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Abstract

Observed genetic associations with educational attainment may be due to direct or indirect genetic influences. Recent work highlights "genetic nurture", the potential effect of a parents' genetics on their child's educational outcomes via rearing environments. To date, few mediating childhood environments have been tested. We use a large sample of genotyped mother-child dyads (N = 2,077) to investigate if genetic nurture occurs via the prenatal environment. We find that mothers with more education-related genes are generally healthier and more financially stable during pregnancy. Further, measured prenatal conditions explain up to one third of the associations between maternal genetics and children's academic and developmental outcomes at ages 4-7. By providing the first evidence of prenatal genetic nurture and showing that genetic nurture is detectable in early childhood, this study broadens our understanding of how parental genetics may influence children and illustrates the challenges of within-person interpretation of existing genetic associations.

Psychologists have long understood that genetic and environmental influences interact to shape human development and produce individual differences (Turkheimer, 2000). However, as genome-wide association studies over the past decade have created new avenues for the study of genetics at the molecular level (Visscher et al., 2017), the line between genetic and environmental influences has begun to blur. There is increasing appreciation that humans are shaped by both direct genetic effects, the influence of their own genes, and social genetic effects, the indirect influences that other peoples' genes have through affecting the shared environment (Domingue & D.W. Belsky, 2017).

Social genetic effects represent a novel mechanism through which individual differences may be transmitted from parents to children. Consider recent genetic discoveries for educational attainment (Lee et al., 2018; Okbay et al., 2016), which correlate with numerous related behavioral and social phenotypes: more prestigious occupations and upward social mobility (D.W. Belsky et al., 2018; Trejo et al., 2018); intelligence, self-control and interpersonal skills (D.W. Belsky et al., 2016); personality (Mõttus, Realo, Vainik, Allik, & Esko, 2017; Smith-Woolley, 20190328; Stephan, Sutin, Kornadt, & Terracciano, 2019); brain development (Elliott et al., 2019; Okbay et al., 2016); attention (de Zeeuw et al., 2014) and prosocial behavior (Wertz et al., 2018). Parental genes related to educational attainment may be associated with child educational attainment due to the correlation between maternal and child genetics that results from genetic inheritance (Ayorech, Krapohl, Plomin, & von Stumm, 2017; Conley et al., 2015). However, parental genes related to educational attainment may also become associated with child educational attainment as a result of an environmentally mediated social genetic effect, where parental genes causally influence their child's educational outcomes via genetically associated parental behaviors or environmental exposures. Recently, non-transmitted parental

genes have been used to document such social genetic influences from parents to their children, an effect described as genetic nurture (Kong et al., 2018). Because genome-wide association studies do not discriminate between the various pathways through which genes become associated with outcomes, recent genetic discoveries from genome-wide association studies capture both direct genetic effects and genetic nurture effects (Trejo & Domingue, 2019).

Genetic nurture allows genes to be used as a lens for the study of social processes through which parents influence their children. For example, new research has found that parental genetics for educational attainment are associated with warm, stimulating parenting, which partially explained the association between parental genetics and offspring's educational attainment at age 18 (Wertz et al., 2019). However, it is also possible that genetic nurture processes begin even earlier. In particular, we consider the possibility of such a phenomenon occurring at the earliest stage of development, when the child is still in utero.

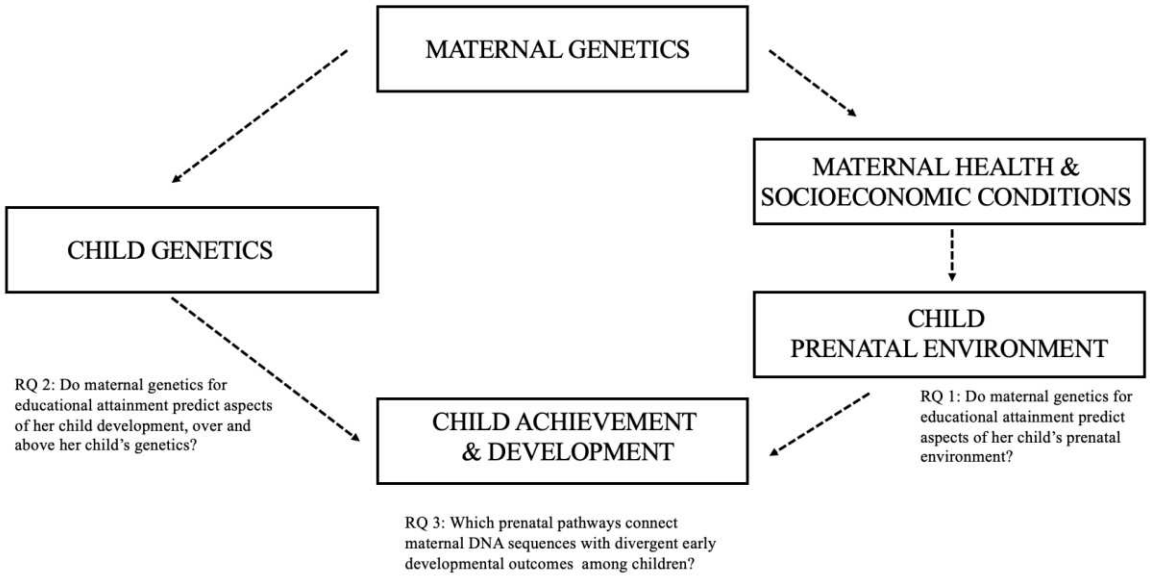
The prenatal period is a promising site for genetic nurture for two reasons. First, the prenatal environment is critical for human development, and prenatal adversity—e.g., maternal stress, poverty, and toxicants—is a well-documented developmental risk factor (Piccolo & Noble, 2018). Second, the conditions inside a mother's womb are the predominant environment for the developing child. External environments may influence the child in utero, but even those are mediated by the mother's biology. This is not true for the postnatal environment, where many environmental processes that affect a child are independent of the mother.

Figure 1 presents a conceptual model for how maternal genetics could influence child development in utero. Maternal genetics are related to both the mother's behaviors and environmental exposures while pregnant; these collectively affect the child in utero and impact the child's downstream outcomes. While identifying the exact causal flows in this graph is

challenging, we note one crucial point. If maternal genetics have a causal effect on child outcomes (independent of genetic transmission), the association between an individual's prenatal environmental exposures and downstream outcomes will be confounded by both direct genetic and social genetic influences. Put plainly, influences on a child's development that stem from their own genetics, maternal genetics, and independent aspects of the prenatal environment will be challenging to separate.

Figure 1

Conceptual model linking maternal genetics with child outcomes through both direct (child genetics) and indirect (child environment) pathways.



Investigating genetic nurturance during the prenatal period is complicated by the paucity of genetically informed studies that contain both information on a mother's behaviors and environmental exposures during pregnancy and measures of the subsequent cognitive and social

development of her children. The study of genetic nurture has been further constrained by the timing of developmental and cognitive outcome measures. Previous research has focused on offspring outcomes later in life (e.g. at ages 17-18; Wertz et al., 2019; Bates et al., 2018), but a complete accounting of genetic nurture would naturally begin earlier in the lifecourse. Can such effects be observed when young children are just entering school?

To investigate whether the prenatal environment is a pathway for genetic nurture, and if these associations are observed early in the child's life, we asked three main questions. First, do maternal genetics for educational attainment predict aspects of a child's prenatal environment? Second, do maternal genetics for educational attainment predict aspects of a child's development in early and middle childhood, over and above the child's own genetics for educational attainment (i.e., genetic transmission)? Third, which social, behavioral, and psychological prenatal pathways connect maternal genetics with divergent early developmental outcomes among children?

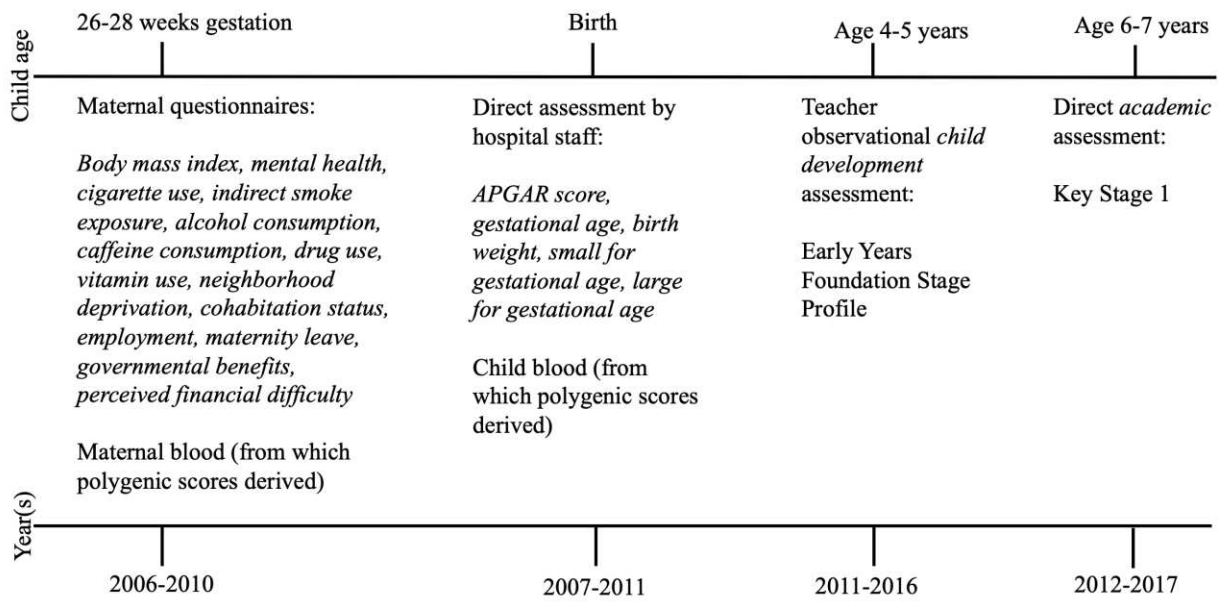
To address these questions, we used rich, prospective data from the Born in Bradford birth cohort (BiB; Wright et al., 2012). To index maternal genetics, we used a maternal polygenic score for educational attainment (PGS; Lee et al., 2019). Via controls for children's genotype, we isolate genetic nurture from direct genetic influences and clarify the contribution of each. Further, we use a high-quality multi-informant method, drawing on parent-reported indexes of prenatal environments, teacher-observations of child development, and direct assessments of child's academics during their first three years of schooling (ages 4-7y). With these robust measures, we offer evidence that maternal genetics are associated with a variety of prenatal exposures and that genetically-associated differences in exposures are predictive of downstream differences in educational development early in the child's life.

Methods

Sample

Our analytic sample is drawn from the Born in Bradford study (BiB), a longitudinal multi-ethnic birth cohort study in northern England (Wright et al., 2012). Compared to national averages, Bradford is more ethnically diverse and has higher levels of socioeconomic deprivation; the cohort is broadly characteristic of the city's maternal population (Wright et al., 2012). BiB enrolled pregnant mothers at 26-28 weeks gestation and has followed them longitudinally. The full study recruited 12,453 women and 3,353 of their partners across 13,776 pregnancies and 13,858 children from 2007 to 2010. Figure 2 shows a timeline of BiB procedures. Upon enrollment during pregnancy, women completed an extensive questionnaire that included information on health behaviors and socioeconomic factors. At the child's birth, genetic samples were assayed from both mother and child, and measures of neonatal health were taken. Administrative educational records were collected for children, which included a structured, teacher-led observational assessment of development at the end of their first year of schooling when students were age 4-5y (Early Years Foundation Stage Profile; EYFSP), and an exam-based direct assessment of academic performance at the end of their third year when students were age 6-7y (Key Stage 1). Of the 13,858 children, genetic data were available for 6,256 mother/child dyads and 6,124 had valid data for prenatal, academic and developmental measures.

Figure 2: Timeline of procedures for BiB cohort.



The cohort was 33.65% White British and 60.35% Pakistani ancestry, and 6.00% other ethnicities. Although a strength of the cohort, diversity raises issues in studies of genetic prediction (Martin et al., 2017). Since the PGS for educational attainment was derived from genome-wide association studies of one million individuals of European ancestry (Lee et al., 2018), we restrict our sample to only mother-child dyads where the mother self-identified as British and was also of European ancestry (N = 2,077, as identified via the first 2 principal components, see Section 1B of Supplemental Information, SI). We briefly report on preliminary analyses in a Pakistani ancestry subsample of the BiB cohort (see Section 3 of SI).

Genotyping & Polygenic Scoring

We used Illumina HumanCore Exome 12 and 24 BeadChip arrays (Version 1/1.1; Illumina, Hayward, CA) to assay common single-nucleotide polymorphism (SNP) variation in the genomes of our cohort members. As with many traits of interest (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015), education is highly polygenic. To capture information from across the dispersed loci, we constructed polygenic scores (Dudbridge, 2013) using Plink (Version 1.9;

Chang et al., 2015). We matched mother and child genotypes from the Born in Bradford data with the most recent genome-wide association study results for educational attainment (Lee et al., 2018); note that the Born in Bradford data was not used in this genome-wide association study. We used 216,542 matched SNPs from BiB members to construct polygenic scores. For each genotype, we counted the number of education-associated alleles (0, 1, or 2), multiplied this count by the effect size estimated in the original genome-wide association study, and then summed weighted counts across all genotypes to calculate each BiB participants' polygenic score. All matched SNPs were used to compute polygenic scores, irrespective of nominal significance for their association with educational attainment. In all analyses, we control for maternal age and the first ten principal components of European ancestry genotype to account for population stratification and increase the robustness of our findings (Price et al., 2006).

Measures

Additional information for all variables used in study is available in the SI (Section 1).

Prenatal Environment. To index salient aspects of the child's prenatal environment, we measured mother's health and socioeconomic status (SES) during pregnancy. Maternal health during pregnancy was indexed via body mass index (BMI; directly assessed by hospital staff), mental health, cigarette use, indirect smoke exposure, alcohol consumption, caffeine consumption, drug use, vitamin use, and sleep problems (maternal self-report). SES during pregnancy was indexed by maternal education, cohabitation status, employment, maternity leave, governmental benefits, perceived financial difficulty (maternal self-report) and neighborhood-level socioeconomic neighborhood deprivation (governmental index). Based on the variables separately described for prenatal health and SES, we constructed two composites via principal components analysis. To maximize sample size in downstream analyses, we used

an algorithm designed to allow for missing data (Stacklies, Redestig, Scholz, Walther, & Selbig, 2007); additional details on their construction are in Section 1 of the SI.

Child outcomes. To index child development, we used children's scores on the Early Years Foundation Stage Profile (EYFSP), a teacher-led observational assessment that indexes physical, personal, social, and emotional development relative to the average child at the end of their first year of schooling with 6 subscales (Whitaker, 2014). We created a single composite measure by first standardizing each subscale and then calculating a mean total score (higher scores indicate greater development). To index children's academic performance, we used children's scores on the Key Stage 1, a standardized school-based exam that includes math, reading and science subscales (National Curriculum Assessments, 2016). We again created a single composite by standardizing each subscale and calculating the total mean (higher scores indicate greater academic performance). Early achievement at age 7 years has been shown to have enduring effects on individual's downstream educational attainment, SES, and well-being (Ritchie & Bates, 2013).

Analytic Sample

Our analytic sample was restricted to mothers and children of European ancestry for whom genetic data and test scores are available (N = 2,077 dyads). Our analytic sample differed from the full BiB sample in several ways (see SI Section 1C for additional detail on sample comparisons); this is to be expected given the diversity of the BiB sample. Given our focus on a genetically homogeneous sample, we focus on comparisons within the full set of self-reported white British BiB respondents. Only a small portion of the self-identified white British respondents are not in the analytic sample (6% of this subsample). Both child and maternal characteristics were largely similar across these two samples (Table A2A). Within our analytic

sample, we observed further missingness of child PGS and developmental and academic outcomes. This missingness is largely due to either children having left Bradford or students being too young to be eligible for the KS1 (additional detail is in Section 1D of SI).

Statistical analysis

We conducted linear regressions with standard errors clustered at the mother-level (74 mothers had two pregnancies) to test how maternal genetics predict both a child's prenatal conditions and their early academic and developmental outcomes. We conducted a power analysis to probe our ability to detect associations between the maternal polygenic score with the child's outcomes (Section 1E of SI). Given our sample size, we are well-powered to detect association estimates larger than 0.06; note that previous work has suggested much larger association estimates of around 0.2 (Wertz et al., 2019).

To test possible prenatal pathways through which maternal genetics may be associated with child outcomes, we then considered mediation models—using a recently developed framework (Imai, Keele, & Tingley, 2010)—to test the extent to which maternal genetics-related differences in early childhood academic performance and development are explained by prenatal conditions and behaviors. We focus on models wherein the composites of prenatal health and SES are separately included as potential mediators linking maternal PGS and children's outcomes (controlling for child PGS). Inference for these analyses is based on the bootstrap. In analyses, all continuous measures were standardized to have M = 0, SD = 1.

We refrain from extensive reliance on p-values in discussion of our results. However, so as to guard against spurious findings, for the core analyses involving the prenatal composites and the child outcomes (i.e., bolded rows of Table 1, standardized estimates for maternal PGS in Table 2, Table 3) we do comment upon p-values relative to the recently suggested conservative

threshold of $p < 0.005$ (Benjamin et al., 2018). Code used for analysis is publicly available (see Section 4 of SI).

Ethical approvals & data sharing

The research project used only existing, de-identified data; institutional review determined that this project's study protocol did not meet the definition of human subject research. The Bradford Leeds NHS Research Ethics Committee provided ethical approval for the BiB study (15/YH/0455), with adult participants providing written consent before data collection. When participants were children, their parents gave informed consent. Researchers retrieved the sensitive biological, medical, and educational records through a managed-access process approved by the BiB Executive Board.

Results

Maternal genotypes are associated with maternal health and SES during pregnancy.

We first tested whether the mother's PGS for educational attainment was associated with mother's health composite scores during pregnancy (Table 1 Panel A). In this model, we do not control for child PGS; these are measures derived from data collected before the child's birth and should thus be largely unaffected by a child's genetics. We found that on average, maternal PGS was positively associated with greater health ($\beta = 0.089$, 95% CI = [0.046-0.132]; $z = 4.077$, $p < 0.005$). To further investigate this, we also tested each prenatal health factor separately in independent models. We found that a greater maternal PGS was associated with lower levels of caffeine consumption, smoking, and indirect smoke exposure and higher levels of vitamin use (effect sizes range from 0.07 to 0.10). This suggests that a larger PGS is generally associated with more optimal health behaviors during pregnancy; however, associations with alcohol consumption are opposite: higher PGS mothers are more likely to have drank alcohol in the last few months than lower PGS mothers.

We then tested whether the mothers' PGS for educational attainment was associated with mother's SES composite scores during pregnancy. We found that on average, maternal PGS was positively associated with greater SES ($\beta = 0.156$, 95% CI = [0.114-0.198]; $z = 7.261$, $p < 0.005$). This association was greater in magnitude than that observed for maternal health. To investigate this further, we also tested each prenatal SES factor separately in independent models. Unsurprisingly, the maternal PGS was positively associated with maternal education. Greater maternal PGS was associated with lower likelihood of the mother being single, being unemployed and receiving governmental benefits (effect sizes range in magnitude from 0.08 to 0.1). Echoing previous findings, higher PGS was also associated with living in a neighborhood with lower levels of deprivation (D.W. Belsky et al., 2019; Domingue, Belsky, Conley, Harris, & Boardman, 2015).

As shown in Table 1 Panel B, these models also revealed that child PGS uniquely contributed to aspects of the prenatal environment, even after controlling for maternal PGS. With respect to health, child PGS was weakly associated with greater health composite scores, as well as increased vitamin usage and decreased smoke exposure. With respect to SES, child PGS was positively associated with the SES composite and mother's education, and negatively associated with likelihood of the mother being single and experiencing financial difficulty. These results provide further evidence for gene-environment correlation.

Table 1. Associations between mother's and children's polygenic scores (from separate models) for educational attainment and prenatal exposures. In Panel A, associations are between maternal PGS and stated outcome, controlling for age and 10 PCs. In Panel B, associations are between child PGS and stated outcome, controlling for maternal PGS, age, and 10 PCs.

	Panel A: Standardized association of outcome with Maternal PGS [controlling for maternal PCs]		Panel B: Standardized association of outcome with Child PGS [controlling for maternal PGS and PCs]		
Outcome	Estimate	95% CI	Estimate	95% CI	N
Health Composite	**0.089**	**0.046, 0.132**	**0.048**	**-0.002, 0.097**	**1986**
BMI	-0.030	-0.077, 0.017	-0.021	-0.074, 0.032	1903
Mental Health	-0.009	-0.056, 0.038	-0.001	-0.055, 0.053	1910
Vitamin use	0.060	0.014, 0.107	0.092	0.042, 0.143	1986
Indirect smoke exposure	-0.076	-0.118, -0.034	-0.050	-0.099, -0.002	1984
Smoking	-0.108	-0.151, -0.065	-0.048	-0.096, 0.000	1986
Alcohol consumption	0.067	0.021, 0.113	0.034	-0.017, 0.085	1986
Caffeine use	-0.070	-0.118, -0.023	-0.008	-0.056, 0.040	1742
Drug use	-0.013	-0.056, 0.031	0.014	-0.040, 0.069	1923
Sleep problems	-0.005	-0.051, 0.041	0.001	-0.052, 0.053	1907
SES Composite	**0.156**	**0.114, 0.198**	**0.096**	**0.048, 0.143**	**1986**
Maternal Education	0.206	0.162, 0.250	0.070	0.019, 0.121	1809
Single	-0.081	-0.123, -0.039	-0.086	-0.135, -0.037	1985
Employed	0.092	0.049, 0.136	0.036	-0.015, 0.086	1986
Maternal Leave	-0.019	-0.069, 0.031	-0.026	-0.080, 0.029	1554
Neighborhood Deprivation	-0.067	-0.112, -0.022	-0.044	-0.094, 0.006	1935
Financial difficulty	-0.030	-0.076, 0.017	-0.058	-0.112, -0.004	1984
Receipt of governmental benefits	-0.102	-0.145, -0.059	-0.052	-0.104, -0.001	1984

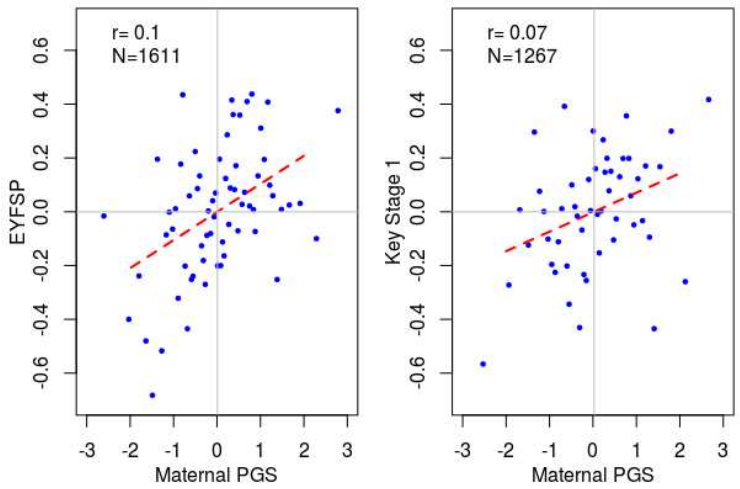
Maternal genotypes predict offspring development net of offspring genes.

To examine the possibility of genetic nurture amongst young children, we next tested whether maternal genetics for educational attainment predicted child development (at age 4-5 years) and academic performance (at age 6-7 years) over and above the child's genetics. As shown in Table 2 and Figure 3, we found that maternal PGS was positively associated with offspring development ($\beta = 0.114$, 95% CI = [0.058, 0.171]; $z = 4.002$, $p < 0.005$) and academic performance ($\beta = 0.087$, 95% CI = [0.020, 0.154]; $z = 2.748$, $p = 0.006$; note that this is marginal in that it is above a conservative threshold of $p = .005$).

Table 2: Mother's and children's polygenic scores for educational attainment uniquely and positively predict children's academic performance and development. Robust CI in parenthesis.

	Child Development (EYFSP)		Academic Performance (KS1)	
Estimates	Mom PGS	Child PGS	Mom PGS	Child PGS
Standardized Outcome	0.114	0.058	0.087	0.083
95% CI	0.058, 0.171	0.002, 0.113	0.020, 0.154	0.016, 0.150
Percentile Ranked Outcome	0.034	0.017	0.030	0.025
95% CI	0.017, 0.050	0.001, 0.033	0.011, 0.049	0.006, 0.044
N	1611		1267	
r2	0.044		0.056	

Figure 3. Maternal PGS for education predicts children's early development and academic performance, accounting for child PGS. Binned scatterplots showing the association between Born in Bradford's mothers' polygenic scores and the developmental and academic outcomes of their children. Maternal polygenic score was residualized on child polygenic score, maternal age, and the first 10 principle components of individual genotype. Maternal polygenic score and both developmental outcomes were standardized within sample to be mean 0 and standard deviation 1. Each point represents roughly 25 mother-child pairs. The red line represents the best linear fit from a regression on the underlying, un-binned data.



In this model, child PGS also uniquely predicted greater academic performance (β = 0.083, 95% CI = [0.016, 0.150]; z = 2.639, p = 0.008) and marginally greater child development (β = 0.058, 95% CI = [0.002, 0.133]; z = 2.020, p = 0.043).

Since the distributions of child outcome variables were highly centralized (see Figure A2 in SI), we also considered analyses based on outcomes converted to percentiles of their respective distributions. Results are qualitatively similar; a one-SD increase in the mother's PGS predicts a gain of around three percentile points in the outcome distribution (β = 0.034 for development, β = 0.030 for academic performance). We also tested whether our findings were potentially due to individual differences in child characteristics measured at birth (Section 2A of SI). Associations between maternal PGS and child's gestational age, APGAR score, and birthweight were null.

As others have observed (Bates et al., 2018; Kong et al., 2018; Wertz et al., 2019), these results are consistent with the hypothesis that mothers' education-associated genetics shape environments that affect offspring outcomes independently of direct mother-child genetic transmission. Our results suggest that such processes are observable during early childhood.

Prenatal environmental exposures mediate associations between maternal genetics and outcomes in early childhood

We next examined whether the observed associations between the maternal PGS and offspring development and academics were explained by conditions experienced during the prenatal period. To do this, we conducted mediation models first with child development as the outcome, and next with academic performance as the outcome. Each model separately included the prenatal health and SES composites as mediators (each model additionally controlled for

child PGS). Note that both the health and SES composites were themselves strongly and positively associated with child development and academic performance (see Section 2B of SI).

For child development, maternal SES during pregnancy explained 27.3% ($p < 0.005$) of the variance in the association between higher maternal PGS and greater child development, and maternal health during pregnancy explained 11.2% ($p < 0.005$) of the variance.

For child academic performance, results were similar. Maternal SES during pregnancy explained (32.1%; $p < 0.005$) of the variance in the association between higher maternal PGS and greater academic performance, and maternal health during pregnancy explained 13.1% ($p < 0.005$) of the variance.

Table 3: Mediation analysis: Proportion of total effect of maternal PGS on outcome that is due to stated mediator (net of child PGS and the alternative prenatal composite).

Outcome	Mediator	Total Effect (maternal PGS on outcome)	95% CI	Proportion mediated	95% CI	N
EYFSP	SES PC	0.113	0.057, 0.164	0.273	0.138, 0.548	1611
EYFSP	Health PC	0.115	0.058, 0.169	0.112	0.039, 0.252	1611
KS1	SES PC	0.087	0.025, 0.146	0.321	0.134, 0.980	1267
KS1	Health PC	0.087	0.024, 0.150	0.131	0.038, 0.484	1267

We considered a supplemental analysis wherein each individual prenatal environmental variable was entered as a mediator, instead of the two composites (Section 2C of SI). Maternal education was an especially salient mediator. One interpretation of these results could be that observed differences are largely mediated by prenatal maternal behaviors that are themselves associated with educational attainment.

Discussion

We investigated whether mother's education-associated genetics are associated with offspring's early development, and whether prenatal environmental factors explain variance in these associations. We drew on a large sample of mother-child dyads followed from 28 weeks gestation through the first 7 years of life. Our results indicate that mothers with more education-associated alleles tended to be healthier (with the exception of alcohol consumption) and more economically secure during pregnancy. Further, these prenatal factors explained about 30% of the positive association between maternal education-associated genetics and child school readiness and early academic performance, even accounting for direct genetic transmission. Together, our results suggest that prenatal exposures are salient environmental pathways through which maternal genetics may influence children's early development and education.

Recent work documents associations between mothers' genetics and their adolescents' education (Bates et al., 2018; Kong et al., 2018; Wertz et al., 2019). We show that maternal genetics are similarly associated with young children's academics and broader developmental milestones, and detectable as young as ages 4-5. The effect size of the association we observed between maternal PGS and child academics is smaller than those from recent studies of adolescent outcomes (effect size of 0.12 compared to 0.23 as observed by Bates et al., 2018 and Wertz et al., 2019 respectively). Our finding adds to growing evidence that genetic variation linked to educational attainment also predicts a constellation of different behaviors and social circumstances across the lifecourse, and even spills into the next generation.

This study suggests that genetic nurture may occur during the prenatal period and leave detectable traces earlier in the child's life than previously observed. Our findings highlight prenatal genetic nurture as a novel pathway through which genetics can confound the observed relationship between prenatal circumstance and child development. For the prenatal environment

to be a period of concern for social policymakers, the documented association between prenatal circumstance and lifecourse development must reflect, at least in part, a causal relationship. However, because a mother's genetics are both transmitted to her offspring and predict her prenatal circumstances, it is unclear the degree to which the relation between prenatal circumstances and child development is correlational versus causal. Most perniciously, such confounding may continue to exist even after controlling for the genetics a child inherits (Rice et al., 2010; Stein et al., 2014). Researchers interested in exploring the causal chain that connect prenatal circumstance to human development would benefit from controlling out the specific pathways we have identified. In particular, we note the crucial role played by the mother's social environment during pregnancy. That said, a mother's SES and other environmental exposures are likely to be relatively unchanging throughout the lifecourse; features of the mother's pregnancy will become the child's environmental surroundings in the first few years of life and beyond. This "stickiness" offers further challenge to research connecting prenatal circumstances to later-life outcomes.

Our research expands on the budding phenotypic annotation literature that uses a top-down approach for unpacking genetic discoveries (D.W Belsky & Harden, 2019). We show that this technique can be applied to indirect genetic influences in addition to direct genetic influences. While findings from genome-wide association studies tend to be a black box, researchers can use data from whole genomes and take a lifecourse development approach to explore how genetics for the discovery of specific phenotypes relate to broader nomological networks (Cronbach & Meehl, 1955). Our analyses embody this approach by utilizing a genome-wide polygenic score for educational attainment as a starting point for exploring the broader nomological network of child development that extends beyond purely educational attainment.

This is important because children's socio-emotional skills are associated with school-readiness and later achievement and wellbeing (Duncan et al., 2007). As such, our results highlight the possibility that maternal genetics may predict a child's capacity to cope and thrive during the transition into formalized education.

We acknowledge limitations. Prenatal environmental measures may be correlated with environmental exposures occurring both before and after pregnancy; e.g., mother's SES may be relatively stable throughout the life course. Thus, prenatal exposures may also inadvertently capture the effect of, for example, persistent exposure to relatively high levels of neighborhood deprivation. Another limitation is that the existing educational attainment polygenic score contains substantial amounts of measurement error, resulting from the finite sample used to obtain the underlying allelic weights. This measurement error attenuates the association between maternal polygenic score and child outcomes, potentially obscuring relevant prenatal pathways. However, this measurement error does not lead to false positives; because mother and child polygenic scores are constructed using the same allelic weights, the child PGS indexes the same genetic pathways as the maternal PGS, and unmeasured child genetics do not confound the association between maternal PGS and child outcomes. In addition, given the complications of interpreting genetic differences across ancestry groups (Martin et al., 2017) our findings only pertain to individuals of White-British ancestry. Finally, though we attempt to reduce confounding through the inclusion of control variables, the findings are observational in nature and do not definitively indicate causal pathways.

The present study illustrates ways in which maternal genetics are interwoven in a complex tapestry of health behaviors and social circumstances. While genes are often used to partition variance in some outcome into genetic and environmental influences, they also

characterize features of the environments that individuals are exposed to. We use genetics to illuminate the important and complex influences on the prenatal environment which in turn shapes children's early development and downstream outcomes. Genetic nurture influences blur the line between genetic and environmental influences, and remind us that genetic influences are not immutable and environments are rarely exogenous.

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