

Contribution of maternal and fetal genetics to fetal weight throughout pregnancy and at birth

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Competing Interests

GS receives/has received research support from Roche Diagnostics, Illumina, and Pfizer (fetal growth restriction, preeclampsia, preterm birth and infection). GS is/has been a paid consultant to Natera Inc (pregnancy screening), Medicines360 (pregnancy screening), Exeltis (preeclampsia) and GSK (preterm birth). GS is/has been a member of a Data Monitoring Committee for GSK (RSV vaccination in pregnancy), Moderna (RSV vaccination in pregnancy) and NGM Biopharmaceuticals, Inc (treatment of hyperemesis gravidarum, committee chair). GS is a named inventor on four patents for the prediction of adverse pregnancy outcome, and these patents have been licensed to Medicines360. GS is an ambassador for the UK stillbirth charity, Sands.

DSC-J is/has been a paid consultant to Medicines360 (screening in pregnancy) and GondolaBio (pregnancy related diagnostics and therapeutics). DSC-J is a named inventor in a series of patents for the prediction of fetal growth restriction, preeclampsia and gestational diabetes mellitus in pregnancy, filed by Cambridge Enterprise and licensed to Medicines360.

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- 1) **Tweetable statement:** Fetal and maternal genetics both influence fetal growth across gestation. Growth-restricted babies have greater differences between their genetically-predicted and observed birthweights compared to those who are constitutionally small.
- 2) **Short title:** Fetal and maternal genetic effects on fetal growth across gestation
- 3) **AJOG at a Glance:**
 - a. **Why was this study conducted?**
 - We used a polygenic risk score (PRS) for birthweight to evaluate the effects of fetal and maternal genetics on estimated fetal weight (EFW) and birthweight across pregnancy and at birth.
 - We also assessed how the difference between genetically-predicted and observed birthweight can help distinguish between small-for-gestational-age (SGA) babies and babies who experience intrauterine growth restriction (IUGR).
 - b. **What are the key findings?**
 - Fetal PRS accounts for ~11-12% of variance in birthweight, while maternal PRS accounts for ~6% in two mother-child cohorts with European ancestry.
 - In a South Asian ancestry cohort, the birthweight variance explained by the joint fetal-maternal PRS was approximately halved compared to European cohorts
 - SGA babies show smaller differences between their predicted and observed birthweights compared to IUGR babies.
 - c. **What does this study add to what is already known?**
 - This study separates the fetal and maternal genetic effects on EFW across gestation, and demonstrates that maternal genetic effects on fetal growth are more impactful at later gestations
 - We demonstrate the need to include more diverse ancestry groups in large-scale genetic studies around pregnancy and birthweight to create more representative risk scores.
 - Our findings suggest the potential use of deviation from genetically-predicted birthweight as a metric to differentiate growth-restricted (IUGR) from constitutionally small (SGA) babies.

Abstract

Word count: 480/500

Background: Both fetal and maternal genomes contribute to birthweight, but the timing and relative magnitude of their effects during gestation remain unclear. Polygenic risk scores (PRSs), constructed from genome-wide association studies (GWAS), capture the cumulative influence of common birthweight-associated variants to quantify genetic predisposition to fetal growth. We constructed fetal and maternal PRSs for birthweight in two UK birth cohorts, the Pregnancy Outcome Prediction Study (POPS) and Born in Bradford (BiB), to evaluate their associations with estimated fetal weight (EFW) throughout pregnancy and with birthweight at delivery. We also investigated whether PRSs could improve risk stratification of infants born below the 10th centile by distinguishing those with pathological intrauterine growth restriction (IUGR) from those who are constitutionally small-for-gestational-age (SGA).

Methods: In POPS and BiB, we used LDpred2-auto to estimate PRSs based on the largest available maternal and fetal GWAS for birthweight. We longitudinally assessed EFW associations with PRSs using linear mixed effects models in POPS and BiB. We evaluated birthweight associations with PRSs using linear models, where birthweight was adjusted for gestational age and fetal sex. We estimated R^2 and conducted variance decomposition analyses for all models. Genetically-predicted birthweights were estimated from joint models of fetal and maternal PRSs plus ten genetic principal components (PCs). BiB analyses were conducted separately for genetically-inferred European (EUR) and South Asian (SAS) ancestry.

Results: While PRS_{fetus} was significantly associated with EFW at baseline (~22 weeks gestation) across cohorts, PRS_{mother} was not. Both the interaction of PRS_{fetus} and PRS_{mother} with gestational age (GA) were significantly associated with EFW. The effect of PRS_{mother} on EFW increased more quickly across gestation than the effect of PRS_{fetus} in POPS, but this finding was not replicated in BiB. Jointly, fetal and maternal polygenic risk explained 4% of variance in EFW in POPS and 1% in BiB-EUR. In POPS, fetal and maternal PRSs showed independent contributions to EFW variance of 3% and 0.5%, respectively. Joint and univariable linear models showed significant positive associations of PRS_{fetus} and PRS_{mother} with observed birthweight. In POPS, PRS_{fetus} and PRS_{mother} accounted for ~10% and ~4% of variance in birthweight over covariates alone, respectively, which was replicated in BiB-EUR. Maternal and fetal genetic effects jointly explained 11% of birthweight variance in POPS, similar to BiB-EUR, at 12%; however, the variance explained was reduced by half in BiB-SAS, at 6%. Among POPS babies

born <10th birthweight centile, the magnitude of the difference between observed and genetically-predicted birthweight was greater in the group judged clinically to be IUGR vs. SGA (p=0.008; point estimate=0.29, 95%CI: 0.12, 0.47).

Conclusions: Maternal and fetal PRSs jointly account for ~11-12% of birthweight variance in European ancestry groups, but much less in a South Asian cohort. In POPS, the effect of birthweight-associated SNPs on estimated fetal weight increases more rapidly across pregnancy for maternal than for fetal genetic effects. Deviation from genetically-predicted birthweight may be a useful metric to help distinguish growth-restricted from constitutionally small babies.

Introduction

Fetal growth is a dynamic developmental process shaped by fetal, placental, and maternal factors. It is an important determinant of perinatal outcomes and health across the life course¹⁻⁷. Improving understanding of processes that shape fetal growth may provide insight into mechanisms underlying pregnancy complications and support identification of pregnancies at risk of adverse perinatal outcomes.

Birthweight reflects cumulative effects of fetal growth trajectories across gestation and timing of delivery. Epidemiological and genetic studies demonstrate that fetal and maternal factors contribute to birthweight variation⁸⁻¹⁰. SNP-based heritability for birthweight is 15-40%^{10,11}, and genome-wide association studies (GWAS) show that birthweight is influenced by genetic variants carried by both mother and fetus¹⁰. Fetal genetic effects may capture influences acting through the fetus or placenta, whereas maternal genetic effects may act indirectly, shaping the intrauterine environment. Although both contribute, fetal genetic factors likely explain more of the total birthweight variance¹⁰.

However, using birthweight as a stand-alone metric provides limited insight into when influences on fetal growth emerge, how they vary across pregnancy, or whether they affect fetal size, gestational duration, or both¹². The relative influence of fetal and maternal genetic contributions may vary across gestation¹³. As fetal nutrient demand increases, placental transport capacity and maternal nutrient supply are likely to become increasingly relevant to fetal size^{14,15}. However, the lack of cohorts with maternal and fetal genetic data alongside universal serial ultrasound measures has prevented systematic understanding of how genetics shape fetal growth trajectories.

A key reason for seeking further insight into genetic influences on fetal growth is that it remains complex to distinguish between small (<10th centile birthweight) babies that fail to meet their genetic growth potential (intrauterine growth restriction, or IUGR) and constitutionally small, healthy babies (small-for-gestational-age, or SGA). These groups exhibit different risk profiles for immediate and long-term adverse outcomes¹⁶⁻¹⁸. Existing clinical approaches to identifying IUGR¹⁹⁻²² are heterogeneous and fail to accurately classify all cases. We assess whether the difference between observed and genetically-predicted birthweight can be useful to distinguish IUGR from SGA babies.

Further, birthweight distributions differ across ethnic groups²³, yet most genetic studies of birthweight are conducted in individuals of genetically-inferred European ancestry. Previous evidence suggests that while common variant effects acting through the fetus may be consistent across populations¹⁰, there may be differing associations between maternal PRS and birthweight across ethnic groups²⁴. Using data from two ethnically, socio-economically, and geographically distinct UK birth cohorts, the Pregnancy Outcomes Prediction Study (POPS) and Born in Bradford (BiB), we investigated the extent to which maternal and fetal polygenic risk explain variation in (i) estimated fetal weight (EFW) across pregnancy, (ii) birthweight, and (iii) the likelihood of IUGR at birth.

Methods

1. Cohort Overview

a. Pregnancy Outcome Prediction Study (POPS)

POPS is a prospective study of unselected nulliparous women at Rosie Hospital in Cambridge, United Kingdom. Women with a singleton pregnancy were enrolled from January 2008-July 2012 (n=4,212)^{25,26}. All participants underwent standardized, serial ultrasound scans at ~12, ~20, ~28, and ~36 weeks gestation²⁶ (Table S1, Supplemental File 1). Within the analytic sample, all POPS participants self-reported their ethnicity as White British; 25% of participants were in the most deprived socioeconomic quartile (Table S2).

b. Born in Bradford (BiB)

BiB is a multi-ethnic, longitudinal birth cohort (n=12,453) recruited between 2007-2011²⁷. 52% of the cohort reported South Asian ethnicity; 45% of European ethnicity and 68% of South Asian ethnicity participants were from neighborhoods in the most deprived socioeconomic quintile (Table S2). BiB did not include universal serial ultrasound scans, however, many participants had clinically-indicated ultrasound scans after their ~20 week scan (Table S1), the results of which were extracted from maternal health records.

2. Preparation of the phenotype data

Observed birthweight was converted to age- and sex-adjusted birthweight centiles using the UK 1990 growth reference data²⁸. In POPS, n=2543 babies were included in birthweight analyses, compared to n=2075 in BiB-EUR and n=2210 in BiB-SAS (Table S1).

In POPS, gestational age was derived from crown-rump length (CRL) measured by ultrasound (<14 weeks of gestation)²⁰. In BiB, gestational age was determined based on last menstrual period (LMP) and confirmed by ultrasound scan²⁹. Estimated fetal weight (EFW) was calculated using the Hadlock III formula³⁰. In POPS, gestational age (GA)-adjusted z-scores for EFW were estimated using the cohort-specific reference distribution based on all four biometric measurements: abdominal circumference, femur length, head circumference, and biparietal diameter³¹. Data were available for n=2531 children with scans at 18-22 weeks, n=2515 at 26-30 weeks, and n=2396 at 34-38 weeks (Table S1). In BiB, gestational age-adjusted z-scores for EFW were calculated using INTERGROWTH-21st standards³². In BiB-EUR, data were available for n=1358 children with scans at ~20 weeks, compared to n=1435 in BiB-SAS; data were also extracted for a second, later scan for n=728 children in BiB-EUR and n=749 in BiB-SAS (Table S1). We excluded multiple pregnancies and pregnancies for which a congenital anomaly was reported.

3. Processing and preparation of the genotype data

We describe the procedures for genotyping, imputation, kinship analysis, and principal component analysis in POPS and BiB in Supplemental File 2.

4. Construction of polygenic risk scores

We constructed a PRS for birthweight using the largest maternal and fetal GWAS for birthweight by deCODE, which was conducted in individuals of European ancestry^{33,34}. SNP weights were estimated using LDpred2-auto with 1,444,196 HapMap3+ variants^{35,36} and a precomputed LD reference panel provided by the LDpred2 authors.

SNP weights were applied separately in BiB and POPS to calculate fetal and maternal PRSs for birthweight. We used the fetal genotype to estimate a PRS for fetal birthweight (PRS_{fetus}), and the mother's genotypes to estimate a PRS for offspring birthweight (PRS_{mother}), with each PRS standardized (mean = 0, SD = 1) within each analytic cohort.

5. Statistical analysis

a. Estimating genetic associations with Estimated Fetal Weight

EFW_z represents the z-score for estimated fetal weight, standardized for gestational age. Where serial ultrasound data was available, we fit linear mixed effects models using continuous GA, a

full description of which is in Table 1A. Covariates included in adjusted models were: maternal age at first appointment, maternal height, paternal height, and the first 10 genetic principal components (PCs). In BiB, maternal and paternal height were excluded due to high missingness.

In linear mixed effects models, fixed effects represent the individual PRS effects centered at 22 weeks, while the interaction term (PRS $\times$ GA) represents changes in EFW_z over time. We determined independent effects of maternal and fetal genetics on EFW_z by calculating the difference between joint and univariable modelling of PRS_{fetus} and PRS_{mother}. We assessed the interaction effect of PRS_{fetus} and PRS_{mother} using likelihood ratio testing.

b. Estimating genetic associations with birthweight

We tested for associations of birthweight with PRS_{fetus} and PRS_{mother} using a series of five linear models, sequentially including fetal and maternal PRSs to assess their independent and joint effects (Table 1B), including an interaction term (PRS_{fetus} $\times$ PRS_{mother}) to test whether PRS_{mother} modifies the association with PRS_{fetus}.

c. Construction of term for deviation from genetically-predicted birthweight

We used five-fold cross-validation to estimate a deviation term (D) representing deviation of observed birthweight from genetically-predicted birthweight in each cohort. In training folds, we fit the model $BW_z \sim PRS_{fetus} + PRS_{mother} + PC1 \dots 10$. We then predicted $\widehat{BW}_z$ (the genetically-predicted value for BW_z) in the held-out fold and estimated D using the equation $D = BW_z - \widehat{BW}_z$, where D represents the difference between the observed and genetically-predicted birthweight z-score.

We compared polygenic risk across babies born <10th centile in POPS only, due to data availability. IUGR was defined as birthweight <10th centile with clinical evidence of growth restriction (defined in Table S3)³⁷. SGA was defined as birthweight <10th centile without clinical evidence of growth restriction. Other babies were categorized as appropriate for gestational age (AGA; birthweight $\geq 10^{\text{th}}$ and $\leq 90^{\text{th}}$ centile) or large for gestational age (LGA; birthweight >90th percentile).

d. Correction for multiple testing

We corrected for multiple testing using the Benjamini-Hochberg procedure to control the false discovery rate (FDR) at 5%. In EFW models (1-10), we applied the correction to PRS_{fetus} , PRS_{mother} , $PRS \times GA$, and GA . In birthweight models (11-15), we applied the correction to p -values for PRS_{fetus} , PRS_{mother} , and $PRS_{\text{fetus}} \times PRS_{\text{mother}}$. All reported q -values in the results are FDR corrected per the Benjamini-Hochberg method.

Results

1. Influence of fetal and maternal polygenic risk scores on EFW across gestation

Analysis in POPS showed that the strength of association between EFW_z and both fetal and maternal PRS increased as gestation progressed (Figure 1). When only fetal genetics were considered, both PRS_{fetus} ($q=1.2e-18$) and the interaction between PRS_{fetus} and gestational age ($q=1.1e-04$) were associated with EFW_z (Table S4A). Considering only maternal genetics, PRS_{mother} was not significantly associated with EFW_z at baseline (~22 weeks; $q = 0.121$), although there was a significant interaction between PRS_{mother} and increasing gestational age ($q=3.4e-11$) (Table S4B).

When fetal and maternal genetics were assessed in the same model (model 4), PRS_{fetus} ($q=2.1e-16$) but not PRS_{mother} ($q=0.915$) was significantly associated with EFW_z at ~22 weeks. Both the interaction of PRS_{mother} ($q=1.6e-09$) and PRS_{fetus} ($q=0.008$) with GA were significant (Table 2; Table S4C), including after adjustment for socioeconomic status and other covariates (Table S4D). The effect of PRS_{mother} on EFW_z increased significantly more quickly across gestation than that of fetal PRS (contrast estimate = -0.004, $Z = -2.15$, $p = 0.031$; Table S5).

In POPS, PRS_{mother} and PRS_{fetus} accounted for substantially more variance in EFW_z than covariates alone (Figure S1). Fetal and maternal genetic effects jointly explained 3.95% of variance in EFW_z over the covariates-only model (Table S6A). Variance decomposition showed independent contributions of PRS_{fetus} and PRS_{mother} of 2.92% and 0.45%, respectively, to EFW_z (Table S6B). Including an interaction term between PRS_{fetus} and PRS_{mother} did not significantly improve model fit compared to the joint model ($p=0.129$; Table S6C).

We tested whether the associations of maternal and fetal PRSs with EFW at ~22 weeks in POPS were consistent with cross-sectional analysis in BiB. In BiB-EUR and BiB-SAS, we

observed an association between PRS_{fetus} and EFW at ~22 weeks (BiB-EUR, $q=8.83e-05$; BiB-SAS, $q=0.024$) (Table S7A). PRS_{fetus} explained 1.3% and 0.4% of the variance in EFW in BiB-EUR and BiB-SAS, respectively (Figure S2A&B), compared to 3.51% in POPS (Figure S1). In BiB-EUR, like POPS, there was no significant association between PRS_{mother} and EFW at ~22 weeks ($q=0.688$); however, a positive association was observed in BiB-SAS ($q = 0.006$; Table S7B). These trends in PRS_{mother} persisted in the joint model, as did the association of PRS_{fetus} with EFW_z (Table S7C). Jointly, PRS_{fetus} and PRS_{mother} accounted for 1.28% of variance in EFW_z for BiB-EUR and 0.94% for BiB-SAS (Table S8A). Variance decomposition in BiB-EUR showed that PRS_{fetus} and PRS_{mother} independently accounted for 1.24% and 0.01% of variance in EFW_z , respectively (Table S8B).

In the subset of BiB-EUR participants with serial EFW measurements ($n=728$), both the fetal and maternal birthweight PRS associations with EFW strengthened across gestation (Figure 2A; Table 2). When fitted alone, PRS_{fetus} was significantly associated with EFW ~22 weeks ($q=2.84e-05$); this association increased with gestational age ($q=0.013$) (Table S4A). In the joint and univariable models, PRS_{mother} showed no significant association with EFW at ~22 weeks, but there was a significant interaction with increasing gestational age, reflecting an effect of PRS_{mother} on EFW that emerges later in gestation (univariable, $q=0.004$; joint, $q=0.018$) (Table S4B; Table 4C). There was no significant difference between the $PRS_{\text{fetus}} \times \text{GA}$ and $PRS_{\text{mother}} \times \text{GA}$ interaction slopes in either BiB ancestry group (BiB-EUR, $p=0.74$; BiB-SAS: $p=0.82$) (Table S5).

2. Influence of fetal and maternal polygenic risk scores on birthweight

Across cohorts, we observed a significant positive association between PRS_{fetus} and PRS_{mother} and birthweight in univariable (models 12-13) (Table S9A&B) and joint models (models 14-15) (Table 3; Table S9C&D). Variance in birthweight explained by fetal and maternal PRSs was substantially higher in both of the European cohorts (POPS, BiB-EUR) compared to BiB-SAS (Figure S3A, S3B, S3C). In POPS, PRS_{fetus} and PRS_{mother} jointly accounted for 11.18% of the variance in birthweight over covariates alone (Figure 3A; Table S10A), comparable to 12.23% in BiB-EUR (Figure 3B; Table S10A). The corresponding variance explained in BiB-SAS was lower at 6.29% (Figure 3C). Variance decomposition confirmed an independent contribution of each PRS to birthweight variance across cohorts, with lower explanatory power in BiB-SAS (Table S10B).

3. Deviation from genetically-predicted birthweight in POPS

The average birthweight genetic risk score for mother and fetus differed significantly across observed birthweight groups in POPS (AGA, LGA, and SGA/IUGR; Figure S4). Babies born AGA and LGA had higher mean PRSs than babies born <10th birthweight centile (Table S11A); however, there was no significant difference in mean PRS of mother or fetus between the IUGR and SGA groups (Table S11B&C). LGA babies tended to be larger than their genetically-predicted size, whereas both SGA and IUGR babies tended to be smaller (Table S12). Although PRS alone did not differentiate between IUGR and SGA groups, IUGR babies had a significantly more negative mean difference between their predicted and observed birthweights than SGA babies (p=0.008, Table 4).

Discussion

a. Principal Findings

Our findings outline the relative fetal and maternal contributions to fetal weight throughout gestation and at birth. We demonstrate that fetal PRS is associated with EFW measurements from ~22 weeks of pregnancy onwards. In the POPS cohort, using universal serial measurements, the strength of the association between both fetal and maternal genetics and EFW increased as pregnancy progressed. We show that maternal genetic effects on EFW increase over gestation to a greater extent than corresponding fetal genetic effects in POPS. This effect was not replicable in BiB, potentially due to the ultrasound measurements at the second timepoint being on a highly selected sample.

We show independent impacts of the fetal and maternal genomes on birthweight in two European (POPS, BiB-EUR) and one South Asian (BiB-SAS) cohorts. Fetal and maternal genetics together accounted for ~11-12% of variance in birthweight in European ancestry groups, compared to ~6% in the South Asian group.

In POPS, average PRS correlated with clinical groupings of observed birthweights, with larger babies having higher PRSs. Our findings suggest that PRS may be useful in discriminating between different phenotypes of small babies. The difference between observed and genetically-predicted birthweight was greater on average in babies designated as growth-restricted (IUGR) compared to those designated as constitutionally small (SGA).

b. Results in the context of what is known

Current practices in dating pregnancies assume that all fetuses are equal in size at 11-14 weeks, when variation in fetal size is smallest. Thus all babies begin their fetal growth trajectory from a 'standardized' point, negating individual genetic influences on fetal size early in pregnancy^{38,39}. This may partly explain why PRSs explain more variance in EFW later in pregnancy in POPS, where GA was determined based on CRL in a first-trimester scan. In keeping with previous evidence⁴⁰, we show a cumulative effect of fetal genetics that becomes more strongly associated with EFW as gestation progresses, despite reducing accuracy in scan measurements⁴¹⁻⁴⁴. These observations may reflect the fact that EFW measured later in gestation is a better proxy for birthweight, though fetal PRS may become a pragmatic adjunct to predicting true fetal weight as birthweight GWASs become more powerful and it becomes possible to calculate fetal PRSs based on low-coverage NIPT data^{45,46}.

In POPS, we show that while maternal PRS is not associated with EFW at mid-pregnancy, maternal genetic impacts accumulate faster than fetal genetic effects in the second half of pregnancy, although this finding was not replicated in BiB (see below). This may be attributable to the increasing importance of the maternal milieu in driving fetal growth, i.e., genetic propensity to insulin resistance^{47,48} and cardiovascular adaptations^{49,50}.

Our results also suggest that polygenic risk for birthweight can be applied across ethnic groups. Maternal genetic effects on birthweight were comparable across cohorts, an important finding given the under-representation of Asian groups in genetic studies^{51,52}. However, we note that some results in BiB-EUR and BiB-SAS differed qualitatively from each other and from POPS. For example, PRS_{mother} had a significant effect on EFW mid-pregnancy in BiB-SAS but not in BiB-EUR or POPS. Its effect size on EFW at week 22 was significantly bigger in BiB-SAS than BiB-EUR in the joint model (Table S7C; $\Delta\beta=0.088$; $p=0.026$), whereas its effect size on birthweight did not differ significantly between ancestries (Table S9D; ; $\Delta\beta=0.138$; $p=0.17$). Replication in other cohorts and more powerful GWASs in South Asian will be required to confirm there are genuine differences in the impact of birthweight-associated genetic variation on EFW between ancestry groups. Another recent study reported associations of mid-pregnancy EFW with maternal as well as fetal birthweight genetic scores in BiB European and

South Asian women⁵³; several factors could explain the differences in our findings, including how the PRS was constructed as well as differences in sample filtering.

c. Clinical Implications

Our finding that genetic risk scores could be useful in differentiating IUGR from SGA is important because there is no gold standard for distinguishing IUGR from SGA⁵⁴. Clinicians attempt to mitigate risks of stillbirth and neonatal morbidities associated with IUGR by recommending early delivery^{55,56}, though this strategy can drive additional morbidity if applied to miscategorized SGA babies⁵⁷⁻⁵⁹. Conversely, mistaking IUGR for SGA can hinder surveillance and intervention that prevents stillbirth. Future studies should test whether PRSs derived from low-coverage NIPT data could improve diagnostic accuracy beyond existing clinical markers^{37,60,61}.

d. Research Implications

Future studies should consider how birthweight polygenic risk could be incorporated into clinical risk prediction tools for adverse perinatal outcomes. Our findings should also be replicated in cohorts with serial ultrasound data and in other ethnicities. Until new, cheaper approaches to non-invasive fetal sequencing are validated, using maternal data could mitigate fetal genetic testing constraints.

e. Strengths and Limitations

We analyzed birthweight associations in two large, meticulously-phenotyped cohorts, POPS and BiB, with distinct ancestry groupings; POPS and BiB-EUR captured European ancestry groups and BiB-SAS captured South Asian ancestry groups. The availability of standardized, longitudinal whole-cohort EFW data from POPS alongside a comprehensive definition of IUGR is a major strength.

A limitation of research on ultrasonographic fetal weight estimates is that the error associated with measuring fetal size increases as pregnancy progresses^{41,42}, such that fetal growth may be over- or under-estimated in late pregnancy⁴³. Methods for deriving gestational age also differed between POPS and BiB. EFW measurements in BiB should be interpreted cautiously, as a

limited, clinically-selected subset of BiB participants had ultrasound measurements for longitudinal analysis. Application of PRSs in BiB-SAS must account for the limited transferability of PRSs derived from GWAS of European ancestry participants to other ancestry groups⁶².

f. Conclusions

Fetal and maternal genetic factors contribute independently to variation in fetal growth and birthweight, with their effects becoming more apparent as gestation progresses. Fetal genetic influences were detectable from mid-pregnancy, while maternal genetic effects appeared to strengthen later in gestation. We found that the discrepancy between observed and genetically-predicted birthweight may help distinguish growth-restricted from constitutionally-small infants. These findings provide new insight into genetic determinants of fetal growth and support further evaluation of polygenic approaches in perinatal risk assessment.

List of abbreviations

AGA = appropriate for gestational age
 BiB-EUR = Born in Bradford participants of genetically-inferred European ancestry
 BiB-SAS = Born in Bradford participants of genetically-inferred South Asian ancestry
 D = deviation from genetically-predicted birthweight
 EFW = estimated fetal weight
 BW = birthweight
 GA = gestational age
 IUGR = intrauterine growth restriction
 LGA = large for gestational age
 PCs = genetic principal components
 POPS = Pregnancy Outcomes Prediction Study
 PRS = polygenic risk score
 SGA = small for gestational age

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all POPS study participants. The study was approved by the Cambridgeshire 2 Research Ethics Committee (identification number 07/H0308/163). Ethics approval for BiB was obtained from the National Health Service Health Research Authority

Yorkshire and the Humber (Bradford Leeds) Research Ethics Committee reference: 16/YH/0320 and 16/YH/0062). Mothers were consented to participate in the study upon attendance of a routine antenatal clinic appointment at the city's primary maternity unit.

Availability of data or materials

The raw data from the POPS study are not publicly available, due to the nature of the consent given by participants in the original study. Requests for POPS supplemental information, including raw data, can be made to Mrs Sheree Green-Molloy at the Department of Obstetrics and Gynaecology, Cambridge University, UK (paoandghod@medschl.cam.ac.uk). Researchers can apply to access data from BiB (<https://bib.vergelabs.dev/research/how-to-access-data/>).

Data on birth weight has been contributed by the EGG Consortium using the UK Biobank Resource and has been downloaded from www.egg-consortium.org <https://egg-consortium.org/birth-weight-2019.html>

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Table 1A

Model 1	$EFW_z \sim \text{covariates} + GA + (1 pregnancy)$
Model 2	$EFW_z \sim PRS_{fetus} + \text{covariates} + GA + (GA \times PRS_{fetus}) + (1 pregnancy)$
Model 3	$EFW_z \sim PRS_{mother} + \text{covariates} + GA + (GA \times PRS_{mother}) + (1 pregnancy)$
Model 4	$EFW_z \sim PRS_{fetus} + PRS_{mother} + \text{covariates} + GA + (GA \times PRS_{fetus}) + (GA \times PRS_{mother}) + (1 pregnancy)$
Model 5	$EFW_z \sim PRS_{fetus} \times PRS_{mother} + \text{covariates} + GA + (GA \times PRS_{fetus}) + (GA \times PRS_{mother}) + (1 pregnancy)$
Model 6	$EFW_z \sim \text{covariates}$
Model 7	$EFW_z \sim PRS_{fetus} + \text{covariates}$
Model 8	$EFW_z \sim PRS_{mother} + \text{covariates}$
Model 9	$EFW_z \sim PRS_{fetus} + PRS_{mother} + \text{covariates}$
Model 10	$EFW_z \sim PRS_{fetus} \times PRS_{mother} + \text{covariates}$

Table 1A. Longitudinal and cross-sectional models of estimated fetal weight in POPs and BiB. This table describes the linear mixed effects models (1-5) used in POPs and BiB and the linear models (6-10) used in BiB to assess contributions of polygenic risk scores to estimated fetal weight (EFW) across gestation. Covariates included maternal age at first appointment, maternal height, paternal height, and the first ten genetic principal components (PCs). GA is modelled as a continuous variable centered on 22 weeks. $1 | pregnancy$ represents the per-pregnancy random intercept. As a robustness analysis in POPS, we evaluated timepoint as a categorical variable using model 4, where we characterized 3 gestational ages corresponding to POPS scans at 20, 28, and 36 weeks.

For models 1-5 in POPS, we calculated marginal R^2 , conditional R^2 , incremental (Δ) R^2 , and AIC values to assess variance in EFW explained by (1) covariates only, (2) PRS_{fetus} , (3) PRS_{mother} , (4) $PRS_{fetus} + PRS_{mother}$, and (5) $PRS_{fetus} \times PRS_{mother}$. Marginal R^2 represents the variance explained by fixed effects only, while conditional R^2 represents the variance explained by both fixed and random effects. Incremental (Δ) R^2 is defined as the difference in marginal R^2 between each model and the baseline (covariates-only) model (1), quantifying the additional proportion of variance in EFW explained by fixed effects beyond baseline, holding the random-effects structure constant. We determined the independent effects of maternal and fetal genetics on EFW_z by calculating the difference between the joint model (4) and the univariable PRS_{fetus} (2) and PRS_{mother} (3) models, respectively. For cross-sectional models 6-10 in BiB, we calculated R^2 , incremental (Δ) R^2 , and AIC values to assess EFW explained by (6) baseline covariates, (7) PRS_{fetus} , (8) PRS_{mother} , (9) $PRS_{fetus} + PRS_{mother}$, and (10) $PRS_{fetus} \times PRS_{mother}$. In the covariate-only model, BiB included maternal age but not maternal and paternal height due to high missingness.

Table 1B

Model 11	$BW_z \sim \text{covariates}$
Model 12	$BW_z \sim PRS_{\text{fetus}} + \text{covariates}$
Model 13	$BW_z \sim PRS_{\text{mother}} + \text{covariates}$
Model 14	$BW_z \sim PRS_{\text{fetus}} + PRS_{\text{mother}} + \text{covariates}$
Model 15	$BW_z \sim PRS_{\text{fetus}} \times PRS_{\text{mother}} + \text{covariates}$

Table 1B. Linear models for assessing birthweight associations in POPs and BiB. This table describes models used in POPs and BiB to assess associations of polygenic risk scores with birthweight. In these models, BW_z represents birthweight standardised for gestational age and sex. Covariates include maternal age, maternal height, and paternal height in POPs and maternal age in BiB. We calculated R^2 , incremental (Δ) R^2 , and AIC values to assess birthweight explained by (11) baseline covariates, (12) PRS_{fetus} , (13) PRS_{mother} , (14) $PRS_{\text{fetus}} + PRS_{\text{mother}}$, and (15) $PRS_{\text{fetus}} \times PRS_{\text{mother}}$. Incremental R^2 values represent the additional variance in BW_z relative to that explained by the covariates-only model (11). We assessed the independent contributions of maternal and fetal genetics by calculating the difference between the joint model (14) and the univariable PRS_{fetus} (12) and PRS_{mother} (13) models, respectively.

Table 2

Coefficient	POPS			BiB (EUR)			BiB (SAS)			
	Estimate	P-value	Q-value FDR	Estimate	P-value	Q-value FDR	Estimate	SE	P-value	Q-value FDR
(Intercept)	-3.981	7.7e-13		-0.054	0.719		-0.674	0.19	3.83E-04	
PRS _{fetus}	0.156	4.2e-17	2.1e-16	0.155	5.01E-06	2.84E-05	0.06	0.035	0.089	0.1792
PRS _{mother}	-0.002	0.915	0.915	0.915	0.808	0.9146	0.042	0.036	0.243	0.2754
GA at scan	0.002	0.110	0.137	0.001	0.861	0.9146	-0.006	0.003	0.032	0.1056
PRS _{mother} :GA	0.008	6.5e-10	1.6e-09	0.007	0.032	0.0596	0.004	0.003	0.225	0.2754
PRS _{fetus} :GA	0.004	0.005	0.008	0.008	0.007	0.0178	0.003	0.003	0.409	0.4095

Table 2. Joint model (4) of longitudinal associations between PRS_{fetus} and PRS_{mother} and EFW_z with continuous GA in POPS and BiB. Gestational age (GA) was modeled as a continuous variable to assess changes across gestation in the associations of PRS_{mother} and PRS_{fetus} with EFW_z using model 4. Regression coefficients represent fixed effects from the joint model, including PRS x GA interaction terms. Estimates are presented with Wald test p-values and false discovery rate (FDR) q-values. FDR correction was applied using the Benjamini-Hochberg method. Here we show only predictors of interest but the full model is reported in Table S2C.

Table 3

Coefficient	POPS			BiB (EUR)			BiB (SAS)		
	Beta	P-value	Q-value FDR	Beta	P-value	Q-value FDR	Beta	P-value	Q-value FDR
(Intercept)	-4.166	3.31e-14		-0.706	1.15e-13		-1.157	2.08e-26	
PRS _{fetus}	0.246	3.67e-48	1.14e-47	0.277	1.25e-40	3.51e-40	0.192	1.61e-21	3.75e-21
PRS _{mother}	0.11	3.58e-11	5.02e-11	0.138	1.65e-11	1.93e-11	0.1	5.05e-07	7.08e-07

Table 3. Associations between fetal and maternal polygenic risk scores (PRS) and observed birthweight z-scores across POPS, BiB-EUR, and BiB-SAS (Model 14). We assessed the cross-sectional associations of PRS_{mother} and PRS_{fetus} using the joint model (Model 14) across cohorts. Estimates are presented with Wald test p-values and false discovery rate (FDR) q-values. FDR correction was applied using the Benjamini-Hochberg method to generate q-values. Adjustments in POPS included maternal age at booking, maternal height, paternal height, PCs 1-10, while BiB adjusted for maternal age at booking and PCs 1-10. Here we show only predictors of interest but the full model is reported in Table S8D.

Table 4

Comparison	Mean diff in mean D	CI	Cohen's d	P-value
IUGR vs AGA	1.67	[1.51, 1.84]	2.73	p = 2.1e-26
SGA vs AGA	1.38	[1.3, 1.46]	2.27	p = 1.8e-80
LGA vs AGA	-1.54	[-1.65, -1.44]	-2.52	p = 3.4e-57
IUGR vs SGA	0.29	[0.12, 0.47]	0.57	p = 0.008
IUGR vs LGA	3.22	[3.03, 3.4]	5.75	p = 4.3e-54
SGA vs LGA	2.92	[2.79, 3.05]	5.56	p = 1.6e-114

Table 4. Pairwise differences in deviation from genetically predicted birthweight across fetal growth classifications. Pairwise t-tests comparing mean deviation between fetal growth categories (IUGR, SGA, AGA, and LGA). Deviation represents the difference between the observed and genetically-predicted birthweight z-score, where $D = BW_z - \widehat{BW}_z$. For each comparison, we report the mean difference in D (second group as reference), 95% confidence intervals, Cohen's d effect size, and associated p-values. Positive values indicate higher deviation in the first-listed group relative to the reference group, while negative values indicate lower deviation. We applied the Bonferroni correction to P-values.

References

1. Wang T, Huang T, Li Y, et al. Low birthweight and risk of type 2 diabetes: a Mendelian randomisation study. *Diabetologia*. 2016;59(9):1920-1927. doi:10.1007/s00125-016-4019-z
2. BIRTH-GENE (BIG) Study Working Group, Huang T, Wang T, et al. Association of Birth Weight With Type 2 Diabetes and Glycemic Traits: A Mendelian Randomization Study. *JAMA Netw Open*. 2019;2(9):e1910915. doi:10.1001/jamanetworkopen.2019.10915
3. Zanetti D, Tikkanen E, Gustafsson S, Priest JR, Burgess S, Ingelsson E. Birthweight, Type 2 Diabetes Mellitus, and Cardiovascular Disease: Addressing the Barker Hypothesis With Mendelian Randomization. *Circ Genomic Precis Med*. 2018;11(6):e002054. doi:10.1161/CIRCGEN.117.002054
4. Moen GH, Brumpton B, Willer C, et al. Mendelian randomization study of maternal influences on birthweight and future cardiometabolic risk in the HUNT cohort. *Nat Commun*. 2020;11(1):5404. doi:10.1038/s41467-020-19257-z
5. Liang J, Xu C, Liu Q, et al. Association between birth weight and risk of cardiovascular disease: Evidence from UK Biobank. *Nutr Metab Cardiovasc Dis NMCD*. 2021;31(9):2637-2643. doi:10.1016/j.numecd.2021.05.017
6. Fung C, Zinkhan E. Short- and Long-Term Implications of Small for Gestational Age. *Obstet Gynecol Clin North Am*. 2021;48(2):311-323. doi:10.1016/j.ogc.2021.02.004
7. Ashorn P, Ashorn U, Muthiani Y, et al. Small vulnerable newborns-big potential for impact. *Lancet*. 2023;401(10389):1692-1706. doi:10.1016/S0140-6736(23)00354-9
8. Arabzadeh H, Doosti-Irani A, Kamkari S, Farhadian M, Elyasi E, Mohammadi Y. The maternal factors associated with infant low birth weight: an umbrella review. *BMC Pregnancy Childbirth*. 2024;24(1):316. doi:10.1186/s12884-024-06487-y
9. Jenabi E, Salehi AM, Farashi S, Salimi Z. The environmental risk factors associated with fetal macrosomia: An umbrella review. *Pediatr Neonatol*. 2024;65(3):217-221. doi:10.1016/j.pedneo.2023.09.007
10. Warrington NM, Beaumont RN, Horikoshi M, et al. Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nat Genet*. 2019;51(5):804-814. doi:10.1038/s41588-019-0403-1
11. Horikoshi M, Beaumont RN, Day FR, et al. Genome-wide associations for birth weight and correlations with adult disease. *Nature*. 2016;538(7624):248-252. doi:10.1038/nature19806
12. Hindmarsh PC, Geary MPP, Rodeck CH, Kingdom JCP, Cole TJ. Intrauterine growth and its relationship to size and shape at birth. *Pediatr Res*. 2002;52(2):263-268. doi:10.1203/00006450-200208000-00020
13. Workalemahu T, Grantz KL, Grewal J, Zhang C, Louis GMB, Tekola-Ayele F. Genetic and Environmental Influences on Fetal Growth Vary during Sensitive Periods in Pregnancy. *Sci Rep*. 2018;8(1):7274. doi:10.1038/s41598-018-25706-z

14. Aplin JD, Myers JE, Timms K, Westwood M. Tracking placental development in health and disease. *Nat Rev Endocrinol*. 2020;16(9):479-494. doi:10.1038/s41574-020-0372-6
15. Cindrova-Davies T, Sferruzzi-Perri AN. Human placental development and function. *Semin Cell Dev Biol*. 2022;131:66-77. doi:10.1016/j.semcdb.2022.03.039
16. Beaumont RN, Kotecha SJ, Wood AR, et al. Common maternal and fetal genetic variants show expected polygenic effects on risk of small- or large-for-gestational-age (SGA or LGA), except in the smallest 3% of babies. *PLoS Genet*. 2020;16(12):e1009191. doi:10.1371/journal.pgen.1009191
17. Sharma D, Shastri S, Sharma P. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. *Clin Med Insights Pediatr*. 2016;10:67-83. doi:10.4137/CMPed.S40070
18. Morris RK, Johnstone E, Lees C, Morton V, Smith G, Royal College of Obstetricians and Gynaecologists. Investigation and Care of a Small-for-Gestational-Age Fetus and a Growth Restricted Fetus (Green-top Guideline No. 31). *BJOG Int J Obstet Gynaecol*. 2024;131(9):e31-e80. doi:10.1111/1471-0528.17814
19. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. *Am J Obstet Gynecol*. 1985;151(3):333-337. doi:10.1016/0002-9378(85)90298-4
20. Olga L, Sovio U, Wong H, Smith G, Aiken C. Association between antenatal diagnosis of late fetal growth restriction and educational outcomes in mid-childhood: A UK prospective cohort study with long-term data linkage study. *PLoS Med*. 2023;20(4):e1004225. doi:10.1371/journal.pmed.1004225
21. Hughes AE, Sovio U, Gaccioli F, Cook E, Charnock-Jones DS, Smith GCS. The association between first trimester AFP to PAPP-A ratio and placentally-related adverse pregnancy outcome. *Placenta*. 2019;81:25-31. doi:10.1016/j.placenta.2019.04.005
22. Sovio U, Gaccioli F, Cook E, Hund M, Charnock-Jones DS, Smith GCS. Prediction of Preeclampsia Using the Soluble fms-Like Tyrosine Kinase 1 to Placental Growth Factor Ratio: A Prospective Cohort Study of Unselected Nulliparous Women. *Hypertension*. 2017;69(4):731-738. doi:10.1161/HYPERTENSIONAHA.116.08620
23. Opondo C, Jayaweera H, Hollowell J, Li Y, Kurinczuk JJ, Quigley MA. Variations in neonatal mortality, infant mortality, preterm birth and birth weight in England and Wales according to ethnicity and maternal country or region of birth: an analysis of linked national data from 2006 to 2012. *J Epidemiol Community Health*. 2020;74(4):336-345. doi:10.1136/jech-2019-213093
24. Nongmaithem SS, Beaumont RN, Dedaniya A, et al. Babies of South Asian and European Ancestry Show Similar Associations With Genetic Risk Score for Birth Weight Despite the Smaller Size of South Asian Newborns. *Diabetes*. 2022;71(4):821-836. doi:10.2337/db21-0479
25. Mack JA, Sovio U, Day FR, et al. Genetic Variants Associated With Preeclampsia and Maternal Serum sFLT1 Levels. *Hypertension*. 2025;82(5):839-848. doi:10.1161/HYPERTENSIONAHA.124.23400

26. Gaccioli F, Lager S, Sovio U, Charnock-Jones DS, Smith GCS. The pregnancy outcome prediction (POP) study: Investigating the relationship between serial prenatal ultrasonography, biomarkers, placental phenotype and adverse pregnancy outcomes. *Placenta*. 2017;59(Suppl 1):S17-S25. doi:10.1016/j.placenta.2016.10.011
27. McEachan RRC, Santorelli G, Watmuff A, et al. Cohort Profile Update: Born in Bradford. *Int J Epidemiol*. 2024;53(2):dyae037. doi:10.1093/ije/dyae037
28. Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med*. 1998;17(4):407-429.
29. Norris T, Johnson W, Petherick E, et al. Investigating the relationship between fetal growth and academic attainment: secondary analysis of the Born in Bradford (BiB) cohort. *Int J Epidemiol*. 2018;47(5):1475-1484. doi:10.1093/ije/dyy157
30. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. *Am J Obstet Gynecol*. 1985;151(3):333-337. doi:10.1016/0002-9378(85)90298-4
31. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet*. 2015;386(10008):2089-2097. doi:10.1016/S0140-6736(15)00131-2
32. Stirnemann J, Salomon LJ, Papageorghiou AT. INTERGROWTH-21st standards for Hadlock's estimation of fetal weight. *Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol*. 2020;56(6):946-948. doi:10.1002/uog.22000
33. Warrington NM, Beaumont RN, Horikoshi M, et al. Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nat Genet*. 2019;51(5):804-814. doi:10.1038/s41588-019-0403-1
34. Juliusdottir T, Steinthorsdottir V, Stefansdottir L, et al. Distinction between the effects of parental and fetal genomes on fetal growth. *Nat Genet*. 2021;53(8):1135-1142. doi:10.1038/s41588-021-00896-x
35. Privé F, Albiñana C, Arbel J, Pasaniuc B, Vilhjálmsson BJ. Inferring disease architecture and predictive ability with LDpred2-auto. *Am J Hum Genet*. 2023;110(12):2042-2055. doi:10.1016/j.ajhg.2023.10.010
36. Privé F, Arbel J, Vilhjálmsson BJ. LDpred2: better, faster, stronger. *Bioinformatics*. 2021;36(22-23):5424-5431. doi:10.1093/bioinformatics/btaa1029
37. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. *Lancet*. 2015;386(10008):2089-2097. doi:10.1016/S0140-6736(15)00131-2
38. Papageorghiou AT, Kennedy SH, Salomon LJ, et al. International standards for early fetal size and pregnancy dating based on ultrasound measurement of crown-rump length in the

- first trimester of pregnancy. *Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol*. 2014;44(6):641-648. doi:10.1002/uog.13448
39. Papageorgiou AT, Ohuma EO, Altman DG, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. *Lancet*. 2014;384(9946):869-879. doi:10.1016/S0140-6736(14)61490-2
40. Vermeulen MJ, Gaillard R, Miliku K, et al. Influence of genetic variants for birth weight on fetal growth and placental haemodynamics. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(4):393-398. doi:10.1136/archdischild-2019-317044
41. Milner J, Arezina J. The accuracy of ultrasound estimation of fetal weight in comparison to birth weight: A systematic review. *Ultrasound*. 2018;26(1):32-41. doi:10.1177/1742271X17732807
42. Parikh LI, Iqbal SN, Jelin AC, Overcash RT, Tefera E, Fries MH. Third trimester ultrasound for fetal macrosomia: optimal timing and institutional specific accuracy. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet*. 2019;32(8):1337-1341. doi:10.1080/14767058.2017.1405385
43. Kumarasiri S, Wanigasekara R, Wahalawatta L, Jayasinghe L, Padeniya T, Dias T. Accuracy of ultrasound estimated fetal weight formulae to predict actual birthweight after 34 weeks: prospective validation study. *Ceylon Med J*. 2013;58(3):116-121. doi:10.4038/cmj.v58i3.6104
44. Dudley NJ, Jindal S, Varley H. An evaluation of systematic and random errors in ultrasound estimated fetal weight during serial ultrasound. *Ultrasound J Br Med Ultrasound Soc*. 2023;31(4):259-265. doi:10.1177/1742271X221139796
45. Biagini SA, Becelaere S, Aerden M, et al. Genotype imputation from low-coverage data for medical and population genetic analyses. *Genome Res*. 2025;35(9):1929-1941. doi:10.1101/gr.280175.124
46. Li Z, Albrechtsen A, Davies RW. Flexible read-aware genotype imputation from sequence using biobank sized reference panels. *Nat Commun*. 2025;17:524. doi:10.1038/s41467-025-67218-1
47. Kampmann U, Knorr S, Fuglsang J, Ovesen P. Determinants of Maternal Insulin Resistance during Pregnancy: An Updated Overview. *J Diabetes Res*. 2019;2019:5320156. doi:10.1155/2019/5320156
48. Angueira AR, Ludvik AE, Reddy TE, Wicksteed B, Lowe WL, Layden BT. New insights into gestational glucose metabolism: lessons learned from 21st century approaches. *Diabetes*. 2015;64(2):327-334. doi:10.2337/db14-0877
49. Hunt K, Polydoros I, van Loon R, Townsend RC, Reynolds RM. Modelling maternal cardiovascular adaptation to pregnancy: a scoping review. *BMC Pregnancy Childbirth*. 2025;26(1):88. doi:10.1186/s12884-025-08270-z

50. Rizi SS, Wiens E, Hunt J, Ducas R. Cardiac physiology and pathophysiology in pregnancy. *Can J Physiol Pharmacol*. 2024;102(10):552-571. doi:10.1139/cjpp-2024-0010
51. Nguyen HAT, Zheng A, Gugel A, Kistin CJ. Asians and Asian Subgroups are Underrepresented in Medical Research Studies Published in High-Impact Generalist Journals. *J Immigr Minor Health*. 2021;23(3):646-649. doi:10.1007/s10903-021-01142-6
52. Dokuru DR, Horwitz TB, Freis SM, Stallings MC, Ehringer MA. South Asia: The Missing Diverse in Diversity. *Behav Genet*. 2024;54(1):51-62. doi:10.1007/s10519-023-10161-y
53. Purdy RA, Feng J, Luo Z, et al. Genetic and maternal environmental contributions to estimated fetal weight at 20 weeks gestation compared with birthweight. *medRxiv*. Preprint posted online June 22, 2026:2026.06.18.26355970. doi:10.64898/2026.06.18.26355970
54. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol*. 2016;48(3):333-339. doi:10.1002/uog.15884
55. Malhotra A, Allison BJ, Castillo-Melendez M, Jenkin G, Polglase GR, Miller SL. Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol*. 2019;10:55. doi:10.3389/fendo.2019.00055
56. Smith GCS. Universal screening for foetal growth restriction. *Best Pract Res Clin Obstet Gynaecol*. 2018;49:16-28. doi:10.1016/j.bpobgyn.2018.02.008
57. Zeitlin J, Ancel PY, Saurel-Cubizolles MJ, Papiernik E. The relationship between intrauterine growth restriction and preterm delivery: an empirical approach using data from a European case-control study. *BJOG Int J Obstet Gynaecol*. 2000;107(6):750-758. doi:10.1111/j.1471-0528.2000.tb13336.x
58. Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases morbidity and mortality among premature neonates. *Am J Obstet Gynecol*. 2004;191(2):481-487. doi:10.1016/j.ajog.2004.01.036
59. Selvaratnam RJ, Wallace EM, Treleaven S, Hooper SB, Davis PG, Davey MA. Does detection of fetal growth restriction improve neonatal outcomes? *J Paediatr Child Health*. 2021;57(5):677-683. doi:10.1111/jpc.15310
60. Hughes AE, Sovio U, Gaccioli F, Cook E, Charnock-Jones DS, Smith GCS. The association between first trimester AFP to PAPP-A ratio and placentally-related adverse pregnancy outcome. *Placenta*. 2019;81:25-31. doi:10.1016/j.placenta.2019.04.005
61. Sovio U, Gaccioli F, Cook E, Hund M, Charnock-Jones DS, Smith GCS. Prediction of Preeclampsia Using the Soluble fms-Like Tyrosine Kinase 1 to Placental Growth Factor Ratio: A Prospective Cohort Study of Unselected Nulliparous Women. *Hypertension*. 2017;69(4):731-738. doi:10.1161/HYPERTENSIONAHA.116.08620
62. Duncan L, Shen H, Gelaye B, et al. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat Commun*. 2019;10(1):3328. doi:10.1038/s41467-019-11112-0

Figure 1

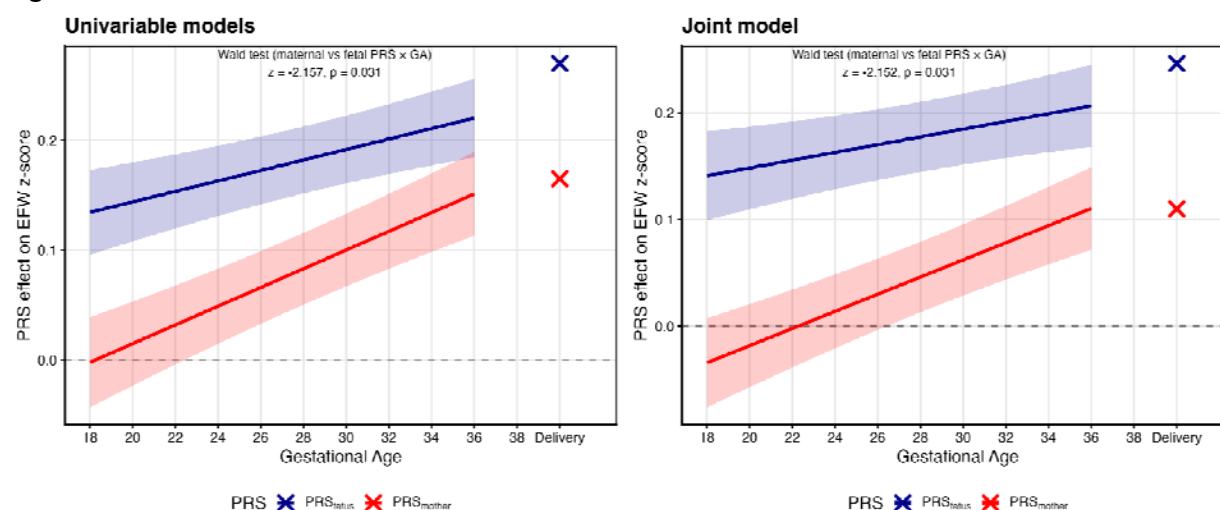
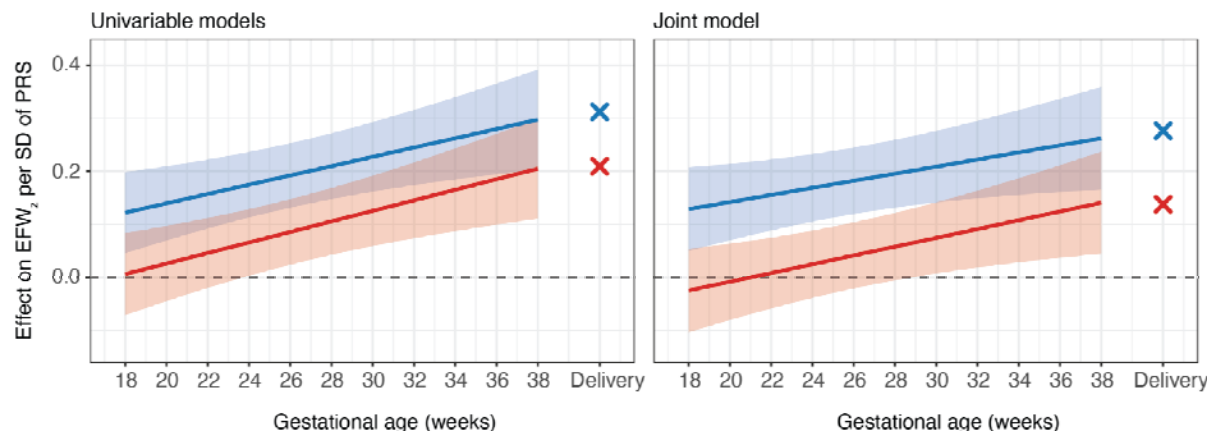


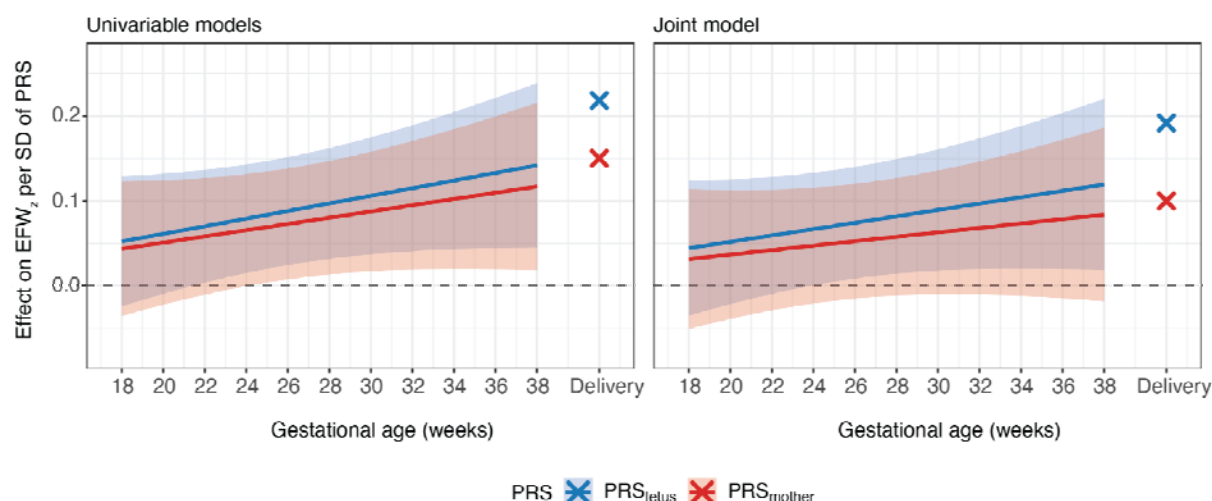
Figure 1: Birthweight PRS associations with EFW_z across gestation from univariable and joint linear mixed-effects models (POPS). Lines show the estimated effect of each birthweight PRS on EFW at each gestational week derived from linear mixed-effects models including a PRS × gestational age interaction term. The left panel shows estimates from univariable models in which PRS_{fetus} and PRS_{mother} were fitted in separate mixed-effects models. The right panel shows trajectories from a joint mixed-effects model in which both PRSs were included simultaneously. Ribbons show 95% confidence intervals. The cross at “Delivery” shows the corresponding PRS association with observed birthweight.

Figures 2A&B

A. BiB-EUR

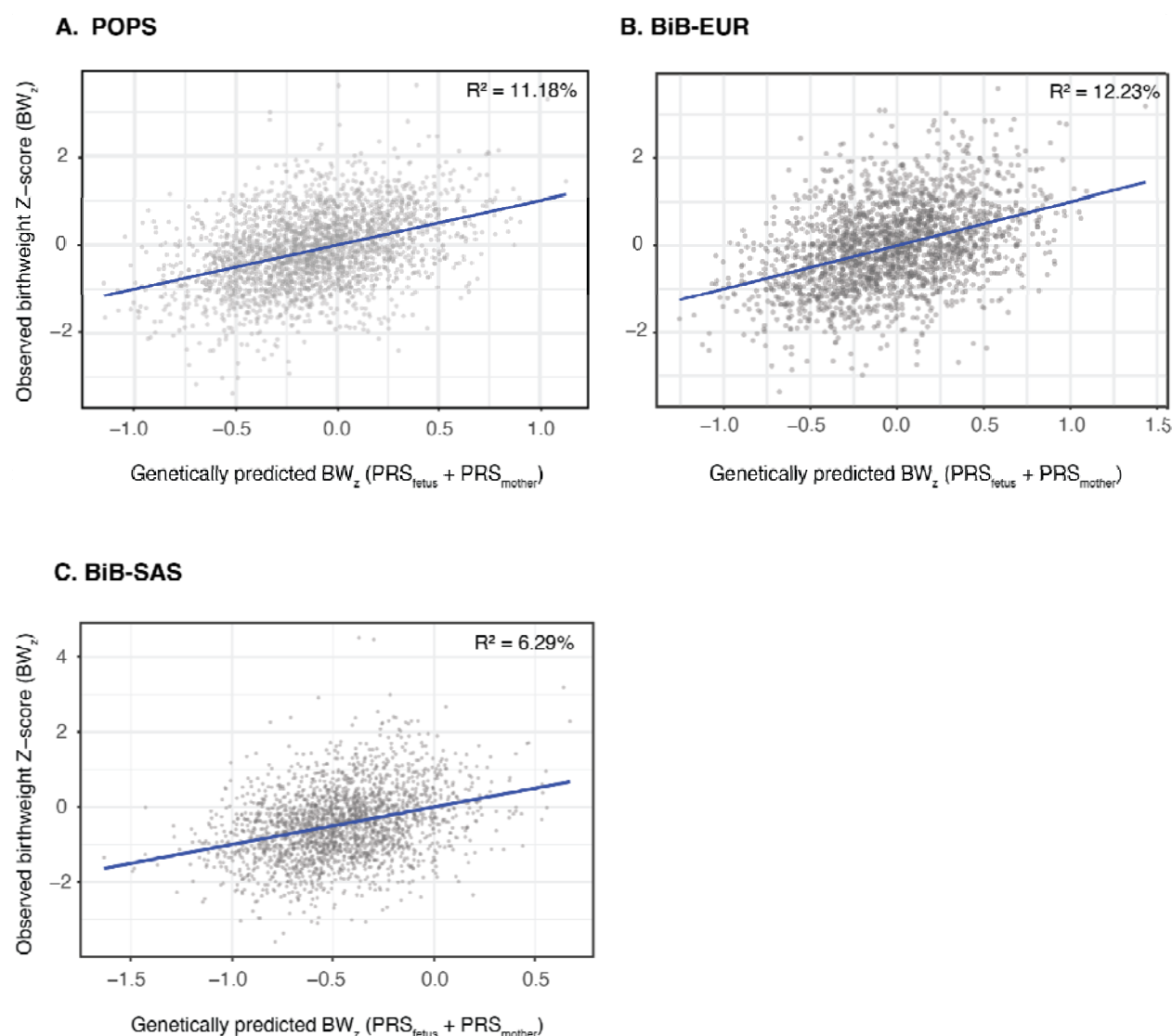


B. BiB-SAS



Figures 2A&B. PRS associations with EFW across gestation from univariable and joint linear mixed-effects models in BiB. Lines show the estimated effect of each birthweight PRS on EFW at each gestational week derived from linear mixed-effects models including a PRS $\times$ gestational age interaction term. The left panel shows estimates from univariable models in which PRS_{fetus} and PRS_{mother} were fitted in separate mixed-effects models. The right panel shows trajectories from a joint mixed-effects model in which both PRS were included simultaneously. Ribbons show 95% confidence intervals. The cross at "Delivery" shows the corresponding PRS association with observed birthweight. EUR: genetically-inferred European ancestry (N=728); BiB-SAS: genetically-inferred South Asian ancestry (N=749).

Figure 3A,B&C



Figures 3A,B,&C. The association between observed birthweight Z-score (BW_z) and genetically-predicted BW_z . Predicted values were fitted from a linear model regressing BW_z on PRS_{fetus} , PRS_{mother} , and covariates in each cohort (model 14, Methods). R^2 is the incremental variance explained by PRS_{fetus} and PRS_{mother} over covariates alone. BiB-EUR: genetically-inferred European ancestry participants from Born in Bradford (N=2,075); BiB-SAS: genetically-inferred South Asian ancestry from Born in Bradford (N=2,210); POPS: Pregnancy outcomes prediction study (N=2,537).