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Testing a Maternal Genetic Risk Score for Birth Weight for Generalizability Across Races: Secondary analysis of a prospective observational cohort.

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1 Introduction

Fetal growth restriction (FGR), traditionally defined as estimated fetal weight <10th percentile, is a leading risk factor for stillbirth and a major focus of antenatal ultrasound use.(1) Current diagnostic strategies for FGR perform poorly to predict perinatal morbidity and mortality, such that most fetuses diagnosed with FGR

do not experience any perinatal morbidity.(2) Efforts have been made to customize fetal growth assessments using maternal and fetal factors that are associated with variation in fetal growth, including maternal race.(3) However, race is a socially defined construct that is fluid over time and subject to considerable admixture and therefore is a problematic proxy for genetic growth potential.(4) Furthermore, its use has the potential to exacerbate disparities by conflating the effect of imposed deprivations with genetics, potentially reclassifying abnormal growth as normal and causing necessary surveillance and interventions to be withheld.(5, 6)

Instead, the integration of genetic data may be a more valid and effective approach to personalize fetal growth assessments and thereby improve recognition of abnormal growth. Recent studies identified genetic markers associated with fetal growth that could be used for such purposes.(7-9) However, it is increasingly recognized that genetic findings in predominantly European cohorts do not generalize to more diverse populations.(10-12) Therefore, the objective of this study was to assess a genetic risk score (GRS) for birth weight (GRS_{BW}), recently developed from a European cohort, for generalizability within groups defined by self-identified race and genetically predicted ancestry.

Because the rationale to use a GRS_{BW} to customize fetal growth assessment is to obviate the impulse to customize using race/ethnicity, our secondary objective was to determine whether self-identified race/ethnicity remains associated with birth weight (BW) after accounting for the GRS_{BW}.

2 Methods

2. Study Setting and Population

Our study was a secondary analysis of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), a large prospective observational cohort study designed to assess contributors to adverse pregnancy outcomes. Detailed nuMoM2b protocols were previously published and are briefly summarized here.(13) Participants in the parent study were recruited at 8 geographically diverse U.S. sites from 2010-2013 and were included if they had a singleton pregnancy between 6 weeks 0 days and 13 weeks days' gestation and no prior pregnancies lasting 20 weeks or more. Potential participants were excluded for age <13 years, 3 or more prior miscarriages, suspected fetal malformation at the time of enrollment, known fetal aneuploidy, conception using a donor oocyte, multifetal reduction, plan for pregnancy termination, or participation in an intervention study to influence pregnancy outcomes. Participants had 4 study visits: during approximately the first, second, and early third trimesters of pregnancy, as well as one after delivery. For this secondary analysis, we included all participants with a live birth at [?]24 weeks with available maternal single nucleotide polymorphism (SNP) array data, derived from unselected maternal blood collection that was part of the protocol for all parent study participants. Participants were excluded if they did not complete any of the 3 research ultrasounds or were missing key variables including fetal sex and BW.

2.2 Outcomes

The primary outcome of this study was association of one's genetic risk score for infant BW with race. Race was divided into self-identified race and genetic ancestry. The secondary outcome of this study was to assess the relationship and overlap between self-identified race and genetic ancestry.

Race designations were self-identified from among the following: White, Black/African American, Asian, Native Hawaiian/Other Pacific Islander, American Indian/Alaskan Native, Multiracial, and Unknown/not reported. Genetic ancestry was ascertained using *Peddy,* a software package that uses an individual's DNA to predict the predominant continental ancestry(14) with the following categorical outputs: AFR, African; AMR, American (Indigenous); EAS, East Asian; EUR, European; SAS, South Asian; UNK, unknown. We assessed the distribution of predicted genetic ancestry within self-identified racial groups.

Maternal DNA was isolated from blood collected at visit 1. Genotyping was performed using a commercially available kit (Infinium Multi-Ethnic Global D2 Bead Chip; Illumina), from which SNP arrays were conducted based on the Genome Reference Consortium human build 38 (CRCh38).(15) 86 BW-associated SNPs that were identified using GRCh37(7) were mapped to GRCH38 for compatibility, yielding 73 SNPs. Maternal

SNP arrays were used to compute the GRS_{BW} for each maternal participant using the weighted sum of BW-associated variants present in each person, such that the score represents the cumulative effect size without traditional units, expressed as $\Gamma P \Sigma = (\breve{}_1 * \beta_1) + (\breve{}_2 * \beta_1) + \ldots (\breve{}_{73} * \beta_{73})$, where V_1 is variant 1 and β_1 is the effect size for variant 1.

2.3 Statistical Analysis

A log-linear model was used to test the association between maternal GRS_{BW} with infant BW, controlling for fetal sex and gestational age at birth. To assess generalizability of the GRS_{BW} across self-identified racial groups, the association between GRS_{BW} and BW was assessed for each self-identified racial subgroup using stratified log-linear models. This same approach was repeated across groups defined by genetic continental ancestry. Finally, self-identified race and genetic ancestry were included as predictor variables in separate log-linear models to test whether they remained independently associated with BW after controlling for GRS_{BW}, infant sex, and gestational age.

3 Results

There were 8,147 participants that met inclusion criteria(**Fig. 1**). Participants' demographic and obstetric characteristics are shown in **Table 1** . Maternal GRS_{BW} values ranged from -0.214 to 0.713 and were positively associated with infant BW (p 0.06, meaning that a change in GRS_{BW} of 1.0 (essentially the entire range of possible GRS_{BW} values) is associated with a 6% increase in BW. The measures of association for terms in the initial model are shown in **Table 2** .

Among the included nuMoM2b participants, the largest self-identified racial group was White, (n=5394, 64.1%), followed by Black/African American (n= 1139, 14.0%), unknown (n=699, 8.6%), multiracial (n=508, 6.2%), and Asian (n=358, 4.4%). Genetically predicted continental ancestry groups, in order of decreasing size, were EUR (n=5,099, 62.6%), AFR (n=1,383, 17.0%), AMR (n=1028, 12.6%), EAS (n=274, 3.4%), UNK (n=264, 3.2%), and SAS (n=99, 1.2%). Within each self-identified racial group, the most common genetic ancestry was as follows: White: EUR (91.6%); Black/African American: AFR (98.8%); Unknown/not reported: AMR (69.4%); multiracial: AFR (30.1%); Asian: EAS (66.5%); Native Hawaiian/Pacific Islander: EAS (68.8%); American Indian/Alaska Native: AMR (76.5%). Overlap between race and predicted ancestry is reported in **Table 3** .

Figure 2 shows the results of our primary analysis our assessing the generalizability of the association between GRS_{BW} and infant BW by self-identified race. The association between GRS_{BW} and infant BW was only significant among participants who self-identified as White (=0.036, 95% CI 0.01-0.062) or more than one race (=0.096, 95% CI 0.008-0.184).

Across racial groups, the magnitude of the association between GRS_{BW} and infant weight varied widely; the magnitudes of the association in Asian and multi-racial groups (0.09 and 0.1, respectively) were more than double that of White and Black groups (0.04 for both). The variation in the magnitude of the association and statistical association across racial groups is shown in **Figure 2.**

Figure 3 demonstrates the results for analyses assessing the association between GRS_{BW} and infant weight within genetically predicted ancestry groups rather than self-identified race. GRS_{BW} was associated with BW in the EUR (=0.044, 95% CI 0.017-0.07, p=0.007) and AMR (=0.073, 95% CI 0.012-0.135, p=0.007) ancestry groups but not AFR, EAS, SAS, or unknown groups (**Figure 3**).

Two final log-linear models each assessed the association between self-identified race or genetically predicted ancestry and BW after controlling for GRS_{BW} in the entire included cohort, using the largest groups in each category (White race, EUR predicted ancestry) as the referent groups. For all groups except American Indian/Alaska Native, self-identified race was independently associated with lower BW after controlling for GRS_{BW}, gestational age, and infant sex (**Table 4**). All genetically predicted ancestry groups except for UNK remained independently associated with lower BW (**Table 4**). Coefficients and confidence intervals for all included terms in each of the models in Table 4 are shown in**Supplementary Tables 1 and 2** .

4 Discussion

4.1 Main Findings

In a cohort of well-characterized nulliparous pregnant people, a GRS_{BW}, derived from a set of previously was modestly associated with infant BW. However, its association with BW was not statistically significant among participants who self-identified as Black, Asian, or had an unknown race, or among those with AFR, EAS, SAS, or UNK genetically predicted ancestry. Our findings suggest that the GRS_{BW} does not fully generalize to racially or genetically diverse groups.

4.2 Interpretation

Our findings are concordant with other studies assessing the relationship between race and fetal growth. Across a variety of contexts, studies have found that race is associated with differences in fetal growth among both unselected and low risk groups.(16-18) In our study, both self-identified race and genetically predicted ancestry were associated with gestational age-adjusted BW, even after controlling for sex and GRS_{BW}. Our finding that the GRS_{BW} was not consistently associated with BW across non-European ancestry groups is also consistent with existing studies of other conditions. Polygenic risk scores derived in primarily European cohorts perform significantly less well in participants of non-European descent for multiple conditions, including venous thromboembolism, coronary artery disease, heart disease, hypertension, chronic kidney disease, and cancer.(19-25) The non-generalizability of genetic findings to diverse populations is a critical gap with the potential to exacerbate existing disparities.(26, 27) Our findings add to this important body of work by extending it to fetal growth, which holds considerable clinical relevance in perinatal medicine.

Our findings have several implications for future efforts in this area. First, our results demonstrating that GRS_{BW} is not associated with BW in many ancestry groups, and that genetically predicted ancestry remains independently associated with BW after controlling for $GRS_{BW,}$ suggests that additional work is needed to achieve equity in the performance of genetic risk scores for BW prediction. Methods to support multi-ancestry polygenic risk score derivation are now available and are promising in their ability to equitably leverage genotypes for trait prediction. However, but such methods still depend on the availability of discovery cohorts that themselves are diverse, if not globally representative.(28-32) As precision medicine advances its ability to improve recognition of diseases such as fetal growth restriction and thereby allow for earlier surveillance or treatment, genetic risk scores that perform better in some populations than others have the potential to exacerbate inequities in adverse pregnancy outcomes. Second, two results suggest that there are additional unaccounted-for factors linking race to fetal growth: the lack of association between GRS_{BW} and BW in multiple self-identified racial groups, and that self-identified race remains associated with BW after controlling for GRS_{BW}. As noted, the GRS_{BW} is likely insufficiently capturing the genetic components of this association. However, as race is a social construct, the persistent association between race and BW can also be linked to systematic differences in environmental and social exposures that are known to contribute to racial health disparities. It is also plausible that there are epigenetic influences reflecting the transgenerational impact of racism and other forms of deprivation, oppression, and hardship imposed on minoritized populations. These factors and their complex relationships to the genetics of fetal growth remain to be clarified and warrant further investigation.

4.3 Strengths and Limitations

Strengths of our study included the use of a large, multicenter U.S. obstetric cohort with geographical and racial diversity. The nuMoM2b protocol provides both standardized specimen collection and validated outcomes ascertainment, and we used externally derived BW-associated SNPs for GRS_{BW} assessment, adding to the rigor and validity of our analysis. Additionally, our assessment of GRS_{BW} using two distinct approaches (both self-identified race and genetically predicted continental ancestry groups) demonstrates that the lack of generalizability is a robust finding.

Our study also had limitations. The need to map SNPs derived from reference build GRCh37 to GRCh38,

ultimately leading to the use of 73 rather than 86 SNPs may have reduced the strength of the overall association between the GRS_{BW} and BW. Also, it is possible that the lack of association between the $GRS_{BW}$and BW is due to the sample sizes of each group, especially for the smallest groups, such as Native Hawaiian/Pacific Islander or American Indian/Alaska Native. However, sample size limitations are unlikely to fully explain the lack of association, as the GRS_{BW} was associated with BW in the multiracial group (n=508) and was very nearly significant among those of SAS predicted ancestry (n=274), both of which had smaller sample sizes than the largest groups in which GRS_{BW} was not associated with BW.

Author Contributions

Each author fulfils the requirements for authorship, with contributions as follows: parent cohort study design and execution: R.M.S., D.H., G.S.; study conception, design, and planning: N.B., L.P., M.J., J.M.; data analysis L.P., M.J., B.M.; results interpretation: B.T., L.P., M.Z., M.P.D., R.G., B.M., R.M.S, D.H., T.W., J.G.S., G.S., N.B.; manuscript drafting: B.T., N.B.; manuscript editing and final approval: B.T., L.P., M.J., M.Z., M.P.D., J.M., R.F., B.M., R.M.S., T.W., D.H., J.G.S., G.S., N.B.

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Ethics Statement

This work was designated by the University of Utah Institutional Review Board (protocol # 00113635) as exempt based on the U.S. Department of Health and Human Services 45 CFR 46 definition of human subjects research.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Table 1. Demographic and obstetric characteristics of nuMoM2b participants meeting secondary analysis inclusion criteria.

Birth weight (g), mean +-SD & 3239.5 (559.1) BW <10th percentile, n (%) 773 (9.5) BW >90th percentile, n (%) 351 (4.3) Newborn sex male, n (%) 4190 (51.4)**Table 2** . Association between infant birth weight and

maternal GRS_{BW}, infant sex, and gestational age at delivery, nuMoM2b cohort, 2010-2013

Parameter	Estimate (95% CI)	t value	p
Intercept	-1.164 (-1.561, -0.767)	-5.74	<.0001
Maternal GRS_{BW}	0.063 (0.041, 0.085)	5.69	<.0001
Female sex (vs male)	-0.042 (-0.047, -0.036)	-14.34	<.0001
Gestational age	0.419 (0.397, 0.441)	37.49	<.0001
Gestational age^2	-0.005 (-0.005, -0.004)	-30.14	<.0001

CI= Confidence Interval

GRS_{BW} = Growth restriction score for birth weight

Table 3 . Alignment between self-identified race and genetically predicted ancestry in a nulliparous cohort of pregnant people

	White	Black/African American	Unknown	Multi-racial	Asian	Nativ
All participants N (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
(n=8147)	5394 (66.2)	1139 (14.0)	699 (8.6)	508 (6.2)	358 (4.4)	32 (0.4
Genetic Ancestry (N%)						
EUR 5099 (62.6)	4949 (91.8)	6 (0.5)	30 (4.3)	111 (21.9)	1 (0.3)	1 (3.1)
AFR 1383 (17.0)	8 (0.2)	1125 (98.8)	90 (12.9)	153 (30.1)	2 (0.6)	2 (6.3)
AMR 1028 (12.6)	388 (7.2)	4 (0.4)	485 (69.4)	118 (23.2)	16 (4.5)	4 (12.5
EAS 274 (3.4)	1 (0)	0 (0)	4 (0.6)	9 (1.8)	238 (66.5)	22 (68
UNK 264 (3.2)	48 (0.9)	3 (0.3)	86 (12.3)	114 (22.4)	10 (2.8)	3 (9.4)
SAS 99 (1.2)	0 (0)	1 (0.1)	4 (0.6)	3 (0.6)	91 (25.4)	0 (0)

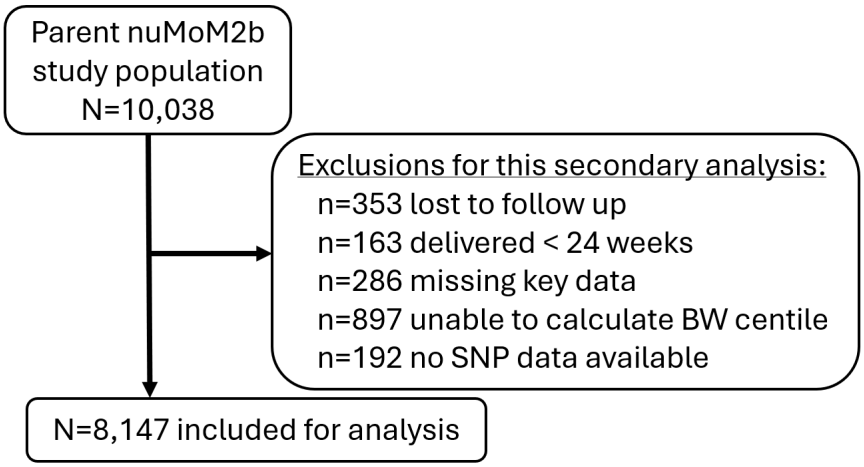
Percentages for genetic ancestry within each self-identified race use the total n from the self-identified race as the denominator.*Peddy* predicts the predominant continental genetic ancestry in single categories. Percentages for total genetic ancestry (far left column) use the overall N (8147) as the denominator. Abbreviations: EUR, European; AFR, African; AMR, American; EAS, East Asian; UNK, Unknown; SAS, South Asian.

Table 4 . Associations between self-identified race or genetically predicted ancestry with BW after controlling for GRS_{BW}.

Self-Identified Race (ref: White)	Estimate (95% CI)	P
American Indian/ Alaskan Native	-0.01 (-0.071, 0.052)	0.76
Asian	-0.037 (-0.051, -0.023)	<0.0001
Black/African American	-0.042 (-0.051, -0.034)	<0.0001
More than one race	-0.015 (-0.027, -0.003)	0.011
Native Hawaiian/Pacific Islander	-0.052 (-0.097, -0.007)	0.023
Unknown	-0.023 (-0.033, -0.013)	<0.0001
Genetically predicted continental ancestry (ref: EUR)		
AFR	-0.042 (-0.049, -0.034)	<0.0001
AMR	-0.018 (-0.027, -0.010)	<0.0001
EAS	-0.020 (-0.036-|-0.004)	0.012
SAS	-0.093 (-0.119, -0.067)	<0.0001
UNK	-0.009 (-0.025, 0.007)	0.255

Caption: Estimates reflect the beta coefficients for each term in the log linear model in comparison to the reference group. AFR, African; AMR, American; EAS, East Asian; SAS, South Asian; UNK, unknown.

Figure 1 . Inclusion flow diagram.



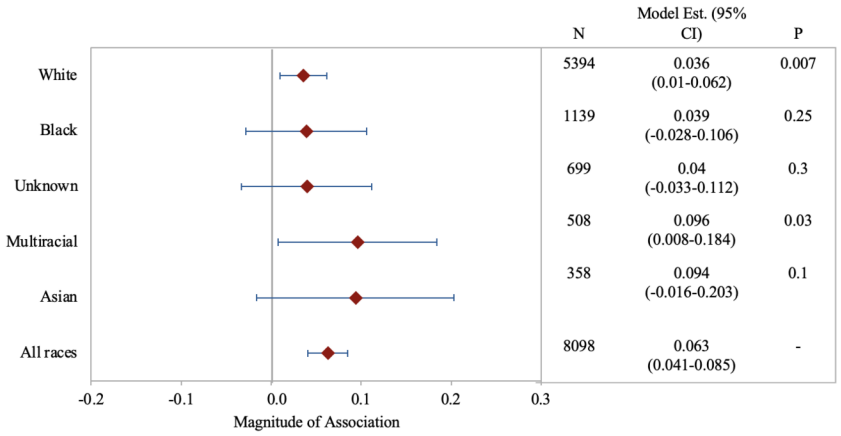


Figure 2: Association of GRS_{BW} with BW in self-identified racial groups.

Caption: The forest plot shows the range of the magnitudes of association, with error bars reflecting the 95% confidence intervals for the association. The magnitude of association means that in the model, an increase in GRS_{BW} of 1.0 is associated with an increase in BW of 3.6% the White race participants, for example. BW, birth weight; EST, estimate; LCL, lower bound of the confidence interval; UCL, upper bound of the confidence interval, P= P value.

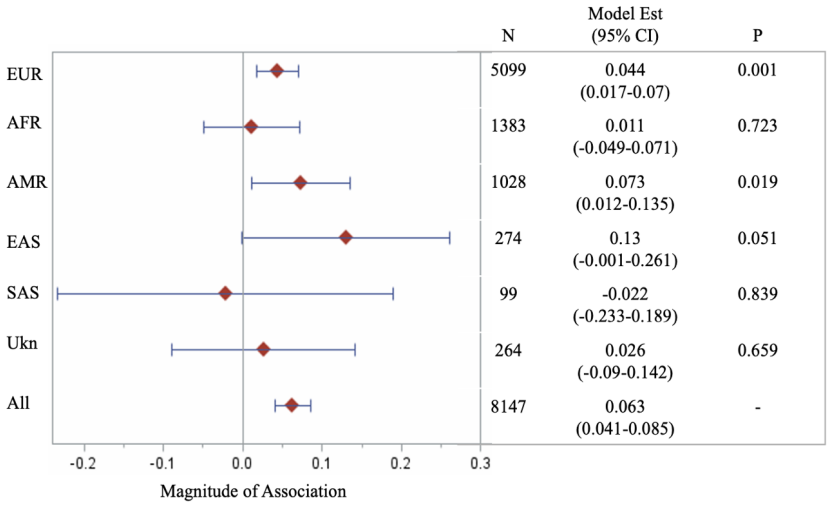


Figure 3 . Association of GRS_{BW} with BW in genetically predicted continental ancestry groups.

Caption: The forest plot shows the range of magnitudes of association, with error bars reflecting the 95% confidence intervals. The magnitude of association means that in the model, an increase in GRS_{BW} of 1.0 is associated with an increase in BW of 4.4% in the EUR group, for example. The estimate, lower bound of the confidence interval and upper bound of the confidence interval is shown in the table to the right.