3.25)	0.677
HOMA-beta	314	120.3 (80.6 to 193.0)	121.4 (81.8 to 170.0)	102.0 (69.8 to 146.3)	0.042
hs-CRP (mg/L)	313	3.45 (5.20)	3.20 (4.94)	2.26 (3.39)	0.137
MVPA (min/week)	186	61.3 (38.6 to 100.9)	63.4 (41.5 to 85.7)	68.4 (43.3 to 99.5)	0.606
HFII (points)	274	9.23 (2.70)	9.62 (2.61)	9.39 (2.89)	0.626
Smoking, n (%)	314	15 (15.0)	14 (13.5)	12 (10.9)	0.672
Body fat percentage (%)	284	39.0 (9.59)	39.5 (9.17)	37.3 (8.97)	0.236
Intervention group, n (%)	314	46 (46)	56 (53.8)	48 (43.6)	0.299

BMI, body mass index; BP, blood pressure; fP-glucose, fasting plasma glucose; GDM, gestational diabetes; GHbA1c, glucose metabolism; HFII, Healthy Food Intake Index; HOMA-IR, homeostasis model assessment for insulin resistance; hs-CRP, high-sensitivity C reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MVPA, moderate-to-vigorous physical activity.

age-matched and BMI-matched women without GDM indicating that a higher PRS increases the risk of both GDM and later progression to type 2 diabetes.[31] Reasons for the undetectable associations in this study could be due to our smaller study population. Differences in the PRSs and selected SNPs could also influence the results.

In our total study population, the HLS showed no significant association with glycemic abnormalities. In many previous studies, on the other hand, HLS has been linked to glycemic abnormalities both during pregnancy and in general population.[33–35] Among pregnant women, adhering to each additional lifestyle factor (diet, PA, stress level, and smoking) lowered the risk of GDM by 23%.[33] Moreover, a large study in the general population (500 000 participants) demonstrated that an HLS consisting of BMI, alcohol consumption, PA, diet, and smoking status was associated with a lower risk of diabetes, regardless of genetic background.[34]

There have been, however, only a limited number of studies assessing the association between an HLS and glycemic abnormalities among postpartum women. Importantly, in our study the HLS showed a significant association with both BMI and body fat percentage which possibly indicates a positive influence on the overall metabolic health. Body fat percentage and BMI both significantly associate with CVD risk highlighting the importance of healthy lifestyle in all postpartum women.[36]

Lifestyle may have individual effects on people.[15 16 20] In a large cohort study, all participants benefitted from achieving lifestyle goals, for example, by improving glycemic health, but the participants at higher genetic risk benefitted the most.[37] Also, in a gene-lifestyle interaction study, the individuals at higher genetic risk of diabetes were more likely to have a successful lifestyle modification.[38] Our current results are well in line with these studies demonstrating a statistically significant interaction between HLS and type 2 diabetes PRS on glycemic abnormalities,[15 16] showing a greater benefit among the participants at highest genetic risk. Also, during pregnancy and first year postpartum, the exact same PRS for type 2 diabetes modified the response to

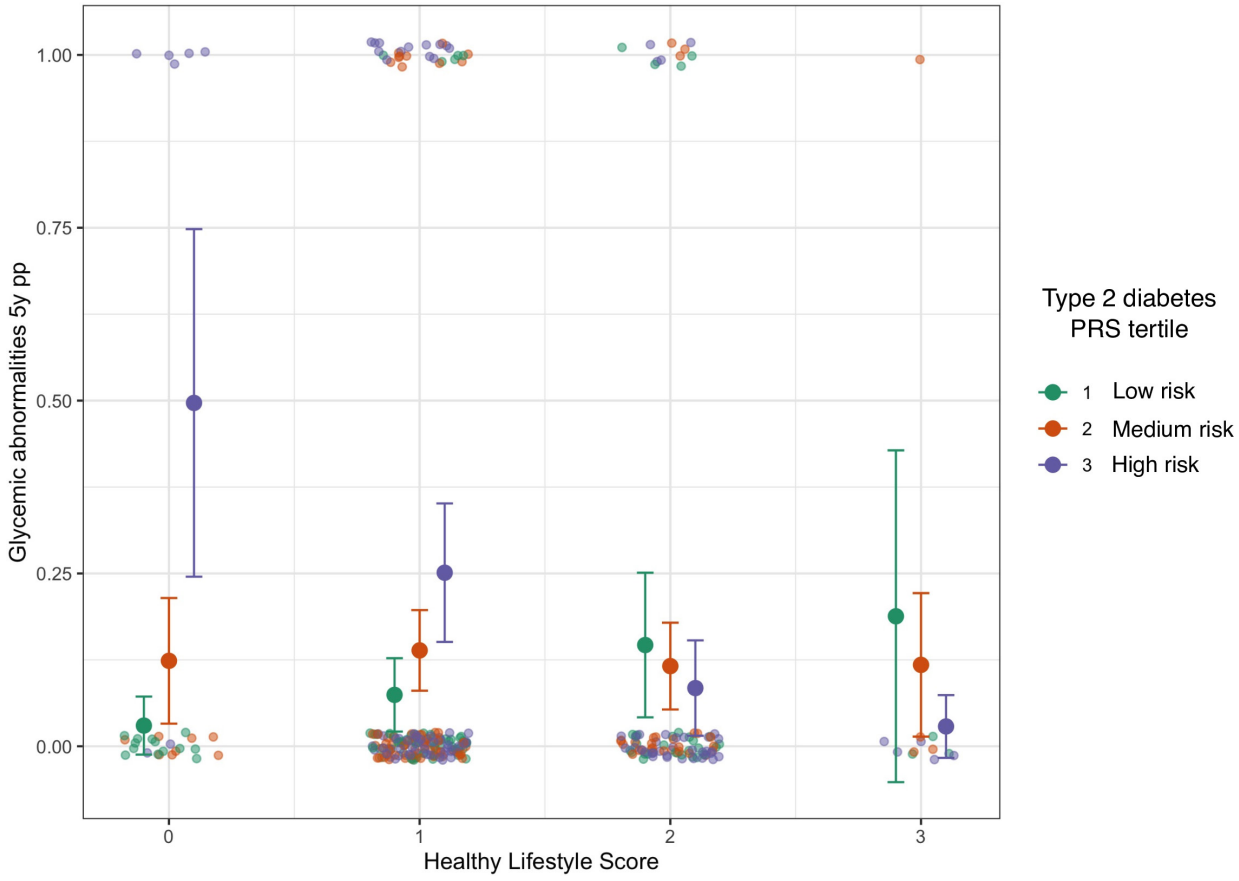

Figure 1 Association between the Healthy Lifestyle score (HLS) and occurrence of glycemic abnormalities among participants grouped according to their type 2 diabetes PRS tertile; low, medium, or high genetic risk. pp, postpartum; PRS, polygenic risk score.

lifestyle intervention, lending credence to this current finding.[19]

Overall, there has not been many studies focusing on gene-environment interactions in women with prior GDM, and none of them has used a PRS for assessing genetic risk. In one randomized study, women with prior GDM and a *CDKAL1* risk variant received more benefit from the lifestyle intervention.[17] Also *MC4R* has shown an interaction with lifestyle intervention on changes in fasting insulin and HOMA-IR 1–3 years postpartum: again, individuals with the risk allele responded to a lifestyle intervention with improvements in insulin resistance.[39] In the RADIEL study, 5 years postpartum lifestyle was associated with better glycemic health only among women with prepregnancy obesity.[20] In this current study, however, there were no differences in clinical characteristics, for example, BMI, between genetic risk groups suggesting that this gene-lifestyle interaction might not explain our prior findings.

One of the strengths in our study comes down to the well-characterized cohort, consisting of an early pregnancy randomized lifestyle intervention with a follow-up continuing up to 5 years postpartum. Our strength also lies in the methods of measuring lifestyle: objective measurement of PA with Armband and the standardized recording of diet with FFQ. Calculating the HFII gave us a comprehensive understanding of an individual's diet as an entity. Another notable strength is the use of a PRS for assessing the genetic risk, offering a more comprehensive estimate of the genetic risk than just individual SNPs.

There are, however, some limitations in our study; one is genotyping only preselected SNPs. A genome-wide genotyping would have given a larger view of the genetic risk, but on the other hand, 50 SNPs could be more affordable for future clinical use. Another limitation is relying solely on calculated indices of insulin secretion and resistance. This may cause varying results due to a partial alteration of hepatic insulin extraction caused by obesity. Unfortunately, we also lack reliable data on pregnancies following the study period which limits the possibilities for assessing the influence of parity. Although the participation rate in the follow-up study was surprisingly good, the number of women is still limited. This might have an influence on the effect of healthy lifestyle in the lowest and middle tertiles where the occurrence of glycemic abnormalities is lower. There was also some missing data on the lifestyle variables included in the HLS which required multiple imputation. The results were, however, well in line when using either the original HLS or the imputed HLS, confirming the reliability of our results.

Women with prior GDM are at markedly increased risk for type 2 diabetes postpartum and therefore form an important group for preventive interventions. As our study demonstrates, clinical characteristics are not enough for identifying those at the highest risk of type 2 diabetes and benefitting the most from lifestyle interventions. From this perspective, all women with GDM history, independent of their BMI, deserve a postpartum follow-up program. Assessing the genetic background could offer one means for selecting candidates for individualized and more intensive preventive interventions. We still need longer and larger follow-up studies focusing on women with GDM history to assess whether this interaction is still evident 10–20 years postpartum. By time, age increases the risk of diabetes even further and gradually rising BMI by age and the menopausal transition compromise metabolic health even further. After delivery, we should not only focus on the child, but also remember the long-term health of the mothers.

Contributors ST participated in the design of the study, literature search, data interpretation, and drafting and editing of the article. EH participated in the design and implementation of the study, literature search, statistical analysis, data interpretation, and drafting and editing of the article. SK, the principal investigator of the study, initiated, participated in the design of, and coordinated the study, participated in the analysis of the results, and advised on drafting and editing the article. JL participated in the design of the study, in the statistical analysis of the results, in data interpretation, and in drafting and editing of the article. EE participated in the design of the study, in data interpretation, and in drafting and editing of the article. HL is the principal investigator of the genetic substudy and participated in the analysis of the results and drafting and editing of the article. All authors have read and approved the final version of the manuscript. EH is the guarantor of this work and, as such, had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

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