Ancestry-Matched and Cross-Ancestry Genetic Risk Scores of Type 2 Diabetes in Pregnant Women and Fetal Growth: A Study in an Ancestrally Diverse Cohort

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Maternal genetic variants associated with offspring birth weight and adult type 2 diabetes (T2D) risk loci show some overlap. Whether T2D genetic risk influences longitudinal fetal weight and the gestational timing when these relationships begin is unknown. We investigated the associations of T2D genetic risk scores (GRS) with longitudinal fetal weight and birth weight among 1,513 pregnant women from four ancestral groups. Women had up to five ultrasonography examinations. Ancestry-matched GRS were constructed separately using 380 European- (GRS*eur*), 104 African- (GRS*afr*), and 189 East Asian- (GRS*eas*) related T2D loci discovered in different population groups. Among European Americans, the highest quartile GRS*eur* was significantly associated with 53.8 g higher fetal weight (95% CI 19.2–88.5) over the pregnancy. The associations began at gestational week 24 and continued through week 40, with a 106.8 g (95% CI 6.5–207.1) increase in birth weight. The findings were similar in analysis further adjusted for maternal glucose challenge test results. No consistent association was found using ancestry-matched or cross-ancestry GRS in non-Europeans. In conclusion, T2D genetic susceptibility may influence fetal growth starting at midsecond trimester among Europeans. Absence of similar associations in non-Europeans urges the need for further genetic T2D studies in diverse ancestries.

Abnormal fetal growth is associated with an increased risk of childhood morbidity and adult cardiometabolic diseases, including type 2 diabetes (T2D) (1–3). Complex interactions of maternal and fetal genetic and environmental factors contribute to fetal growth variations (4). Associations between T2D risk alleles and birth weight could vary depending on whether the maternal T2D risk allele is or is not transmitted to the fetus (5,6). Recent estimates show that maternal genotypes account for 7.6–11.1% of variations in birth weight (7,8). Genome-wide association studies (GWAS) found several overlaps between genetic variants on the maternal genome associated with higher offspring birth weight and known T2D susceptibility loci such as *MTNR1B*, *GCK*, *TCF7L2*, *ADCY5*, and *CDKAL1* (7,8). However, whether T2D genetic risk influences longitudinal fetal weight trajectories and, if so, the gestational timing when these relationships begin, is unknown. Further, such data in diverse ancestral populations are lacking. Addressing this research question will help us achieve a better understanding on the etiology of aberrant fetal growth.

T2D risk alleles in the maternal genome may affect fetal growth indirectly by altering maternal glycemia during pregnancy (9) and thereby influencing fetal insulin secretion, or directly by sharing the genetic variant to the offspring (8,10). In previous studies among European ancestry populations, maternal genetic variants at T2D risk loci have been associated with higher offspring birth weight (7,11). Another study that aggregated the known T2D risk variants among African ancestry populations into a genetic risk score (GRS) found that higher maternal T2D-related GRS is associated with increased birth weight (10). Genetic associations on birth weight may not be directly transferable to fetal weight because the genetic contribution to fetal growth varies during gestation (4), with gestation time-specific effect (12).

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Genetic effects may also vary by ancestry (13,14). Moreover, GRS constructed using genetic variants associated with T2D in GWAS conducted in European populations has limited validity in non-European populations due to differences in variant distributions and genetic structure (15). Therefore, an investigation of maternal genetic contribution to fetal growth generalizable to diverse populations warrants GRS constructed from genetic variants validated in the respective ancestral population, longitudinal fetal growth measures, and multiancestral cohorts. To date, the role of maternal genetic predisposition to T2D on longitudinal fetal weight among ancestrally diverse populations has not been studied.

In this study, we used a cohort of pregnant women from four ancestral populations in the U.S. to investigate the association between maternal genetic predisposition to T2D and fetal weight. For each ancestral population, we examined these associations using a GRS constructed from T2D risk variants identified by GWAS involving a population group with matching ancestry (ancestry-matched GRS). We also evaluated associations in each ancestral population using GRS constructed from T2D risk variants identified by GWAS involving a different population group (cross-ancestry GRS).

RESEARCH DESIGN AND METHODS

Study Population

Women with low-risk status were enrolled in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies–Singleton cohort from July 2009 to January 2013 at 12 clinic sites in the U.S. as previously reported (16). To ensure low-risk for adverse pregnancy outcomes, women with chronic diseases, previous pregnancy complications, or self-reported use of cigarettes, illicit drugs, or alcohol during the months before enrollment were not included in the study (16). Briefly, women from four self-identified racial/ethnic groups (i.e., White, hereafter referred to as European American, Hispanic [Hispanic American], Black [African American], East Asian [East Asian American]) were recruited between 8 weeks 0 days and 13 weeks 6 days of pregnancy and followed along the pregnancy.

DNA Extraction, Genotyping, and Genotype-Based Principal Components

DNA was extracted from stored blood samples collected during study visits. Genotyping was performed using the Infinium Multi-Ethnic Global BeadChip array (Illumina) that has >1.7 million single-nucleotide polymorphisms (SNPs). Genotypes were imputed with the Michigan Imputation Server implementing Eagle2 for haplotype phasing, followed by Minimac2 for imputing nontyped SNPs with 1000 Genomes Phase 3 reference sequence data. Individuals whose ancestry was an outlier from the distribution of the Hispanic, African, European, and East Asian clusters of the 1000 Genomes reference population were removed. Details of the quality control process have previously been described (12). Genotype data were used to estimate genotype-based principal components (PCs) representing population structure (17).

GRS Construction

GRS construction was based on previous GWAS that reported T2D risk variants. The causal variants tagged by a GWAS variant involving one ancestral population may be on a different block of haplotype (segment of correlated genetic markers) in other populations (18). Therefore, we constructed three ancestry-specific GRS related to T2D, GRS*eur* using 380 SNPs from GWAS of T2D in European populations (19), GRS*afr* using 104 SNPs from GWAS of T2D in African American populations (20), and GRS*eas* using 189 SNPs from GWAS of T2D in East Asian populations (Supplementary Tables 1, 2, and 3, respectively). Weighted GRS were calculated by multiplying the dosage of the T2D-increasing allele for each SNP (range 0–2) by its published effect estimate (19–21), followed by summing the resulting values.

Fetal Growth Parameters

After the first ultrasonography to confirm gestational age with self-reported last menstrual period, participants were randomized to one of four schedules for five ultrasonography appointments (22). All of the women included in this study had at least two ultrasound measurements with estimation of fetal growth. This randomization scheme was designed to capture gestational weeks 16 to 40 without having to expose women to weekly ultrasonography. Measurement of fetal growth was performed using standardized obstetrical ultrasonography protocols and identical equipment (Voluson E8; GE Healthcare). All dedicated sonographers underwent an intensive training and evaluation period (23). The quality control showed that measurements between site sonographers and experts had high correlation (>0.99) and a low coefficient of variation (<3%) (24).

Outcomes

For each ultrasound, fetal weight was estimated from head circumference, abdominal circumference, and femur length using the Hadlock formula (25). The creation of the fetal growth curve has been previously described (22). Briefly, ultrasound measurement of fetal growth was used to compute race/ethnic-specific fetal growth curves with weekly estimation using linear mixed models with cubic spline mean structures and a cubic polynomial random effect. Three knot points were chosen based on the Akaike information criterion and fixed at 25th, 50th, and 75th percentiles to evenly distributed gestation weeks, and percentiles were estimated considering normal distribution of the random effects and error structure, ultimately estimating the growth curves (22). The same models were used to obtain ancestry-specific weekly

estimation of fetal growth from gestational week 13 to 40 for all enrolled women. Birth weight was measured using an electronic infant scale or beam balance scale. Birth weight was recorded in grams (g).

Glucose Tolerance Results

Women with gestational diabetes mellitus (GDM), impaired glucose tolerance (IGT), and normal glucose tolerance (NGT) were identified using the medical record review (26). GDM was defined by the oral glucose tolerance test results based on the Carpenter-Coustan criteria (27) (at least two values met or exceeded 95 mg/dL at fasting, 180 mg/dL at 1 h, 155 mg/dL at 2 h, 140 mg/dL at 3 h), or by receipt of GDM medications. IGT was defined as having a plasma glucose concentration 2 h after oral glucose tolerance test between 140 mg/dL and 199 mg/dL, but not meeting the criteria for GDM (27). NGT was defined as women without GDM, without IGT, and with all glucose tolerance test values <140 mg/L.

Statistical Analyses

Analyses were stratified by maternal ancestry group (i.e., European, Hispanic, African, and East Asian American) to avoid spurious associations or distortions in effect estimates between genetic susceptibility and fetal growth because of allele frequency differences between ancestry groups (28). Post hoc statistical power was calculated using the G*Power 3 program with $\alpha = 0.05$, eight predictors, and an effect size f^2 of 0.04 (29). Power ranged from 80.7% for East Asian Americans (smallest sample size, n = 202), to 98.9% for European Americans (largest sample size, n = 471).

We considered GRS as categorical quartiles because, as in Rahman et al. (10), the relationship between GRS of T2D and birth weight examined using penalized cubic splines (adjusted for maternal prepregnancy BMI, five first genotype PCs, and fetal sex and gestational age at delivery) was nonlinear. Linear regressions were used to test the association between GRS quartiles 2, 3, and 4 compared with quartile 1 and weekly fetal growth and birth weight, adjusted for maternal prepregnancy BMI, five first genotype PCs, and fetal sex; association between GRS and birth weight was further adjusted for gestational age at delivery. Given the number of comparisons in weekly fetal growth analysis, we implemented the Benjamini and Yekutieli false discovery rate correction for multiple testing (30). Longitudinal linear mixed models were used to estimate the association between GRS and longitudinal fetal weight adjusted for maternal prepregnancy BMI, five first genotype PCs, fetal sex, and gestational age on the ultrasonogram coded using linear and quadratic terms and random effect corresponding to the mother-child pair. We calculated the linear trend over increasing mean GRS quartiles (i.e., the mean of the GRS quartile was assigned to all women from the quartile) adjusted for the abovementioned covariates and reported the *P* value of trend (*P*-trend).

For each ancestry group, we examined ancestry-matched GRS and cross-ancestry GRS. Specifically, ancestry-matched GRS included GRS*eur* among European Americans, GRS*afr* among African Americans, and GRS*eas* among East Asian Americans. Cross-ancestry GRS included GRS*afr* and GRS*eas* among European Americans, GRS*afr*, GRS*eur*, and GRS*eas* among Hispanic Americans, GRS*eur* and GRS*eas* among African Americans, and GRS*eur* and GRS*afr* among East Asian Americans.

We performed two ancestry-matched GRS sensitivity analyses *1*) further adjusting for the value of the glucose challenge test and *2*) restricting to women with NGT (all glucose tolerance tests <140 mg/L). This was done by excluding women with IGT, women with GDM, and women who had any elevated values (>140 mg/dL) in the oral glucose tolerance test or glucose challenge test but did not meet the criteria for GDM or IGT, resulting in the exclusion of 165 women.

Finally, we assessed the additional variance in fetal weight and birth weight explained by GRS by calculating the differences in adjusted coefficient of determination (adjusted R^2) between the regression model that included GRS as well as covariates and the model that included covariates only. The covariates considered were maternal prepregnancy BMI, first five PCs, fetal sex, and gestational age on the ultrasonogram or at birth.

Data and Resource Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. No applicable resources were generated or analyzed during the current study.

RESULTS

Analyses were performed among 471 European Americans, 418 Hispanic Americans, 422 African Americans, and 202 East Asian Americans. The average fetal weight was highest among European Americans throughout pregnancy and lowest among East Asian Americans until late in pregnancy when the mean fetal weight became lowest among African Americans ($P < 0.001$). Mean birth weight ranged from 3,189 (SD 535) g among African Americans to 3,418 (SD 489) g among European Americans ($P = 9.8 \times 10^{-12}$) (Table 1). The distribution of GRS differed between ancestry groups, with the exception that mean (SD) GRS*eur* was similar between European Americans (22.79 [0.68]) and Hispanic Americans (22.76 [0.66]) (Supplementary Fig. 1). Similarly, the minor allele frequency distribution of the individuals SNPs used to construct the GRS varied between ancestry groups (Supplementary Fig. 2).

Ancestry-Matched GRS

Among European Americans, the highest quartile GRS*eur* was associated with 53.8-g higher longitudinal fetal weight (95% CI 19.2, 88.5; *P*-trend = 0.01) compared with the lowest quartile GRS*eur* (Fig. 1). The findings were unchanged when the analysis was adjusted for glucose tolerance results

Table 1—Description of the study population (1,513 pregnant women from the NICHD Fetal Growth Studies–Singleton cohort)

	European American *n* = 471	Hispanic American *n* = 418	African American *n* = 422	East Asian American *n* = 202	*P* value*
Age, years	30.6 (4.3)	27.0 (5.6)	25.3 (5.3)	31.0 (4.5)	2.8×10^{-66}
Prepregnancy BMI, kg/m^2	23.3 (3.1)	24.3 (3.1)	24.2 (3.4)	22.2 (2.6)	5.5×10^{-17}
NGT, *n* (%)	430 (91.3)	374 (89.5)	382 (90.5)	162 (80.2)	1.9×10^{-4}
Gestational age at delivery, weeks	39.2 (1.6)	39.4 (1.9)	39.0 (2.0)	39.3 (1.2)	0.126
Term birth (≥37 weeks), *n* (%)	442 (93.8)	398 (95.2)	385 (91.2)	194 (96.5)	0.032
Infant male sex, *n* (%)	233 (55)	169 (51)	137 (50)	52 (54)	0.297
Estimated fetal weight, g					
At 13 weeks	70.3 (6.0)	69.2 (6.5)	70.0 (6.2)	68.4 (6.9)	0.001
At 20 weeks	335.1 (29.6)	326.8 (32.4)	327.8 (30.8)	322.0 (33.2)	1.1×10^{-06}
At 28 weeks	1,202.5 (113.3)	1,158.8 (124.5)	1,148.4 (116.2)	1,138.1 (121.2)	4.3×10^{-14}
At 40 weeks	3,769.1 (452.6)	3,567.8 (476.1)	3,452.9 (419.2)	3,496.1 (442.0)	1.0×10^{-25}
Birth weight, g	3,417.7 (488.8)	3,340.3 (521.8)	3,189.4 (534.9)	3,341.5 (443.6)	9.8×10^{-12}
Ancestry-matched GRS	GRS*eur*		GRS*afr*	GRS*eas*	
First quartile	21.95 (0.34)	NA	16.52 (0.70)	12.13 (0.41)	NA
Second quartile	22.61 (0.12)	NA	18.04 (0.27)	12.29 (0.51)	NA
Third quartile	23.04 (0.12)	NA	18.91 (0.28)	12.57 (0.50)	NA
Fourth quartile	23.68 (0.68)	NA	20.24 (0.68)	12.90 (0.49)	NA

Data are presented as mean (SD) unless indicated as *n* (%). NA, not applicable. *P value derived from ANOVA or χ^2 test comparing four groups.

(Supplementary Fig. 3) and among women with NGT (Supplementary Fig. 4). Analysis at each gestational week from 24 to 40 weeks showed that the highest quartile GRS*eur* was associated with higher fetal weight beginning at week 24 (an increase in fetal weight of 15.8 g [95% CI 0.1, 31.4] at week 24 to 196.0 g [95% CI 80.7, 311.4] at week 40, among women with the highest GRS*eur* compared with women with the lowest GRS*eur*) (Fig. 2). The findings were similar in a sensitivity analysis except that associations were significant beginning at week 22 when analysis was

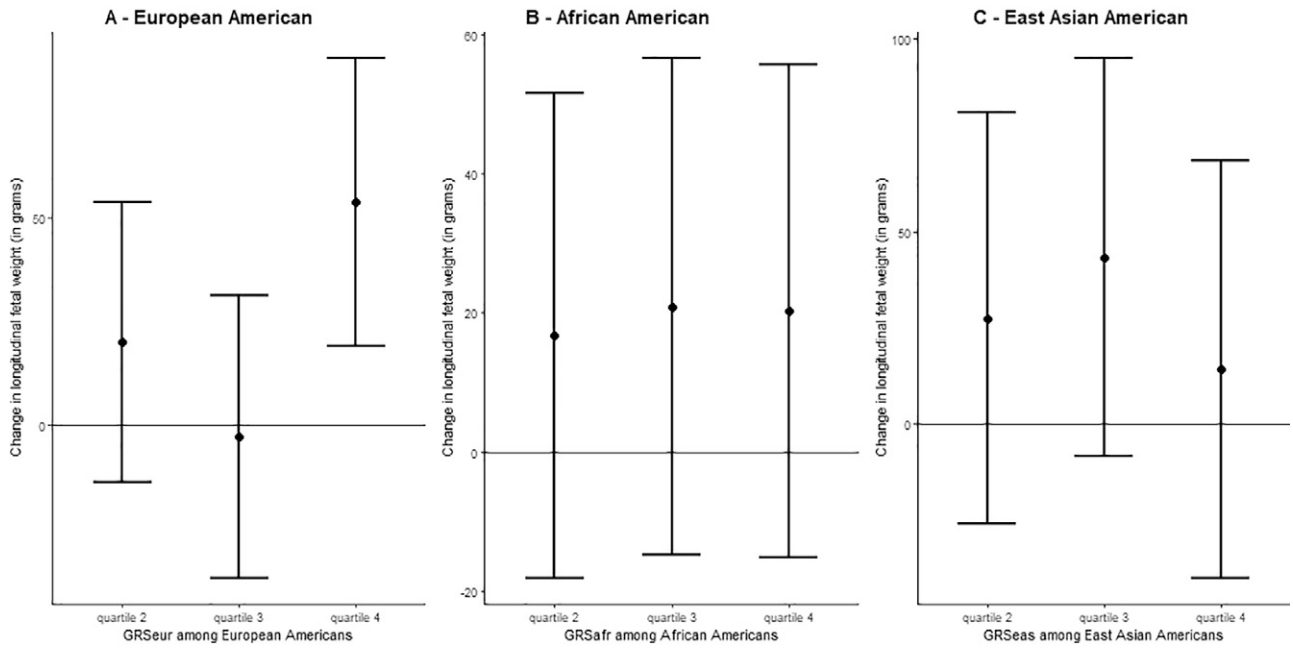

Figure 1—Changes in longitudinal fetal weight (in grams) for quartile increase in ancestry-matched GRS-related T2D (*N* = 1,513 from the NICHD Fetal Growth Studies–Singleton cohort). Adjusted for prepregnancy BMI, offspring sex, gestational age at measurements, and for the first five genetic PCs. Dots indicate the estimates, vertical lines indicate the 95% CIs, and horizontal lines indicate the null.

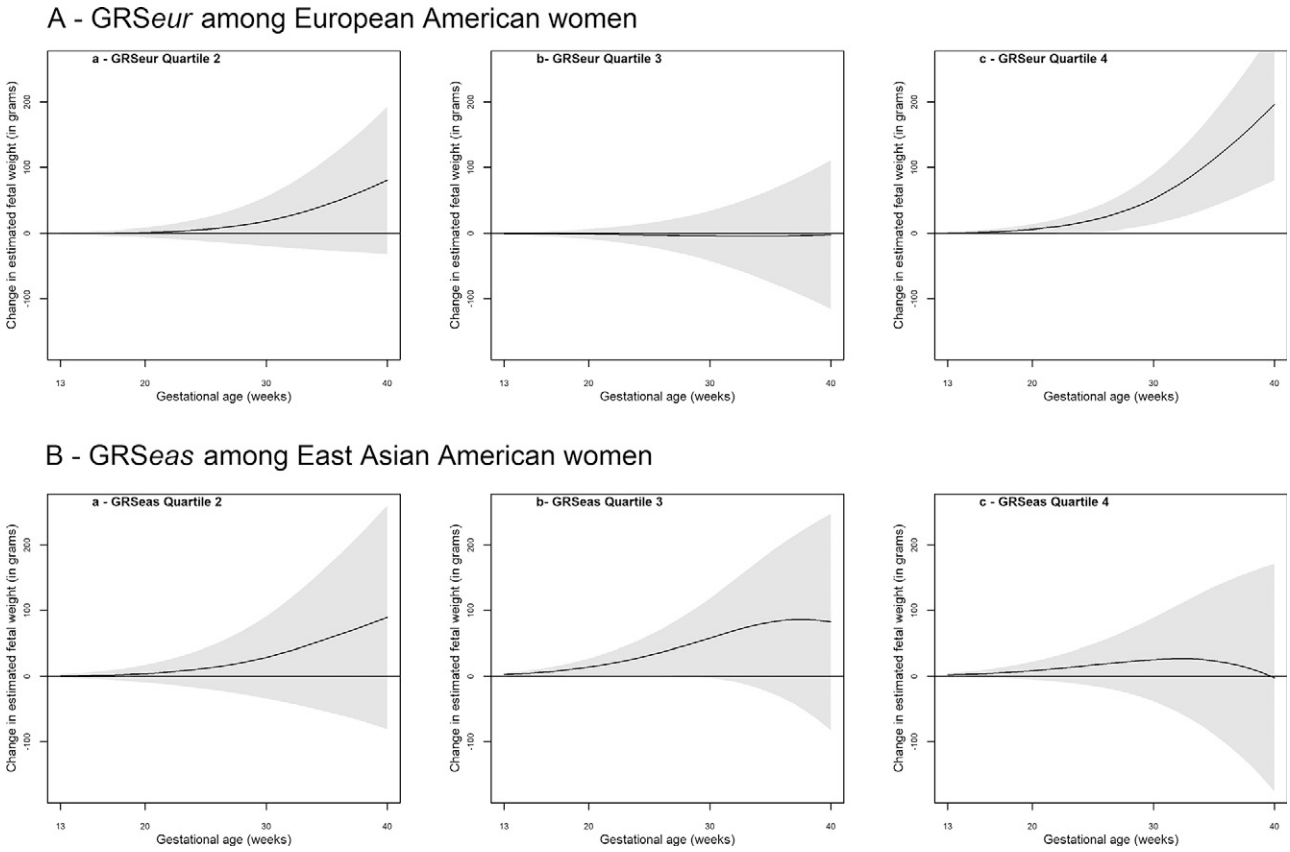

Figure 2—Weekly change in estimated fetal weight (in grams) for quartile increase in GRS*eur*-related T2D among European American women (*A*), and GRS*eas*-related T2D among East Asian American women (*B*) (*N* = 1,513 from the NICHD Fetal Growth Studies–Singleton cohort). Adjusted for maternal age, prepregnancy BMI, offspring sex, and for the first five genetic PCs. Black curved lines indicate the estimates, gray zones indicate the 95% CIs, and the horizontal lines indicate the null.

further adjusted for glucose tolerance test results and was significant beginning at week 27 among women with NGT (Table 2). At birth, the highest quartile GRS*eur* was associated with 106.8-g higher birth weight (95% CI 6.5, 207.1; *P*-trend = 0.11) (Fig. 3).

Among other ancestry groups, ancestry-matched GRS (i.e., GRS*afr* among African Americans and GRS*eas* among East Asian Americans) were not associated with longitudinal fetal weight (Fig. 1) or birth weight in the main analysis (Fig. 3) and sensitivity analysis (Supplementary Figs. 3 and 4). In the weekly analysis, GRS*afr* among African Americans was not associated with weekly estimated fetal weight (Supplementary Table 4). The third quartile GRS*eas* among East Asian Americans was associated with higher fetal weight from 13 to 28 weeks (an increase in fetal weight of 2.9 g [95% CI 0.2, 5.6] at week 13 to 46.8 g [95% CI 0.46, 93.2] at week 40) compared with women with the lowest GRS*eas*, but the highest quartile GRS*eas* was not associated with fetal weight (Fig. 2 and Supplementary Table 5).

Cross-Ancestry GRS

Among European Americans, the highest quartile GRS*afr* was associated with 38.4-g higher longitudinal fetal weight (95% CI 3.7, 73.1 g; *P*-trend = 0.07) compared with the lowest quartile GRS*afr* (Supplementary Fig. 5). The third quartile GRS*eas* was associated with 53.9-g higher longitudinal fetal weight (95% CI 19.5, 88.3; *P*-trend = 0.01) and 117.8-g higher birth weight (95% CI 17.8, 217.8; *P*-trend = 0.09) compared with the lowest quartile GRS*eas* (Supplementary Fig. 6).

Among African Americans, the second quartile GRS*eas* was associated with 37.0-g lower longitudinal fetal weight (95% CI −72.32, −1.59; *P*-trend = 0.22) compared with the lowest quartile GRS*eas*. The second quartile GRS*eur* was associated with 36.3-g higher longitudinal fetal weight (95% CI 0.86, 71.7; *P*-trend = 0.61) compared with the lowest quartile GRS*eur*. The second and third quartiles of GRS*eur* were associated with 108.9-g (95% CI 7.5, 210.3) and 131.7-g (95% CI 29.4, 233.9) higher birth weight, respectively (*P*-trend = 0.34).

All of the cross-ancestry GRS associations had lower precision as observed from the wide CIs. Other cross-ancestry GRS (i.e., GRS*eur*, GRS*afr*, and GRS*eas* among Hispanic Americans and GRS*eur* and GRS*afr* among East Asian Americans) were not associated with longitudinal fetal weight and birth weight.

Table 2—Weekly estimated fetal weight change (in grams) associated with the highest quartile of GRS*eur* compared with the lowest quartile among European American women

	Among European American women (n = 471)			Among European American women further adjusted for glucose challenge test results (n = 471)			Among European American women with NGT (n = 430)		
Gestational week	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
13	0.55	−1.02, 2.11	0.491	0.90	−0.76, 2.56	0.286	0.47	−1.17, 2.10	0.575
14	0.81	−1.18, 2.79	0.425	1.25	−0.86, 3.35	0.245	0.69	−1.38, 2.76	0.510
15	1.17	−1.35, 3.69	0.363	1.72	− 0.95, 4.39	0.207	1.01	−1.61, 3.64	0.448
16	1.66	−1.53, 4.86	0.307	2.35	−1.04, 5.73	0.173	1.46	−1.87, 4.78	0.390
17	2.34	− 1.69, 6.36	0.255	3.18	− 1.09, 7.45	0.144	2.06	−2.14, 6.25	0.335
18	3.22	−1.82, 8.26	0.210	4.25	−1.08, 9.59	0.118	2.85	−2.39, 8.09	0.285
19	4.36	−1.88, 10.6	0.170	5.60	−1.00, 12.21	0.096	3.88	−2.6, 10.36	0.240
20	5.80	−1.83, 13.44	0.136	7.28	−0.80, 15.37	0.077	5.18	−2.75, 13.11	0.200
21	7.60	−1.66, 16.86	0.107	9.34	−0.46, 19.14	0.062	6.81	−2.81, 16.42	0.165
22	9.82	−1.31, 20.94	0.084	11.83	0.05, 23.61	0.049	8.81	−2.73, 20.36	0.134
23	12.51	−0.75, 25.77	0.064	14.82	0.78, 28.85	0.039	11.26	−2.49, 25.02	0.108
24	15.76	0.08, 31.44	0.049	18.37	1.76, 34.98	0.030	14.22	−2.05, 30.49	0.087
25	19.64	1.21, 38.07	0.037	22.56	3.03, 42.08	0.024	17.76	−1.36, 36.88	0.069
26	24.24	2.70, 45.78	0.027	27.47	4.64, 50.29	0.018	21.96	−0.39, 44.30	0.054
27	29.67	4.62, 54.71	0.020	33.19	6.64, 59.74	0.014	26.91	0.92, 52.91	0.042
28	36.03	7.02, 65.04	0.015	39.84	9.08, 70.60	0.011	32.74	2.62, 62.85	0.033
29	43.45	9.96, 76.95	0.011	47.52	12.00, 83.05	0.009	39.54	4.76, 74.32	0.026
30	52.03	13.52, 90.55	0.008	56.31	15.44, 97.18	0.007	47.41	7.40, 87.43	0.020
31	61.82	17.73, 105.91	0.006	66.25	19.44, 113.06	0.006	56.40	10.56, 102.25	0.016
32	72.83	22.62, 123.05	0.005	77.32	23.98, 130.66	0.005	66.53	14.27, 118.79	0.013
33	85.04	28.18, 141.90	0.003	89.47	29.04, 149.91	0.004	77.77	18.53, 137.01	0.010
34	98.34	34.36, 162.31	0.003	102.58	34.55, 170.62	0.003	90.03	23.31, 156.74	0.008
35	112.58	41.09, 184.06	0.002	116.48	40.41, 192.55	0.003	103.17	28.53, 177.81	0.007
36	127.68	48.30, 207.05	0.002	131.07	46.54, 215.59	0.002	117.13	34.14, 200.11	0.006
37	143.59	55.93, 231.26	0.001	146.29	52.87, 239.70	0.002	131.85	40.08, 223.62	0.005
38	160.29	63.91, 256.68	0.001	162.10	59.33, 264.87	0.002	147.32	46.29, 248.36	0.004
39	177.76	72.18, 283.35	0.001	178.49	65.84, 291.13	0.002	163.53	52.70, 274.36	0.004
40	196.03	80.70, 311.37	0.001	195.47	72.34, 318.59	0.002	180.50	59.27, 301.72	0.004

Data are for n = 471 from the NICHD Fetal Growth Studies–Singleton cohort. Adjusted for prepregnancy BMI, offspring sex, and for the first five genetic PCs. All results were not significant after Benjamini and Yekutieli correction.

Additional Variance Explained by GRS

Additional variance (change in adjusted R^2) in longitudinal fetal weight and birth weight explained by GRS was very small across all ancestry groups. The highest change in the adjusted R^2 was a 0.44% increase in variance of birth weight explained by GRS*eur* among European Americans (Supplementary Table 6).

DISCUSSION

In this study of maternal genetic predisposition to T2D and fetal growth, we observed that GRS of T2D derived from GWAS involving European ancestry populations was significantly and positively associated with fetal weight starting at week 24 and birth weight among European American women. Consistent associations were found among European American women with NGT. However, among women with non-European ancestry, GRS of T2D derived from ancestry-matched and cross-ancestry GWAS were not associated with fetal weight or birth weight.

Maternal genetic susceptibility to T2D can influence fetal growth via different mechanisms. The best described mechanism is increased maternal blood glucose, which crosses the placenta and stimulates secretion of fetal

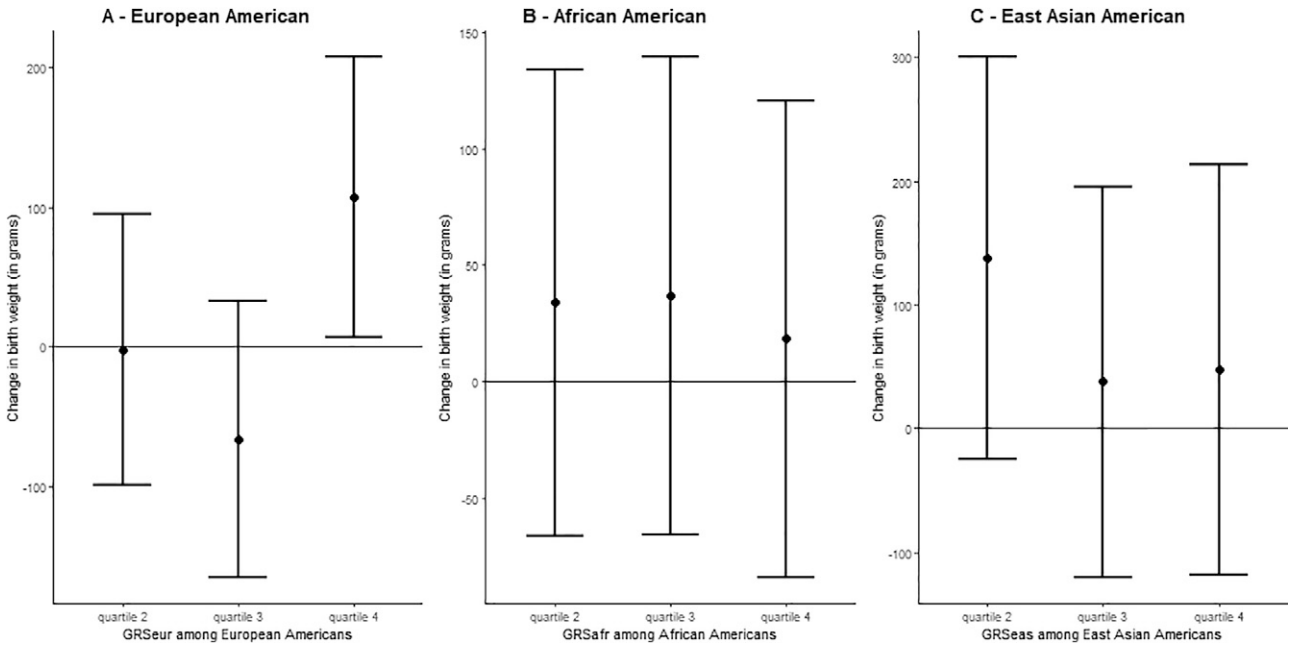

Figure 3—Change in birth weight (in grams) for quartile increase in ancestry-matched GRS-related T2D (*N* = 1,513 from the NICHD Fetal Growth Studies–Singleton cohort). Adjusted for maternal age, prepregnancy BMI, offspring sex, gestational age at delivery, and for the first five genetic PCs. Dots indicate the estimates, vertical lines indicate the 95% CIs, and horizontal lines indicate the null.

insulin (31–34), which is a well-known fetal growth factor (35). A study among African American women suggested that maternal GRS influenced fetal growth independent of maternal blood glucose levels (10). In the current study, we observed that GRS of T2D was associated with higher fetal weight even among women with NGT. Fetal insulin-induced growth can in part explain our finding in the later gestational weeks. Although earlier studies reported that fetal pancreatic insulin secretion is not glucose sensitive until ∼28 gestational weeks (36), more recent studies showed that fetal insulin response to glucose can be established at an earlier gestational age (37–39). Moreover, our study's associations in European Americans were stronger among women with NGT, suggesting that maternal genetic susceptibility to T2D can impact fetal growth independently of maternal glycemia. This is consistent with a study among Afro-Caribbean women that found the association of maternal T2D GRS with birth weight is not mediated via maternal fasting and postchallenge glucose levels measured during oral glucose tolerance test in late second trimester (10).

Our observations of increased fetal growth associated with maternal T2D GRS could be explained by several factors. First, maternal genetic variants can be implicated in the intrauterine environment via changes in maternal metabolic status, placental vascular function, and transfer of nutrients to the fetus, thereby affecting the intrauterine environment (40).

Second, several T2D risk alleles included in the GRS overlap with genetic loci associated with gestational diabetes (41), obesity (42), gestational weight gain (43), metabolic syndrome (44) and blood lipids (45,46); each of these traits can influence fetal growth (47). Therefore, the SNPs included in the T2D GRS may influence fetal growth beyond the contribution of maternal blood glucose levels.

Third, the associations may partly be due to parentally inherited fetal T2D-related alleles. For example, a recent GWAS on birth weight reported 15 SNPs pleiotropic with T2D, of which 2 had directionally consistent fetal and maternal effects (7). Future larger studies using the Mendelian randomization analyses framework are needed to separate the direct fetal effect from the indirect maternal effect. Examining the overlapping and independent effects of GRS for multiple cardiometabolic traits, such as lipids and blood pressure (48,49), may help our understanding of the complex pathways involved in fetal growth regulation.

No consistent association was found between ancestry-matched or cross-ancestry GRS and fetal and birth weights in non-Europeans. It has been demonstrated that cross-ancestry analysis can cause unpredictable biases (50). In our analysis, the relationship between GRS and birth weight among African Americans showed a nonlinear trend, consistent with a previous study among Afro-Caribbeans (10). Given the genetic heterogeneity of the African American population, a more refined GRS from multiple African populations may be required to improve prediction. Broadly, however, the performance of GRS is more reassuring among populations with close ancestry (51), although different environmental exposures

may alter the genetic effect. Although some T2D GWAS loci discovered in Europeans were replicated in Hispanics (52,53) and East Asians (21), recent studies emphasize the need for representation of diverse ancestral populations in genetic studies of T2D (54). Studies conducted among Hispanic populations have reported only a handful signals at previously known regions from European GWAS of T2D (52,53). This limited our ability to generate ancestry-specific GRS for Hispanic American women, highlighting the critical necessity of large-scale genetic studies of T2D in Hispanic and Indigenous populations. Absence of well-powered GWAS in diverse ancestries is a prevailing issue in genomics (50). Our study's null findings in non-Europeans, despite tests using ancestry-matched GRS, is likely because fewer SNPs were included in ancestry-matched GRS for non-Europeans than Europeans (3.7- and 2.0-fold fewer in Africans and East Asians, respectively, compared with Europeans). We also acknowledge that our sample size for East Asian Americans is the smallest of all groups and that statistical power is marginal, potentially limiting the reliability of the estimates.

Although GRS could be a promising potential biomarker in future precision medicine, it is critical to validate its performance using studies with larger sample sizes before translation into clinical practice (55). Inclusion of ancestrally diverse populations in genetic studies is also crucial to improve the reliability of GRS for risk prediction across population groups (55). Furthermore, because GRS can explain only part of the variability in fetal growth, it should be integrated with environmental factors to improve its predictive utility in clinical decisions (4).

To our knowledge, this is the first study to test the association between maternal T2D genetic risks derived from diverse ancestry GWAS and fetal growth in diverse ancestry groups. We recognize that our study has limitations, we did not have fetal genotype, fetus insulin level, or maternal glucose level to investigate mediation; however, our findings were consistent even after adjusting for maternal glucose challenge test values or after exclusion of women with abnormal glucose tolerance.

The NICHD Fetal Growth Study has many strengths, including its longitudinal design, involvement of ancestry-diverse populations, and implementation of standardized ultrasound protocols with established quality control (23, 24). The study recruited healthy pregnant women without previous pregnancy complications and prepregnancy diabetes (16), minimizing confounding related to abnormal maternal blood glucose.

In conclusion, genetic susceptibility to T2D was associated with increased fetal weight starting at week 24 and birth weight among European American women even with NGT. These results suggest that maternal genetic susceptibility to T2D may be related to fetal growth beyond the contribution of maternal blood glucose levels. Absence of similar associations in non-European women urges the need for further genetic studies to understand the genetic architecture of T2D in diverse ancestries.

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