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ORIGINAL RESEARCH

The Genes We Inherit and Those We Don't: Maternal Genetic Nurture and Child BMI Trajectories

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Abstract

Recently, methods have been introduced using polygenic scores (PGS) to estimate the effects of genetic nurture, the environmentally-mediated effects of parental genotypes on the phenotype of their child above and beyond the effects of the alleles which are transmitted to the child. We introduce a simplified model for estimating genetic nurture effects and show, through simulation and analytical derivation, that our method provides unbiased estimates and offers an increase in power to detect genetic nurture of up to 1/3 greater than that of previous methods. Subsequently, we apply this method to data from the Avon Longitudinal Study of Parents and Children to estimate the effects of maternal genetic nurture on childhood body mass index (BMI) trajectories. Through mixed modeling, we observe a statistically significant age-dependent effect of maternal PGS on child BMI, such that the influence of maternal genetic nurture appears to increase throughout development.

Keywords Genetic nurture · BMI · Polygenic score · Cultural transmission · ALSPAC

Introduction

Global trends in body weight are alarming, with rates of childhood obesity increasing and underweight rates remaining high (Yanovski 2018), both of which are linked to severe negative health outcomes and even mortality when continued into adulthood (GBD 2015 Obesity Collaborators et al. 2017; Strand et al. 2012). Thus, it is important to identify potential points for early intervention to prevent extremes of body mass index (BMI), a common proxy measure for adiposity often used in underweight and obesity classification.

Ultimately, any phenotypic similarity among family members can be attributed to two broad sources of direct effects: genetic transmission ("nature") and cultural transmission ("nurture"). The proportion of trait variance which can be explained by transmitted genetic factors is termed heritability and can be estimated through classical family-based modeling of phenotypic correlations or by studies involving direct measurement of genotypes. These methods are also able to estimate the proportion of phenotypic variance attributable to cultural transmission (Cavalli-Sforza and Feldman 1973; Eaves 1976), the effects of one individual's phenotype on another's, for example through knowledge, behavioral modeling, or other lifestyle or environmentally mediated factors. An important extension of cultural transmission is the special case of maternal effects (Wolf and Wade 2009), which include all effects of the maternally provided environment, including the prenatal environment, on the phenotype of her child. The remaining phenotypic variance not accounted for by these two broad sources, which accounts for any dissimilarity among relatives, is attributed to the contribution of non-shared genetic or environmental factors, or measurement error.

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Genetic and cultural sources of familial resemblance are confounded in studies of parents and their children, thus extended twin, family, and adoption models have historically been used to partition the variance explained in offspring traits due to genetic, environmental, and cultural transmission processes (Cavalli-Sforza and Feldman 1973; Nance and Corey 1976). The two most recent meta analyses of twin studies have estimated the heritability of BMI in adults to be 0.73 and 0.75, although there is substantial variation across studies (Elks et al. 2012; Min et al. 2013) and recent genome-wide methods suggest these may be overestimates (Hemani et al. 2013; Yang et al. 2015). Conflicting results prevent a definitive conclusion as to whether sex differences exist in the heritability of BMI. Results from meta analyses which include younger twins have shown that genetic and unique environmental effects tend to become stronger throughout development, while the effect of the shared environment tends to decrease until adolescence where it becomes near zero (Nan et al. 2012; Silventoinen et al. 2010). Across three studies using extended twin or family designs, the effects of cultural transmission have been estimated to account for between 0 and 2% of the variance in BMI (Maes et al. 1997; Tambs et al. 1991) or BMI fluctuation (Bergin et al. 2012).

The interest in parental effects through cultural transmission has not been lost in the genome-wide era. Maternal genome wide complex trait analysis was developed to estimate the variance in an offspring's phenotype attributable to the effects of maternal genotype using genome-wide single nucleotide polymorphism (SNP) data (Eaves et al. 2014). Importantly, the authors also note that methods which fail to model the effects of cultural transmission when present may result in upwardly biased estimates of direct genetic effects. While some groups have sought to estimate parental effect sizes for individual genetic variants (Warrington et al. 2018, 2019), others have leveraged progress in genome-wide association studies (GWAS) to obtain estimates of the causal effects of parental exposures on offspring outcomes using Mendelian randomization (MR; Evans et al. 2019; Zhang et al. 2015). Additional progress has been made in elucidating the power and bias characteristics of parental effect models, with important implications for approaches to data collection and analysis (Lawlor et al. 2017; Moen et al. 2019; Tubbs et al. 2020).

Recently, two groups independently developed a method utilizing polygenic scores (PGS) for modeling the contribution of non-transmitted parental alleles on the phenotype of their child, which Kong and colleagues termed "genetic nurture" (Bates et al. 2018; Kong et al. 2018). This method involves creating a PGS for each offspring calculated from the alleles they inherited from their parents and another PGS derived from the remaining non-transmitted alleles. Both PGSs can be further partitioned into those of maternal and paternal origin. The two studies demonstrated a statistically significant effect of non-transmitted parental alleles on educational attainment (EA) with effect size estimates of 29.9% and 38% that of the transmitted PGS.

However, the genetic architecture of EA may differ significantly from that of BMI, with EA heritability estimated through meta-analysis of twin studies to be 0.4, but with high heterogeneity between studies (Branigan et al. 2013). While Kong and colleagues examined the effect of EA PGS on other offspring phenotypes, including body mass index, we are not aware of another study which has examined the effects of genetic nurture on BMI. The Avon Longitudinal Study of Parents and Children (ALSPAC) provides an ideal dataset for examining the effects of maternal cultural transmission on BMI. Not only does this resource provide genetic data on a large sample of mother–child pairs, but also repeated measures of BMI over childhood and adolescence, allowing the contribution of these effects to be modelled across development.

Under the familiar paradigm of the transmission disequilibrium test (Spielman et al. 1993), it appears natural to partition genotype data from trios into transmitted and non-transmitted components. However, this may be unnecessary or even unhelpful when we are interested in estimating the effects of cultural transmission. Thus, here we first propose another possible model for estimating maternal effects which does not separate transmitted and non-transmitted parental components to be calculated, and compare it analytically and through simulation with the models from Kong et al. (2018) and Bates et al. (2018). We then apply the best performing model to data from ALSPAC to estimate the effects of maternal genetic nurture on BMI trajectory through development.

Subjects and Methods

Simulation Study and Analytic Derivation for Model Comparison

We performed a simple simulation study to compare the performance of three potential regression models to predict offspring phenotype, with the goal of comparing the statistical power, variance explained, standard error, and bias of maternal effects estimated using only the non-transmitted maternal genotype versus the complete maternal genotype. Figure 1 shows a path diagram visualizing these three models.

$$M1: \; y \sim h_s G_O + \beta_p G_P + \beta_m G_M,$$
$$M2: \; y \sim h_s G_O + \beta_{np} G_{PNT} + \beta_{nm} G_{MNT},$$
$$M3: \; y \sim \beta_{tp} G_{PT} + \beta_{np} G_{PNT} + \beta_{tm} G_{MT} + \beta_{nm} G_{MNT}.$$

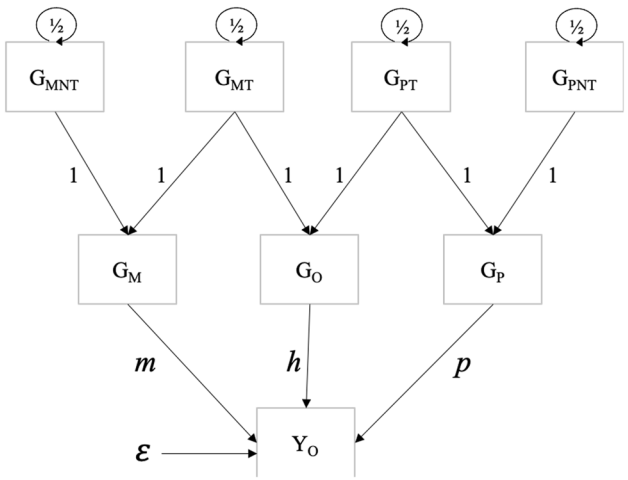

Fig. 1 Path diagram of genetic nurture models. Y_O denotes the phenotype of the child. G_O, G_M, and G_P are the polygenic scores for phenotype Y for the offspring, mother, and father, respectively. G_{MNT}, and G_{MT} are the polygenic scores for the non-transmitted and transmitted maternal alleles, whereas G_{PNT}, and G_{PT} are those for the father. *h*, *m*, and *p* represent the effects of the offspring, maternal, and paternal polygenic scores on the offspring phenotype. is the random error variance in Y

M1 is our proposed model, which regresses the phenotype *y* on offspring PGS (G_O) and paternal PGS (G_P) and maternal PGS (G_M). M2 differs from M1 in that the two parental PGSs (G_{PNT} and G_{MNT}) are based on alleles not transmitted to the offspring, and was employed in a mixed model framework by Bates et al. (2018). Lastly M3 differs from M2 by further partitioning the offspring PGS into components transmitted from the two parents (G_{PT} and G_{MT}), and was used by Kong et al. (2018) to estimate parent-of origin effects of genetic nurture and by Bates et al. (2018) in a structural equation model.

The full simulation procedures and closed-form model comparison are detailed in the Supplementary Material. Briefly, we randomly sampled non-transmitted and transmitted PGS for hypothetical mothers and fathers, subsequently using these to calculate the offspring phenotype and the following PGS: G_O, G_M, G_P, G_{MT}, G_{MNT}, G_{PT} ,and G_{PNT}. In the supplement, we show the derivation of expected regression estimates, error variance, and non-centrality parameters of the beta estimates for each model.

Direct Genetic and Genetic Nurture Effects on BMI in ALSPAC

The complete ALSPAC study design and dataset have been described in detail elsewhere (Boyd et al. 2013; Fraser et al. 2013) and a description of the study numbers provided by ALSPAC is included in the supplement. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). Briefly, this longitudinal observational study recruited over 14,000 pregnant women and their partners from the Bristol, UK area in the early 1990s. These families provided psychological, physiological, and genetic data through questionnaires and clinical visits over the past 29 years. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The present analysis utilized standard demographic variables, genotype data from mothers and children, BMI measurements from mothers at 2 clinical visits and BMI measures from children invited to clinical visits at ages 7, 9, 10, 11, and 17.

Following standard genotyping quality control measures, maternal and child genotype data were harmonized by ALSPAC researchers (see Supplementary Material). We performed an additional principal component analysis using PLINK version 1.9 (Chang et al. 2015) (www.cog-genomics.org/plink/1.9/) to control for population stratification, which identified four individuals who appeared as outliers on the first and second genetic principal components and were thus excluded from the sample. After these quality control measures, our analytic sample consisted of 3120 genotyped mother–child pairs of European ancestry with at least 1 maternal and child clinical visit, representing a total of 14,022 child BMI observations. Maternal and child BMI distributions exhibited a heavy rightward skew towards higher BMI measurements. Thus, for use in our model selection procedure, we applied a logarithmic transformation to these variables with an added constant chosen to minimize the skew of the distributions.

Polygenic Score Construction

Lassosum (Mak et al. 2017), a machine-learning based program, was used to calculate PGS for mothers and offspring in our sample from the most recent GWAS meta-analysis for BMI (Yengo et al. 2018). Lassosum employs penalized regression on summary statistics while accounting for linkage disequilibrium, producing more accurate polygenic risk prediction than other popular techniques (Allegrini et al. 2019; Mak et al. 2017). For the tuning parameter optimization step in Lassosum, the mean maternal BMI across two clinical visits and a randomly drawn child BMI measurement from all available clinical visits were used as the phenotype for mothers and children, respectively, to maximize the number of available phenotypic observations.

Mixed Models

Mixed models are often used in longitudinal data analysis for their ability to estimate average fixed effects across individuals while simultaneously accounting for random effects within individuals arising from the covariance between repeated measurements across time. As our dataset also contains a small number of sibling pairs, mixed models have the added benefit of being able to control for covariance between siblings. Therefore, we constructed a mixed model to estimate the fixed effects of child age, age^2, sex, PGS_C, PGS_M, and all meaningful multiplicative interactions between these predictors on child BMI. In a follow-up analysis, a similar mixed model was constructed to estimate the effects of maternal BMI. For all models, variables were standardized to have a mean of zero and standard deviation of one, with age subsequently squared, as this increases the likelihood of mixed model convergence when using the *lme4* package (Bates et al. 2015).

To determine the most appropriate random effects structure and whether to use the transformed BMI variables, we employed a model selection procedure (see Supplementary Material) to identify a best-fitting model which minimizes the AIC and best satisfies the underlying mixed model assumptions, while avoiding models which arrive at a singular fit or fail to converge. This procedure identified the best-fitting model as that which predicted log-transformed child BMI as a function of child age, age^2, and sex, along with PGS_C, PGS_M, and all possible pairwise multiplicative interactions apart from age * age^2. Random intercepts and slopes controlled for the effects of age and age^2 within each child and within sibling pairs. Models were fit by maximum likelihood using the *lme4* package version 1.1.21 (Bates et al. 2015) for R version 3.5.3 (R Core Team 2019), while p-values were calculated using the *lmerTest* package version 3.1.0 (Kuznetsova et al. 2017), and the *r2glmm* package (Jaeger et al. 2017) was used to calculate partial R^2 for each predictor based on the method of Nakagawa and Schielzeth (2013).

Results

Simulation Results and Analytic Derivation

Figure 2 plots the squared partial correlation (i.e. the variance uniquely explained in y by a variable) of G_M versus G_{MNT} across 1000 simulations with varying magnitude of maternal effects, indicating that the full maternal PGS consistently explains a greater proportion of variance in the phenotype of the child than a PGS of the non-transmitted maternal alleles alone while statistically controlling for the effects of the transmitted alleles by inclusion of G_O as a predictor in the regression. Supplementary Fig. S1 similarly plots the bias and standard error (SE) of G_M versus G_{MNT}, demonstrating that while both are unbiased predictors of maternal genetic nurture effects, the SE of G_M is smaller compared to G_{MNT}. Figure 3 compares the statistical power of β_m and β_{nm} to estimate the genetic maternal effects and the combined power of all predictors, measured as model F-statistic, across the three regression equations for 1000 simulations of varying sample size and fixed maternal, paternal, and child PGS effects. Figure 3 demonstrates that β_m of M1 had greater power to detect the maternal genetic effects than β_{nm} of M2 or M3. In terms of combined power of all independent variables, M1 and M2 had equal power to predict the offspring phenotype, which was greater than that of M3.

Comparison of the asymptotic properties of these three models demonstrates that M1 correctly estimates the direct effect of the child's genotype and the effects of genetic nurture. With M1, these effects can be interpreted straightaway, whereas the direct effect estimates from M2 and M3 are initially biased by parental effects, and must be "de-biased" before interpretation. At the same time, M1 affords the greatest statistical power to detect genetic nurture effects as compared to M2 and M3. The non-centrality parameter per offspring-parent trio is increased by $\frac{1\sigma_1^2}{3\sigma_2^2}$ in model M1 compared to model M2, and by 1/3 when compared to model M3, where σ_1^2 is the residual variance in y of model M1 and σ_2^2 is that of model M2. In the supplement, we further show that given a complete mediation of genetic nurture effects through a maternal phenotype, a modified M1 is able to accurately partition these effects.

Mixed Model Results of BMI from ALSPAC

Table 1 provides descriptive statistics for the sample prior to variable standardization and log-transformation of child and mother BMI. Table 2 summarizes the results of our best-fitting mixed model (Model A) predicting log-transformed child BMI as a function of child age, age^2, and sex, along with PGS_C, PGS_M, and all possible multiplicative interactions except for age * age^2 while controlling for random variation within child BMI measurements across time and for correlation among siblings. Table 2 also shows the results from Model B, an extension of Model A which includes log-transformed maternal BMI and its interactions with age, age^2, and sex as predictors. Model A supports the presence of a significant age-dependent effect of maternal genetic nurture on child BMI (Age * PGS_M; $\beta = 0.014, SE = 0.005, p = 0.007$) with an effect size 39% that of the similar interaction between age and child PGS (Age * PGS_C; $\beta = 0.036, SE = 0.005, p = 6.20e-13$). With the inclusion of maternal BMI as a predictor in Model B, this Age * PGS_M interaction term becomes non-significant, but

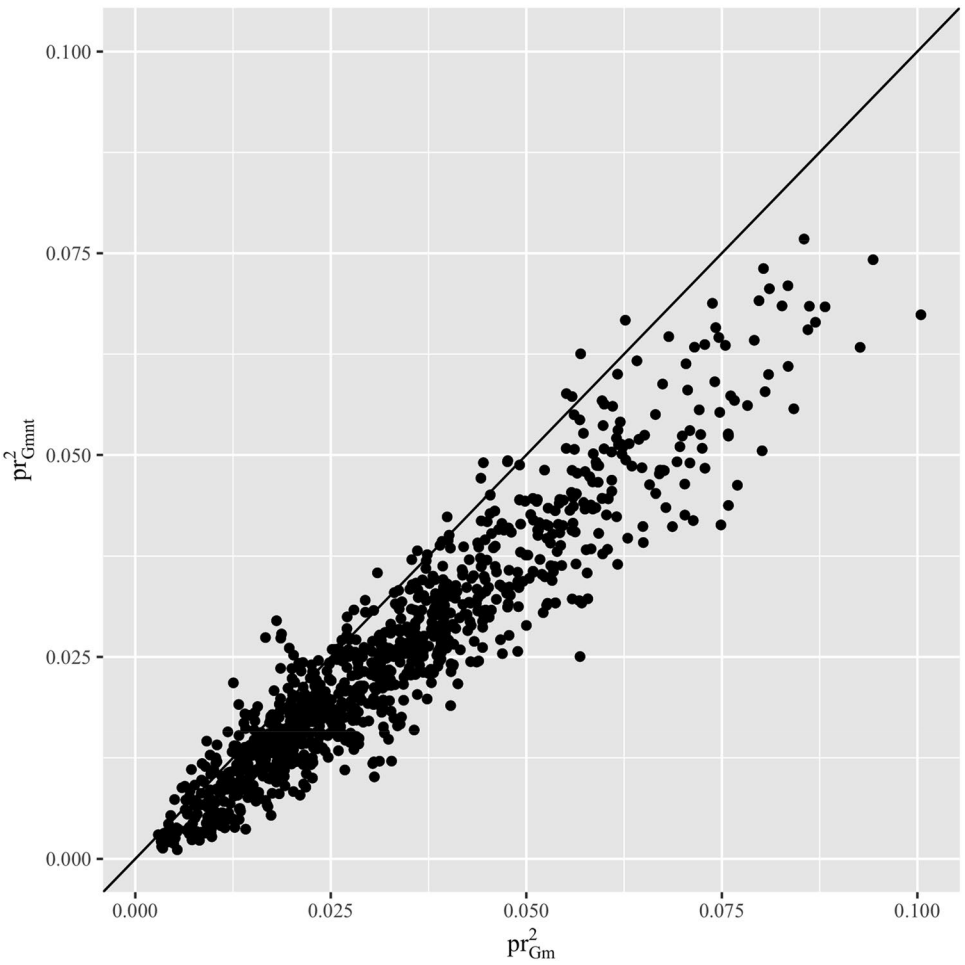

Fig. 2 Partial correlation squared of G_M vs G_{MNT} across 1000 simulations. *Note.* This figure plots the variance uniquely explained by G_M versus G_{MNT} across 1000 simulations with varying maternal effect sizes, showing that the complete maternal PGS consistently explains a greater proportion of variance in the phenotype of the child than a PGS of the non-transmitted maternal alleles alone while statistically controlling for the effects of the transmitted alleles by inclusion of G_O as a predictor in the regression model

the previously non-significant $Age^2 * PGS_M$ term becomes statistically significant with a p-value of 0.033. Figure 4 visualizes the predicted effect of PGS_C and PGS_M on child BMI across age from Model A, showing that while the effects of maternal BMI risk variants only appear to be relevant in later stages of child development, the PGS_C tends to decrease in importance in determining the phenotype towards later stages of development.

Discussion

Our major objectives were to determine an optimal model for estimating the polygenic effects of maternal genetic variants on a child's phenotype and subsequently apply a similarly constructed mixed model to longitudinal BMI measurements. The results of our analysis have implications for future research into genetic nurture effects estimation and for our understanding of the genetic and environmental contributors to BMI across development. Here, we discuss the benefits of our proposed model, results from mixed models applied to BMI in the context of previous findings from twin studies, potential limitations of our approach, and the practical relevance of our results.

We have shown through simulation and derivation that while controlling for the direct effects of the transmitted alleles, a full maternal polygenic risk score has greater power, smaller SE, and explains a greater proportion of the variance in a child's phenotype than a maternal polygenic score computed for the non-transmitted alleles alone. Previous methods (Bates et al. 2018; Kong et al. 2018) have focused on estimating the effects of genetic nurture arising from non-transmitted genetic variants. However, transmitted alleles may also contribute to a parental effect on the child's phenotype above and beyond the direct effects of the child's own genotype. In other words, the environmental effects of half of the parental genotype do not disappear after formation of the zygote. We have shown that our proposed model is able to give unbiased estimates of the direct effects of transmitted variants and the genetic nurture effects of both transmitted and non-transmitted parental genetic variants without the need to partition the component PGS, resulting in greater statistical power and easier interpretation

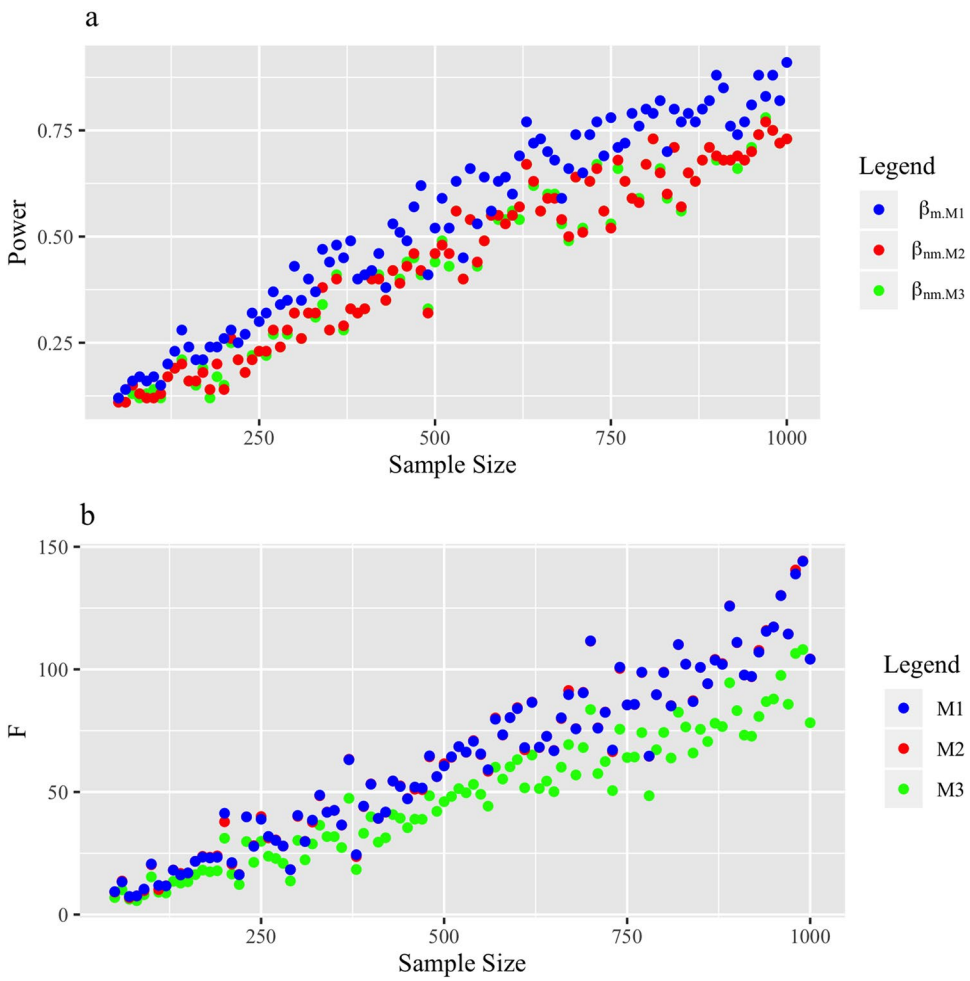

Fig. 3 Power of β_m vs β_{nm}, and overall regression model power (measured by F-statistic). Results are from 1000 simulations of varying sample size with fixed direct, maternal genetic nurture and paternal genetic nurture effects. Model M1 regresses the phenotype *y* on offspring PGS, paternal PGS, and maternal PGS. M2 differs from M1 in that the two parental PGSs are based on alleles not transmitted to offspring. Lastly M3 differs from M2 by further partitioning the offspring PGS into components transmitted from the two parents. Panel **a** compares the statistical power to detect the presence of a maternal effect utilizing a PGS computed from all maternal alleles (β_m) versus a PGS constructed from only the maternally non-transmitted alleles (β_{nm},) across the three regression models. We show that of M1 had greater power to detect the maternal genetic effects than of M2 or M3. Panel **b** compares the F-statistics of each model. In terms total model power, M1 and M2 had equal power to predict the offspring phenotype, which were both greater than that of M3

Table 1 Descriptive statistics of clinical measures and PGS calculated from genotype data in our analytic sample of the ALSPAC dataset

Clinical measures	N	BMI		Age	
		Mean (SD)	Min–max	Mean (SD)	Min–max
Mothers					
Average of 2 clinic visits	3120	26.67 (5.26)	15.30 to 55.04	48.74 (4.38)	34 to 62.79
Children (48% male)					
7 year clinic visit	2858	16.12 (1.97)	10.85 to 31.65	7.49 (0.26)	6.83 to 9.42
9 year clinic visit	2890	17.52 (2.75)	12.64 to 34.25	9.81 (0.27)	8.75 to 11.33
10 year clinic visit	2889	18.01 (2.95)	12.36 to 34.72	10.60 (0.22)	9.92 to 12.17
11 year clinic visit	2891	18.85 (3.26)	12.44 to 36.08	11.71 (0.21)	10.75 to 13.58
17 year clinic visit	2494	22.54 (3.87)	13.00 to 50.05	17.74 (0.39)	16.25 to 19.75
BMI polygenic scores		Mean (SD)			Min–max
Mothers		0.61 (0.90)			− 2.74 to 3.62
Children		0.60 (0.89)			− 2.91 to 3.68

than models which propose separate transmitted and non-transmitted PGS.

The results of our mixed models show a statistically significant age-dependent effect of maternal genetic nurture on child BMI which is 39% that of the similar interaction effect of a child's own polygenic risk with age. Our results suggest that the effects of maternal genetic nurture on child BMI become stronger throughout development. This

Table 2 Results from a mixed effects model predicting log-transformed child BMI

Predictors	BMI_C Model A			BMI_C Model B		
	Estimates	CI	p	Estimates	CI	p
Fixed effects						
Intercept	− 0.072	− 0.163 to 0.018	0.118	− 0.093	− 0.181 to − 0.005	**0.039**
Age	0.617	0.589 to 0.644	**< 0.001**	0.613	0.585 to 0.640	**< 0.001**
Sex (1 = M, 2 = F)	0.086	0.029 to 0.142	**0.003**	0.099	0.044 to 0.154	**< 0.001**
PGS_C	0.278	0.194 to 0.361	**< 0.001**	0.270	0.189 to 0.352	**< 0.001**
PGS_M	0.030	− 0.054 to 0.113	0.489	− 0.024	− 0.111 to 0.064	0.597
Age^2	− 0.020	− 0.041 to 0.000	0.055	− 0.018	− 0.039 to 0.003	0.088
Age * Sex	0.009	− 0.008 to 0.026	0.288	0.012	− 0.005 to 0.029	0.168
Age * PGS_C	0.036	0.026 to 0.046	**< 0.001**	0.035	0.025 to 0.044	**< 0.001**
Age * PGS_M	0.014	0.004 to 0.023	**0.007**	0.000	− 0.010–0.011	0.948
Age^2 * Sex	− 0.022	− 0.035 to − 0.009	**0.001**	− 0.024	− 0.037 to − 0.011	**< 0.001**
Age^2 * PGS_C	− 0.037	− 0.045 to − 0.030	**< 0.001**	− 0.036	− 0.043 to − 0.028	**< 0.001**
Age^2 * PGS_M	− 0.000	− 0.008 to 0.007	0.897	0.009	0.001 to 0.017	**0.033**
Sex * PGS_C	0.023	− 0.028 to 0.074	0.386	0.021	− 0.029 to 0.070	0.418
Sex * PGS_M	− 0.010	− 0.061 to 0.041	0.703	− 0.027	− 0.081 to 0.026	0.316
BMI_M				0.141	0.061 to 0.221	**0.001**
Age * BMI_M				0.033	0.024 to 0.042	**< 0.001**
Age^2 * BMI_M				− 0.023	− 0.030 to − 0.016	**< 0.001**
Sex * BMI_M				0.038	− 0.009 to 0.086	0.116
Random effects						
σ^2	0.04			0.04		
τ_{00}	$0.23_{ID:FID}$			$0.23_{ID:FID}$		
	0.40_{FID}			0.36_{FID}		
τ_{11}	$0.02_{ID:FIDage}$			$0.02_{ID:FIDage}$		
	$0.01_{ID:FIDage\text{^}2}$			$0.01_{ID:FIDage\text{^}2}$		
	0.02_{FIDage}			0.02_{FIDage}		
	$0.02_{FIDage\text{^}2}$			$0.02_{FIDage\text{^}2}$		
ρ_{01}	0.58			0.59		
	− 0.83			− 0.83		
	− 0.06			− 0.13		
	− 0.59			− 0.57		
ICC	0.94			0.94		
N	3120_{ID}			3120_{ID}		
	3099_{FID}			3099_{FID}		
Observations	14,022			14,022		
Marginal/conditional R^2	0.419/0.965			0.446/0.965		

Bold font indicates p-value less than 0.05

All variables (apart from age^2) were standardized to have a mean of 0 and standard deviation of 1

BMI_C log-transformed child BMI, *BMI_M* log-transformed maternal BMI, *CI* 95% confidence interval, *FID* unique family ID, *ID* unique child ID, *PGS_C* offspring polygenic score, *PGS_M* maternal polygenic score

is somewhat surprising, as twin studies suggest that the effects of the shared environment, which would partially subsume the effects of genetic nurture, decrease throughout childhood and adolescence (Nan et al. 2012; Silventoinen et al. 2010). However, maternal genetic nurture may also contribute to the unique environment component if one twin is treated differently from their co-twin, which may happen with greater frequency through development, potentially explaining our seemingly disparate results. Alternative explanations may include a cumulative effect of genetic nurture or an increasing similarity to maternal diet as children approach adulthood and become less picky or relatively less constrained in their choice of food.

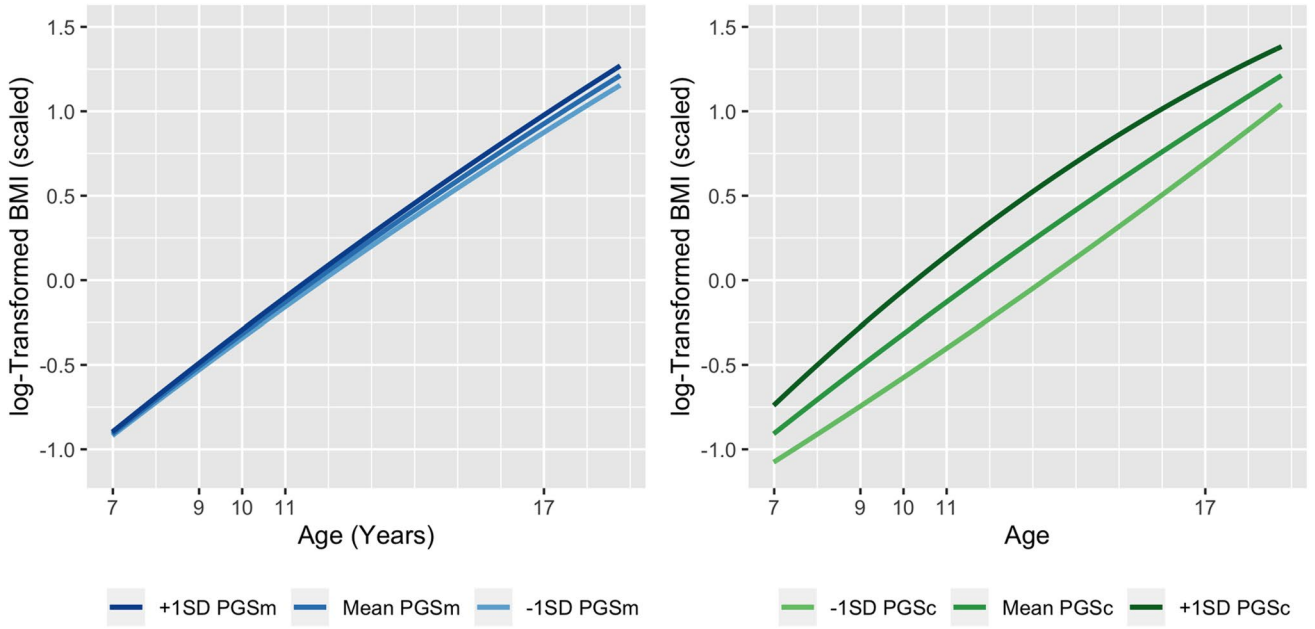

Fig. 4 Simple slope of the predicted effect of PGS_M and PGS_C on BMI across age. *Note*. Tick marks correspond to target assessment ages of children in years. Child BMI is log-transformed and standardized. Lines represent the predicted value of child BMI from child age, age^2, respective PGS, PGS * age, and PGS * age^2

Although the age-dependent effect of maternal genetic nurture is statistically significant, the combined effects of PGS_M and its interactions with age as predicted by Model A uniquely explain about 0.02% of the variance in child BMI. In comparison, the combined effects of PGS_C and its interactions with age from Model A are able to uniquely explain 1.15% of the variance in child BMI, about 50 times greater than the combined PGS_M effects. Further, maternal genetic nurture increases in relative importance throughout development. For instance, the combined effect size estimates for PGS_M and its interactions with age are 5% that of those estimates for PGS_C predicted at the mean age for year 7 follow-up visit, but 26% as large as the PGS_C effect size estimates predicted at the mean age for the 18-year follow-up. This suggests that the effects of maternal genetic nurture on child BMI may be relatively unimportant in practical applications compared to the influence of other risk factors including the child's own genetic risk.

After inclusion of maternal BMI as a predictor in the base Model A, the effect of Age * PGS_M was no longer statistically significant, but the Age^2 * PGS_M became significant. Thus, it is unclear whether the genetic factors responsible for the effects of genetic nurture may be mediated by the manifest maternal BMI, which would suggest shared genetic factors contributing both to the maternal BMI and indirectly to the child's BMI.

In contrast to results from previous twin modeling (Nan et al. 2012; Silventoinen et al. 2010) showing that the influence of additive genetic factors increases throughout child development, our model results suggest that polygenic effects on BMI may actually decrease slightly in importance as children get older. One potential explanation for these seemingly divergent findings is that while twin studies are able to model the effects of all additive genetic factors, polygenic scores based on GWAS results are unable to adequately capture the effects of rare or structural genetic variants, which might have cumulative or developmentally-dependent effects on BMI risk.

The apparent discrepancy between some of our results and those of previous twin studies highlights some potential limitations of our approach. As previously discussed, the common variants examined by SNP-based genotyping are not ideal for capturing the effects of rare or structural genetic variants, which may have a larger effect on the phenotype, and may even fail to capture a large proportion of the variance explained by non-typed common SNPs as well. Additionally, our polygenic scores for both mothers and children were calculated using summary statistics from GWAS examining BMI in adults. Although they are likely to overlap greatly, it is possible that the genetic variants which influence childhood BMI differ from those which are important in adulthood. However, GWAS of BMI in children lack the statistical power of their adult BMI counterparts of significantly larger sample size (Felix et al. 2016). As our sample consists only of British mother–child pairs of European ancestry, the applicability to other populations with different cultural or ancestral backgrounds is limited. Future work should

strive to collect and analyze such longitudinal family data in understudied populations.

A number of obstacles may bias the estimation of maternal genetic nurture in our study. First, our estimates of genetic nurture effects could be downwardly biased by utilizing a BMI-based PGS, as maternal genetic variants which affect the child's BMI may not be restricted to the same factors important in determining the mother's own BMI. As discussed by Kong et al. (2018), bias in the estimates of maternal effects can clearly occur in the presence of un-modelled paternal effects that are correlated with maternal effects due to assortative mating, which has been shown to exist for BMI in humans (Robinson et al. 2017; Silventoinen et al. 2003). However, recent theoretical work by our group has shown that collider bias can occur even when un-modelled paternal effects are independent of maternal effects (Tubbs et al. 2020).

We have shown that utilizing a combined maternal PGS to estimate the effects of genetic nurture represents an improvement in the techniques introduced by Kong et al (2018) and Bates et al. (2018). By utilizing the full child, mother, and father polygenic scores, we show a 1/3 increase in power to detect a genetic nurture effect over models which separate these scores into non-transmitted and transmitted component scores. Further, in applying this model to developmental BMI trajectories, we have shown a statistically significant age-dependent effect of maternal PGS on child BMI, such that the effects of maternal genetic nurture appear to increase throughout development and into late adolescence. Although the size of observed maternal genetic nurture effects on child BMI are miniscule compared the effects of transmitted alleles present in the child, the current analysis does not negate the potential importance of the parentally provided environment on the child's BMI, which warrants continued future study.

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Compliance with Ethical Standards

Conflict of interest Justin D. Tubbs, Robert M. Porsch, Stacey S. Cherny and Pak C. Sham declares that they have no conflict of interest to report.

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