



Deposited via The University of York.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/201551/>

Version: Published Version

Article:

von Stumm, Sophie, Kandaswamy, Radhika and Maxwell, Jessye (2023) Gene-environment interplay in early life cognitive development. *Intelligence*. 101748. ISSN: 0160-2896

<https://doi.org/10.1016/j.intell.2023.101748>

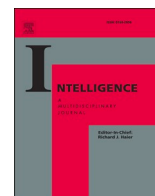
Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



Gene-environment interplay in early life cognitive development

Sophie von Stumm^{a,*}, Radhika Kandaswamy^b, Jessye Maxwell^b

^a Department of Education, University of York, Heslington, York, UK

^b King's College London, Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, London, UK

ARTICLE INFO

Keywords:

Gene-environment interplay
Polygenic scores
Cognitive development
Gene-environment interaction
TEDS

ABSTRACT

Children's differences in early life cognitive development are driven by the interplay of genetic and environmental factors, but identifying replicable gene-environment interactions (GxE) has proven difficult. We systematically tested GxE effects in the prediction of cognitive development from 2 to 4 years, using polygenic scores (PGS) for years spent in education and 39 measures of the home and neighborhood environment. Data came from up to 6973 unrelated individuals from the Twins Early Development Study (TEDS), a UK population-representative cohort. The environmental measures accounted together for 20.6% of the variance in cognitive development, while the PGS accounted for 0.5% ($p < .001$). We observed substantial gene-environment correlations but found no conclusive evidence for GxE effects. While associations between PGS and cognitive development were weak, genetic and environmental factors had direct and additive (i.e., main effects) rather than interactive influences on early life cognitive development.

1. Introduction

Children's differences in cognitive development are evident early on in life (Deary, 2012; Tucker-Drob & Briley, 2014; von Stumm & Plomin, 2015). By the time they start formal education, children's differences in cognitive ability are powerful predictors of their contemporaneous and future academic achievement (Honzik, Macfarlane, & Allen, 1948; von Stumm, 2017). Identifying the causes of children's differences in early life cognitive development is therefore key to designing and implementing effective interventions that improve children's life chances.

Differences in early life cognitive development stem from the complex interplay between genetic factors and the rearing environment. This interplay includes gene-environment correlations (rGE) and gene-environment interactions (GxE). rGE refer to the covariance between genes and environments that occurs when genotypes are assorted to the environments that they are found in (e.g., Abdellaoui, Hugh-Jones, Yengo, et al., 2019; Avinun, 2020). GxE imply moderation effects, with the genetic predispositions for phenotypic traits developing differently in different environments (i.e., being moderated by the environment; Plomin, DeFries and Loehlin, 1977). While rGE effects have often been observed (Abdellaoui et al., 2019; Avinun, 2020; Kravitz et al., 2017), finding replicable GxE in the prediction of early life cognitive development has proven difficult. Even the popular Scarr-Rowe hypothesis (Scarr-Salapatek, 1971), which suggests that family

socioeconomic status (SES) moderates the influence of genetics on cognitive development, has not been conclusively demonstrated (Figlio, Freese, Karbownik, & Roth, 2017; Hanscombe et al., 2012; Tucker-Drob & Bates, 2016; von Stumm et al., 2020).

GxE effects are typically interpreted according to one of three conceptual frameworks. First, children with the genetic risk for poor cognitive outcomes may be disproportionately negatively affected by early life adversity, such as chaotic family homes or malnutrition (cf. diathesis-stress model; Sigelman & Rider, 2009). Alternatively, enriched environments may maximise the expression of genetic differences, while environmental stress masks them (cf. bioecological model; Bronfenbrenner & Morris, 2006; Ronda et al., 2022); for example, children with or without a genetic propensity for intelligence may show reduced cognitive growth in unsupportive learning environments. The third concept is a cross-over interaction, where susceptible children are disproportionately affected by both negative and positive experiences (cf. differential susceptibility model; Greven et al., 2019).

Several reasons account for the persistent struggle to empirically substantiate GxE effects in the prediction of cognitive development. A key one is statistical power: Modelling GxE effects requires very large sample sizes (Dick et al., 2015; Duncan & Keller, 2011; Keers & Pluess, 2017). For example, 2500 pairs of monozygotic and dizygotic twins are needed to detect GxE of medium effect size with 80% power in a twin model (Hanscombe et al., 2012). Yet few studies that tested GxE in the

* Corresponding author.

E-mail address: sophie.vonstumm@york.ac.uk (S. von Stumm).

<https://doi.org/10.1016/j.intell.2023.101748>

Received 21 May 2022; Received in revised form 1 March 2023; Accepted 1 March 2023

Available online 11 March 2023

0160-2896/© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

prediction of cognitive development even approximated such sample sizes (Figlio et al., 2017; Tucker-Drob & Bates, 2016). The most seminal study in this area, cited >1800 times at the time of writing, analyzed data from only 114 monozygotic and 205 dizygotic twin pairs (Turkheimer, Haley, Waldron, d'Onofrio, & Gottesman, 2003), yielding <30% power to detect a sizeable GxE effect.

Second, prior studies of GxE in the prediction of cognitive development typically modelled only one or two environmental factors, an approach that (a) ignores the breadth and diversity of environments, (b) precludes the possibility of multiple GxE being simultaneously at play, and (c) leads to residual confounding (Keller, 2014; von Stumm & d'Apice, 2022). Few environments are truly exogenous to the individual, which is known as the endogeneity problem (Dick, 2011; Duncan, Magnuson, & Ludwig, 2004; Schmitz & Conley, 2017; von Stumm & d'Apice, 2022) and complicates disentangling truly environmental from truly genetic effects. Because many environmental measures show substantial genetic influences, it is plausible that environments and a target phenotype (i.e., cognitive development) have shared genetic etiology.

A third challenge lies in operationalizing genetic influence. The classical twin model infers heritability by comparing the phenotypic resemblance of monozygotic twins to that of dizygotic twins (Plomin, 2019). In this model, GxE are evident when the heritability estimates of a trait (e.g., cognitive development) vary as a function of a putatively environmental measure (e.g., family SES; Tucker-Drob & Bates, 2016). An alternative approach is to use person-specific estimates of genetic propensities and to directly test their interplay with environments. For example, the candidate-gene approach to GxE analyzed if a pre-specified genetic variant manifested differently depending on the environmental context (Duncan & Keller, 2011; Saltz et al., 2018). Yet most psychological traits are polygenic – that is, their expression is influenced by many thousands of DNA variants rather than by a few candidate genes. These DNA variants can be aggregated as polygenic scores (PGS) that are person-specific estimates of genetic propensity for a target phenotype (Plomin & von Stumm, 2018). PGS allow for directly testing gene-environment interplay, although they do not solve all problems pertaining to GxE analyses (Schmitz & Conley, 2017; Ronda et al., 2022).

In this preregistered study, we analyzed data from a large, well-powered sample of children from the Twins Early Development Study (TEDS). We tested a broad range of early life experiences or environmental measures as moderators of the relation between PGS and cognitive development from age 2 to 4 years. Our environmental measures ranged widely from parent-reports of twins' sleeping patterns and chaos in the family home to postcode-based indicators of neighborhood quality, such as local employment rates and air pollution levels. We did not make predictions about specific interactions between environmental measures and PGS, adopting an a-hypothetical approach that mirrors that of genome-wide association (GWA) studies, which test DNA-phenotype associations across the genome, independent of the DNA variants' location or function (Plomin & von Stumm, 2018; von Stumm & d'Apice, 2022). We used a PGS based on the summary statistics from a large GWA study for years spent in education with 1.1 million participants (Lee et al., 2018). In previous analyses, polygenic scores based on this GWA study predicted 7% and 10% of the variance in cognitive ability at age 12 and 16 years, as well as 7% and 15% of the variance in school performance at age 12 and 16 years (Allegrini et al., 2019). Although we made no predictions about specific GxE effects, we did hypothesize that the PGS based on Lee et al.'s (2018) GWA study for years spent in education is significantly associated with early life cognitive development.

2. Method

2.1. Sample

Participants came from the Twins Early Development Study (TEDS), for which over 10,000 twin pairs were recruited from England and

Wales between 1994 and 1996. At the twins' age of 18 months, 13,759 families participated; this first assessment wave included data about demographics, pregnancy, childbirth, and zygosity. Zygosity was assigned using a parent-reported questionnaire of physical similarity, which is over 95% accurate when compared to DNA testing (Price et al., 2000). For cases where zygosity was unclear, DNA testing was conducted. At the twins' ages 2, 3, and 4 years, data were collected on cognitive and socio-emotional development as well as environmental factors, including parenting, family homes, and early life experiences. Of the families who participated during the first assessment wave, 83.5% (i.e., 10,336 families) also provided data at the ages 2, 3, and 4 years. In addition to phenotypic data, a subsample of 10,346 TEDS twins (i.e., one twin per 3706 pairs and 3320 DZ co-twins) were genotyped using two different genotyping platforms (AffymetrixGeneChip 6.0 and Illumina HumanOmniExpressExome-8v1.2) in two waves, 5 years apart. The present analyses included a subsample of one randomly selected twin per pair with genotype data ($N = 6973$ unrelated individuals), for 6084 of whom cognitive test scores at age 2 to 4 years were available.

TEDS families were representative of other UK families in 1990s (Rimfeld et al., 2019). For example, 93% of the TEDS families identified as white versus 93% UK families, and 44% of TEDS mothers being employed at twins' ages 2–4 years versus 50% of UK mothers (Rimfeld et al., 2019). In our analysis sample, 94% of the TEDS families identified as white, and 47% of mothers reported being employed (Table S1). The analysis sample's SES, a composite of mothers' and fathers' education and occupation, as well as mothers' age at first birth (not necessarily the twins'), assessed when the families were first contacted, was at mean = 0.09 (SD = 1; Table S1) marginally higher than that of the full sample (mean = 0, SD = 1). Parents provided written informed consent prior to data collection. TEDS project approval (05.Q0706/228) was granted by the ethics committee for the Institute of Psychiatry, Psychology and Neuroscience at King's College London.

2.2. Power

Sample size recommendations for achieving sufficient statistical power in GxE studies are scarce (e.g., Hanscombe et al., 2012; Manuck & McCaffery, 2014), but some suggested that reliably detecting interactions requires at least 16 times the sample size needed for testing direct effects (Gelman, 2018). Using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009), detecting direct effects of $f = 0.15$ by 40 predictors (i.e., 39 environments and PGS) with 80% power requires $N = 214$, which comes to $N = 3424$ after multiplying by 16 to include the 40 interaction terms. If we include the covariates in our power calculation (i.e., gender, 10 PCs, genotype array, and batch), the 53 predictors require $N = 244$ to for detecting direct effects and $N = 3904$ for their interactions at 80% power. These sample requirements are lower than those available for the current analyses (i.e., maximum $N = 6084$).

2.3. Measures

2.3.1. Cognitive development

Parent-administered tests and parent-reported observations were used to assess twins' cognitive ability at the ages 2, 3, and 4 years. These measures have been validated against standard tests administered by trained testers (Oliver et al., 2002; Saudino et al., 1998). Nonverbal cognitive performance was assessed using age-appropriate versions of the Parent Report of Children's Abilities (PARCA; Oliver et al., 2002, Saudino et al., 1998), an hour-long test that includes three parent-administered tasks: a "find the pair" task, a drawing task, and a matching task. Tasks' items assessed number, shape, size, conceptual grouping, and orientation skills. Some items were newly created for administration in TEDS; others were adapted from previously well-validated measures, such as the McCarthy Scales of Children's Abilities (McCarthy, 1972) or the Bayley Scales of Infant Development (Bayley, 1993). The parent-administered PARCA component was supplemented

by eight parent-report items anchored on concrete behaviors and requiring simple yes or no answers. Some of these items were newly created; others were adapted from the Minnesota Child Development Inventory (MCDI; Ireton & Thwing, 1974) and the Ages and Stages Questionnaires (Bricker, Squires, & Mounts, 1995). Verbal ability, specifically vocabulary and grammar, was assessed by parent reports on the CDI-III, an extension of the short form of the MacArthur Communicative Development Inventories: Words and Sentences, which has been shown to have excellent internal consistency and test-retest reliability, as well as concurrent validity with tester-administered measures (Fenson et al., 2007). Overall, the PARCA has been well established as a valid and reliable measure of children's cognitive abilities (Bayley, 1993; Blagman et al., 2014; d'Apice, Latham, & von Stumm, 2019; Martin et al., 2013; McCarthy, 1972; Oliver et al., 2002; Saudino et al., 1998); also, the United Kingdom's National Institute for Clinical Excellence (NICE, 2017)

uses a revised version (PARCA-R) in their developmental assessment guidelines. At each age, scores were standardized and summed to form z-scores of cognitive ability.

2.3.2. Environmental measures

A total of 39 environmental measures were included in our analyses that were recorded in TEDS for twins aged 2 to 4 years, which broadly assessed the family home, early life adversity, neighborhood environment, and local pollution (Fig. 1). The grouping of the environmental measures is preliminary to organize the measures, rather than to infer an empirical or theoretical taxonomy. Details on each of the environmental measures can be found in the Supplementary Methods.

2.3.3. Polygenic scores (PGS)

Saliva and buccal cheek swab samples were collected, and DNA was

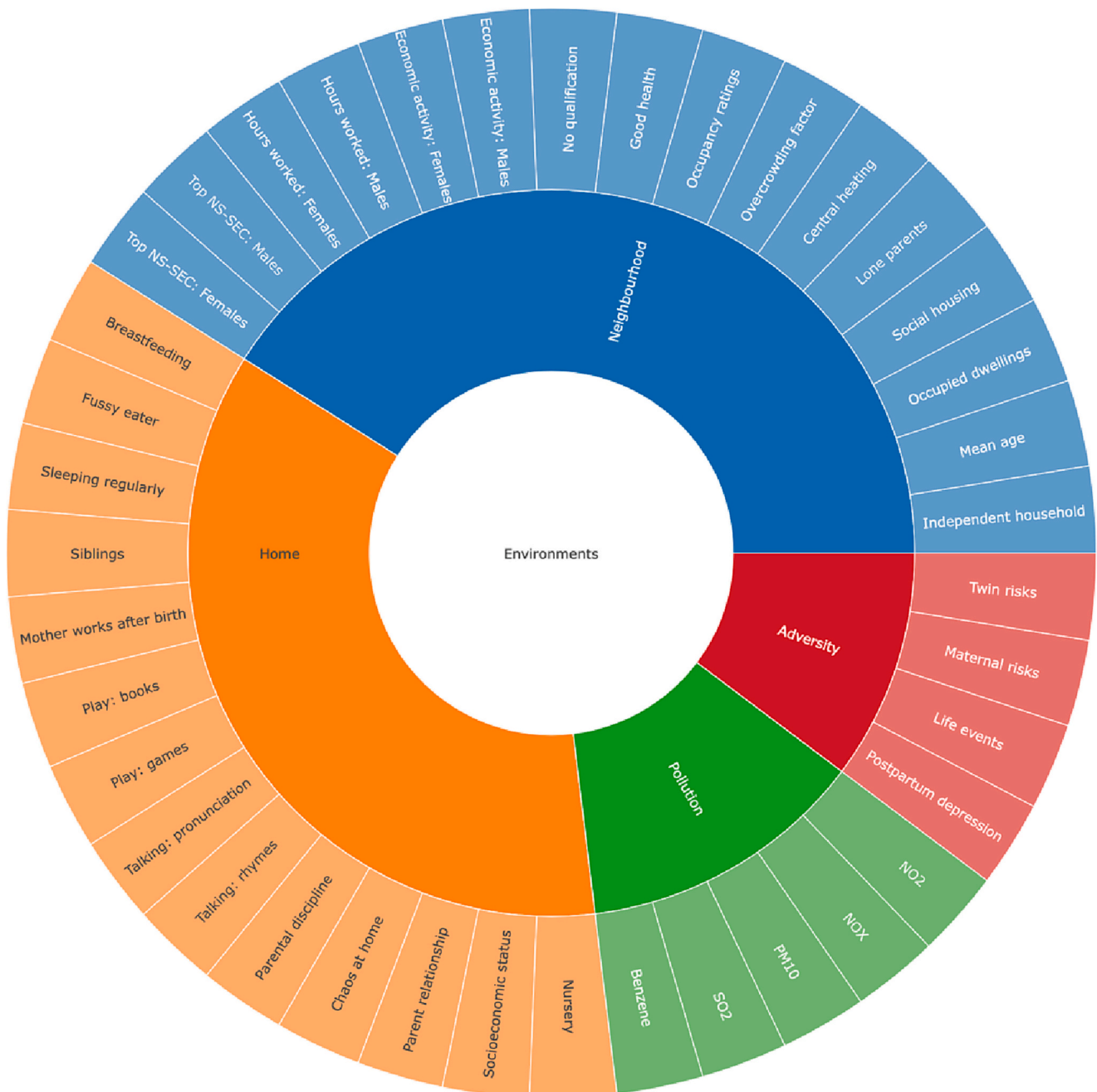


Fig. 1. Overview of the 39 environment measures used in the current analyses of Twins Early Development Study data.

extracted and genotyped to compute genome-wide polygenic scores (PGS) based on the latest genome-wide association (GWA) study for years of education (Lee et al., 2018). PGS were constructed using the Bayesian LDpred approach, which estimates causal effect sizes from GWA summary statistics by assuming a prior for the genetic architecture and LD information from a reference panel (Vilhjalmsson et al., 2015; (see Supplementary Methods for details).

2.4. Statistical analyses

All analyses were conducted using R statistical software (R Core Team, 2020). The analyses were preregistered at <https://osf.io/sg4rf/>. All variables were standardized (i.e., z-scores) prior to analysis. The cognitive ability scores at ages 2, 3, and 4 years were respectively corrected for within-assessment age differences, and the residuals were summed to a cognitive development score. We fitted our model using lavaan (Rosseel, 2012), which applies full-information maximum

likelihood (FIML) estimation to missing data.

We sought to answer three primary research questions: (1) Do GxE effects exist in the prediction of cognitive development in early life? (2) If they exist, to what extent do GxE effects account for children's differences in cognitive development, independent of the main effects of PGS and environmental variables? (3) What environmental variables, if any, are particularly relevant to the observation of GxE effects? To answer these questions, we applied a stepwise analysis approach. First, Pearson correlations tested associations between the PGS and environmental variables. Second, individual linear regression models were fitted to test independently the predictive validity of the PGS for years in education and our 39 environmental measures for phenotypic early life cognitive development (i.e., the composite that combined cognitive ability scores from 2, 3, and 4 years of age). We adjusted our models for gender, as well as the PGS model for the first 10 principal components (PCs), genotyping array, and batch. We Bonferroni-corrected the p-values associated with the regression coefficients ($p_{conventional} = 0.05 /$

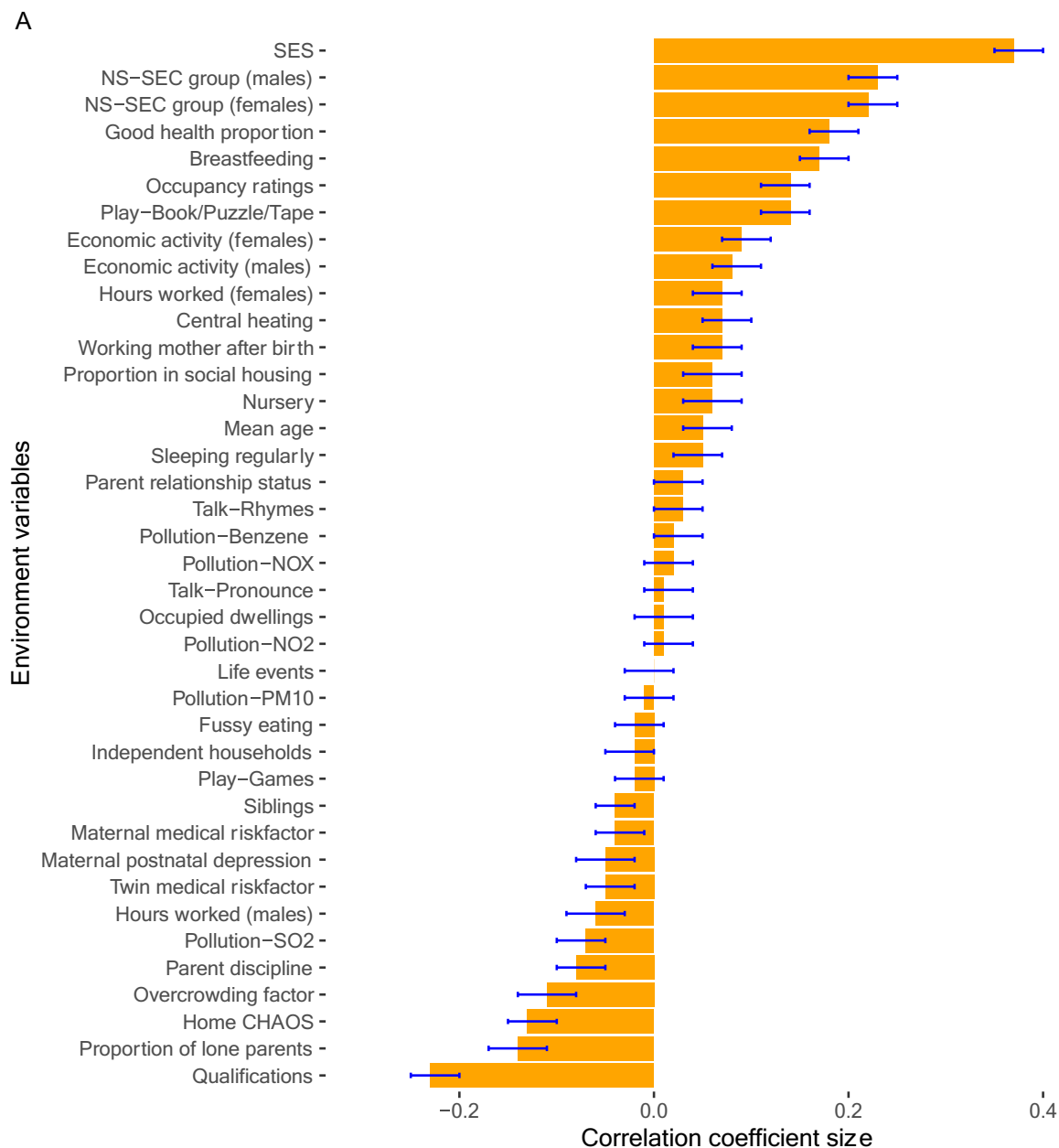


Fig. 2. Correlations of PGS for years spent in education and of cognitive development at age 2, 3, and 4 years with 39 environmental measures. The lines indicate 95% Confidence Intervals (CI).

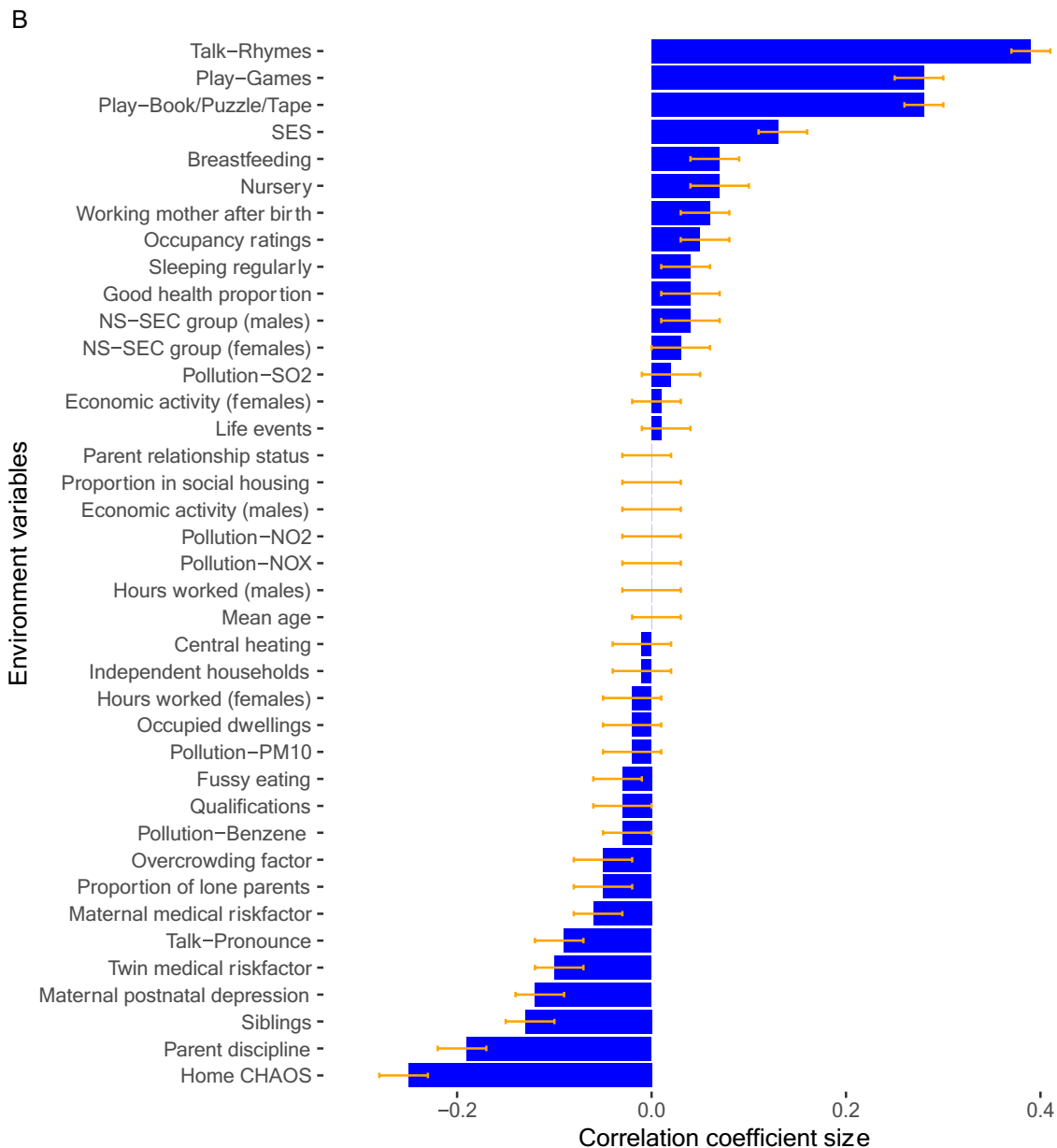


Fig. 2. (continued).

40 (i.e., 39 environments plus PGS); $p_{corrected} = 0.001$) to reduce the risk of Type I errors. Third, we fitted a linear regression model with all 39 environmental variables to predict early life cognitive development, after adjusting for gender. Fourth, we modelled all environmental measures and the PGS, with its covariates gender, 10 PCs, genotyping array, and batch, as predictors of cognitive development. Fifth, we built interaction terms between PGS and the 39 environmental measures and added them to our individual linear regression models in addition to the respective direct effects of PGS and environmental measures and the covariates gender, 10 PCs, genotyping array, and batch. If one of the interaction terms was significant, we would fit a model that also controlled for the interactions between the direct predictors and the covariates (cf. Barr et al., 2019). Our final, sixth model included all direct effects and interaction terms for 39 environmental variables and the PGS to test their combined predictive power for early life cognitive development. Again, we controlled for gender, 10 PCs, genotyping array, and batch. For the models from step three, four and six, we applied the conventional p-value of 0.05 to infer significance for the beta coefficients of main and interaction effects. Across all models, standard

errors were corrected for multiple hypotheses testing. We interpreted our model results using adjusted R^2 values.

3. Results

The correlations between the PGS for years spent in education and the environmental variables are displayed in Fig. 2a, while correlations between cognitive development and the environmental variables are shown in Fig. 2b (see also Table S1 for descriptives and Fig. S1 for the study measures' inter-correlations). The correlations between the environmental measures and PGS ranged from -0.23 to 0.37 (i.e., r_{GE}), while correlations between environmental measures and cognitive development ranged from -0.25 to 0.39 . The PGS correlated $r = 0.07$ ($p < .001$) with cognitive development. For cognitive development, the strongest correlations were observed with home environment measures (e.g., positive correlations with talking to and playing with twin, negative correlations with CHAOS and parental discipline). For the PGS, the strongest correlations emerged for family SES and neighborhood variables (e.g., population proportion of postcode classified as high

professional status, low qualification, and lone parent). Overall, substantial gene-environment and phenotype-environment correlations were evident.

The PGS significantly predicted cognitive development (i.e., composite score of cognitive ability assessments at age 2, 3, and 4 years), $\beta = 0.064$, CI 95% from 0.041 to 0.087, $p < .001$, accounting for 0.5% of the variance, independent of the covariates. Of the 39 environmental measures, $n = 21$ significantly predicted cognitive development ($p < .001$) in their independent models, accounting for 0.2% up to 11.2% of the variance (Table S2). Mirroring the correlational findings, cognitive development was most strongly predicted by talking to (11.2%) and playing with the child (7% and 8.1%), as well as chaos in the family home (5.4%) and parental discipline (2.8%). None of the interaction terms between PGS and the environmental measures in the individual regression models was associated with the Bonferroni-corrected p -value of < 0.001 for the prediction of cognitive development (Table S3). Only two interaction terms were associated with p -values $< .05$, including the annual mean of nitrogen oxide ($p = .032$) and nitrogen dioxide ($p = .027$).

Together, the environmental variables accounted for 20.6% of the variance in cognitive development, after adjusting for gender (Fig. 3;

Table S4). When PGS was added to the model (i.e., in addition to all environmental predictors and covariates, all effects estimated simultaneously), it no longer emerged as a significant predictor of cognitive development ($\beta = 0.009$, $p = .428$, Table S5), probably due to confounding from rGE. The final sixth model, which included all interaction terms between the environmental variables and the PGS as well as their main effects, accounted for 21.2% of the variance in cognitive development (Table S6), with the interaction terms accounting for 0.6% of the variance after controlling for main effects and covariates (Fig. 3). This increment in R^2 was not significant. Two of the interaction terms were associated with p -values lower than 0.05: Correcting the child's pronunciation of sentences and words ($p = .019$) and the proportion of males in the top NS-SEC group (i.e., higher managerial, administrative, and professional occupations; $p = .042$), a marker of occupational status, significantly moderated the association between PGS and cognitive development. Both these interactions term accounted for 0.1% or less of the variance.

4. Discussion

Our study systematically tested gene-environment interplay in early

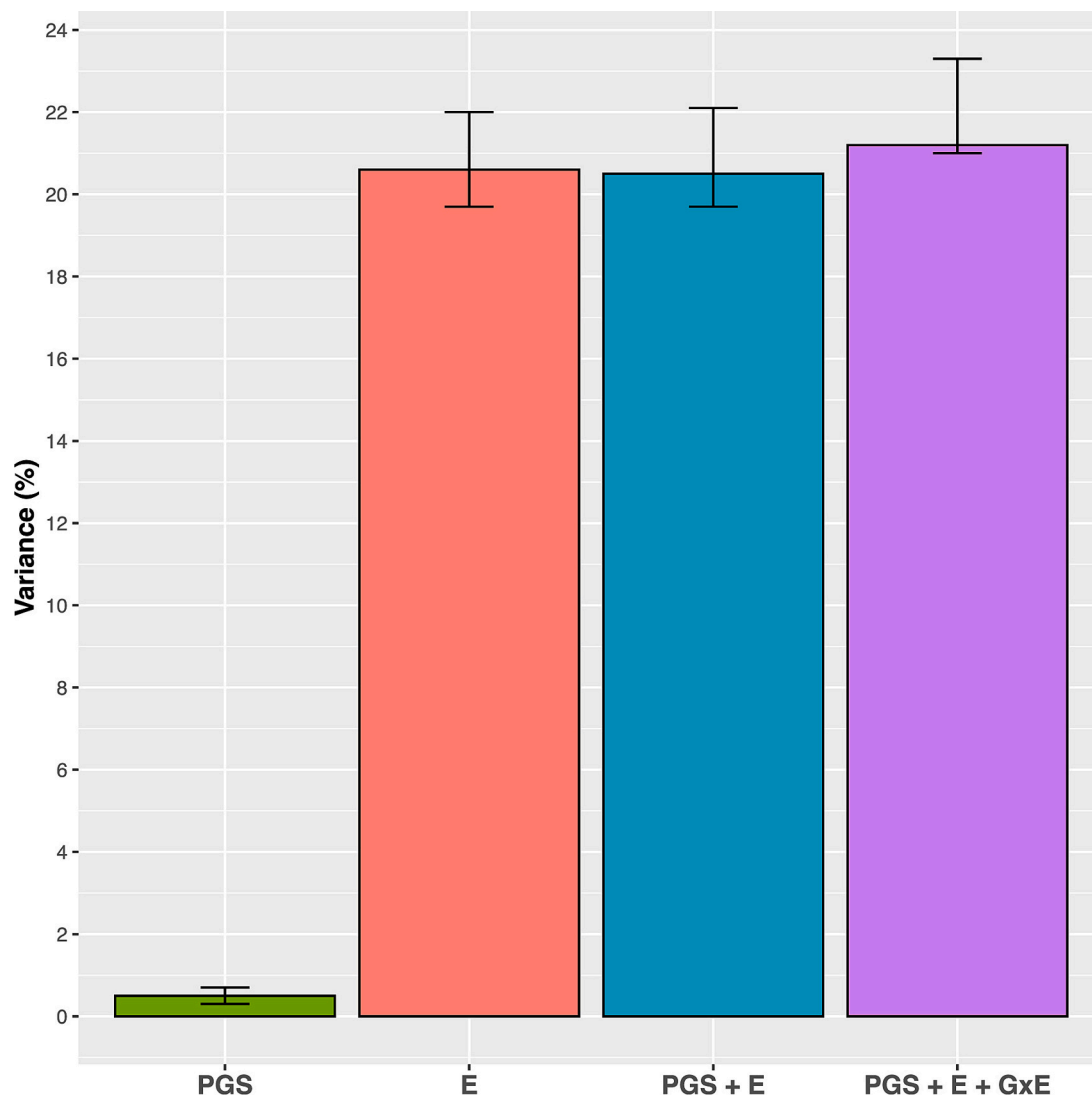


Fig. 3. Adjusted R^2 values across models with direct and interaction effects of PGS and 39 environmental measures.

Error bars are 95% Confidence Intervals based on bootstrapping from 100 samples. The first bar from the left (green) shows the R^2 for PGS, the second (red) for all 39 environmental measures, the third (blue) for PGS and environmental measures, and the last one (purple) combines all direct and interaction effects from PGS and environmental measures.

life cognitive development using PGS to capture children's genetic propensities and 39 home and neighborhood measures that broadly mapped children's environments. The PGS based on the GWAS for years in education (Lee et al., 2018) significantly predicted early life cognitive development, accounting for 0.5% of the variance. This effect size is smaller than those reported for the prediction of ability scores at later ages, for example at age 12 and 16 years when PGS based on the GWAS for years in education (Lee et al., 2018) account for 7% and 10% of the variance in intelligence, respectively (Allegrini et al., 2019). The discrepancy in effect sizes is likely in part due to the age-related increase of genetic influences on cognitive ability (Haworth et al., 2010; Plomin & Deary, 2015). Accordingly, the predictive validity of PGS is low when children are young but magnifies as they become older. Another reason for the discrepancy in prediction effect sizes from PGS is that cognitive ability differences in early life are less stable and more difficult to assess reliably than at later ages (Bayley, 1955; Bartels, Rietveld, Van Baal, & Boomsma, 2002; Feinstein, 2003). Thus, cognitive ability differences in early life are generally less predictable than at later ages.

The 39 environmental measures accounted together for a fifth of the variance in cognitive development, with the strongest predictions coming from talking to (11.2%) and playing with the child (7% and 8.1%), as well as chaos in the family home (5.4%) and parental discipline (2.8%). Although we treated these and our other measures as 'environmental', they are not truly exogenous to the individual (Dick, 2011, Schmitz & Conley, 2017). Indeed, we found evidence for widespread rGE, akin to previous studies (Abdellaoui et al., 2019; Krapohl et al., 2017), because the PGS correlated significantly with 29 of our 39 environmental measures. Several of these rGE were greater than the prediction from PGS to cognitive development, reflecting that genetics exert much of their influences through the environment (cf. genetic confounding; Wertz et al., 2020). For example, our putatively environmental measures of cognitive stimulation from the parents, including playing games, jointly reading books, and talking rhymes, correlated between 0.26 and 0.37 with PGS, suggesting that children's genetic propensities for cognitive development are drivers of the cognitive stimulation that they receive. In other words, children actively construct their environmental experiences for genetic reasons, rather than being passive recipients of environmental inputs. In general, rGE are referred to as passive, when they result from parents providing environments that correspond to their genetic propensities that they passed on to their children, as active, when children actively select themselves into environments that match their genetics, and as evocative, when children shape their environment according to their genetic propensities (Avinun, 2020; Plomin et al., 1977). rGE are the likely cause of the pervasiveness of genetic influences for lifespan development, as children increasingly construct, select, and shape their environments as they grow up.

We did not find conclusive evidence for significant GxE effects in our analyses, even though this was our primary research aim. In our environment-specific interaction models, no PGS x environment interaction term was associated with a p -value below the Bonferroni-corrected threshold of $p < .001$, with the only two interaction terms that were associated with p -values below 0.05, the conventional standard in significance testing, pertaining to air pollution. In our models that included direct (i.e., main) effects of all environmental measures and PGS, as well as their interactions, two interaction terms were associated with p -values of below 0.05 but these were not related to air pollution. In fact, one referred to correcting children's pronunciation of sentences and the other to the proportion males in top occupations in the post-code area. Both interaction terms accounted for marginal amounts of variance. We have no theoretical rationale to explain why these two variables would emerge as significant moderators of the association between PGS and cognitive development, rather than any of our other environmental measures, including the proportion of women in top occupations in the post-code area. Although our study was sufficiently powered to simultaneously model large number of environments and

their interactions with PGS, we are cautious to interpret the significance of these two interaction terms as true finding, rather than one by chance. The two measures' moderating effects must be replicated in other samples before any conclusions about their roles are warranted.

The modest predictive validity of PGS for children's differences in early life cognitive development in the current study is not necessarily the cause for failing to identify significant GxE effects. That is, the sensitivity of analyses to detect an interaction effect is relatively independent of the main effect's effect size (Duncan & Keller, 2011; Keller, 2014). For example, recent Monte Carlo Simulation studies, which estimated the power of GxE models with PGS for indexing genetic propensities, showed that the magnitude of the predictor's direct effects and their inter-correlation affected only negligibly the probability of detecting significant GxE (von Stumm, Lyon, & Nancarrow, 2022).

Not finding significant GxE effects aligns with other studies that failed to detect meaningful moderations of genetic influences on phenotypic traits (e.g., Allegrini et al., 2020; Figlio et al., 2017; Kandaswamy et al., 2022; Plomin, Gidziela, Malanchini, & von Stumm, 2022). This and other research suggest that identifying replicable GxE effects in the prediction of complex traits that are influenced by many genetic and environmental factors, like cognitive but also social-emotional development, may be impossible, at least with the methods that are currently available. Yet, some recent studies have reported significant GxE effects in samples of young adults from Scandinavia in the prediction of educational achievement (e.g., Cheesman et al., 2022; Ronda et al., 2022), a phenotype that correlates strongly with cognitive development (von Stumm, 2017). Future research will elucidate if the ability to detect significant GxE effects varies as a function of target phenotype (e.g., cognitive development versus educational achievement), assessment age (e.g., early life versus adulthood), and cultural context (e.g., national and geographical differences).

4.1. Limitations

Our study suffered three main limitations. The first concerns the assessment of children's early life environment. Although we included 39 broad measures of the home and neighborhood environment, data on all environmental factors that affect children's cognitive development were not available, for example fathers' mental health or children's dietary habits. Also, our environmental variables differed in their scope and unit of measurement: Some were assessed by single items and some by established psychometric scales (e.g., chaos at home) or composite indices (e.g., SES). This problem affects all studies that seek to model environmental influences across levels and domains (von Stumm & d'Apice, 2022). Second, we operationalized genetic propensities as PGS but it is possible that GxE happen at a different level of measurement, perhaps at the level of a single gene or even single-nucleotide polymorphism (SNP). If that were the case, our environmental measures are also likely to be too high-level and coarse to detect interactions, but time-sensitive, momentary measures of environmental exposures would be needed. Furthermore, compared to heritability estimates from twin studies (e.g., Haworth et al., 2010), currently available PGS capture only a fraction of the genetic influences on cognitive development, a phenomenon known as the 'missing heritability gap' (Maher, 2008; Manolio et al., 2009). It is therefore possible that current PGS are suboptimal measures of genetic influences on early life cognitive development. Third, the discovery GWA study (Lee et al., 2018) for creating the PGS and the target sample were both composed mainly of European ancestry making our findings less generalizable to other ancestry populations.

5. Conclusion

We used PGS to capture children's genetic propensities and 39 home and neighborhood measures to map their environments in a UK-representative population cohort to study the gene-environment interplay in cognitive development. We observed widespread rGE, suggesting

that children are assorted to environments in line with their genetic propensities, but found no evidence for significant GxE effects. The current results suggest that genetic influences, as indexed by PGS based on Lee et al.'s (2018) GWAS for years spent in education, on early life cognitive development are not conditioned by environments, and conversely that environmental effects on cognitive development do not vary as a function of genetics. Alas, it is premature to conclude that environmental interventions will benefit children's cognitive development equally regardless of their genetic differences. The hypothesis that GxE effects exist in the prediction of cognitive development is too compelling to reject it, even in the face of the current null findings.

Data availability

Data came from the Twins Early Development Study (TEDS), which researchers can access after completing a data access request form: <https://www.teds.ac.uk/researchers/teds-data-access-policy>.

Acknowledgements

We gratefully acknowledge the ongoing contribution of the participants in the Twins Early Development Study (TEDS) and their families. TEDS has been supported by a program grant from the UK Medical Research Council (MR/M021475/1 and previously G0901245), with additional support from the US National Institutes of Health (AG046938). This project was supported by a Nuffield Foundation award (EDO/44110) to SvS, who is also supported by a British Academy Mid-career Fellowship (2022) and a CRISP Fellowship from the Jacobs Foundation (2022-2027).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.intell.2023.101748>.

References

- Abdellaoui, A., Hugh-Jones, D., Yengo, L., ... Visscher, P. M. (2019). Genetic correlates of social stratification in Great Britain. *Nature Human Behaviour*, 1332–1342. <https://doi.org/10.1038/s41562-019-0757-5>
- Allegrini, A. G., Karhunen, V., Coleman, J. R. I., Selzam, S., Rimfeld, K., von Stumm, S., ... Plomin, R. (2020). Multivariable G-E interplay in the prediction of educational achievement. *PLoS Genetics*. <https://doi.org/10.1371/journal.pgen.1009153>
- Allegrini, A. G., Selzam, S., Rimfeld, K., von Stumm, S., Pingault, J. B., & Plomin, R. (2019). Genomic prediction of cognitive traits in childhood and adolescence. *Molecular Psychiatry*, 24(6), 819–827. <https://doi.org/10.1038/s41380-019-0394-4>
- Avinun, R. (2020). The E is in the G: Gene-environment-trait correlations and findings from genome-wide association studies. *Perspectives on Psychological Science*, 15(1), 81–89. <https://doi.org/10.1177/1745691619867107>
- Barr, P. B., Kuo, S. I. C., Aliev, F., Latvala, A., Viken, R., Rose, R. J., & Dick, D. M. (2019). Polygenic risk for alcohol misuse is moderated by romantic partnerships. *Addiction*, 114(10), 1753–1762. <https://doi.org/10.1111/add.14712>
- Bartels, M., Rietveld, M. J., Van Baal, & Boomsma, D. I. (2002). Genetic and environmental influences on the development of intelligence. *Behavior genetics*, 32(4), 237–249. <https://doi.org/10.1023/a:1019772628912>
- Bayley, N. (1955). On the growth of intelligence. *American Psychologist*, 10, 805–818.
- Bayley, N. (1993). *Bayley Scales of Infant Development* (2nd ed.). San Antonio, TX: Psychological Corporation.
- Blaggan, S., Guy, A., Boyle, E. M., Spata, E., Manktelow, B. N., Wolke, D., & Johnson, S. (2014). A parent questionnaire for developmental screening in infants born late and moderately preterm. *Pediatrics*, 134(1), 55–62. <https://doi.org/10.1542/peds.2014-0266>
- Bricker, D., Squires, J., & Mounts, L. (1995). *Ages and stages questionnaire: A parent-completed, child-monitoring system*. Baltimore: Brookes.
- Bronfenbrenner, U., & Morris, P. A. (2006). The bioecological model of human development. In W. Damon, & R. M. Lerner (Eds.), *Handbook of child psychology and developmental science: Vol 1. Theoretical Models of Human Development* (pp. 793–828). New York: John Wiley & Sons. <https://doi.org/10.1002/9780470147658>
- Cheesman, R., Borgen, N. T., Lyngstad, T. H., Eilertsen, E. M., Ayorech, Z., Torvik, F. A., ... Ystrom, E. (2022). How genes, schools, and residential areas shape achievement: A population-wide gene-environment interaction study. Preprint: Doi:10.31234/osf.io/r9vzp.
- d'Apice, K., Latham, R. M., & von Stumm, S. (2019). A naturalistic home observational approach to children's language, cognition, and behavior. *Developmental Psychology*, 55(7), 1414–1427. <https://doi.org/10.1037/dev0000733>
- Deary, I. J. (2012). *Intelligence. Annual Review of Psychology*, 63, 453–482.
- Dick, D. M. (2011). Gene-environment interaction in psychological traits and disorders. *Annual Review of Clinical Psychology*, 7, 383–409. <https://doi.org/10.1146/annurev-clinpsy-032210-104518>
- Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., ... Sher, K. J. (2015). Candidate gene-environment interaction research: Reflections and recommendations. *Perspectives on Psychological Science*, 10(1), 37–59. <https://doi.org/10.1177/1745691614556682>
- Duncan, G. J., Magnuson, K. A., & Ludwig, J. (2004). The endogeneity problem in developmental studies. *Research in Human Development*, 1(1–2), 59–80. <https://doi.org/10.1080/15427609.2004.9683330>
- Duncan, L. E., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry*, 168(10), 1041–1049. <https://doi.org/10.1176/appi.ajp.2011.11020191>
- Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G* power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, 41(4), 1149–1160. <https://doi.org/10.3758/BRM.41.4.1149>
- Feinstein, L. (2003). Inequality in the Early Cognitive Development of British Children in the 1970 Cohort. *Economica*, 70(277), 73–97.
- Fenson, L., Marchman, V. A., Thal, D. J., Dale, P. S., Reznick, J. S., & Bates, E. (2007). *MacArthur-Bates communicative development inventories: User's guide and technical manual* (2nd ed.). Baltimore, MD: Brookes.
- Figlio, D. N., Freese, J., Karbownik, K., & Roth, J. (2017). Socioeconomic status and genetic influences on cognitive development. *Proceedings of the National Academy of Sciences*, 114(51), 13441–13446. <https://doi.org/10.1073/pnas.1708491114>
- Gelman, A. (2018, March 15). You need 16 times the sample size to estimate an interaction than to estimate a main effect. *Statistical Modeling, Causal Inference, and Social Science*. <https://statmodeling.stat.columbia.edu/2018/03/15/need-16-times-sample-size-estimate-interaction-estimate-main-effect/>.
- Greven, C. U., Lionetti, F., Booth, C., Aron, E. N., Fox, E., Schendan, H. E., & Homberg, J. (2019). Sensory processing sensitivity in the context of environmental sensitivity: A critical review and development of research agenda. *Neuroscience & Biobehavioral Reviews*, 98, 287–305. <https://doi.org/10.1016/j.neubiorev.2019.01.009>
- Hanscombe, K. B., Trzaskowski, M., Haworth, C. M., Davis, O. S., Dale, P. S., & Plomin, R. (2012). Socioeconomic status (SES) and children's intelligence (IQ): In a UK-representative sample SES moderates the environmental, not genetic, effect on IQ. *PLoS One*, 7(2), Article e30320. <https://doi.org/10.1371/journal.pone.0030320>
- Haworth, C. M., Wright, M. J., Luciano, M., Martin, N. G., de Geus, E. J., van Beijsterveldt, C. E., ... Plomin, R. (2010). The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Molecular Psychiatry*, 15(11), 1112–1120. <https://doi.org/10.1038/mp.2009.55>
- Honzik, M. P., Macfarlane, J. W., & Allen, L. (1948). The stability of mental test performance between two and eighteen years. *The Journal of Experimental Education*, 17(2), 309–324. <https://doi.org/10.1080/00220973.1948.11010388>
- Ireton, H., & Thwing, E. (1974). *The Minnesota child development inventory*. Minneapolis, MN: Behavior Science Systems.
- Kandaswamy, R., Allegrini, A., Nancarrow, A. F., Cave, S. N., Plomin, R., & von Stumm, S. (2022). Predicting alcohol use from genome-wide polygenic scores, environmental factors, and their interactions in young adulthood. *Psychosomatic Medicine*, 84(2), 244–250. <https://doi.org/10.1097/PSY.0000000000001005>
- Keers, R., & Pluess, M. (2017). Childhood quality influences genetic sensitivity to environmental influences across adulthood: A life-course gene x environment interaction study. *Development and Psychopathology*, 29(5), 1921–1933. <https://doi.org/10.1017/S0954579417001493>
- Keller, M. C. (2014). Gene x environment interaction studies have not properly controlled for potential confounders: The problem and the (simple) solution. *Biological Psychiatry*, 75(1), 18–24. <https://doi.org/10.1016/j.biopsych.2013.09.006>
- Krapohl, E., Hannigan, L. J., Pingault, J. B., Patel, H., Kadeva, N., Curtis, C., & Plomin, R. (2017). Widespread covariation of early environmental exposures and trait-associated polygenic variation. *Proceedings of the National Academy of Sciences*, 114(44), 11727–11732. <https://doi.org/10.1073/pnas.1707178114>
- Lee, J. J., et al. (2018). Gene discovery and polygenic prediction from a 1.1-million person GWAS of educational attainment. *Nature Genetics*, 50, 1112–1121. <https://doi.org/10.1038/s41588-018-0147-3>
- Maher, B. (2008). Personal genomes: The case of the missing heritability. *Nature*, 456(7218), 18–21. <https://doi.org/10.1038/456018a>
- Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorf, L. A., Hunter, D. J., ... Visscher, P. M. (2009). Finding the missing heritability of complex diseases. *Nature*, 461(7265), 747–753. <https://doi.org/10.1038/nature08494>
- Manuck, S. B., & McCaffery, J. M. (2014). Gene-environment interaction. *Annual Review of Psychology*, 65, 41–70. <https://doi.org/10.1146/annurev-psych-010213-115100>
- Martin, A. J., Darlow, B. A., Salt, A., Hague, W., Sebastian, L., McNeill, N., & Tarnow-Mordi, W. (2013). Performance of the Parent Report of Children's Abilities-Revised (PARCA-R) versus the Bayley Scales of Infant Development III. *Archives of disease in childhood*, 98(12), 955–958. <https://doi.org/10.1136/archdischild-2012-303288>
- McCarthy, D. (1972). *McCarthy scales of Children's abilities*. New York: The Psychological Corporation.
- National Institute for Clinical Excellence. (2017). Developmental follow-up of children and young people born preterm, NICE guideline [NG72]. Retrieved from <http://www.nice.org.uk/guidance/ng72/chapter/Recommendations#providing-enhanced-developmental-support>.
- Oliver, B., Dale, P. S., Saudino, K. J., Petrill, S. A., Pike, A., & Plomin, R. (2002). The validity of a parent-based assessment of cognitive abilities in 3-year-olds. *Early Child Development and Care*, 172(4), 337–348. <https://doi.org/10.1080/03004430212713>
- Plomin, R. (2019). *Blueprint: How DNA makes us who we are*. MIT Press.

- Plomin, R., & Deary, I. (2015). Genetics and intelligence differences: Five special findings. *Molecular Psychiatry*, 20, 98–108. <https://doi.org/10.1038/mp.2014.105>
- Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin*, 84(2), 309–322. <https://doi.org/10.1037/0033-2909.84.2.309>
- Plomin, R., & von Stumm, S. (2018). The new genetics of intelligence. *Nature Reviews Genetics*, 19(3), 148–159. <https://doi.org/10.1038/nrg.2017.104>
- Price, T. S., Freeman, B., Craig, I., Petrill, S. A., Ebersole, L., & Plomin, R. (2000). Infant zygosity can be assigned by parental report questionnaire data. *Twin Research*, 3, 129–133.
- R Core Team. (2020). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from <https://www.R-project.org>.
- Rimfeld, K., Malanchini, M., Spargo, T., Spickernell, G., Selzam, S., McMillan, A., ... Plomin, R. (2019). Twins early development study: A genetically sensitive investigation into behavioral and cognitive development from infancy to emerging adulthood. *Twin Research and Human Genetics*, 22, 508–513. <https://doi.org/10.1017/thg.2019.56>
- Ronda, V., Agerbo, E., Bleses, D., Mortensen, P. B., Borglum, A., Mors, O., ... Werge, T. (2022). Family disadvantage, gender, and the returns to genetic human capital. *Journal of Economics*, 124, 550–578. <https://doi.org/10.1111/sjoe.12462>
- Rossee, Y. (2012). Lavaan: An R package for structural equation modeling and more. Version 0.5–12 (BETA). *Journal of Statistical Software*, 48(2), 1–36.
- Saltz, J. B., Bell, A. M., Flint, J., Gomulkiewicz, R., Hughes, K. A., & Keagy, J. (2018). Why does the magnitude of genotype-by-environment interaction vary? *Ecology and Evolution*, 8(12), 6342–6353. <https://doi.org/10.1002/ece3.4128>
- Saudino, K. J., Dale, P. S., Oliver, B., Petrill, S. A., Richardson, V., Rutter, M., ... Plomin, R. (1998). The validity of parent-based assessment of the cognitive abilities of 2-year-olds. *British Journal of Developmental Psychology*, 16, 349–363. <https://doi.org/10.1111/j.2044-835X.1998.tb00757.x>
- Scarr-Salapatek, S. (1971). Race, social class, and IQ. *Science*, 174(4016), 1285–1295. <http://www.jstor.org/stable/1733128>.
- Schmitz, L., & Conley, D. (2017). Modeling gene-environment interactions with quasi-natural experiments. *Journal of Personality*, 85(1), 10–21. <https://doi.org/10.1111/jopy.12227>
- Sigelman, C. K., & Rider, E. A. (2009). Developmental psychopathology. In *Life-span human development* (6th ed., pp. 468–495). Belmont, CA: Wadsworth Cengage Learning.
- von Stumm, S. (2017). Socioeconomic status amplifies the achievement gap throughout compulsory education independent of intelligence. *Intelligence*, 60, 57–62. <https://doi.org/10.1016/j.intell.2016.11.006>
- von Stumm, S., & d'Apice, K. (2022). From genome-wide to environment-wide: capturing the environome. *Perspectives on Psychological Science*, 17(1), 30–40. <https://doi.org/10.1177/1745691620979803>
- Plomin, R., Gidziela, A., Malanchini, M., & von Stumm, S. (2022). Gene-environment interaction using polygenic scores: Do polygenic scores for psychopathology moderate predictions from environmental risk to behavior problems? *Development and Psychopathology*, 1–11. Advance online publication <https://doi.org/10.1017/S0954579422000931>.
- von Stumm, S., Lyon, K., & Nancarrow, A. F. (2022). New methods, persistent issues, and one solution: Gene-environment interaction studies of childhood cognitive development. [Doi:10.31234/osf.io/zxfng](https://doi.org/10.31234/osf.io/zxfng).
- von Stumm, S., & Plomin, R. (2015). Socioeconomic status and the growth of intelligence from infancy through adolescence. *Intelligence*, 48, 30–36. <https://doi.org/10.1016/j.intell.2014.10.002>
- von Stumm, S., Smith-Woolley, E., Ayorech, Z., McMillan, A., Rimfeld, K., Dale, P. S., & Plomin, R. (2020). Predicting educational achievement from genomic measures and socioeconomic status. *Developmental Science*, 23(3), Article e12925. <https://doi.org/10.1111/desc.12925>
- Tucker-Drob, E. M., & Bates, T. C. (2016). Large cross-national differences in gene x socioeconomic status interaction on intelligence. *Psychological Science*, 27(2), 138–149. <https://doi.org/10.1177/0956797615612727>
- Tucker-Drob, E. M., & Briley, D. A. (2014). Continuity of genetic and environmental influences on cognition across the life span: A meta-analysis of longitudinal twin and adoption studies. *Psychological Bulletin*, 140, 949–979.
- Turkheimer, E., Haley, A., Waldron, M., d'Onofrio, B., & Gottesman, I. I. (2003). Socioeconomic status modifies heritability of IQ in young children. *Psychological Science*, 14(6), 623–628. <https://doi.org/10.1046/j.0956-7976.2003.psci.1475.x>
- Vilhjálmsdóttir, B. J., Yang, J., Finucane, H. K., Gusev, A., Lindström, S., Ripke, S., ... Marsal, S. (2015). Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *The American Journal of Human Genetics*, 97(4), 576–592. <https://doi.org/10.1016/j.ajhg.2015.09.001>
- Wertz, J., Moffitt, T. E., Agnew-Blais, J., Arseneault, L., Belsky, D. W., Corcoran, D. L., ... Caspi, A. (2020). Using DNA from mothers and children to study parental investment in Children's educational attainment. *Child Development*, 91(5), 1745–1761. <https://doi.org/10.1111/cdev.13329>