Genetic Determinants of Glycemic Traits and the Risk of Gestational Diabetes Mellitus

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Many common genetic polymorphisms are associated with glycemic traits and type 2 diabetes (T2D), but knowledge about genetic determinants of glycemic traits in pregnancy is limited. We tested genetic variants known to be associated with glycemic traits and T2D in the general population for associations with glycemic traits in pregnancy and gestational diabetes mellitus (GDM). Participants in two cohorts (Genetics of Glucose regulation in Gestation and Growth [Gen3G] and Hyperglycemia and Adverse Pregnancy Outcome [HAPO]) underwent oral glucose tolerance testing at 24–32 weeks' gestation. We built genetic risk scores (GRSs) for elevated fasting glucose and insulin, reduced insulin secretion and sensitivity, and T2D, using variants discovered in studies of nonpregnant individuals. We tested for associations between these GRSs, glycemic traits in pregnancy, and GDM. In both cohorts, the fasting glucose GRS was strongly associated with fasting glucose. The insulin secretion and sensitivity GRSs were also significantly associated with these traits in Gen3G, where insulin measurements were available. The fasting insulin GRS was weakly associated with fasting insulin (Gen3G) or C-peptide (HAPO). In HAPO (207 GDM case subjects), all five GRSs (T2D, fasting glucose, fasting insulin, insulin secretion, and insulin sensitivity) were significantly associated with GDM. In Gen3G (43 GDM case subjects), both the T2D and insulin secretion GRSs were associated with GDM; effect sizes for the other GRSs were similar to those in HAPO. Thus, despite the profound changes in glycemic physiology during pregnancy, genetic determinants of fasting glucose, fasting insulin, insulin secretion, and insulin sensitivity discovered outside of pregnancy influence GDM risk.

Pregnancy produces marked changes in glycemic physiology that predispose to the development of glucose intolerance (1,2). By late pregnancy, adaptations include elevated postprandial glucose, reduced insulin sensitivity, and enhanced insulin secretion (2,3). In some pregnant women, an abnormal degree of fasting or postprandial hyperglycemia develops, leading to the diagnosis of gestational diabetes mellitus (GDM). GDM is associated with adverse perinatal and long-term outcomes for mothers and their children, including a high risk of future maternal type 2 diabetes (T2D) (4,5). The extent to which genetic factors contribute to alterations in gestational glycemic physiology and the development of GDM is unknown.

Multiple large studies in the general population have identified common genetic polymorphisms associated with T2D (6–8). The mechanisms by which some T2D-associated variants lead to hyperglycemia has been further elucidated by examining variant associations with physiologic traits related to glucose metabolism (glycemic traits), including insulin secretion and sensitivity (9–13). Many common genetic polymorphisms associated with T2D act by directly or indirectly affecting insulin secretion from the

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pancreatic β-cell. Thus, a genetic predisposition to β-cell dysfunction is now well established as one of the key mechanisms leading to the development of T2D (7).

In contrast to T2D, the role of genetic factors in gestational glycemic physiology and GDM is not well understood (14). There is only one previous genome-wide association study (GWAS) of quantitative glycemic traits in pregnancy. In this study, five variants associated with glycemic traits in the general population were associated with glucose or C-peptide levels in pregnant women; two variants not associated with glycemic traits in the general population were discovered (15). In a GWAS for GDM conducted in Korean women, several variants known to be associated with T2D in the general population were associated with a history of GDM (16). Two previous studies have also shown that genetic risk scores (GRSs) built from variants associated with T2D and/or glycemic traits in the general population are associated with GDM (17,18). However, previous studies have not assessed the aggregate effect of physiologically based groups of genetic variants on GDM risk.

We therefore aimed to use discoveries from glycemic trait genomics in the general population to gain insight into the physiologic mechanisms that contribute to GDM. We tested the hypothesis that genetic determinants of glycemic traits (fasting glucose, fasting insulin, insulin secretion, and insulin sensitivity) outside of pregnancy are also associated with these traits in pregnancy. Further, we tested whether the genetic determinants of each glycemic trait are associated with GDM, with the goal of identifying the key physiologic processes that lead to hyperglycemia in pregnancy.

RESEARCH DESIGN AND METHODS

Genetics of Glucose regulation in Gestation and Growth Cohort

Genetics of Glucose regulation in Gestation and Growth (Gen3G) is a prospective cohort study of pregnant women based in Sherbrooke, Québec, Canada, previously described in detail by Guillemette et al. (19). Participating women were enrolled in the first trimester of pregnancy. Exclusion criteria included history of overt diabetes or laboratory evidence of overt diabetes at the first trimester study visit (hemoglobin A1C ≥6.5% or glucose ≥185 mg/dL after a 50-g glucose load), multiple pregnancy, and use of medications that affect glucose metabolism. All women underwent a 75-g oral glucose tolerance test (OGTT) between 24 and 30 weeks' gestation. The ethics review committee at Centre Hospitalier Universitaire de Sherbrooke approved the study, and participants gave written informed consent.

Hyperglycemia and Adverse Pregnancy Outcome Cohort

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study is an international multicenter prospective study of maternal glucose metabolism, previously described in detail by Metzger et al. (4). Pregnant women underwent a 75-g OGTT between 24 and 32 weeks' gestation. Exclusion criteria included known diabetes and multiple pregnancy. Women with fasting glucose >105 mg/dL or 2-h glucose >200 mg/dL were excluded from further study. The institutional review board at each HAPO field center approved the protocol, and subjects provided written informed consent.

Glycemic Trait Measurements

In Gen3G, we measured glucose levels fasting and at 60 and 120 min after oral glucose administration using the hexokinase method (Roche Diagnostics, Indianapolis, IN). Insulin and C-peptide levels were measured at the same time points using multiplexed particle-based flow cytometric assays (Human Milliplex MAP kits; EMD Millipore).

In HAPO, glucose (fasting and at 60- and 120-min postglucose load) and C-peptide (fasting and at 60-min postglucose load) were measured in a central laboratory using a chemical analyzer (VITROS 750; Ortho Clinical Diagnostics) and immunoassay (AutoDELFIA; PerkinElmer), respectively (20).

In Gen3G, the Stumvoll first-phase estimate was used to estimate insulin secretion, and the Matsuda index was used to estimate insulin sensitivity (the opposite of insulin resistance) (21,22). In both cohorts, insulin sensitivity was also assessed using a C-peptide–based measurement derived in the HAPO study (23).

GDM Classification

Participants were classified as having GDM if their OGTT results met the International Association of the Diabetes in Pregnancy Study Group's criteria, endorsed by the World Health Organization in 2013 (24,25).

Genotyping

In Gen3G, we isolated DNA from maternal blood buffy coat using the Gentra Puregene Blood Kit (Qiagen, Mississauga, Canada). Genomic data were obtained from the Expanded Multi-Ethnic Global Array (Illumina) at the Genome Quebec Innovation Center (Montreal, Canada). Single nucleotide polymorphisms (SNPs) included in the analyses had a call rate of >95% and did not depart from the Hardy-Weinberg equilibrium ($P > 0.01$). Samples included had a call rate of >98%. SNPs were checked for discrepancies between mother and child or between two pregnancies in the same subject; samples with biologically implausible results were removed. We performed imputations using ShapeIT v2.r7990 phasing, HRC r1.1 2016 reference panel, and minimac3 software provided by the Michigan imputation server. For the present analysis, we included all women who had both genomic data and full glucose and insulin results from the OGTT.

In HAPO, we extracted DNA from blood collected during the OGTT. We performed genotyping using the Illumina Human610-Quad v1B SNP array at the Broad Institute. Quality control for genomic data consisted of removing samples and/or SNPs with male sex, chromosomal anomalies, sample duplicates, low call rate, Mendelian errors,

departures from the Hardy-Weinberg equilibrium, duplicate discordance, and low minor allele frequencies. Genotypes were imputed using SHAPEIT v.2 and IMPUTE2 v.2.3.0 with 1000 Genomes phase III data. For the present analysis, we included women with European ancestry enrolled at sites in the U.K. (Belfast), Australia (Newcastle/Brisbane), and Canada (Toronto).

GRS

We studied 150 genetic variants known to be associated with glycemic traits or T2D from previous studies in the general population. All selected variants were associated with at least one trait at genome-wide significance in the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) or DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium data (8–12).

Supplementary Tables 1–5 list the 150 SNPs used in the five GRSs. For the fasting glucose and insulin GRSs, we studied all SNPs known to be associated with their respective trait at genome-wide significance in Europeans, based on data from MAGIC (9–11). For the T2D GRS, we studied 85 SNPs known to be associated with T2D at genome-wide significance and with at least a nominally significant association with T2D in Europeans from DIAGRAM, as selected by Udler et al. (26) using data from Morris et al. (8). For the insulin secretion GRS, we used 8 SNPs associated with insulin secretion (as measured by corrected insulin response [CIR] in MAGIC OGTT data, available in up to 5,318 individuals) at genome-wide significance, plus 16 SNPs from the fasting glucose, fasting insulin, or T2D GRSs that had nominally significant associations with the CIR in the same data (9,12). For the insulin sensitivity GRS, we used 2 SNPs associated with insulin sensitivity (as measured by the Stumvoll Insulin Sensitivity Index applied to OGTT data) in a recent MAGIC GWAS and 12 SNPs from the fasting glucose, fasting insulin, or T2D GRSs that had nominally significant associations with the Matsuda index in MAGIC OGTT data (12,13).

Effect alleles were defined as fasting glucose–raising, fasting insulin–raising, insulin secretion–lowering, or insulin sensitivity–lowering alleles. A SNP score for each locus was calculated for each subject by multiplying the number of risk alleles carried (0, 1, or 2) by the effect size (β) for each variant's association with the relevant trait/disease in MAGIC data (available for fasting glucose, fasting insulin, and Matsuda index) or DIAGRAM data (T2D) (8,9,12). For insulin secretion, effect sizes for each SNP and CIR were used, as there were no summary statistics available for the Stumvoll first-phase estimate (12). The SNP scores for the SNPs in each trait GRS were summed to obtain the subject's GRS for each trait. All GRSs were rescaled such that the highest possible score was equal to two times the number of SNPs included to give a more interpretable score "per risk allele" after weighing each allele's effect size; for example, the possible score range for the T2D GRS was 0 to 170.

We conducted a sensitivity analysis using unweighted GRSs (assigning one point for each fasting glucose– or fasting insulin–raising, insulin secretion– or insulin sensitivity–lowering, or T2D risk–increasing allele carried, without weighting), as assumptions about relative effect sizes derived in studies of nonpregnant individuals may not apply to pregnant women.

Subjects who had greater than 10% missing SNPs for a given GRS were not assigned a score. Subjects with equal to or less than 10% missing alleles received a GRS adjusted for the number of missing SNPs, such that the highest possible score for each person was equivalent to the highest possible score for an individual without missing SNPs.

Statistical Analysis

We used *t* tests (for continuous variables) and χ^2 tests (for categorical variables) to compare the characteristics of women with and without GDM in each cohort. We used linear regression to test for associations between GRSs and corresponding glycemic traits at 24–32 weeks' gestation, with and without multivariate adjustment for BMI, maternal age, and gestational age at the time of the OGTT. The multivariate model with insulin secretion (Stumvoll first-phase estimate) as the response variable was also adjusted for insulin sensitivity (Matsuda index). We transformed the C-peptide levels and the HAPO insulin sensitivity index into *z*-scores prior to analysis to aid in comparisons between the two cohorts, given differing C-peptide assays and units of measurement. We natural log transformed fasting insulin, the Matsuda insulin sensitivity index, and the Stumvoll first-phase estimate in Gen3G to meet assumptions for parametric analyses.

We tested for associations between the glycemic trait and T2D GRSs and GDM using logistic regression, with and without multivariate adjustment for BMI, maternal age, and gestational age at the time of the OGTT.

Given our hypothesis-based approach, two-tailed *P* values < 0.05 were considered significant. Analyses were conducted using R 3.5.1.

RESULTS

Subject Characteristics

In both cohorts, women with GDM, as compared with women who maintained normal glucose tolerance, were older and had higher BMI, higher glucose levels, higher fasting insulin and/or C-peptide levels, and lower insulin sensitivity (Table 1). In Gen3G, women with GDM were less likely to be primigravid. In HAPO, women with GDM were more likely to have a family history of diabetes. Women studied in both cohorts were predominantly of European descent.

Associations Between Weighted Glycemic Trait GRSs and Late-Pregnancy Glycemic Traits

Table 2 shows the associations between each glycemic trait GRS and its respective glycemic trait in late pregnancy.

The fasting glucose GRS was strongly associated with fasting glucose in both cohorts and explained 7% of the variation in this trait ($P = 1.6 \times 10^{-10}$ in Gen3G, $P = 2.7 \times 10^{-23}$ in

Table 1—Characteristics of Gen3G and HAPO participants

	All	NGT	GDM
Gen3G cohort			
N	551	508	43
Age (years)*	28.2 ± 4.3	28.1 ± 4.1	30.0 ± 5.8
Primigravid*	189 (34.3)	178 (35.0)	11 (25.6)
European ethnicity	535 (97.1)	492 (96.9)	43 (100)
Family history of diabetes	107 (19.4)	95 (18.7)	12 (29)
Gestational age at OGTT (weeks)	26.4 ± 1.0	26.4 ± 1.0	26.2 ± 1.0
BMI at OGTT(kg/m^2)*	28.1 ± 5.4	27.9 ± 5.2	31.0 ± 7.0
Fasting glucose (mg/dL)*	75.6 ± 6.9	74.9 ± 5.7	84.5 ± 12.0
1-h Glucose (mg/dL)*	128.6 ± 28.8	124.6 ± 25.4	175.4 ± 25.9
2-h Glucose (mg/dL)*	104.7 ± 23.7	101.4 ± 20.2	143.6 ± 27.3
Fasting insulin (μU/mL)*	8.8 ± 8.0	8.5 ± 8.1	11.3 ± 6.8
Fasting C-peptide (pg/mL)*	970.3 ± 542.2	951.0 ± 535.1	1,197.7 ± 579.0
Insulin secretion (Stumvoll first-phase estimate)	1,190.8 ± 433.6	1,197.8 ± 430.0	1,107.5 ± 471.4
Matsuda insulin sensitivity index*	7.7 ± 5.3	9.1 ± 5.3	5.2 ± 2.8
HAPO insulin sensitivity index*	2.2 ± 0.5	2.3 ± 0.4	1.9 ± 0.4
HAPO cohort			
N	1,380	1,173	207
Age (years)*	31.3 ± 5.3	31.1 ± 5.3	32.6 ± 4.9
Primigravid	782 (56.8)	679 (57.9)	103 (50.5)
European ethnicity	1,380 (100)	1,173 (100)	207 (100)
Family history of diabetes*	229 (16.6)	176 (15)	53 (26)
Gestational age at OGTT (weeks)	28.5 ± 1.4	28.5 ± 1.4	28.4 ± 1.3
BMI at OGTT (kg/m^2)*	28.5 ± 4.8	28.0 ± 4.5	31.0 ± 5.8
Fasting glucose (mg/dL)*	82.1 ± 6.7	80.5 ± 5.3	91.1 ± 6.8
1-h Glucose (mg/dL)*	132.0 ± 29.5	125.9 ± 24.6	166.4 ± 31.4
2-h Glucose (mg/dL)*	109.3 ± 21.7	105.3 ± 18.4	131.6 ± 25.5
Fasting C-peptide (μg/L)*	1.98 ± 0.81	1.85 ± 7.0	2.70 ± 1.0
HAPO insulin sensitivity index*	3.7 ± 1.5	3.9 ± 1.5	2.5 ± 0.9

Data are mean ± SD or *n* (%), unless stated otherwise. OGTT was performed between 24 and 32 weeks' gestation. HAPO: *N* = 1,376 for subjects with information on gravidity, *N* = 1,364 for subjects with HAPO insulin sensitivity index results. NGT, normal glucose tolerance. *Significantly different between NGT and GDM ($P < 0.05$).

HAPO), with each unit increase in the GRS raising fasting glucose by approximately 0.4 mg/dL. This association persisted after multivariate adjustment. The fasting insulin GRS associated with increased fasting insulin in Gen3G, but this was not significant after adjustment for covariates, including maternal BMI ($P = 0.12$). The fasting insulin GRS was not associated with fasting C-peptide *z*-score in Gen3G but was associated with fasting C-peptide *z*-score in HAPO after multivariate adjustment ($P = 0.01$).

In the Gen3G cohort, the insulin secretion GRS was associated with reduced insulin secretion, explaining 1.3% of the variation in this trait in univariate analysis ($P = 0.007$). The relationship between the insulin secretion GRS and the Stumvoll first-phase estimate strengthened after multivariate adjustment, including for insulin sensitivity ($P = 3.8 \times 10^{-7}$). The insulin sensitivity GRS was associated with reduced insulin sensitivity in Gen3G as measured by the Matsuda index, explaining 0.6% of the variation in this trait in univariate analysis ($P = 0.04$). The relationship between the GRS and the Matsuda index strengthened after multivariate adjustment ($P = 0.009$). There was no significant association between the insulin sensitivity GRS and the HAPO (C-peptide–based) insulin sensitivity index in either cohort ($P = 0.22$ and $P = 0.40$ in Gen3G and HAPO, respectively).

Associations Between Trait GRSs and GDM

The T2D GRS was associated with GDM in both cohorts (Gen3G: adjusted odds ratio [OR] [95% CI] 1.06 [1.01, 1.10], HAPO: 1.03 [1.01, 1.06]) (Fig. 1 and Supplementary Table 6).

In HAPO, the fasting glucose, fasting insulin, insulin secretion, and insulin sensitivity GRSs were all associated with GDM independent of maternal age, BMI, and gestational age at the time of the OGTT, with a 1-unit increase in each score raising the odds of GDM by 6%–14% (Fig. 1 and Supplementary Table 6). In Gen3G, the insulin secretion GRS was associated with GDM (OR [95% CI] 1.14 [1.02, 1.26], $P = 0.02$ in multivariate model) (Fig. 1). We did not observe significant associations between the other glycemic trait GRSs and GDM in Gen3G, but the OR estimates were similar to those in HAPO.

Sensitivity Analyses

The associations between unweighted GRSs and their respective traits in pregnancy and GDM were similar or slightly weaker than associations with the weighted GRSs described above (Supplementary Tables 7 and 8).

DISCUSSION

Here, we demonstrate that physiologically based sets of genetic variants known to be associated with fasting glucose,

Table 2—Associations of glycemic trait GRSs with their respective traits in pregnancy

GRS	SNPs (*N*)	Trait	Univariate			Multivariate	
			β (95% CI)	*P*	r^2	β (95% CI)	*P*
Gen3G cohort							
Fasting glucose	38	Fasting glucose (mg/dL)	0.42 (0.30, 0.55)	1.6×10^{-10}	7.0%	0.39 (0.27, 0.51)	3.0×10^{-10}
Fasting insulin	18	Fasting insulin (μU/mL)	0.02 (0.002, 0.04)	0.03	0.6%	0.01 (−0.003, 0.03)	0.12
Fasting insulin	18	Fasting C-peptide z-score	0.02 (−0.01, 0.05)	0.24	0.07%	0.008 (−0.02, 0.04)	0.60
Insulin secretion	24	Stumvoll first-phase estimate	−0.01 (−0.02, −0.003)	0.007	1.3%	−0.02 (−0.02, −0.009)	3.8×10^{-7}
Insulin sensitivity	14	Matsuda index	−0.02 (−0.04, −0.0007)	0.04	0.6%	−0.03 (−0.04, −0.006)	0.009
Insulin sensitivity	14	HAPO insulin sensitivity index z-score	−0.02 (−0.06, 0.01)	0.22	0.01%	−0.03 (−0.06, 0.008)	0.13
HAPO cohort							
Fasting glucose	38	Fasting glucose (mg/dL)	0.43 (0.35, 0.52)	2.7×10^{-23}	7.0%	0.42 (0.06, 0.18)	5.2×10^{-25}
Fasting insulin	18	Fasting C-peptide z-score	0.01 (−0.006, 0.04)	0.16	0.1%	0.02 (0.005, 0.038)	0.01
Insulin sensitivity	14	HAPO insulin sensitivity index z-score	−0.01 (−0.04, 0.01)	0.40	0.05%	−0.02 (−0.04, 0.005)	0.14

Multivariate models included age, BMI, and gestational age as covariates. The model with the Stumvoll first-phase estimate as the response variable also includes insulin sensitivity (Matsuda index) as a covariate.

insulin secretion, and insulin sensitivity in the general population influence glycemic traits in pregnancy. Fasting glucose–raising, fasting insulin–raising, insulin secretion–reducing, and insulin sensitivity–reducing genetic risk alleles, assessed in aggregated scores, are associated with higher GDM risk. Our work suggests that the genetic architecture of glycemic traits in pregnancy is, to some extent, shared with the genetic architecture of these traits outside pregnancy, despite the profound changes that occur in glycemic physiology during gestation.

In a previous GWAS that included HAPO and Gen3G participants from this analysis, among others, we searched for genetic loci associated with fasting glucose and other glycemic traits in pregnancy, identifying five loci known to be associated with glycemic traits in the general population and two novel variants with associations limited to pregnancy (15). In this previous study, we found that SNPs at or near *GCKR*, *G6PC2*, *PCSK1, PPP1R3B*, and *MTNR1B* (all included in the fasting glucose GRS in the current study) were associated with fasting glucose at genome-wide significance. The present work extends these findings, suggesting that fasting glucose–associated genetic variants identified in the general population, in aggregate, are a strong determinate of fasting glucose in pregnancy. Based on published reports, our fasting glucose GRS had a similar effect on fasting glucose in pregnancy to that reported outside of pregnancy, though we did not have data to directly compare the effect sizes in and outside of pregnancy in the same women (27,28).

Despite including SNPs at loci identified as associated with fasting C-peptide in pregnancy in our prior study (*PPP1R3B* and *GCKR*) (15) plus 16 other loci associated with fasting insulin in the general population, the fasting insulin GRS was weakly associated with fasting C-peptide after multivariate analysis in HAPO only; the fasting insulin GRS explained only 0.1% of the variation in fasting C-peptide in HAPO in univariate analysis. The weak association between the fasting insulin GRS and fasting insulin in Gen3G was no longer statistically significant after multivariate adjustment. Thus, there may be genetic and nongenetic determinants of fasting insulin/C-peptide that are unique to pregnancy. Consistent with this, our previous investigation identified a SNP at the *BACE2* locus as associated with fasting C-peptide levels specifically in pregnancy.

GRSs for insulin sensitivity and insulin secretion were also significantly associated with these traits in Gen3G, where insulin measurements were available. Although both insulin sensitivity and secretion are known to change markedly over the course of gestation, our work suggests that the genetic determinates of these traits in nonpregnant individuals continue to influence glycemic physiology in pregnancy. Additional research is needed to determine whether there are genetic variants that have a specific effect on the dramatic pregnancy-associated longitudinal changes in glycemic physiology.

The observed significant associations between T2D-associated variants and GDM risk are consistent with

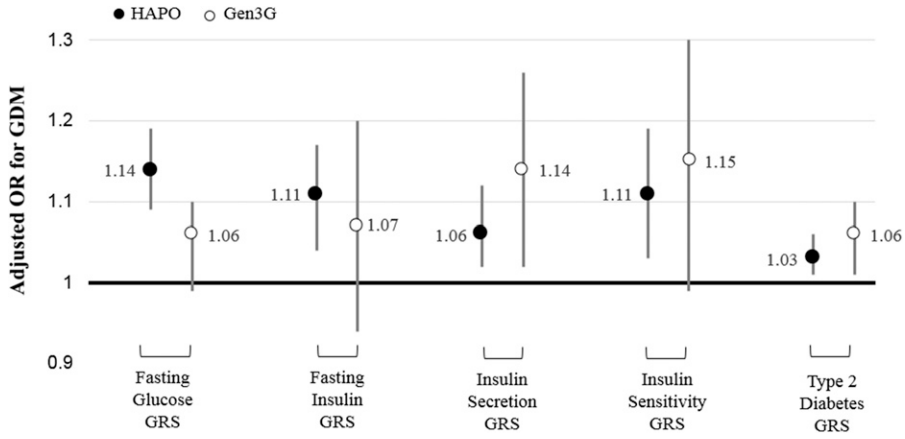

Figure 1—Association between glycemic trait GRSs and GDM. The graph depicts the increase in odds per 1-unit increase in GRS (circles), with the 95% CI for the increase in odds (bars). A 1-unit increase in the GRS is equal to one additional risk allele carried when that risk allele has an average effect on the glycemic trait of interest in nonpregnant individuals. A 1-unit increase in the T2D GRS increased the odds of GDM in both Gen3G and HAPO by 3%–6%. A 1-unit increase in the GRS for each glycemic trait significantly increased the odds of GDM by 6%–14% in HAPO.

results from prior studies. A study conducted in women with a history of GDM used both an unbiased (GWAS) and hypothesis-based approach and found that many T2D-associated alleles were associated with GDM (16). Previous investigations, as reviewed by Lowe et al. (14), have examined the associations of some individual known T2D-associated variants with GDM risk, with positive findings (including SNPs at loci included in the current study: *CDKAL1, IGF2BP2, TCF7L2, KCNQ1, MTNR1B*) (29,30). Finally, two previous studies used GRSs to test whether T2D susceptibility alleles were also associated with GDM, finding an effect consistent with that observed here (17,18). Of note, some previously conducted studies used case populations with a history of GDM and control populations free of glucose intolerance outside of pregnancy but without known pregnancy history, potentially biasing the results (16,18). Despite these potential biases, our results support the conclusions of this prior research.

Although previous studies have examined individual genetic variants known to be associated with glycemic traits outside of pregnancy, we are the first, to our knowledge, to demonstrate associations between GDM and physiologically based groups of genetic variants that determine fasting glucose, fasting insulin, insulin secretion, and insulin sensitivity. Our observations lend support to the hypothesis that at least a proportion of the risk for GDM is conferred by chronic defects in insulin secretion or sensitivity that manifest during gestation. Despite prior suggestions that women with GDM primarily have genetic defects in insulin secretion, our data suggest that genetic predisposition to GDM also involves genetic defects in insulin sensitivity.

Strengths of the current study include the use of all known glycemic trait–associated variants in each score, the glycemic physiology profiling in each pregnancy, and the use of contemporaneous control subjects with objective glycemic measurements during gestation. Limitations include the lack of insulin measurements in the HAPO participants and the small sample size in comparison with studies designed to examine common genetic variation in nonpregnant individuals; this limited the power to demonstrate associations of small magnitude, particularly in Gen3G. The design of the HAPO study may have led to the exclusion of women with severe GDM, further decreasing power; even so, we were able to detect significant associations between each of our GRSs and GDM in this cohort. Finally, data were not available to derive weights specific for the Stumvoll first-phase estimate in the insulin secretion GRS; however, like the Stumvoll estimate, CIR is a measure of early insulin response to a glucose load and both are highly correlated with gold standard measures (22,31,32).

In conclusion, our results show that genetic determinants of fasting glucose, insulin secretion, and insulin sensitivity in the general population affect these traits in pregnancy; in particular, fasting glucose appears to have largely shared genetic architecture between the pregnant and nonpregnant state. Further, women who carry fasting glucose–raising, fasting insulin–raising, insulin secretion–reducing, or insulin sensitivity–reducing alleles are at higher risk for GDM. Clinically, precision approaches based on common genetic variation, currently being considered for prevention and treatment of T2D, may also apply to hyperglycemia in pregnancy.

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