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Maternal BMI-increasing genetic risk score and fetal weights among diverse US ethnic groups

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Abstract

Objective: We examined associations between maternal genetic risk for obesity and fetal weight at the end of first (13 weeks and 6 days), second (27 weeks and 6 days), and third (40 weeks and 0 days) trimesters among four race/ethnic group U.S. women.

Methods: For 603 White, 591 Black, 535 Hispanic, and 216 Asian women, maternal genetic risk score (GRS) was calculated as the sum of 189 BMI-increasing alleles and was categorized into high or low GRS. Associations between GRS (continuous and categorical) and estimated fetal weight were tested overall, and stratified by pre-pregnancy BMI, gestational weight gain (GWG), and fetal sex.

Results: High GRS, compared to low GRS, was associated with increased fetal weight at end of second (β :22.73 g; 95% CI:2.35,43.11, $p=0.03$) and third trimesters (β :88.28 g; 95% CI: 9.01,167.56, $p=0.03$) among Hispanics. The effect of GRS was stronger among Hispanics with normal pre-pregnancy weight, adequate first trimester GWG, or inadequate second trimester GWG ($p<0.05$). Among Asians, high GRS was associated with increased weight among male fetuses but decreased weight among female fetuses ($p<0.05$).

Conclusion: Maternal obesity-genetic risk was associated with fetal weight with potential effect modifications by maternal pre-pregnancy BMI, GWG, and fetal sex.

Keywords

obesity; genetic risk score; fetal weight; fetal growth; small-for-gestational age birthweight (SGA)

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Introduction

Fetal growth trajectories are important indicators of fetal health and a strong determinant of health and disease during childhood and adulthood (1). Recent reports have revealed that genetic factors associated with obesity in adults also influence variations in birthweight (2, 3, 4). It is increasingly understood that birthweight is not a good proxy for longitudinal fetal growth (5) and there is very little understanding of how genetic susceptibility to obesity influences fetal weight at different windows of gestation. A better and comprehensive understanding of the influence of genetics of obesity on fetal weight may help inform future lifestyle interventions designed not only to optimize fetal growth and prevent perinatal morbidity or mortality but also to improve health in adulthood.

Genome-wide association studies (GWAS) have successfully identified multiple polymorphisms associated with the risk of obesity in Europeans and East Asians (6, 7, 8, 9). About 21% of variation in body mass index (BMI) can be accounted for by common genetic variations (6). Genetic risk scores (GRS) are being increasingly used as a tool to summarize risk-associated variation across the genome by aggregating information from multiple single nucleotide polymorphisms (SNPs) for a particular phenotype (10) and are particularly helpful in stratifying individuals into high or low genetic risk groups (11).

Maternal genetic risk for obesity plays an important role in the relationship between maternal pre-pregnancy obesity status and birthweight (3). Maternal pre-pregnancy BMI and gestational weight gain (GWG) are among established factors associated with fetal growth (12). Furthermore, sex-specific differences have been found with regards to genetic influence on childhood BMI trajectory (13, 14).

No study has investigated the relationship between maternal GRS and fetal growth at clinically relevant gestation windows. In the current study we examined association of maternal GRS that included 189 SNPs (6, 7, 8) with 1) fetal weight at end of first trimester of pregnancy (13 weeks 6 days), 2) fetal weight at end of second trimester (27 weeks 6 days), 3) fetal weight at end of third trimester (40 weeks 0 day), 4) odds of small-for-gestational age (SGA) compared to appropriate-for-gestational-age (AGA) at birth, and 5) odds of LGA compared to AGA at birth. We also assessed whether these associations vary by pre-pregnancy BMI (obese, overweight and normal), GWG (inadequate, adequate, excessive), and fetal sex (male, female).

Methods

Study participants

The present analysis involved participants of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies – Singletons, a prospective longitudinal cohort of 2802 pregnant woman recruited between July 2009 and January 2013 from 12 participating clinical sites in the US. Women self-reported their race/ethnic group as non-Hispanic White (hereafter referred to as White), non-Hispanic Black (Black), Hispanic, or Asian/Pacific Islander (Asian). Details of the cohort profile have been previously reported (15). The study protocol was reviewed and approved by institutional

review boards at NICHD and each of the clinical sites. Written informed consent was obtained from all participants.

Gestational age was determined using the date of the last menstrual cycle and confirmed by ultrasound between 8–13 weeks gestation. A total of 2215 woman consented for future genetic research and were successfully genotyped, of which 1945 samples passed genotyping quality control and had fetal sonography measurements, meeting eligibility for the present analysis.

Fetal weight, pre-pregnancy BMI and gestational weight gain

Details of study population, participant recruitment and clinical measurements have been described elsewhere (15). In brief, after the first ultrasound to confirm gestational age, pregnant women underwent five standardized ultrasounds at *a priori* defined gestational ages to measure fetal biometry. For each visit, estimated fetal weight was calculated from ultrasound measurement of fetal head circumference, abdominal circumference, and femur length using the Hadlock formula (16). Our primary outcomes were fetal weight at 13 weeks 6 days (end of first trimester), 27 weeks 6 days (end of second trimester) and 40 weeks (end of third trimester) separately. We considered independent tests at these gestation time points consistent with previous studies that have shown that fetal growth trajectories are nonlinear (16), and the growth patterns significantly vary by each trimester (17). Offspring birthweight was abstracted from the medical chart and determined to be SGA if birthweight was less than the 10th percentile for gestational age, LGA if birthweight was greater than or equal to the 90th percentile for gestational age, or AGA if birthweight was between the 10th and 90th percentile for gestational age according to sex-specific birthweight references (18). Pre-pregnancy BMI was calculated using self-reported pre-pregnancy weight in kilograms divided by measured height in meters squared and was categorized as normal weight (<25 kg/m²), overweight (25–<30 kg/m²), or obese (≥30 kg/m²). Participant's weight was recorded at each research visit and abstracted from prenatal care records. Trimester-specific GWG was determined to be inadequate, adequate or excessive as defined by the 2009 Institute of Medicine recommended pre-pregnancy BMI specific guidelines (19).

Genotyping, imputation, and calculation of genetic risk score

Genotypes were imputed with the Michigan Imputation Server (20) implementing Eagle2 for haplotype phasing, followed by Minimac2 for imputing non-typed SNPs with 1000 Genomes Phase 3 reference sequence data (<http://www.internationalgenome.org>). In brief, DNA was successfully extracted from stored buffy coat specimens obtained from 652 Blacks, 641 Whites, 582 Hispanics, and 340 Asians. SNPs were genotyped using the Infinium Multiethnic Global BeadChip microarray (Illumina). Quality control of SNP genotypes was carried out using PLINK version 1.9 (<https://www.cog-genomics.org/plink2>). We removed samples with more than 5% missing SNP genotypes, high degree of relatedness ($\text{Pi hat} \geq 0.25$), excess heterozygosity (≥ 3 S.D. from the mean), and outliers from the distribution of the European, Hispanic, East Asian, and African clusters of the 1000 Genomes reference population based on multi-dimensional scaling plots. We removed insertion-deletions, multi-allelic and duplicated SNPs. We also removed SNPs that had more than 5% missing values, minor allele frequency <0.5%, and not in Hardy-Weinberg

equilibrium ($P < 10^{-4}$). After quality control, 622 Whites genotyped at 825,185 SNPs, 637 Blacks genotyped at 1,078,089 SNPs, 568 Hispanics genotyped at 1,044,163 SNPs, and 238 Asians genotyped at 748,179 SNPs remained. Imputation of genotypes was performed with Minimac2 using the 1000 Genomes Phase 3 genotype reference. After removal of insertion-deletion sites, SNPs with minor allele frequency $< 0.5\%$ and dosage $r^2 < 0.3$, ~18 million SNP genotypes remained. Data from a total of 603 Whites, 591 Blacks, 535 Hispanics, and 216 Asians with live birth data were taken forward for analyses.

A list of 214 SNPs associated with adult BMI at genome-wide significance thresholds ($p < 5 \times 10^{-8}$) in three previous large-scale GWAS (6, 7, 8) was used to extract genotype data from our study samples. A total of 189 SNPs was found across all race/ethnic groups in our datasets. We then constructed an unweighted maternal GRS for each participant by summing the dosage of the BMI-increasing allele for each SNP (range: 0–2) from the 189 SNPs. We preferred using an unweighted GRS because it has been shown to be more robust to errors arising from differences in effect size and population structure, particularly among our ancestrally diverse race/ethnic groups as recommended by Dudbridge (2013) (21). Maternal GRS was determined to be high GRS when it was at or above the median value and low GRS when it was below the median value per race/ethnic group. Subsequent analyses implemented categorical GRS by comparing high GRS to low GRS as well as continuous GRS.

Statistical Analysis

Multivariate linear regression analyses were performed to test associations between categorical maternal GRS (high GRS compared to low GRS) and fetal weight at the end of each trimester, estimating the change in fetal weight and 95% confidence interval (CI). Multinomial logistic regression analyses were performed to test associations between categorical GRS and odds of SGA compared to AGA, and odds of LGA compared to AGA. The aforementioned analyses were repeated using continuous GRS. Analyses were adjusted for fetal sex (except in models that included SGA or LGA for which sex-specific references were used as part of their definition (18)), mother's education (high school and less, some college degree or higher), nativity status (US born, long-term-resident immigrant, short-term-resident immigrant), parity (continuous), health insurance (private or managed care, other), marital status (married or living with partner, not married), employment (employed or full time student, other), and the first five genetic principal components. Analyses were then stratified by maternal pre-pregnancy BMI (normal weight, overweight, and obese), trimester-specific GWG adequacy (inadequate, adequate, and excessive), and neonatal sex (male and female). Interactions between GRS and pre-pregnancy BMI, between GRS and GWG, and between GRS and offspring sex were tested by including multiplicative interaction terms in the models.

We examined whether the relationship between GRS and fetal weight was mediated via pre-pregnancy BMI or GWG for each subgroup of obesity status using two sets of models: models for fetal weight (outcome model) and models for the potential mediator (mediator model) at each trimester. The mediator and outcome models were combined to estimate the direct, indirect, and total effects of maternal GRS on fetal weight at each trimester.

Proportion mediated was calculated as indirect effect divided by total effect, expressed in percentage, which represents the proportion of the total effect of maternal GRS on fetal weight that is mediated via respective mediators. Analyses included GRS-mediator interaction term, and assumed that conditional on the study covariates, there is no confounding of 1) the GRS-fetal weight relation, 2) GRS-mediator relation, 3) mediator-fetal weight relation, and that 4) GRS did not confound the mediator-fetal weight relation (22). All analyses were implemented using PLINK 1.9 (<https://www.cog-genomics.org/plink2>), and SAS version 9.4 (SAS Institute Inc). *P-Value* < .05 was considered statistically significant.

All analyses were stratified by maternal race/ethnicity to avoid population stratification bias in effect estimates between genetic susceptibility and fetal growth due to allele frequency differences between race/ethnic groups. Genetic principal components were generated from multi-dimensional scaling analysis of a set of uncorrelated SNPs for further adjustment during analysis to account for population structure (23).

Results

Characteristics of the study participants are presented in Table 1. The mean maternal GRS was 181.3 (range: 166–252) among Whites, 179.8 (range: 163–248) among Blacks, 180.2 (range: 165–243) among Hispanics, and 181.1 (range: 170–236) among Asians. The mean pre-pregnancy BMI (in kg/m²) was 25.1 among Whites, 26.6 among Blacks, 26.0 among Hispanics and 22.2 among Asians. The distributions of trimester-specific GWG varied by race/ethnic groups. Offspring sex distributions were similar across all race/ethnic groups (Table 1).

Compared to low GRS, high GRS was significantly associated with increased fetal weight at end of second (β :22.7 grams, 95% CI: 2.3 to 43.1) and end of third trimester (β :88.3 grams, 95% CI: 9.0 to 167.6, $p=0.03$) among Hispanics only. Similar findings were found when GRS was used on the continuous scale. Each unit increase in maternal GRS was associated with increased fetal weight at end of second (β : 1.4 grams, 95% CI: 0.1 to 2.6) and end of third trimester (β : 5.2 grams, 95% CI: 0.4 to 10.0) among Hispanics (Table 2). Among Asian fetuses, high GRS was significantly associated with increased fetal weight among males (end of first trimester β :3.6 grams, 95% CI: 0.1 to 7.0), but decreased fetal weight among females (end of first trimester β : -5.3 grams, 95% CI: -8.6 to -2.0, *P-for-interaction*=0.0007; end of second trimester β :-46.2 grams, 95% CI: -91.8 to -0.6, *P-for-interaction*=0.01). Among Hispanic fetuses, high GRS was significantly associated with increased fetal weight among males only (end of first trimester β : 2.2 grams, 95% CI: 0.4 to 4.1; end of second trimester β : 43.9 grams, 95% CI: 12.5 to 75.4; end of third trimester β : 164.3 grams, 95% CI: 39.5, 289.2). However, *P-for-interaction* was not statistically significant (Table 3).

High GRS was significantly associated with 2.6 times increased odds of SGA (95% CI: 1.1 to 6.1, *P-for-interaction*=0.001) among male Black offspring and 80% reduced risk of LGA (95% CI: 0.1 to 0.8, *P-for-interaction*=0.02) among female Black offspring (Table 4).

Analyses stratified by pre-pregnancy BMI found that high GRS was significantly associated with increased fetal weight among Hispanics with normal pre-pregnancy weight only (first trimester β :3.1 grams; 95% CI: 1.1 to 5.1, *P-for-interaction*=0.003; Second trimester β :36.4 grams; 95% CI: 6.7 to 66.2, *P-for-interaction*=0.17) (Table 5).

Analyses stratified by GWG adequacy found that high GRS was associated with increased fetal weight among Hispanics who had adequate first trimester GWG (β :2.9 grams; 95% CI: 0.4 to 5.3), and inadequate second trimester GWG (β :35.3 grams; 95% CI: 4.8 to 65.7) (Table 6). However, there was no significant mediation effect of GRS on fetal weight through pre-pregnancy BMI or GWG (Supplementary Table S1).

Discussion

In the current study of associations between maternal GRS and fetal weight, we examined the influence of maternal BMI-increasing genetic risk on fetal weight at three gestation times and on SGA and LGA risk among four race/ethnic groups in the US. Our study revealed three key findings. First, we observed that high GRS was significantly associated with increased fetal weight only among Hispanics at end of second and end of third trimesters of pregnancy. Second, the effects of maternal GRS on fetal weight at ends of first and second trimesters were stronger among Hispanic mothers with normal pre-pregnancy BMI. Further, maternal GRS increased fetal weight among Hispanics mothers with adequate first trimester GWG and inadequate second trimester GWG. Lastly, we found an offspring sex-dependent effect of high GRS, particularly among Asians and Blacks. Among Asians, high GRS was associated with increased fetal weight among male offspring but decreased fetal weight at ends of first and second trimester among female offspring. Among Blacks, high GRS was associated with increased SGA risk among male offspring and decreased LGA risk among female offspring.

We found that maternal BMI genetic risk has a direct and significant effect on fetal weight which was not mediated through mother's pre-pregnancy BMI or GWG. The possibility of a direct genetic effect on fetal weight cannot be overlooked. Nevertheless, it should be noted that obesity is a multifactorial disorder where obesity and GWG may influence other metabolic markers of adiposity, especially early in life. Furthermore, several SNPs associated with BMI (6, 7, 8) have also been shown to be associated with GWG (24) and other cardio-metabolic traits (e.g., rs13107325 in *SLC39A8* for blood pressure (25), multiple SNPs from *KCNQ1*, *TCF7L2*, *SLC30A8*, *KCNJ11*, *CDKN2A*, *CDKN2B* gene in type 2 diabetes) (26, 27). BMI-associated SNPs such as rs1558902 in the *FTO* genes are known to have role in birthweight (28). Placental function is also known to be influenced by maternal obesity status by increasing oxidative stress, change in cell turn over, vascular endothelium thickening, and maternal inflammatory lesion turning placenta to be less mature compared to fetus gestational age. This may lead to altered transport of nutrients that may include increased glucose transport (via increased insulin resistance), increased amino acid transport (via pro-inflammatory cytokines) and increased lipid transport (via fat mobilization) (29, 30).

The stronger effect of maternal genetic risk on fetal weight among Hispanics, particularly among normal BMI mothers and mothers with adequate or inadequate GWG is noteworthy. Several studies have shown that in mothers with obesity, the intrauterine environment has higher inflammatory markers, oxidative stress, and an altered hormonal milieu (30) leading to fetal overgrowth with high fat mass (31). Therefore, the birthweight-increasing effect of high GRS may be diminished as a result of compensatory effects to maintain fetal weight homeostasis. Consistent with this observation, we previously found that offspring born to African ancestry women who were overweight or obese had significantly higher birthweight among mothers with low genetic risk but not among mothers with high genetic risk (3). A study that implemented Mendelian randomization has also found that genetically elevated maternal BMI is potentially causally associated with higher offspring birthweight (4). In addition, the effect of the *FTO* gene genetic variants on longitudinal BMI has been found to be more evident among individuals with lower birthweight than among individuals with higher birthweight (32). These observations may explain our current study finding that the fetal weight-increasing effect of high GRS was more evident among women who did not have excessive GWG. Future studies are needed to confirm these findings and to unravel the complex interactions among maternal genetic factors, adiposity and weight gain during pregnancy, and fetal growth.

We found directionally opposite associations between offspring sex-dependent effects of BMI genetic risk on fetal weight and birth size among Asians and Blacks, respectively. Male and female fetuses respond differently to adverse intrauterine exposures, which has been increasingly linked to placental function (29, 33). Our finding that high GRS was associated with increased odds of SGA among male Black offspring but not in female Black offspring is consistent with recent evidence that male fetuses are more susceptible to adverse outcomes of intrauterine insults (33, 34). A study in predominantly Hispanic participants revealed that male fetuses of lean women have the highest antioxidant activity, a protection which is lost with obesity perhaps contributing to the increased incidence of adverse outcomes with a male fetus (34). Both SGA and LGA babies are more likely to accumulate excess fat mass in early childhood and are at increased risk for obesity in adulthood (35). Although our finding needs to be cautiously interpreted because of the small number of SGA and LGA neonates, it highlights the potential contribution of maternal genetic risk for obesity in orchestrating sex differences in fetal growth and subsequent risk of adulthood chronic diseases.

The main strength of our study was the longitudinal design and implementation of a standardized ultrasound protocol with established quality control (36), that allowed us to characterize the dynamics of in-utero fetal growth among four US racial/ethnic groups (16). To our knowledge, our study is the first to provide trimester-specific investigation on the effect of maternal BMI-increasing genetic risk on fetal weight and how these relationships are modified by pre-pregnancy BMI, GWG, and fetal sex at different gestational windows.

There are some limitations to this study. First, we utilized SNPs associated with BMI, discovered in predominantly in European (6) and East Asian ancestry populations (7) to construct our GRS and applied it to four ancestrally diverse race/ethnic populations. Although, the allele frequencies and patterns of linkage disequilibrium is not consistent

across the race/ethnic groups, a study reported that cumulative information across the human genome can be used to characterize individual level risk for obesity with small variation in BMI among Whites and Black young adults and supports the use of GRS in the transethnic replication (37). There is evidence that ten SNPs in *FTO* previously associated with BMI in European population could not be replicated in individuals of African population, probably due to both the study's sample size and the genetic structure of the population studied (38). Identification of race/ethnic group specific variants (e.g., African-specific variant in *SEMA4D* associated with BMI) (39) implies the need for ancestry-specific genomic studies and careful interpretation of polygenic risk scores based on trait-associated SNPs found only in one ancestry. Although there may be different possible explanations such as race/ethnicity-specific differences in effect size or heritability (40, 41), insulin-regulation pathways (42), and multi-dimensional socio-cultural factors (43, 44), future studies with a large sample are needed to comprehensively understand the mechanisms involved. Second, adjusting for fetal BMI increasing GRS may be needed to separate direct maternal GRS effects from direct effects of fetal genetic risk. Previous studies have shown that the variance in birthweight explained by autosomal fetal genetic loci is higher than maternal genetic loci (45). In addition, fetal genotypes and parent-of-origin effects significantly influence the relationship between maternal GRS and offspring birthweight (2, 3). However, we did not adjust for fetal GRS because of absence of data. Third, replication of the findings in an independent data set was not possible because of the uniqueness of the cohort with respect to race/ethnic diversity and longitudinal measures of fetal biometry. Lastly, the number of genetic loci associated with BMI is continuously growing (9), including loci that were not part of the present study, but present opportunities for more comprehensive studies in the future.

In summary, this study found that high BMI increasing genetic risk was associated with increased fetal weight among Hispanics, with stronger effects among those with normal pre-pregnancy weight and inadequate first trimester or adequate second trimester GWG. The effect of GRS on fetal weight and abnormal birth size varied by offspring sex among Asians and Blacks. Our findings suggest that genetic risk of pregnant mothers is potentially informative to understanding variations in fetal weight.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject?

- Maternal BMI-increasing genetic risk score (GRS) is associated with offspring's birthweight; however, the association of GRS with longitudinal fetal weight is not known.

What does your study add?

- This is the first study to find relations between maternal GRS constructed using the largest number of BMI-increasing variants and fetal weight across gestation among race/ethnic diverse pregnant women.
- Among Hispanics, high BMI-increasing GRS was significantly associated with increased fetal weight; when stratified by pre-pregnancy BMI and gestational weight gain, high BMI-increasing GRS was associated with increased fetal weight among women who had normal pre-pregnancy BMI and inadequate gestational weight gain (GWG) in first trimester and adequate GWG in second trimester.
- Among Asians, the association of BMI-increasing GRS on fetal weight varied by fetal sex; high BMI-increasing GRS was associated with increased weight of male fetuses but decreased weight of female fetuses.

Table 1:

Characteristics of study participants

Characteristics	Whites	Blacks	Hispanics	Asians	<i>p</i> ^a
	603	591	535	216	
Maternal age in years, mean $\pm$ s. d	30.35 $\pm$ 4.50	25.38 $\pm$ 5.28	27.01 $\pm$ 5.57	30.80 $\pm$ 4.56	<.0001
Parity, mean $\pm$ s. d	0.64 $\pm$ 0.83	0.82 $\pm$ 0.96	1.06 $\pm$ 1.08	0.59 $\pm$ 0.64	<.0001
Pre-pregnancy BMI, kg/m ² , mean $\pm$ s. d	25.09 $\pm$ 5.18	26.56 $\pm$ 5.68	26.04 $\pm$ 4.99	22.17 $\pm$ 2.72	<.0001
Normal (<25 kg/m ²), n (%)	366 (60.70)	281 (47.55)	270 (50.47)	180 (83.11)	<.0001
Overweight (25-30 kg/m ²)	133 (22.06)	165 (27.92)	172 (32.15)	35 (16.41)	
Obese ($\geq$ 30 kg/m ²)	104 (17.25)	145 (24.53)	93 (17.38)	1 (0.46)	
GWG (1 st trimester), n (%)					<.0001
Inadequate	34 (5.64)	105 (17.77)	98 (18.32)	13 (6.02)	
Adequate	200 (33.17)	174 (29.44)	185 (34.58)	118 (54.63)	
Excessive	369 (61.19)	312 (52.79)	252 (47.10)	85 (39.35)	
GWG (2 nd trimester), n (%)					<.0001
Inadequate	230 (38.14)	274 (46.36)	265 (49.53)	121 (56.02)	
Adequate	215 (35.66)	134 (22.67)	136 (25.42)	67 (31.02)	
Excessive	158 (26.20)	183 (30.96)	134 (25.05)	28 (12.96)	
GWG (3 rd trimester), n (%)					<.0001
Inadequate	98 (16.25)	163 (27.58)	156 (29.16)	51 (23.61)	
Adequate	255 (42.29)	177 (29.95)	176 (32.90)	118 (54.63)	
Excessive	250 (41.46)	251 (42.47)	203 (37.94)	47 (21.76)	
GWG (total pregnancy period), n (%)					<.0001
Inadequate	140 (24.10)	176 (31.43)	187 (36.52)	78 (38.24)	
Adequate	204 (35.11)	157 (28.04)	137 (26.76)	82 (40.20)	
Excessive	237 (40.79)	227 (40.54)	188 (36.72)	44 (21.57)	
Median GRS (IQR)	181.92 (11.86)	179.87 (11.21)	180.07 (11.84)	181.09 (10.77)	0.03
Low GRS, mean $\pm$ s. d	174.26 $\pm$ 5.62	173.26 $\pm$ 4.65	173.46 $\pm$ 4.67	174.76 $\pm$ 5.13	1.00
High GRS, mean $\pm$ s. d	188.27 $\pm$ 5.05	186.37 $\pm$ 5.02	186.66 $\pm$ 5.28	187.39 $\pm$ 5.02	
Mother's education, n (%)					<.0001
High school or less	43 (7.13)	244 (41.29)	278 (51.96)	42 (20.83)	
Some college or more	560 (92.87)	247 (58.71)	257 (48.04)	171 (79.17)	
Married, n (%)	562 (93.20)	309 (52.37)	395 (73.83)	203 (93.98)	<.0001
Private or Managed insurance, n (%)	545 (93.16)	265 (46.57)	180 (34.75)	175 (84.54)	<.0001
Employed or student, n (%)	493 (81.76)	439 (74.28)	306 (57.30)	133 (61.57)	<.0001
Nativity status, n (%)					<.0001
US born	565 (93.70)	547 (92.55)	228 (42.70)	34 (15.74)	
Immigrants-long term resident	19 (3.15)	24 (4.06)	163 (30.52)	94 (43.52)	
Immigrants-short term resident	19 (3.15)	20 (3.38)	143 (26.78)	88 (40.74)	
Fetal sex, male, n (%)	312 (53.70)	276 (49.29)	257 (50.20)	105 (51.22)	0.47
Fetal weight by trimester, g, mean $\pm$ s. d					

Characteristics	Whites	Blacks	Hispanics	Asians	p^a
	603	591	535	216	
End of 1 st trimester	85.89 ± 7.61	85.18 ± 7.62	84.32 ± 8.19	83.30 ± 8.42	<.0001
End of 2 nd trimester	1180.18 ± 112.84	1128.38 ± 113.79	1138.20 ± 123.45	1114.09 ± 117.18	<.0001
End of 3 rd trimester	3776.95 ± 454.40	3475.67 ± 425.42	3589.72 ± 477.87	3491.04 ± 431.24	<.0001
Birth size compared to reference, n (%)					
Appropriate for gestational age	473 (81.41)	453 (81.04)	424 (82.81)	168 (82.35)	<.0001
Small for gestational age	30 (5.16)	71 (12.70)	46 (8.98)	21 (10.29)	<.0001
Large for gestational age	77 (13.25)	31 (5.55)	41 (8.01)	15 (7.35)	<.0001

GWG, gestational weight gain based on Institute of Medicine (IOM) criteria 2009; BMIGRS, BMI increasing genetic risk score;

End of 1st trimester (13weeks 6 days gestation); End of 2nd trimester (27weeks 6 days gestation); End of 3rd trimester (40week gestation);

^a p value, by chi-square test or student t test or non-parametric approach, as appropriate

Table 2
Association between maternal BMI GRS and fetal weight in four race/ethnic groups

	Whites (n= 603)		Blacks (n=591)		Hispanics (n= 535)		Asians (n=216)	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
End of 1st trimester								
<i>High GRS compared to low GRS</i>	-0.4 (-1.7, 0.8)	0.51	0.5 (-0.8, 1.8)	0.44	1.1 (-0.4, 2.5)	0.14	-0.2 (-2.6, 2.3)	0.89
<i>Per unit increase in GRS</i>	-0.00 (-0.1, 0.1)	0.99	0.02 (-0.1, 0.1)	0.58	0.1 (-0.0, 0.2)	0.12	-0.03 (-0.2, 0.1)	0.69
End of 2nd trimester								
<i>High GRS compared to low GRS</i>	-10.6 (-28.8, 7.7)	0.26	5.9 (-12.8, 24.6)	0.54	22.7 (2.4, 43.1)	0.03	1.8 (-30.9, 34.5)	0.91
<i>Per unit increase in GRS</i>	-0.4 (-1.4, 0.7)	0.45	0.1 (-1.0, 1.3)	0.85	1.4 (0.1, 2.6)	0.02	-0.3 (-2.4, 1.8)	0.77
End of 3rd trimester								
<i>High GRS compared to low GRS</i>	-39.7 (-113.8, 34.4)	0.29	8.7 (-62.8, 80.1)	0.81	88.3 (9.0, 167.6)	0.03	21.6 (-96.9, 140.2)	0.72
<i>Per unit increase in GRS</i>	-2.3 (-6.6, 1.9)	0.28	-0.6 (-5.0, 3.8)	0.77	5.2 (0.4, 10.0)	0.03	0.3 (-7.3, 7.9)	0.93

GRS, BMI increasing genetic risk score;

End of 1st trimester (13 weeks 6 days gestation); End of 2nd trimester (27 weeks 6 days gestation); End of 3rd trimester (40 weeks 0 day gestation)

Model adjusted for mothers age, infant sex, maternal education, marital status, health insurance, parity, nativity status and 5 genetic principal components

Table 3

Association between maternal BMI GRS and fetal weight among male and female fetuses

	Whites (n= 603)			Blacks (n=591)			Hispanics ^a (n= 535)			Asians ^a (n=216)		
	β (95% CI)	P		β (95% CI)	P		β (95% CI)	P		β (95% CI)	P	
End of 1st trimester												
<i>High GRS compared to low GRS</i>												
Male	0.1 (-1.7, 1.8)	0.94		0.73 (-1.2, 2.7)	0.47		2.2 (0.0, 4.4)	0.04		3.6 (0.1, 7.0)	0.04	
Female	-0.9 (-2.8, 0.9)	0.30		0.28 (-1.4, 2.0)	0.74		0.4 (-1.5, 2.2)	0.71		-5.3 (-8.6, -2.0)	0.001	
<i>Per unit increase in GRS</i>												
Male	0.01 (-0.1, 0.1)	0.85		0.1 (-0.1, 0.2)	0.27		0.1 (-0.0, 0.2)	0.11		0.1 (-0.1, 0.3)	0.40	
Female	-0.01 (-0.1, 0.1)	0.88		-0.03 (-0.1, 0.1)	0.58		0.04 (-0.1, 0.2)	0.51		-0.3 (-0.5, -0.1)	0.01	
End of 2nd trimester												
<i>High GRS compared to low GRS</i>												
Male	-1.0 (-26.7, 24.7)	0.93		2.8 (-26.4, 31.9)	0.85		43.9 (12.5, 75.4)	0.01		39.9 (-6.7, 86.7)	0.09	
Female	-20.3 (-46.9, 6.3)	0.13		8.7 (-16.4, 33.7)	0.49		8.8 (-18.8, 36.3)	0.53		-46.2 (-91.8, -0.6)	0.04	
<i>Per unit increase in GRS</i>												
Male	-0.2 (-1.8, 1.3)	0.76		0.5 (-1.2, 2.2)	0.59		2.2 (0.4, 4.1)	0.01		0.5 (-2.6, 3.6)	0.75	
Female	-0.6 (-2.0, 0.9)	0.45		-0.3 (-1.9, 1.3)	0.72		0.7 (-1.1, 2.4)	0.45		-2.5 (-5.5, 0.5)	0.09	
End of 3rd trimester												
<i>High GRS compared to low GRS</i>												
Male	-6.1 (-108.9, 96.7)	0.90		-28.9 (-134.6, 76.8)	0.59		164.3 (39.5, 289.2)	0.01		46.2 (-127.8, 220.2)	0.59	
Female	-69.4 (-178.1, 39.2)	0.20		44.1 (-56.4, 144.5)	0.38		34.4 (-70.4, 139.1)	0.51		14.1 (-150.2, 178.5)	0.86	
<i>Per unit increase in GRS</i>												
Male	-2.1 (-8.4, 4.2)	0.51		-0.9 (-7.0, 5.3)	0.78		8.8 (1.4, 16.1)	0.01		-2.9 (-14.4, 8.6)	0.61	
Female	-2.8 (-8.7, 3.2)	0.35		-0.1 (-6.6, 6.4)	0.97		2.1 (-4.4, 8.6)	0.53		1.2 (-9.6, 11.9)	0.83	

GRS, BMI increasing genetic risk score; End of 1st trimester (13weeks 6 days gestation); End of 2nd trimester (27weeks 6 days gestation); End of 3rd trimester (40week 0 day gestation)

Model adjusted for maternal age, education, marital status, health insurance, parity, nativity status and 5 genetic principal components

^a *P*-for-interaction (High compared to low GRS) for first, second and third trimester among Hispanics 0.27, 0.17, 0.20, respectively^a *P*-for-interaction (High compared to low GRS) for first, second and third trimester among Asians 0.0007, 0.01, 0.80, respectively

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^a *P₁-for-interaction* (per unit increase in GRS) for first, second and third trimester among Hispanics 0.61, 0.31, 0.22, respectively

^a *P₁-for-interaction* (per unit increase in GRS) for first, second and third trimester among Asians 0.01, 0.13, 0.61, respectively

Table 4

Association between maternal BMI GRS and SGA or LGA

	SGA compared to AGA					LGA compared to AGA				
	High GRS compared to low GRS		Per unit increase in GRS			High GRS compared to low GRS		Per unit increase in GRS		
	n	OR (95% CI)	P	OR (95% CI)	P	n	OR (95% CI)	P	OR (95% CI)	P
Whites	30/473	1.1 (0.5, 2.4)	0.81	1.0 (1.0, 1.0)	0.84	77/473	1.1 (0.7, 1.8)	0.79	1.0 (1.0, 1.0)	0.85
Male	17/254	0.6 (0.2, 1.9)	0.40	0.9 (0.9, 1.0)	0.28	40/254	1.4 (0.7, 2.9)	0.38	1.0 (0.9, 1.1)	0.72
Female	13/219	2.5 (0.6, 9.8)	0.19	1.1 (0.9, 1.1)	0.17	37/219	0.9 (0.4, 1.8)	0.67	1.0 (0.9, 1.0)	0.45
Blacks ^a	71/452	1.1 (0.6, 1.8)	0.84	1.0 (1.0, 1.0)	0.76	31/452	0.8 (0.4, 1.7)	0.54	1.0 (0.9, 1.0)	0.67
Male	32/225	2.6 (1.1, 6.1)	0.02	1.1 (1.0, 1.1)	0.06	16/225	2.9 (0.9, 9.7)	0.07	1.0 (0.9, 1.1)	0.28
Female	39/228	0.5 (0.2, 1.0)	0.05	1.0 (0.9, 1.0)	0.11	15/228	0.2 (0.1, 0.8)	0.02	1.0 (0.9, 1.1)	0.89
Hispanics	45/424	0.7 (0.4, 1.3)	0.24	1.0 (0.9, 1.0)	0.18	41/424	1.1 (0.5, 2.2)	0.80	1.0 (1.0, 1.0)	0.97
Male	24/211	0.7 (0.3, 1.9)	0.49	0.9 (0.9, 1.0)	0.32	22/211	1.4 (0.5, 4.2)	0.53	1.0 (0.9, 1.1)	0.22
Female	22/213	0.7 (0.3, 1.7)	0.37	0.9 (0.9, 1.0)	0.39	19/213	1.3 (0.4, 4.0)	0.66	0.9 (0.9, 1.0)	0.09
Asians	21/168	0.6 (0.2, 1.5)	0.24	1.0 (0.9, 1.1)	0.76	15/168	1.2 (0.3, 3.9)	0.80	1.0 (1.0, 1.1)	0.48
Male	9/89	0.5 (0.1, 3.1)	0.43	1.1 (0.9, 1.2)	0.41	6/89	4.6 (0.3, 62.3)	0.25	1.1 (0.9, 1.4)	0.29
Female	12/79	0.5 (0.1, 2.7)	0.39	1.0 (0.9, 1.2)	0.69	9/79	0.7 (0.1, 6.4)	0.72	1.0 (0.9, 1.1)	0.84

GRS, BMI increasing genetic risk score; SGA, small for gestational age at birth; LGA, large for gestational age at birth; AGA, appropriate for gestational age at birth

Model adjusted for maternal age, education, marital status, health insurance, parity, nativity status and 5 genetic principal components

^a *P*-for-interaction (High GRS compared to low GRS) among Blacks: SGA compared to vs AGA = 0.001 and LGA compared to vs. AGA = 0.02^a *P*-for-interaction (per unit increase in GRS) among Blacks: SGA compared to AGA = 0.009 and LGA compared to vs. AGA = 0.07

Table 5
Association between maternal BMI GRS and fetal weight in four race/ethnic groups by pre-pregnancy BMI

	Whites (n= 603)			Blacks (n=591)			Hispanics (n= 535)			Asians (n=216)		
	β (95% CI)	P		β (95% CI)	P		β (95% CI)	P		β (95% CI)	P	
End of 1st trimester												
<i>High GRS compared to low GRS</i>												
Normal	-0.5 (-2.1, 1.1)	0.51		0.2 (-1.6, 2.0)	0.81		3.1 (1.1, 5.1)	0.003		-0.1 (-2.7, 2.5)	0.95	
Overweight	-0.5 (-3.2, 2.2)	0.73		1.4 (-1.2, 4.0)	0.29		0.02 (-2.4, 2.4)	0.99		1.4 (-7.1, 9.8)	0.74	
Obese	1.3 (-2.4, 4.9)	0.50		0.2 (-2.6, 2.9)	0.89		-3.6 (-7.6, 0.3)	0.07		NA		
<i>Per unit increase in GRS</i>												
Normal	-0.01 (-0.1, 0.1)	0.83		0.03 (-0.1, 0.1)	0.61		0.2 (0.0, 0.3)	0.01		-0.01 (-0.2, 0.2)	0.88	
Overweight	0.1 (-0.1, 0.2)	0.47		0.1 (-0.1, 0.2)	0.48		0.02 (-0.1, 0.2)	0.81		0.1 (-0.5, 0.6)	0.86	
Obese	0.1 (-0.2, 0.3)	0.67		-0.03 (-0.2, 0.1)	0.76		-0.1 (-0.4, 0.1)	0.28		NA		
End of 2nd trimester												
<i>High GRS compared to low GRS</i>												
Normal	-14.9 (-38.6, 8.8)	0.22		5.7 (-20.9, 32.3)	0.67		36.4 (6.7, 66.2)	0.02		-2.2 (-36.1, 31.7)	0.90	
Overweight	8.0 (-32.4, 8.4)	0.70		12.9 (-25.6, 51.3)	0.51		17.8 (-18.8, 54.5)	0.34		48.9 (-79.8, 177.6)	0.44	
Obese	-10.5 (-61.1, 40.2)	0.68		2.3 (-39.4, 43.9)	0.91		-20.9 (-74.3, 32.5)	0.44		NA		
<i>Per unit increase in GRS</i>												
Normal	-0.7 (-2.0, 0.7)	0.34		0.1 (-1.5, 1.7)	0.92		1.6 (-0.1, 3.4)	0.07		-0.6 (-2.7, 1.6)	0.60	
Overweight	0.5 (-1.8, 2.8)	0.65		0.6 (-1.8, 3.0)	0.61		1.1 (-1.3, 3.4)	0.37		4.6 (-4.3, 13.5)	0.29	
Obese	-0.8 (-4.0, 2.3)	0.60		-0.3 (-2.9, 2.4)	0.83		0.5 (-2.7, 3.7)	0.74		NA		
End of 3rd trimester												
<i>High GRS compared to low GRS</i>												
Normal	-65.5 (-159.1, 28.1)	0.17		26.1 (-73.3, 125.5)	0.61		58.0 (-52.4, 168.4)	0.30		-11.2 (-128.3, 105.8)	0.85	
Overweight	94.8 (-83.9, 273.6)	0.30		0.9 (-143.4, 145.3)	0.99		116.7 (-29.9, 263.3)	0.12		246.4 (-253.6, 746.4)	0.31	
Obese	-140.3 (-336.3, 55.7)	0.16		-0.4 (-164.2, 163.4)	1.00		73.7 (-148.3, 295.6)	0.51		NA		
<i>Per unit increase in GRS</i>												
Normal	-3.7 (-9.0, 1.6)	0.17		-1.0 (-7.0, 5.1)	0.75		2.0 (-4.5, 8.6)	0.53		-2.8 (-10.3, 4.6)	0.45	
Overweight	0.5 (-9.7, 10.6)	0.92		0.3 (-8.5, 9.2)	0.94		5.6 (-3.8, 15.1)	0.24		29.1 (-4.0, 62.2)	0.08	

	Whites (n= 603)			Blacks (n=591)			Hispanics (n= 535)			Asians (n=216)		
	β (95% CI)	P		β (95% CI)	P		β (95% CI)	P		β (95% CI)	P	
Obese	-8.2 (-20.5, 4.2)	0.19		-0.4 (-10.9, 10.0)	0.93		11.4 (-1.5, 24.3)	0.08		NA		

GRS, BMI increasing genetic risk score;
End of 1st trimester (13weeks 6 days gestation); End of 2nd trimester (27weeks 6 days gestation); End of 3rd trimester (40weeks 0 day gestation)
Model adjusted for mothers age, infant sex, maternal education, marital status, health insurance, parity, nativity status and 5 genetic principal components
^a P for interaction (*High GRS compared to low GRS*) for first, second and third trimester among Hispanics 0.002, 0.17, 0.91 respectively
^a P for interaction (*per unit increase in GRS*) for first, second and third trimester among Hispanics 0.07, 0.81, 0.30 respectively

Table 6

Association between maternal BMI GRS and fetal weight in four race/ethnic groups by GWG

Whites (n= 603)			Blacks (n=591)			Hispanics (n= 535)			Asians (n=216)		
	β (95% CI)	P		β (95% CI)	P		β (95% CI)	P		β (95% CI)	P
End of 1st trimester											
<i>GRS (High GRS compared to low GRS)</i>											
Inadequate	-1.8 (-8.8, 5.2)	0.60		2.5 (-0.8, 5.8)	0.14		0.6 (-3.4, 4.7)	0.75		NA	
Adequate	0.3 (-1.9, 2.5)	0.81		0.2 (-2.4, 2.8)	0.88		2.9 (0.4, 5.3)	0.02		-0.1 (-3.6, 3.3)	0.94
Excessive	-0.3 (-1.9, 1.3)	0.72		-0.3 (-1.9, 1.3)	0.69		0.2 (-1.8, 2.3)	0.81		0.6 (-3.4, 4.5)	0.77
<i>GRS (per risk allele)</i>											
Inadequate	-0.1 (-0.6, 0.3)	0.49		0.1 (-0.2, 0.3)	0.59		-0.03 (-0.3, 0.2)	0.83		NA	
Adequate	0.03 (-0.1, 0.2)	0.68		0.01 (-0.2, 0.2)	0.94		0.2 (0.0, 0.3)	0.02		-0.1 (-0.3, 0.1)	0.48
Excessive	0.03 (-0.1, 0.1)	0.50		-0.00 (-0.1, 0.1)	0.92		0.02 (-0.1, 0.1)	0.81		0.02 (-0.2, 0.3)	0.89
End of 2nd trimester											
<i>GRS (High GRS compared to low GRS)</i>											
Inadequate	-11.9 (-42.9, 19.2)	0.45		12.2 (-15.7, 40.1)	0.39		35.3 (4.8, 65.7)	0.02		8.1 (-32.4, 48.7)	0.69
Adequate	-16.2 (-46.8, 14.4)	0.30		25.9 (-14.2, 66.1)	0.20		16.4 (-25.4, 58.1)	0.44		-22.2 (-90.5, 46.1)	0.52
Excessive	5.8 (-30.4, 41.9)	0.75		-6.8 (-43.2, 29.7)	0.72		-10.9 (-51.2, 29.5)	0.60		29.7 (-108.5, 167.8)	0.65
<i>GRS (per risk allele)</i>											
Inadequate	-1.7 (-3.5, 0.1)	0.06		0.3 (-1.5, 2.0)	0.77		1.6 (-0.2, 3.3)	0.08		0.2 (-2.3, 2.6)	0.88
Adequate	-0.5 (-2.1, 1.2)	0.57		1.7 (-0.7, 4.1)	0.16		1.7 (-0.9, 4.1)	0.19		-2.9 (-7.3, 1.4)	0.18
Excessive	1.2 (-1.1, 3.5)	0.30		-0.9 (-3.1, 1.3)	0.42		-0.3 (-3.0, 2.4)	0.81		2.6 (-7.8, 13.0)	0.59
End of 3rd trimester											
<i>GRS (High GRS compared to low GRS)</i>											
Inadequate	77.2 (-90.3, 244.7)	0.36		6.2 (-73.3, 205.7)	0.35		100.2 (-53.3, 253.7)	0.20		10.6 (-234.6, 255.9)	0.93
Adequate	-96.1 (-209.7, 17.5)	0.10		-8.6 (-137.3, 120.1)	0.90		127.7 (-2.8, 258.1)	0.06		37.8 (-114.0, 189.7)	0.62
Excessive	-8.6 (-127.9, 110.8)	0.89		-18.0 (-134.5, 98.4)	0.76		20.4 (-113.1, 153.9)	0.76		13.0 (-399.1, 425.1)	0.95
<i>GRS (per risk allele)</i>											
Inadequate	-2.9 (-12.5, 6.7)	0.55		3.3 (-5.4, 12.0)	0.40		2.6 (-6.2, 11.4)	0.56		-0.4 (-16.4, 15.6)	0.95
Adequate	-6.4 (-12.8, 0.0)	0.05		-2.9 (-10.9, 5.0)	0.46		6.6 (-1.0, 14.1)	0.08		1.2 (-8.0, 10.5)	0.79

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	Whites (n= 603)			Blacks (n=591)			Hispanics (n= 535)			Asians (n=216)		
	β (95% CI)	P		β (95% CI)	P		β (95% CI)	P		β (95% CI)	P	
Excessive	0.1 (-7.1, 7.2)	0.98		-1.3 (-8.3, 5.7)	0.71		4.9 (-4.0, 13.8)	0.28		1.4 (-31.3, 34.0)	0.93	

GWG, gestational weight gain based on Institute of Medicine (IOM) criteria 2009; BMIGRS, BMI increasing genetic risk score;
End of 1st trimester (13weeks 6 days gestation); End of 2nd trimester (27weeks 6 days gestation); End of 3rd trimester (40week 0day gestation)
Model adjusted for mothers age, infant sex, maternal education, marital status, health insurance, parity, nativity status and 5 genetic principal components