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Associations of maternal blood pressure-raising polygenic risk score with fetal weight

Tsegaselassie Workalemahu[1], **Mohammad L. Rahman**[2], **Marion Ouidir**[1], **Jing Wu**[1], **Cuilin Zhang**[1], **Fasil Tekola-Ayele**[1]

[1]Epidemiology Branch, Division of Intramural Population Health Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA;

[2]Harvard Medical School, Department of Population Medicine and Harvard Pilgrim Healthcare Institute, Boston, MA, USA

Abstract

Maternal blood pressure (BP) is associated with variations in fetal weight, an important determinant of neonatal and adult health. However, the association of BP-raising genetic risk with fetal weight is unknown. We tested the associations of maternal BP-raising polygenic risk score (PRS) with estimated fetal weights (EFWs) at 13, 20, 27, and 40 weeks of gestation. This study included 622 White, 637 Black, 568 Hispanic, and 238 Asian pregnant women with genotype data from the NICHD Fetal Growth Studies. PRSs of systolic (SBP) and diastolic BP (DBP) were calculated for each participant based on summary statistics from a recent genome-wide association study. Linear regression models were used to compare mean EFW differences between the highest versus lowest tertile of PRS, adjusting for maternal age, education, parity, genetic principal components and fetal sex. Hispanics in the highest DBP PRS tertile, compared to those in the lowest, had 8.1g (95% CI: −15.1,−1.1), 32.4g (−58.4,−6.4) and 119.4g (−218.1,−20.7) lower EFW at 20, 27 and 40 weeks, respectively. Similarly, Asians in the highest DBP PRS tertile had 137.2g (−263.5,−10.8) lower EFW at week 40, and those in the highest tertile of SBP PRS had 3.2g (−5.8,−0.7), 12.9g (−23.5,−2.4), and 39.8g (−76.9,−2.7) lower EFWs at 13, 20 and 27 weeks. The findings showed that pregnant women's genetic susceptibility to high BP contributes to reduced fetal growth, suggesting a potential future clinical application in perinatal health.

Keywords

blood pressure; fetal weight; polygenic risk score; pregnancy; gestation

Corresponding author details: Fasil Tekola-Ayele (F.T.-A.); ayeleft@mail.nih.gov; 6710B Rockledge Dr., BG 6710B RM 3204, Bethesda MD 20892, Tel: 301-827-6518.

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Introduction

Fetal weight is an important determinant of neonatal and adult health, and reduced offspring weight at birth is associated with lifetime risk of coronary heart disease and stroke.[1, 2] Most previous studies used birthweight as a marker of fetal growth. However, it is increasingly recognized that birthweight is a poor proxy for fetal growth,[3] and the pattern of fetal growth across pregnancy is nonlinear.[4, 5] Previous studies have demonstrated that higher maternal blood pressure during pregnancy is associated with reduced ultrasound-measured fetal weight and higher perinatal mortality.[6, 7] Despite evidence for associations between genetically elevated maternal blood pressure with lower birthweight,[8] and strong genetic contributions to fetal growth variations,[9, 10] the relationship between blood pressure-raising genetic risk and fetal growth during pregnancy is unknown.

Genome-wide associations studies (GWASs) have discovered single nucleotide polymorphisms (SNPs) that were associated with systolic (SBP) and diastolic blood pressure (DBP) in the general population.[11, 12] Maternal blood pressure-raising genetic variants have also been reported to have shared effect on offspring birthweight.[13] Specifically, using a Mendelian Randomization approach, a study has reported that SBP-raising maternal SNPs are causally related to lower offspring birthweight.[8]

Quantifying the combined effects of SNPs across the entire genome using polygenic risk scores (PRSs)[14] has increasingly being used because of its potential application in clinical care, including stratified disease prevention.[15–21] However, to our knowledge, no studies have evaluated the relationship between maternal genetic propensity for elevated blood pressure and fetal weight during pregnancy. In the present study, we investigated the associations of maternal SBP- and DBP-increasing PRSs with longitudinal estimated fetal weights (EFWs) from ultrasonography measurements at four time points across pregnancy, i.e. at 13 weeks and 6 days (13w6d or end of first trimester of pregnancy), 20 weeks (20w0d or mid-gestation), 27 weeks and 6 days (27w6d or end of second trimester), and 40 weeks (40w0d or end of third trimester) among ethnically diverse study participants.

Methods

Study design and population

Our study included participants of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies – Singletons, a prospective longitudinal cohort study of 2755 ethnically diverse women with singleton pregnancies. Women were recruited between July 2009 and January 2013 from 12 participating clinical sites in the United States.[4, 22] The study included women without chronic disease, previous pregnancy complications, use of illicit drugs, cigarettes, or alcohol in the months before pregnancy and mothers with no fetal anomalies at birth. Women self-reported their race/ethnicity as Hispanic (N=813), non-Hispanic White (N=740; hereafter referred as White), non-Hispanic Black (N=762; hereafter referred as Black), or Asian/Pacific Islander (N=440; hereafter referred as Asian). The present study included 2215 women who consented for future genetic research and were subsequently genotyped. The study profile details have been previously reported.[22] The study protocol was reviewed and approved by the

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

Phenotype and covariate measurement

Pregnant women in the NICHD Fetal Growth Studies had five standardized ultrasounds measured at *a priori* defined gestational ages to measure fetal biometry. For each visit, estimated fetal weight was calculated using the Hadlock formula that incorporated standardized ultrasonography measurement of fetal head circumference, abdominal circumference, and femur length with established quality control.[10, 22] Main outcomes included in this study were estimated fetal weight at 13 weeks 6 days or end of first trimester (hereafter referred as 13 week), 20 week or mid gestation, 27 weeks 6 days or end of second trimester (hereafter referred as 27 week) and 40 weeks or end of third trimester. These gestational week-specific fetal weights were calculated from linear mixed models with a cubic spline mean structure and a random effects structure that were used to model growth trajectories across gestation, as described in our previous study.[10] SBP and DBP measurements in millimeters of mercury (mmHg) were abstracted from routine blood pressure measurements taken during prenatal visits and blood pressure measurements taken during study visits scheduled at 8–13, 16–22, 24–29, and 34–37 weeks of gestation. For each visit, if blood pressure was measured more than once, the highest measurement that was recorded was abstracted. The 1st, 2nd and 3rd trimester SBP was calculated to be the average of SBP measurements abstracted during 0–13 weeks, 14–27 weeks and 28–40 weeks of gestation, respectively, as similarly defined previously.[23] Trimester-specific DBP was also calculated similarly. The rational for defining trimester-specific blood pressure is that blood pressure is shown to vary by trimester, where it nadirs towards mid-gestation and sharply rises in the third trimester.[24] Gestational age at delivery was determined using the date of the last menstrual period and confirmed by ultrasound-based fetal biometry measures taken between the gestation periods of 8 weeks and 0 days to 13 weeks and 6 days.[4, 22] Maternal age and weight at antenatal clinical visits were abstracted from the prenatal records. Recalled pre-pregnancy weight and measured height were used to calculate pre-pregnancy BMI in kg/m^2, defined as a continuous variable and a categorical variable (normal weight: <25 kg/m^2; overweight: 25–30 kg/m^2; and obese: >30 kg/m^2).

Genotyping, imputation and quality control

DNA was successfully extracted from stored buffy coat specimens obtained from each participant (582 Hispanics, 641 Whites, 652 Blacks, and 340 Asians). SNPs were genotyped using the Infinium Multiethnic Global BeadChip microarray (Illumina). SNP genotype quality control (QC) analyses removed samples with more than 5% missing SNP genotypes, high degree of relatedness (Pi hat ≥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 upon evaluation of multi-dimensional scaling plots. Insertion-deletions, multi-allelic and duplicated SNPs were removed. In addition, SNPs with more than 5% missing values, minor allele frequency <0.5%, and not in Hardy-Weinberg equilibrium (P-value <10–4) were removed. After QC, 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 for further analyses. Imputation of our SNP data was carried out using the Michigan Imputation Server,[25] implemented using Eagle2 for haplotype phasing, followed by Minimac2 to impute non-typed SNPs to the 1000 Genomes Phase 3 reference sequence data (http://www.internationalgenome.org). Principal components (PC) were generated from the multi-dimensional scaling analysis of a set of uncorrelated SNPs to obtain population structure for each participant. After examining the scree plots of the components, the first five PCs were selected as the most significant components capturing population structure in our data.

Estimation of polygenic risk scores (PRSs)

To generate PRS, we used publicly available summary statistics of a recent GWAS that identified and validated several genetic variants associated with SBP and DBP in 145 315 individuals of European ancestry.[12] The summary data included >9.8 million SNPs with minor-allele-frequency ≥1%. The GWAS summary statistics were obtained from the UK Biobank data repository (http://biota.osc.ox.ac.uk) and was made accessible to us through the UK Biobank Resource (under application number 44203).

We generated PRSs separately for the four race/ethnic groups, SBP and DBP measurements and for each of the four gestational time points. PRSs were calculated by summing the blood pressure-increasing alleles across genome-wide SNPs at P-value thresholds between 0 and 1e-4 at increments of 5e-5 using a “high resolution scoring” approach that provided the most predictive PRS for each EFWs. An $r^2 \geq 0.1$ (250-kilo base window) was used for clumping to remove SNPs that are in linkage disequilibrium as implemented in PRSice-2, a PRS analysis tool.[14] The PRSs were not weighted by the effect estimates of the GWAS summary statistics. An unweighted genetic risk scoring approach is recommended in situations where (1) no GWAS meta-analyses have yet been performed on the trait of interest (the UK biobank study sample excluded pregnant women and GWASs on blood pressure during pregnancy are non-existent), and (2) existing GWAS meta-analyses are comprised of studies with different ethnicities (the UK biobank study sample is primarily based on individuals of European ancestry).[26] In addition, unweighted risk scores are found to be more robust to errors arising from differences in effect size and population structure, particularly among our ancestrally diverse race and ethnic groups.[27]

Statistical analysis

PRSs-EFWs associations were conducted using linear regression models that included each PRS (grouped into tertiles) as the predictor, each corresponding EFW as the outcome, adjusting for maternal age (in years), parity (nulliparous vs other), education (≤12 vs >12 years of education), population structure (five PCs as continuous variables) and fetal sex. The tests at each gestational period were considered independent tests because fetal growth trajectories were shown to be nonlinear,[4] and the growth patterns significantly vary by trimester.[5] Blood pressure also varies by trimester,[24] and different associations of DBP and SBP on fetal growth or birthweight were reported elsewhere.[2, 28] Additionally, the analyses were stratified by the four self-identified race/ethnic groups to account for underlying fetal weight differences as demonstrated previously[4] and address population stratification bias. We did not adjust for pre-pregnancy BMI or maternal weight, as obesity may mediate

the associations between genetic risk for increased blood pressure and fetal weight.[29] Moreover, genetic variants are associated with BMI and blood pressure, as demonstrated by GWAS studies.[12, 30] We considered analyses showing P-value <0.05 as statistically significant. Regression models estimated change in grams of EFWs and the corresponding 95% confidence interval (CI), comparing groups in second and highest PRS tertile to those in the lowest PRS tertile. All analyses were conducted using PLINK 1.9, PRSice-2 2.1.3.beta,[14] R and SAS version 9.4 (SAS Institute Inc).

Results

The characteristics of our study participants by race/ethnicity groups are presented in Table 1. More details about the study participants has been described previously.[31] The mean±SD maternal age was 27.1±5.5, 30.3±4.5, 25.4±5.3 and 30.7±4.6 years for Hispanics, Whites, Blacks and Asians, respectively. The mean±SD gestational age was approximately 39±2 weeks for each race/ethnicity group. Approximately 34.9% of Hispanics, 53.2% of Whites, 47.1% of Blacks and 47.7% of Asians were nulliparous and 18.0% of Hispanics, 17.4% of Whites, 24.3% of Blacks, and 0.4% of Asians were obese (pre-pregnancy BMI ≥ 30.0 kg/m^2). Approximately, 52.1% of Hispanics, 7.2% of Whites, 41.3% of Blacks, and 21.9% of Asians had ≤12 years of education. The distributions of offspring sex were similar across all race/ethnic groups. EFWs at 13, 20, 27 and 40 weeks gestation were highest among Whites and lowest among Asians. The mean SBP and DBP measurements were slightly lower in the second (13–27 weeks gestation) and higher in the third (28–40 weeks gestation) trimester across groups, similar to the expected changes in blood pressure pattern in non-hypertensive women.[32] Summary of the PRSs and their distribution by ancestry group is presented in Supplementary Table 1 and Supplementary Figure 1.

DBP PRS was significantly associated with EFW among Hispanics and Asians. Specifically, Hispanics in the highest tertile of DBP PRS, as compared to those in the lowest, had 1.1g (95%CI:−2.9, 0.69) lower EFW at week 13 (p-for-trend=0.01), 8.1g (95%CI:−15.1, −1.1) lower EFW at week 20 (p-for-trend=0.02), 32.4g (95%CI:−58.4, −6.4) lower EFW at week 27 (p-for-trend=0.01) and 119.4g (95%CI:−218.1, −20.7) lower EFW at week 40 (p-for-trend=0.02). Asians in the highest tertile of DBP PRS, as compared to those in the lowest, had 1.7g (95%CI:−4.2, 0.9) lower EFW at week 13 (p-for-trend=0.04), 8.5g (−19.2, 2.3) lower EFW at week 20 (p-for-trend=0.03), 32.5g (−71.2, 6.1) lower EFW at week 27 (p-for-trend=0.02), and 137.2 (−263.5, −10.8) lower EFW at week 40 (p-for-trend=0.05). SBP PRS was significantly associated with EFW among Asians similar to that of DBP PRS in which, those in the highest SBP PRS had 39.8g (95%CI:−76.9,−2.7) lower EFW at week 27 (p-for-trend=0.05). In contrast to the pattern observed at 13, 20, and 27 weeks, Hispanics in the highest tertile of SBP PRS had 111.5g (95%CI:12.7, 210.3) higher EFW at 40 weeks (Table 2).

Discussion

We constructed maternal PRSs using blood pressure-increasing alleles from GWAS summary statistics and evaluated the associations between the PRSs and EFWs among Hispanic, White, Black and Asian women. There were significant inverse associations

between maternal DBP PRS and EFW among Asians and Hispanics, and between maternal SBP PRS and EFW among Asians. There was also a tendency for inverse associations between SBP and DBP PRSs and EFWs among Blacks.

The observed inverse association between maternal polygenic risk of increased blood pressure and reduced fetal weight are supported by Mendelian Randomization studies,[8, 13] The analyses of the Early Growth Genetics Consortium and the UK Biobank GWA studies showed that higher maternal SBP is causally associated with lower offspring birthweight, independent of the direct fetal effects.[13] A 10 mm Hg genetically higher maternal SBP was associated with a 208g lower offspring birthweight.[8] Beaumont et al found that maternal blood pressure-raising alleles were associated with lower birthweight by acting via the intrauterine environment (e.g. high blood pressure during pregnancy), rather than via effects of shared alleles with the fetus.[29] However, only small changes in SBP were associated with genetic risk score (GRS) of SBP, and a maternal intrauterine factor such as BMI was not found to be mediator of the association between SBP GRS and offspring birthweight.[8, 13]

We observed an inverse association between PRS of DBP-raising alleles and EFW among Hispanics and Asians, but the inverse associations were not apparent among Whites. Heterogeneity in associations of several cardio-metabolic-related genetic risk scores with fetal growth and birthweight have been previously described by studies in our group using the same study population. For example, high GRS of HDL cholesterol-lowering alleles was associated with increased fetal weight among Whites and Asians but decreased fetal weight among Hispanics.[33] High GRS of maternal BMI-increasing alleles was associated with increased fetal weight at week 27 and week 40 among Hispanics.[31]

The mechanisms through which maternal increased blood pressure influences fetal growth are not well understood. Higher blood pressure levels and intrauterine growth restriction may both be the result of placental dysfunction or maternal cardiovascular adaptations to pregnancy.[6] SBP and DBP levels are elevated in non-hypertensive pregnant women with intrauterine growth restriction.[34] The increase in maternal blood pressure levels may affect the development of the placental villous tree, leading to reduced functional capacity of the placenta, and resulting in fetal growth restriction or lower offspring birthweight.[6] In addition, endothelial dysfunction in the maternal circulation is characteristic of pregnancies complicated by preeclampsia or fetal growth restriction.[35]

Differing effects of the SNPs on EFW acting through other cardiometabolic factors *in utero* have been reported.[36] Therefore, the pathways through which high maternal blood pressure GRS influences EFW may involve metabolic processes other than maternal blood pressure itself. The pathways through which maternal genetic risk of metabolic traits are linked to EFW has also been found to be complex in our previous studies examining GRS of maternal pre-pregnancy obesity and type 2 diabetes.[31, 37] Additional studies that elucidate associations between maternal genetic risk of metabolic traits and fetal growth are of great clinical importance because they support efforts to maintain healthy pregnancy for maximizing healthy fetal growth.

Our study has limitations. The PRSs were constructed from a blood pressure GWAS that excluded pregnant mothers and primarily used European ancestry participants.[11, 12] The predictive accuracy of the PRSs in our study population that included diverse ancestries and pregnant women is unknown. Another limitation in our study includes the lack of fetal genotypes, which could help understand the independent effects of maternal and fetal blood pressure-raising PRSs on EFWs. Moreover, the potential interactions between fetal growth-related fetal genetic variants which may vary in distribution by ancestry[38] and blood pressure-raising PRSs could not be evaluated in the present study. However, it was recently demonstrated that the maternal blood pressure-raising allele acting via the intrauterine environment, has birthweight lowering effect.[29] Using placental biopsies taken from fetal side, we have previously shown that maternal blood pressure during pregnancy is associated with placental epigenetic changes in the same population.[23] In that study, women (n=301) who had gestational hypertension and preeclampsia were 8 (2.7%) and 5 (1.7%), respectively. Due to limited sample size, we did not evaluate associations between hypertensive disorders of pregnancy and placental methylation. Similarly, in the present study, gestational hypertensives and women with preeclampsia were 83 (3.0%) and 92 (3.3%) in the population. Hypertension or preeclampsia could be in the causal pathway between maternal blood pressure-raising polygenic risk score and fetal weight. We did not evaluate the direct or indirect associations between maternal blood pressure-raising PRS with fetal weight as well as mediation by hypertension or preeclampsia as the sample size is limited when data is stratified by race/ethnicity. Future studies should examine these associations by considering hypertensive and preeclamptic women who are more at risk for pregnancies complicated by fetal growth abnormalities.

Important strength of our study includes availability of trimester-specific blood pressure data that allowed us to evaluate intrauterine factors affecting the fetus. In addition, we used longitudinal measurement of fetal biometry using standardized ultrasonological protocol with established quality control and conducted by certified sonographers.[22] This allowed assessment of fetal weight at different times during gestation and facilitated identification of critical time period at which the growth of the fetus may be affected due to maternal genetic propensity to elevated blood pressure. Further, during recruitment, several major chronic diseases were used as exclusion criteria, potentially minimizing confounding by unaccounted pre-pregnancy complications that may influence fetal growth.[22]

In conclusion, in this first multi-ethnic study that assessed associations of PRS of blood pressure and fetal growth during pregnancy, the polygenic risk for elevated diastolic and systolic blood pressure was found to be associated with reduced estimated fetal weight in Hispanics and Asians but not in Whites. Future multi-ethnic GWASs of blood pressure are needed to construct risk prediction models for aberrant fetal growth using PRSs. Such efforts will facilitate clinical management of mothers with high genetic risk for increased blood pressure, for whom there is high burden of aberrant fetal growth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary Table

What is known about topic

- Maternal blood pressure is associated with variations in fetal weight, an important determinant of neonatal and adult health.
- Despite evidences for associations of between genetically elevated maternal blood pressure with lower birthweight, and strong genetic contributions to variations in fetal growth, the relationship between blood pressure-raising genetic risk and fetal growth during pregnancy is unknown.

What this study adds

- We constructed maternal polygenic risk scores using blood pressure-increasing alleles from genome-wide association study summary statistics and evaluated the associations between the PRSs and EFWs among Hispanic, White, Black and Asian women.
- Polygenic risks for elevated systolic and diastolic blood pressures were associated with lower fetal weight among Hispanics and Asians.
- Maternal polygenic risk score of elevated blood pressure may provide utility for clinical interventions aimed at preventing aberrant fetal growth in diverse populations.

Table 1.

Characteristics of the study participants

	Hispanics (n=568)	Whites (n=622)	Blacks (n=637)	Asians (n=238)	P-value[1]
Maternal characteristics					
Age, y, mean ± SD	27.1 ± 5.5	30.3 ± 4.5	25.4 ± 5.3	30.7 ± 4.6	<0.001
Gestational age at delivery, weeks, mean ± SD	39.3 ± 1.8	39.2 ± 1.9	39.0 ± 2.2	39.3 ± 1.2	0.07
Nulliparous, n (%)	198 (34.9)	331 (53.2)	300 (47.1)	116 (48.7)	<0.001
Pre-pregnancy body mass index (kg/m^2), n (%)					<0.001
<25.0	279 (49.7)	379 (61.1)	295 (46.6)	197 (83.5)	
25.0–29.9	181 (32.3)	133 (21.5)	184 (29.1)	38 (16.1)	
≥30.0	101 (18.0)	108 (17.4)	154 (24.3)	1 (0.4)	
≤12 years of education, n (%)	296 (52.1)	45 (7.2)	263 (41.3)	52 (21.9)	<0.001
Systolic blood pressure, mmHG, mean ± SD					
First trimester (0–13 weeks gestation)	108.2 ± 10.2	110.8 ± 10.2	112.8 ± 10.3	106.5 ± 10.1	<0.001
Second trimester (14–27 weeks gestation)	107.2 ± 9.0	110.2 ± 8.5	111.6 ± 9.2	105.8 ± 8.2	<0.001
Third trimester (28–40 weeks gestation)	109.6 ± 9.4	113.4 ± 9.5	114.5 ± 9.8	108.4 ± 8.5	<0.001
Diastolic blood pressure, mmHG, mean ± SD					
First trimester (0–13 weeks gestation)	65.2 ± 7.8	67.2 ± 7.5	67.9 ± 7.7	67.3 ± 13.2	<0.001
Second trimester (14–27 weeks gestation)	63.1 ± 6.9	65.4 ± 6.0	65.9 ± 6.5	64.7 ± 5.9	<0.001
Third trimester (28–40 weeks gestation)	65.5 ± 7.1	68.3 ± 6.7	68.4 ± 6.7	67.5 ± 6.8	<0.001
Fetal characteristics					
Female, n (%)	257 (49.6)	271 (46.4)	294 (51.3)	101 (48.8)	0.11
Ultrasound Estimated Fetal Weight, g, mean ± SD					
End of first trimester (13 weeks gestation)	80.7 ± 8.2	82.2 ± 7.6	81.4 ± 7.8	79.4 ± 8.2	0.001
Mid gestation (20 weeks gestation)	332.8 ± 34.8	341.4 ± 32.0	333.7 ± 32.9	326.0 ± 34.1	<0.001
End of second trimester (27 weeks gestation)	1159.1 ± 129.2	1200.1 ± 118.0	1150.6 ± 120.2	1128.6 ± 120.6	<0.001
Third trimester (40 weeks gestation)	3675.9 ± 492.8	3853.3 ± 469.7	3581.4 ± 441.3	3552.9 ± 438.2	<0.001

[1]P-value, by chi-squared test or analysis of variance (ANOVA) test, as appropriate

Table 2.

Associations between SBP and DBP-increasing polygenic risk scores and estimated fetal weight at different gestation weeks

	Hispanics (n=568)	P-value	Whites (n=622)	P-value	Blacks (n=637)	P-value	Asians (n=238)	P-value
Systolic Blood Pressure Polygenic Risk Score								
End of first trimester (13 weeks gestation)								
Tertile 1	ref		ref		ref		Ref	
Tertile 2	−0.82 (−2.55, 0.91)	0.35	0.77 (−0.66, 2.21)	0.29	−0.31 (−1.8, 1.18)	0.68	−1.62 (−4.4, 1.15)	0.25
Tertile 3	−1.53 (−3.18, 0.13)	0.07	1.28 (−0.23, 2.8)	0.1	−0.94 (−2.44, 0.56)	0.22	−1.68 (−4.24, 0.89)	0.2
P-for-trend		0.14		0.13		0.28		**0.02**
Mid gestation (20 weeks gestation)								
Tertile 1	ref		ref		ref		Ref	
Tertile 2	−2.53 (−9.83, 4.77)	0.5	1.84 (−4.37, 8.05)	0.56	−1.46 (−7.74, 4.82)	0.65	−9.05 (−20.2, 2.1)	0.18
Tertile 3	−5.65 (−12.71, 1.41)	0.12	4.33 (−2.01, 10.66)	0.18	−3.6 (−9.99, 2.8)	0.27	−12.93 (−23.46, −2.4)	0.12
P-for-trend		0.2		0.1		0.2		**0.02**
Second trimester (27 weeks gestation)								
Tertile 1	ref		ref		ref		ref	
Tertile 2	1.8 (−25.24, 28.84)	0.9	13.91 (−8.25, 36.08)	0.22	−6.3 (−29.07, 16.47)	0.59	−24.93 (−64.11, 14.25)	0.21
Tertile 3	−5.52 (−31.58, 20.53)	0.68	19.28 (−4.19, 42.75)	0.11	−10.25 (−34.04, 13.53)	0.4	**−39.82 (−76.91, −2.72)**	**0.04**
P-for-trend		0.34		0.08		0.15		0.05
Third trimester (40 weeks gestation)								
Tertile 1	ref		ref		ref		ref	
Tertile 2	**111.52 (12.73, 210.32)**	**0.03**	18.23 (−72.9, 109.35)	0.69	−13.74 (−100.59, 73.12)	0.76	63.34 (−71.65, 198.34)	0.36
Tertile 3	48.63 (−51.45, 148.7)	0.34	50.89 (−41.62, 143.4)	0.28	−59.42 (−139.61, 20.77)	0.15	−62.97 (−194.12, 68.18)	0.34
P-for-trend		0.39		0.06		0.07		0.17
Diastolic Blood Pressure Polygenic Risk Score								
End of first trimester (13 weeks gestation)								
Tertile 1	ref		ref		ref		ref	
Tertile 2	0.92 (−0.76, 2.61)	0.28	0.77 (−0.66, 2.21)	0.29	−0.06 (−1.52, 1.39)	0.93	−1.62 (−4.4, 1.15)	0.25
Tertile 3	−1.1 (−2.9, 0.69)	0.23	1.28 (−0.23, 2.8)	0.1	−0.69 (−2.19, 0.81)	0.37	−1.68 (−4.24, 0.89)	0.2
P-for-trend		**0.01**		0.05		0.05		**0.04**
Mid gestation (20 weeks gestation)								

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	Hispanics (n=568)	P-value	Whites (n=622)	P-value	Blacks (n=637)	P-value	Asians (n=238)	P-value
Tertile 1	ref		ref		ref		ref	
Tertile 2	−3.04 (−9.92, 3.84)	0.39	3.47 (−2.54, 9.49)	0.26	−0.46 (−6.66, 5.74)	0.88	−7.5 (−18.6, 3.6)	0.18
Tertile 3	**−8.07 (−15.07, −1.06)**	**0.02**	4.53 (−1.86, 10.92)	0.16	−3.53 (−9.85, 2.78)	0.27	−8.47 (−19.22, 2.29)	0.12
P-for-trend		**0.02**		**0.04**		0.05		**0.03**
End of second trimester (27 weeks gestation)								
Tertile 1	ref		ref		ref		ref	
Tertile 2	−11.04 (−35.56, 13.48)	0.38	13.91 (−8.25, 36.08)	0.22	−2.28 (−25.27, 20.7)	0.85	−27.79 (−64.98, 9.4)	0.14
Tertile 3	**−32.38 (−58.39, −6.36)**	**0.01**	19.28 (−4.19, 42.75)	0.11	−14.91 (−37.85, 8.02)	0.2	−32.54 (−71.16, 6.07)	0.1
P-for-trend		**0.01**		**0.03**		0.07		**0.02**
Third trimester (40 weeks gestation)								
Tertile 1	ref		ref		ref		ref	
Tertile 2	−8.56 (−100.94, 83.82)	0.86	48.25 (−41.53, 138.04)	0.29	0.86 (−83.58, 85.3)	0.98	62.1 (−68.17, 192.37)	0.35
Tertile 3	**−119.41 (−218.09, −20.73)**	**0.02**	73.62 (−18.61, 165.86)	0.12	−81.35 (−168.19, 5.49)	0.07	**−137.16 (−263.5, −10.82)**	**0.03**
P-for-trend		**0.02**		0.05		0.18		0.05

*Statistically significant estimats are shown in Bold

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