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Genotype–environment interplay in associations between maternal drinking and offspring emotional and behavioral problems

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Abstract

Background. While maternal at-risk drinking is associated with children's emotional and behavioral problems, there is a paucity of research that properly accounts for genetic confounding and gene–environment interplay. Therefore, it remains uncertain what mechanisms underlie these associations. We assess the moderation of associations between maternal at-risk drinking and childhood emotional and behavioral problems by common genetic variants linked to environmental sensitivity (genotype-by-environment [G × E] interaction) while accounting for shared genetic risk between mothers and offspring (GE correlation).

Methods. We use data from 109 727 children born to 90 873 mothers enrolled in the Norwegian Mother, Father, and Child Cohort Study. Women self-reported alcohol consumption and reported emotional and behavioral problems when children were 1.5/3/5 years old. We included child polygenic scores (PGSs) for traits linked to environmental sensitivity as moderators.

Results. Associations between maternal drinking and child emotional ($\beta_1 = 0.04$ [95% confidence interval (CI) 0.03–0.05]) and behavioral ($\beta_1 = 0.07$ [0.06–0.08]) outcomes attenuated after controlling for measured confounders and were almost zero when we accounted for unmeasured confounding (emotional: $\beta_1 = 0.01$ [0.00–0.02]; behavioral: $\beta_1 = 0.01$ [0.00–0.02]). We observed no moderation of these adjusted exposure effects by any of the PGS.

Conclusions. The lack of strong evidence for G × E interaction may indicate that the mechanism is not implicated in this kind of intergenerational association. It may also reflect insufficient power or the relatively benign nature of the exposure in this sample.

Introduction

Mental health problems often start in childhood, compromising children's quality of life and development to such an extent that they are among the leading causes of childhood disability (Erskine et al., 2015; Kessler et al., 2007b). Early-onset mental health problems often persist into adolescence and adulthood (Kessler et al., 2007a), with broad and far-reaching consequences for individuals, their families, and society. About 13% of children have a psychiatric disorder (Barican et al., 2022), e.g. emotional and behavioral problems and disorders (Campbell, 1995; Collishaw, 2015; Weitzman et al., 2015). Given the prevalence and impact of early-onset psychiatric problems, there is a need for reliable knowledge about risk factors associated with children's emotional and behavioral problems that can inform intervention and prevention research.

Maternal at-risk drinking is a risk factor associated with child emotional and behavioral problems (Hill et al., 2008; Hill, Tessner, & McDermott, 2011; Hussong, Huang, Curran, Chassin, & Zucker, 2010; Kim & Sin, 2020; Marmorstein, Iacono, & McGue, 2009; Oro, Goldsmith, & Lemery-Chalfant, 2021). However, as with many observational associations in epidemiological research, it remains uncertain to what extent causal mechanisms underlie these associations. Given the context of this association – typically between related individuals living in the same household –, two potential routes of confounding could inflate or mask exposure-based causal effects in observed associations. First, in genetic transmission of risk, the same genetic factors influence liability to problem drinking in adults and behavior difficulties in children. Within individuals old enough to experience alcohol problems, there is extensive genetic overlap with other mental health problems, such as behavioral, like hyperactivity and conduct difficulties (Karlsson Linnér et al., 2021; Kendler, Prescott, Myers, & Neale, 2003;

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Abbreviations:
ADHD: attention-deficit hyperactivity disorder; AUDIT: alcohol-use disorders identification test; *BDNF*: brain-derived neurotrophic factor; CBCL: Child Behavior Checklist; FDR: false-discovery rate; G × E: genotype-by-environment; GWAS: genome-wide association studies; LRT: likelihood ratio test; MBRN: Medical Birth Registry of Norway; PCA: principal component analysis; PGS: polygenic score; xPGS: polygenic scores interaction; PTSD: post-traumatic stress disorder; SEM: structural equation modeling; SNP: single-nucleotide polymorphism

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Kessler, Crum, Warner, & Nelson, 1997), and emotional, like anxiety and depression (Colbert et al., 2021; Foo et al., 2018; Kushner et al., 2012). Therefore, it is plausible that genetic material shared intergenerationally might give rise to or inflate an observational association between parent and child behaviors; indeed, this has been demonstrated in numerous scenarios (McAdams et al., 2014). Second, *non-genetic* familial vulnerabilities for behavioral outcomes may also wholly or partly explain an association between maternal problem drinking and offspring emotional or behavioral problems. These include observable risks like financial instability, certain physical health problems, or bereavement – more broadly are defined as factors without a genetic basis that increases the likelihood of both parental exposure and child outcome, prompting the two to be associated independently of any causal relationship between them.

Although both genetic and non-genetic familial factors may confound estimates of associations between maternal at-risk drinking and offspring outcomes, truly causal effects relying on children being exposed to problem drinking (or its consequences) and subsequently developing emotional or behavioral problems may nonetheless exist. The causal mechanisms for this may involve a range of maternal behaviors or aspects of family functioning operating as mediators. For example, maternal problem drinking may affect mothers' ability to be sensitive and supportive in interaction with their child(ren) (Renk et al., 2015; Straussner & Fewell, 2018), which in turn increases the risk of emotional and behavioral difficulties in offspring (Christoffersen & Soothill, 2003; Rossow, Lambert, Keating, & McCambridge, 2015). Fetal programming represents an alternative mechanism (Lewis, Austin, Knapp, Vaiano, & Galbally, 2015; Stevenson, Lillycrop, & Silver, 2020); the assumption is that prenatal exposure to stressors during pregnancy, such as alcohol use and mental health problems, causes physiological fetal reprogramming, which can influence offspring health into adulthood. For instance, in-utero exposure to maternal anxiety and depression has been associated with an increased likelihood of behavior and emotional problems in offspring during childhood and adolescence (Lewis, Lewis, & Galbally, 2014). Further, women with poor mental health during pregnancy likely have poorer health behaviors, including being more likely to consume alcohol during pregnancy (Lewis et al., 2015). Studies examining associations between maternal at-risk drinking and offspring emotional and behavioral problems should control for in-utero exposure to alcohol – but few do.

Much of the research on the environmental transmission of risk is based on observational studies (Jennison, 2014; Knudsen, Ystrom, Skogen, & Torgersen, 2015; Mahedy et al., 2017), which are frequently confounded by genotype–environment (GE) correlations (Plomin, Defries, & Loehlin, 1977). However, even studies using traditional behavior genetic studies designs, such as family, adoption, twin, and children-of-twin studies, produce somewhat inconsistent findings about associations between parental at-risk drinking and offspring behavior, and more so for emotional outcomes (Bornovalova, Hicks, Iacono, & McGue, 2010; Kendler et al., 2015; Lund et al., 2020; Oro et al., 2021; Waldron, Martin, & Heath, 2009). These inconsistent findings may result from genuine heterogeneity between study cohorts or measurement issues. They are also likely compounded by the cost, in terms of statistical power, of partitioning variance and covariance for mental health problems into multiple environmental and genetic components. This approach may reduce the precision of exposure-based effect estimates and produce inconsistencies by ignoring the potential for interactions between genes and the environment (Rutter, 2010).

G × E can be explained as (1) an exposure (e.g. maternal drinking) impacting an outcome (e.g. offspring emotional and behavior problems) differently for individuals with different genotypes; or (2) the impact of the genotype on the risk of the outcome varying due to different environmental risk (Dick, 2011) exposures. Genetic variants associated with traits that influence how people respond to changes in their immediate environment are, by definition, involved in producing G × E. For example, common genetic variants explain approximately 10% of the inter-individual variation in neuroticism (Nagel et al., 2018). Individuals with high levels of neuroticism tend to 'respond poorly to environmental stress, interpret ordinary situations as threatening and can experience minor frustrations as hopelessly overwhelming' (Widiger & Oltmanns, 2017). Accordingly, any genetic variants that are causal for higher levels of neuroticism can also be considered biological amplifiers of the effects of environmental stressors. In practical terms, since genome-wide polygenic scores (PGSs) aggregate the cumulative effects on a given trait of common variants across an individual's genome, any PGS for a trait linked to environmental sensitivity may be used to test for G × E (see examples using PGS for neuroticism [Lehto, Karlsson, Lundholm, & Pedersen, 2019; Plomin, Gidziela, Malanchini, & von Stumm, 2022], attention-deficit hyperactivity disorder [ADHD] [Chen et al., 2020; He & Li, 2022], post-traumatic stress disorder [PTSD] [Lipsky et al., 2023], and others [Mullins et al., 2016; Trotta et al., 2016]). G × E may inflate, mask, or partially attenuate estimates of exposure–outcome associations, depending on their magnitude and direction and the composition of the study sample. Moreover, interpreting results from PGS-by-environment models is made challenging by the potential influence of several distinct forms of bias (Pingault et al., 2022). Careful control for dependencies between PGS and measured environments is required – and in all cases, cautious interpretation is warranted (Akimova, Breen, Brazel, & Mills, 2021).

Estimating exposure-based effects of maternal at-risk drinking on offspring's emotional and behavioral problems precisely and without bias requires rigorous and thoughtful control for all GE interplay and non-genetic confounding. In this study, we take on the challenge of providing robust answers about the role of maternal drinking on offspring's emotional and behavioral development by utilizing data from genotyped mother–offspring pairs and mother–offspring–sibling trios. Specifically, we assess the moderation of associations between maternal at-risk drinking and childhood emotional and behavioral problems by common genetic variants linked to environmental sensitivity (G × E) while accounting for shared genetic risk between mothers and their offspring (GE correlation) and potential confounding by non-genetic familial factors and prenatal maternal drinking.

Methods

Sample

MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (Magnus et al., 2016). Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 41% of the pregnancies. The cohort now includes 114 500 children, 95 200 mothers, and 75 200 fathers. The analyses were based on version 12 of the quality-assured data files released for research in

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January 2019. The Regional Committees for Medical and Health Research Ethics provided ethical approval (REK; 2016/1702). We also used data from the Medical Birth Registry of Norway (MBRN), a national health registry containing information about all births in Norway.

Genotyping and quality control

Blood samples were obtained from both parents during pregnancy and mothers and children (umbilical cord) at birth (Paltiel et al., 2014). Procedures for genotyping and subsequent quality control of genotype data are described fully in Corfield et al. (2022). For these analyses, after quality control, genotype data across 6 981 748 single-nucleotide polymorphisms (SNPs) were available for 76 465 children, 77 387 mothers, and 50 462 fathers.

Inclusion/exclusion criteria

We included individuals from MoBa with data available on at least one exposure or outcome variable.

Measures

Exposures

The primary exposure was maternal at-risk drinking. Variables indexing maternal at-risk drinking were derived based on mother reports from questionnaires received when children were 1.5, 3, and 5 years old. The mothers reported how many alcohol units they usually drink when they consume alcohol on weekends and weekdays, respectively. We followed a previously established approach (Lund et al., 2020) for converting these numbers to a three-point ordinal scale, using an average of weekday and weekend drinking scores but with weekday drinking up-weighted as follows: 1–2 units reported = 0/0 (weekday score/weekend score); 3–4 = 1/0.5, 5–6 = 2/1, 7–9 = 3/2, and ⩾10 = 3/3. Abstainers (mothers reporting zero units consumed) were set to missing to account for censoring, as per Lund et al. (2020).

Outcomes

The primary outcomes were children's emotional and behavioral problems, measured using the Child Behavior Checklist (CBCL) behavioral and emotional problems sub-scales. Mothers reported about their children at 1.5, 3, and 5 years old on a three-point response scale ('Never or rarely true', 'Sometimes or somewhat true', 'Often or always true'). The behavior sub-scale included eight items related to aggressive, defiant, inattentive, or impulsive behavior. The emotions subscale included five items related to emotional reactivity, anxiety, and somatic complaints. Scale scores were created at each wave as the mean of all available items multiplied by the number of items in the scale unless more than 50% of items were missing, in which case we set the individual's scale score to missing. See online Supplementary Methods S1 for an overview of what CBCL items we included in the emotional and behavior measures at 1.5, 3, and 5 years.

Moderators

We created PGSs based on summary statistics from the largest recent genome-wide association studies (GWASs) of three traits: ADHD (Demontis et al., 2018), neuroticism (Luciano et al., 2017), and PTSD (Nievergelt et al., 2019). We selected these traits because each plausibly involves sensitivity to the environment in some respect (e.g. the attentional component of ADHD, neuroticism reflecting dispositional concern and worry about many aspects of day-to-day life, and PTSD indexing sensitivity to traumatic environmental exposures). We additionally included height as a negative control (Yengo et al., 2018); as a non-behavioral yet highly polygenic trait, we assume that height-associated variants are unlikely to moderate responses to environmental stress beyond the level of chance. We created all PGSs using PRSice2 (Choi & O'Reilly, 2019) using a clumping and thresholding approach (250 kb window, $p = 1$, $r^2 = 0.1$). The p value thresholds for SNP inclusion were 5×10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, 0.001, 0.01, 0.05, 0.1, 0.5, and 1. The first principal component of scores across all of the p value thresholds (within a trait) was extracted as the PGS for analysis (this is the PGS-principal component analysis [PCA] approach outlined in Coombes, Ploner, Bergen, & Biernacka [2020]).

Covariates

We organized covariates for the analyses into tiers according to their adjustment level. Tier 1 covariates are parity and child sex, extracted from the MBRN. A growing body of research suggests that fetal programming affects the developing fetus (e.g. Lewis et al., 2015; Stevenson et al., 2020). The assumption is that prenatal exposure to various stressors during pregnancy, such as alcohol use, causes physiological fetal reprogramming, which can influence offspring's health into adulthood. In tier 2, we therefore included a measure of prenatal exposure to maternal at-risk drinking, derived similarly to the exposures, based on responses at the 17th and 30th weeks of pregnancy. We used an average of these two scores as the covariate in analyses. Finally, tier 3 covariates were maternal and paternal versions of the relevant PGS, constructed as described above.

All continuous variables were standardized prior to analysis. We prepared data using the phenotools package (0.2.8) (*Phenotools*, n.d.) in R 4.1.0 (R Core Team, 2022).

Analyses

PGS analyses

Multiple linear regression

We describe the basic analytic model in Equation (1). We ran 24 separate models for combining two CBCL outcomes, three measurement waves, and four PGS traits. We added covariates sequentially according to the 'tier' listed in the abovementioned covariate description. Interaction terms for the moderation of exposure and PGS main effects by covariates were included, in line with current recommendations (Domingue, Trejo, Armstrong-Carter, & Tucker-Drob, 2020).

$$\begin{aligned} CBCL_{out_{wave}} = {} & \beta_0 + \beta_1 mARDrink_{wave} + \beta_2 cPGS_{trait} \\ & + \beta_3 mARDrink_{wave}{:}cPGS_{trait} + \beta_4 cov_1 \\ & + \beta_5 mARDrink_{wave}{:}cov_1 + \beta_6 cPGS_{trait}{:}cov_1 + \cdots + \varepsilon \end{aligned} \quad (1)$$

Here, CBCL, Child Behavior Checklist; mARDrink, maternal at-risk drinking; cPGS, child polygenic score; cov, covariate; subscripts 'out' denotes the outcome (either behavioral or emotional);

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subscript 'wave' denotes the wave of measurement (either child age 1.5, 3, or 5 years old); subscript 'trait' denotes the PGS trait (either ADHD, neuroticism, PTSD, or height).

All models for a given PGS trait and CBCL outcome combination were specified concurrently in a structural equation modeling (SEM) framework using lavaan 0.6-9 (Rosseel, 2012) in R. We used cluster robust standard errors were used to account for sibling pairs in the data and full information maximum-likelihood estimation to handle missing data. In the interests of parsimony and reducing the multiple testing burden, we tested whether the exposure and moderator main (β_1, β_2) and interaction (β_3) effects and, subsequently, the residual variances of the outcome could be constrained to be equal across waves. We retained all constraints that did not significantly worsen model fit according to a likelihood ratio test (LRT) with a Bonferroni-corrected critical p value threshold of 0.05/8 = 0.00625, corresponding to the number of combinations of two outcomes and four moderators. All analytic code is publicly available online at https://github.com/psychgen/mdrink-gxe.

Multilevel SEM

We used multilevel SEMs to decompose the main and interaction effects of interest according to the extent to which they are individual-specific ('within' level) or family wide ('between' level). Figure 1 shows the core components of the tested model. An exposure-based main effect of maternal at-risk drinking (β_1) on the child outcome is estimated independently of a direct effect from confounding factors (both genetic and non-genetic in origin) that influence the exposure consistently across siblings in a family (γ_1). Similarly, the interaction effect between the exposure and the PGS is estimated separately within (β_3) and between (γ_3) levels of the model – with the latter absorbing components of the effect that are inconsistent with an exposure-based mechanism.

The multilevel SEM was run, including covariates from all tiers. Given its additional adjustment for unmeasured familial confounding, it is considered the 'fully adjusted' model. As with the standard linear regression models above, we tested the effect of constraining key parameters and residuals to be equal across measurement waves using LRTs. We used the most constrained acceptable model as the basis for inferences relating to our hypotheses. Multilevel models were run in software Mplus 8.3 (Muthén & Muthen, 2017) via R using MplusAutomation 1.0.0 (Hallquist & Wiley, 2018).

xPGS analyses

The polygenic scores interaction (xPGS) approach (Chen et al., 2020) involves re-creating PGS based on the extent to which each SNP in the PGS moderates the association between an exposure and an outcome. For each PGS trait indexing environmental sensitivity (i.e. ADHD, neuroticism, PTSD), we selected SNPs that were included at the threshold at which most variance was explained by the first principal component from the PGS-PCA described above ($SNP_{i\ldots j}$). We ran SNP–exposure interaction models for these SNPs of the form shown in Equation (2).

$$\begin{aligned} CBCL_{out_{wave}} =& \beta_0 + \beta_1 mARDrink_{wave} + \beta_2 SNP_{i\ldots j_{trait}} \\ &+ \beta_3 mARDrink_{wave}{:}SNP_i \ldots j_{trait} + \beta_4 cov_1 \\ &+ \beta_5 mARDrink{:}cov_1 + \beta_6 SNP_{i\ldots j_{trait}}{:}cov_1 + \cdots + \varepsilon \end{aligned} \quad (2)$$

Here, CBCL, Child Behavior Checklist; mARDrink, maternal at-risk drinking; SNP_i, ith individual variant from the original polygenic score; cov, covariate; subscript 'out' denotes the outcome (either behavioral or emotional); subscript 'wave' denotes the wave of measurement (either child aged 1.5, 3, or 5 years old); subscript 'trait' denotes the PGS trait (either ADHD, neuroticism, PTSD, or height).

This model is equivalent to that used in a genome-wide *interaction* study, with one key difference. Rather than looking for interaction effects across the whole genome – a very costly approach in terms of statistical power – here, the testing burden is reduced by restricting to SNPs accounting for most of the direct polygenic effect on the trait(s) in question. Thus, the main assumption that this approach relies upon is that SNP–trait interaction effects are more likely where SNPs are also involved in the main effects on the same trait. To guard against over-fitting, these models were run only in the singleton MoBa children with available genotype data (N = 50 637) as a 'training' sample. Having run the single-SNP interaction models for each outcome at each wave, we created a single xPGS at each of the 11 p value inclusion thresholds listed above (under 'Moderators'), including all SNPs that remained after clumping (250 kb window, $p = 1$, $r^2 = 0.1$) in a single score (i.e. irrespective of which PGS trait a SNP initially come from). We used the betas and p values from the single-SNP interaction models averaged across the three waves of a given outcome to create the xPGS. PGS-PCA was again used to derive the first principal component from the scores at all 11 thresholds, meaning that finally, we included one single xPGS for emotional and one for behavioral problems as moderators in the relevant standard and multilevel linear models described above. The only difference was that these models were run on the siblings only (N = 33 105) – i.e. those individuals not included in the training sample used to generate the xPGS. We also ran models using the original PGS on this sub-sample to check that the results were comparable.

Multiple testing

We applied a false-discovery rate (FDR) correction to p values across the parameters involved in the null hypothesis significance tests using the Benjamini–Hochberg method. At a minimum – i.e. with all constraints over time accepted – this would have been the eight interaction effects (four PGS traits and two outcomes). However, where constraining effects to be equal across time was impossible without a significant reduction in model fit, each effect was included (up to the maximum of 24). Main effects are not subjected to null hypothesis significance tests (and thus not included in the FDR correction) and are only presented with confidence intervals (CIs) as a measure of precision.

Preregistration

We pre-registered the plan for these analyses before the data was analyzed (Hannigan et al., 2022). Deviations from the preregistration are detailed and justified in online Supplementary Methods S2.

Results

See Table 1 for descriptive statistics for the main study variables. Mean levels of all child behavioral and emotional problems and maternal at-risk drinking decreased slightly across the available

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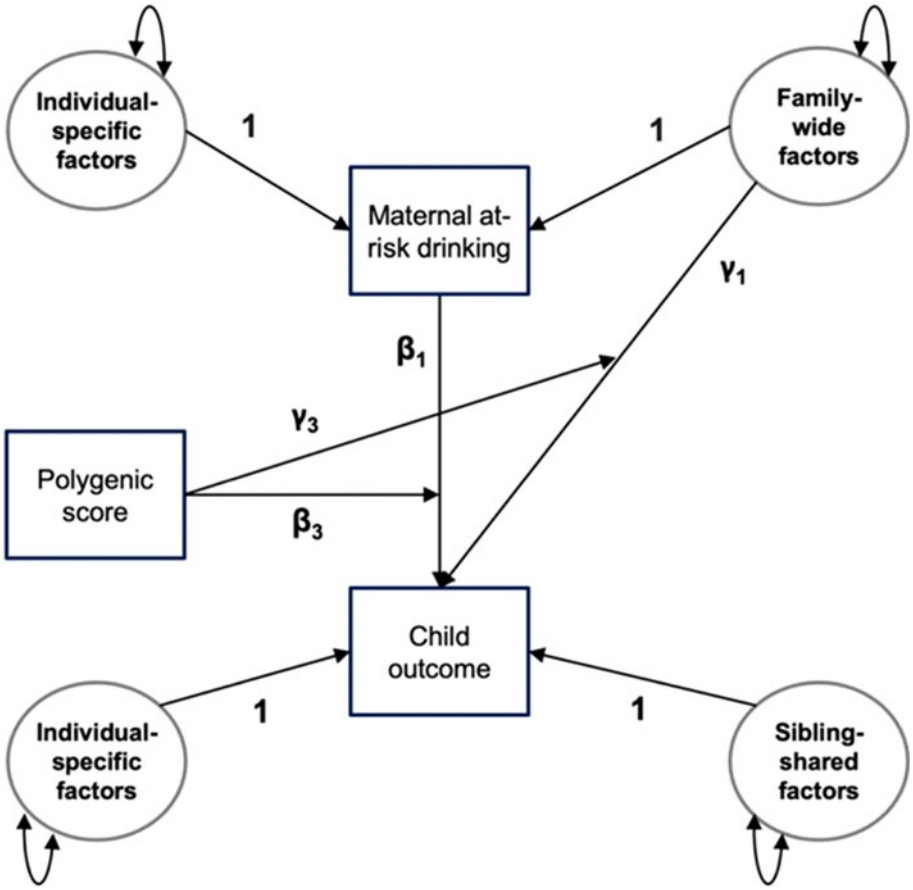

Figure 1. Core components of the multi-level SEM in which main and interaction effects are adjusted for familial confounding.
Note: Observed variables are represented in boxes and latent variables in circles; double-headed arrows indicate the variance of a latent variable estimated; and single-headed arrows indicate estimated paths; the full model includes multiple waves of correlated outcomes and predictors – these are omitted here for clarity.

study waves. We found evidence of selective attrition on all traits and ADHD PGS (see online Supplementary Table S1), partly explaining this trend.

PGS analyses

Model fitting to determine the acceptability of cross-wave constraints

The results of the model fit comparisons to determine the acceptability of constraining core main and interaction effects and residuals to be equal across time are available in online Supplementary Tables S2–S5. Apart from in the ADHD-PGS-as-moderator models, at least the main and interaction effects (and often also the residual variances) could be constrained to be equal across waves in all models. We present results from the most parsimonious model that did not significantly lose fit to the data (compared to an unconstrained model) in all cases.

Main effects

Figure 2 shows the estimated main effects of the exposure, maternal at-risk drinking, and each PGS moderator on childhood emotional and behavioral problems and the extent to which they are attenuated with each additional level of adjustment for confounding. The main effects of maternal at-risk drinking are estimated at $\beta_1 = 0.04$ (95% CI 0.03–0.05) for emotional and $\beta_1 = 0.07$ (0.06–0.08) for behavioral problems when only parity and child sex are included in the models. The magnitude of these effects was reduced when other covariates were added to the models, and are almost attenuated in the most adjusted model when unmeasured familial confounding is accounted for (emotional: $\beta_1 = 0.01$ [95% CI 0.00–0.02]; behavioral: $\beta_1 = 0.01$ [0.00–0.02]). Of the PGS moderators, ADHD showed the strongest direct effect on behavior. This effect was broadly unaffected by all adjustments. The effect also differed markedly across waves, which was why no constraints were acceptable in this model. Small direct effects for other PGS moderators were mostly attenuated in the most adjusted model.

Interaction effects

Figure 3 shows the exposure-by-PGS results from the models adjusted for all covariates and unmeasured familial confounding. The solid lines show the effects of maternal at-risk drinking across different PGS-moderator values, with shaded bands representing 95% CIs based on the estimated interaction term. Dashed lines show the null for each interaction test. Specifically, the effect of maternal at-risk drinking does not change from the overall main effect for an outcome with changes in the PGS-moderator. Raw and FDR-corrected p values for all PGS–exposure interaction terms are presented in Table 2 and confirm that no interactions between maternal at-risk drinking and any of the PGS were observed once multiple testing was accounted for.

xPGS analyses

Exposure-by-SNP models were run in the singleton sub-sample MoBa children ($N = 76\,867$) to be used as the basis of the xPGS creation. Online Supplementary Table S6 provides an overview

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Table 1. Descriptive statistics for the analytic sample

Measure	Waves age (years)	*N*	Mean	s.d.	Min.	Max.
CBCL behavioral problems	1.5	75 737	3.943	2.269	0	16
	3	58 202	3.873	2.432	0	16
	5	41 246	2.502	2.283	0	16
CBCL emotional problems	1.5	70 776	1.327	1.240	0	10
	3	58 196	1.408	1.409	0	10
	5	41 246	1.078	1.309	0	10
Maternal at-risk drinking	1.5	57 985	0.198	0.521	0	3
	3	44 676	0.187	0.511	0	3
	5	21 487	0.115	0.390	0	3

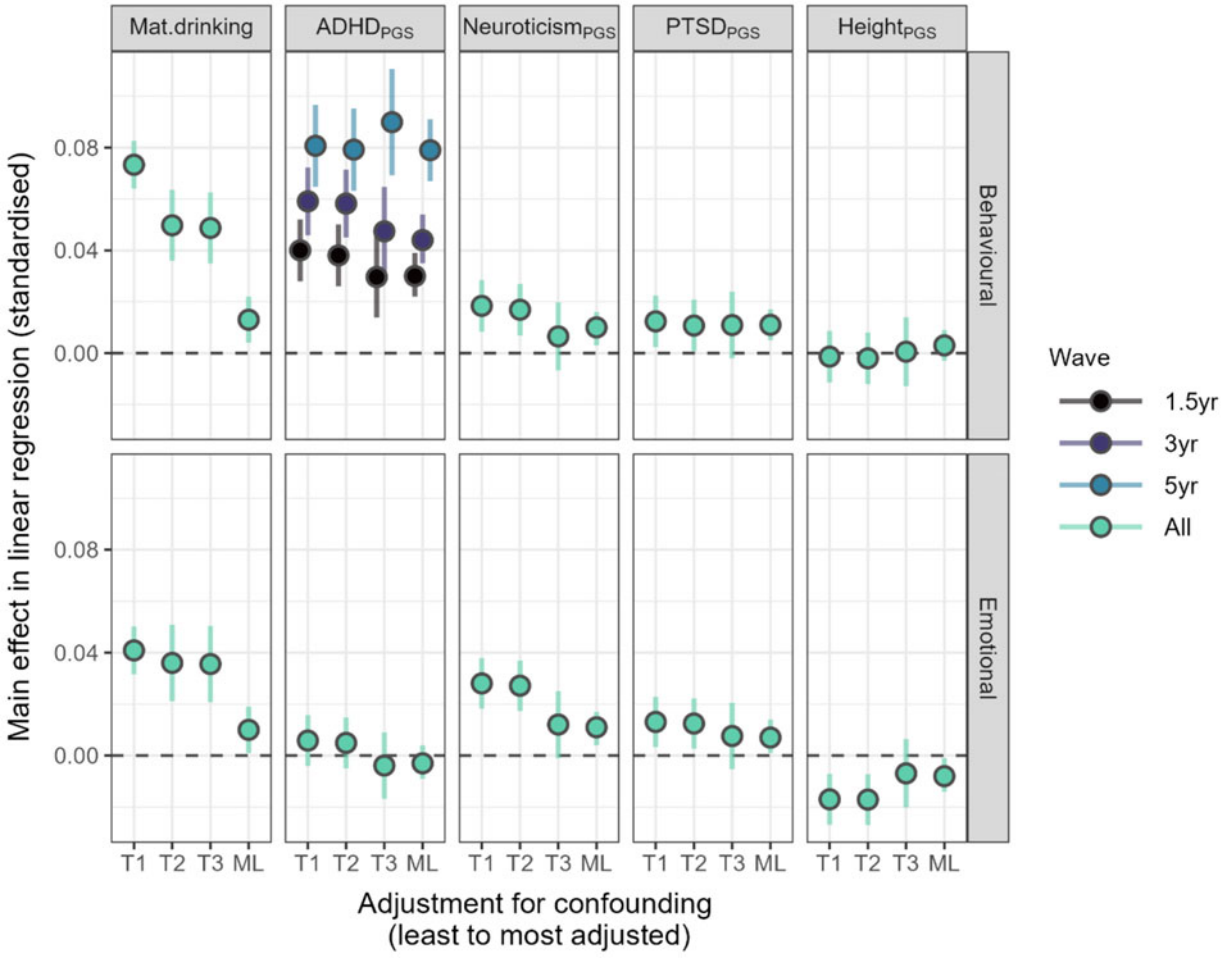

Figure 2. Main effects of exposure and PGS moderators on child emotional and behavioral problems at each level of adjustment.
Note: Effects are displayed separately by wave when constraining them to equality was not possible without a loss of model fit – otherwise the constrained effect estimated at all waves is displayed.
T1, tier 1 covariates (parity and child sex); T2, tier 2 covariates (T1 + prenatal exposure to maternal at-risk drinking); T3, tier 3 covariates (T1, T2 + maternal and paternal PGSs); ML, multilevel.

of the top 15 SNPs from these models, i.e. those with the lowest *p* values for their interaction with the exposure. None of the individual SNPs reached significance after a strict Bonferroni correction based on a combination of the number of independent SNPs tested (17 133) and the number of outcomes (two) and waves (three). Online Supplementary Tables S7–S10 provide an overview of model fit comparisons testing constraints in the xPGS models run in the sibling sub-sample of MoBa children ($N = 37$ 367). In the most adjusted models, the main and interaction effects for maternal at-risk drinking and the xPGS could be

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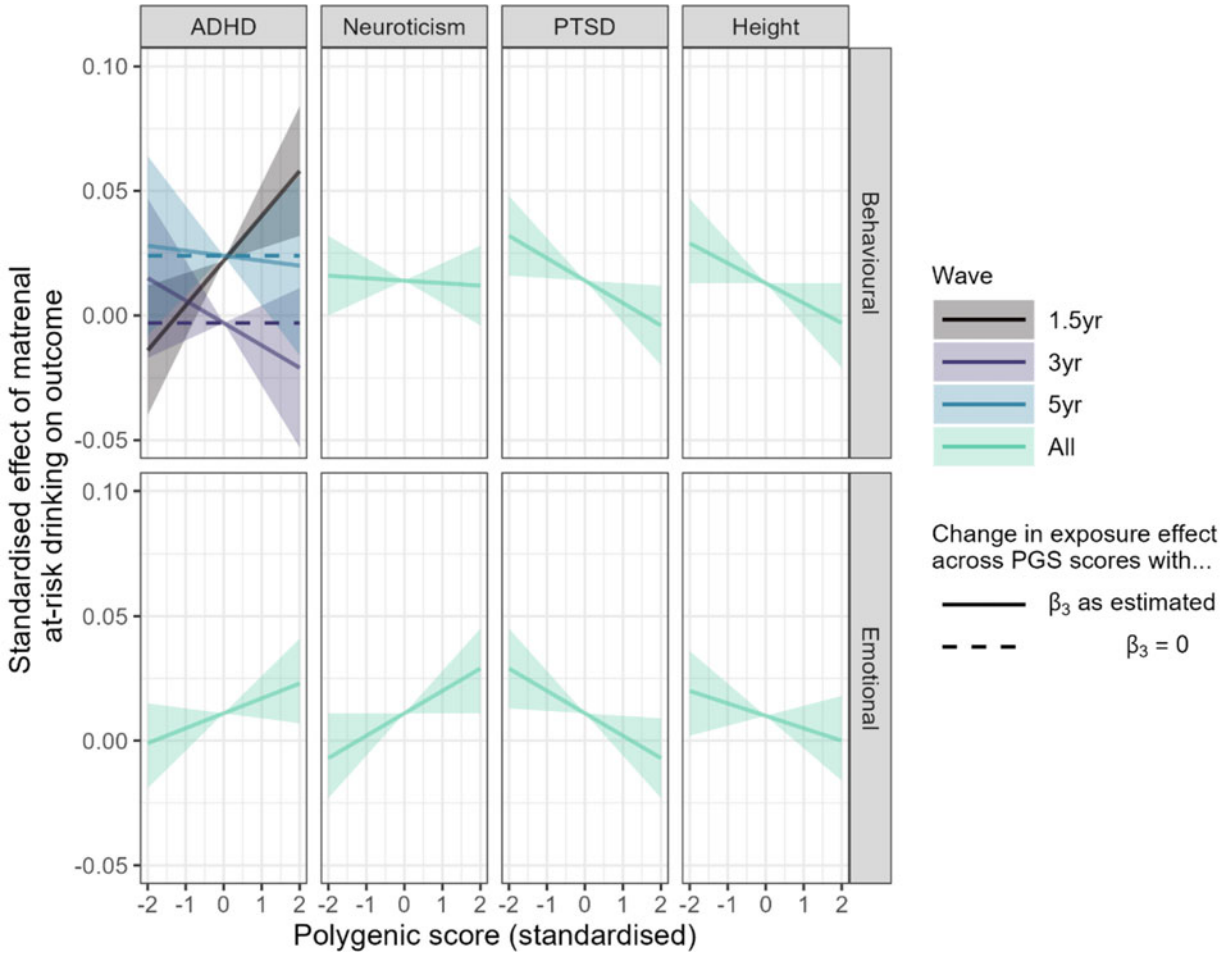

Figure 3. Exposure-by-PGS interaction effects in the most adjusted models presented as changes in the exposure's overall effect at different PGS moderator values. *Note*: Shaded regions represent uncertainty (95% CIs) in the estimation of the exposure-by-PGS interaction effect only (i.e. uncertainty around the estimate of the main effect of the exposure is not represented); effects are displayed separately by wave when constraining them to equality was not possible without a loss of model fit – otherwise the constrained effect estimated at all waves is displayed.

Table 2. Estimates and FDR-corrected *p* values and effect estimates for the interaction between maternal at-risk drinking and PGS from the best-fitting, most parsimonious multilevel models

Outcome	PGS moderator	Accepted constraints	Wave	Beta	*p* value	FDR-corrected *p* value
CBCL behavior	ADHD	None	1.5 years	0.018	0.007	0.070
CBCL behavior	ADHD	None	3 years	−0.009	0.281	0.351
CBCL behavior	ADHD	None	5 years	−0.002	0.854	0.854
CBCL behavior	Neuroticism	Betas and residuals	All	−0.001	0.827	0.854
CBCL behavior	PTSD	Betas and residuals	All	−0.009	0.022	0.073
CBCL behavior	Height	Betas and residuals	All	−0.008	0.054	0.108
CBCL emotion	ADHD	Betas and residuals	All	0.006	0.134	0.223
CBCL emotion	Neuroticism	Betas and residuals	All	0.009	0.040	0.100
CBCL emotion	PTSD	Betas and residuals	All	−0.009	0.021	0.073
CBCL emotion	Height	Betas and residuals	All	−0.005	0.271	0.351

constrained to equality across waves for behavioral but not emotional problems. Online Supplementary Figure S1 shows the estimates of exposure-by-xPGS effects, and online Supplementary Table S11 shows FDR-corrected *p* values. For behavioral problems, the pattern was consistent with the results of the PGS analysis, with no significant or sizeable moderation of the effect of maternal at-risk drinking. For emotional problems, we observed a small, significant interaction effect at age 3 ($\beta_3 = 0.04$ [0.02–0.08],

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FDR-corrected p value = 0.012), with effects at other ages in a consistent direction but not significant

Post-hoc *sensitivity analysis*

In response to reviewer comments we tested the impact of including other forms of maternal prenatal substance use in the models as a covariate. The results – presented as main and interaction effect estimates from tier 2 and tier 2 + maternal prenatal smoking models in online Supplementary Tables S12 and S13 – show that the impact of including maternal prenatal smoking was negligible.

Discussion

We set out to disentangle the mechanisms underlying associations between maternal at-risk drinking and offspring emotional and behavior problems in the context of GE interplay. Specifically, we assessed whether common genetic variants putatively linked to environmental sensitivity moderated the effects of exposure to maternal at-risk drinking on emotional and behavioral problems early in life. The main effects of maternal at-risk drinking weakened substantially after controlling for measured and unmeasured familial confounding. There was no robust evidence for the moderation of these effects by genetic sensitivity. The findings are consistent with the GE correlation that inflates associations between maternal at-risk drinking and child outcomes. However, they provide no support for the hypothesis that G × E makes the causal component of these links stronger in some families than others.

The idea that children with certain genetic makeups are more sensitive to unfavorable environmental influences than children without such genetic makeups is plausible. However, studying the G × E implied by this model is complex and vulnerable to analytical missteps (Domingue et al., 2020). We applied controls for both measured and unmeasured confounding to ensure – as far as possible – that the effect of being moderated was due to exposure and not sources of confounding shared intergenerationally (such as genetics). This was necessary because of the ambiguous evidence regarding whether such exposure-mediated effects exist. Much of previous, genetically informed research on associations between maternal drinking and offspring behavior or/and emotional problems addressed outcomes in adolescent and adult offspring (e.g. Hicks, Foster, Iacono, & McGue, 2013; Kendler et al., 2015, 2012; Kim & Sin, 2020; Knopik et al., 2006; Marmorstein, Iacono, & Mcgue, 2012; Marmorstein et al., 2009; Oro et al., 2021). Most of these studies suggest an association, but the findings are not unambiguous, nor do they necessarily generalize to younger children – the focus of our investigation. Indeed, two large-scale, longitudinal studies that included offspring ages similar to the current study (1.5, 3, and 4 years old) suggested no association (Knudsen et al., 2015; Mahedy et al., 2017) – though their designs do not allow for familial confounding, which can mask and inflate effects.

The attenuation of the exposure effects down almost to zero in the final model of our study demonstrated the significance of adjusting for confounding – which included maternal and paternal PGSs and their interaction terms and prenatal at-risk drinking to account for the possibility of a 'fetal programming' mechanism (Lewis et al., 2015; Stevenson et al., 2020). The results confirm previous findings with these data, both for maternal at-risk drinking (Lund et al., 2020) and other putative sources of intergenerational risk transmission (Cheesman et al., 2020; Eilertsen et al., 2022; Gustavson et al., 2021; Hannigan et al., 2018): namely that processes like GE correlation highly inflate observational associations and that both cautious interpretation and – where possible – statistical adjustment is fundamental.

After systematically removing sources of confounding from our estimated associations between maternal at-risk drinking and child emotional and behavioral outcomes, we estimated G × E effects. We followed a pre-registered analysis plan to control the false-positive rate and accounted for multiple testing. Further, we followed current best practice guidelines and included interaction effects between all covariates and both the exposure and moderators (Domingue et al., 2020). With stringent control of confounding, we found no robust evidence of moderation of the effect of exposure to maternal at-risk drinking on early-life emotional and behavioral development.

We are unaware of previous studies that have addressed genetic moderation of the effect of maternal at-risk drinking on offspring's emotional and behavioral problems. However, considering our findings in the context of prior work on G × E for similar associations, previous research suggests that child genetic variation may moderate the associations between maternal risk factors and offspring's emotional and behavioral outcomes (Chen et al., 2020). For instance, a study that examined whether prenatal depression and the child promoter region of the serotonin transporter gene interacted to predict childhood dysregulation suggested an interaction effect that was stable during the study period from offspring ages 3–36 months (Babineau et al., 2015). Further, while the effect was modest, the difference in dysregulation scores was considered clinically significant for children with particular genetics sensitive to unfavorable environmental influences when examining extremes of exposure (Babineau et al., 2015). Another study examined whether the effects of prenatal anxiety on offspring's emotional symptoms were moderated by genetic variation in the offspring's brain-derived neurotrophic factor (*BDNF*) gene. Offspring emotional symptoms were assessed six times from ages 4 to 15 years. The results showed a main effect of two *BDNF* polymorphisms on emotional symptoms up to age 13; and genetic moderation by other *BDNF* polymorphisms (O'Donnell, Glover, Holbrook, & O'Connor, 2014). These studies indicate that examining G × E remains essential because the approach recognizes that one size does not fit all. What is considered weak environmental effects at the population level could have strong effects on offspring with certain genetic sensitivities to unfavorable environmental influences (Plomin et al., 2022). It is, however, important to contextualize these kinds of results by noting that the current trend in G × E research is moving away from specific candidate gene/variant approaches, which have typically yielded inconsistent results, and toward more polygenic models of GE interplay (Assary, Vincent, Keers, & Pluess, 2018; Barker, Maughan, Allegrini, Pingault, & Sonuga-Barke, 2022). Preliminary applications of such models have tended to find little (Gillett et al., 2022; He & Li, 2022; Plomin et al., 2022), with some notable exceptions (Chen et al., 2020), warranting further investigation and replication attempts. This suggests that such effects do not exist at any meaningful magnitude for the combinations of traits and environments studied, or perhaps we need to adapt our methodologies and fine-tune our polygenic instruments to better detect them.

We further probed the possible presence of interactions by adapting the recently introduced xPGS approach (Chen et al., 2020) to refine PGS based on SNPs most involved in moderating associations. Although our single-SNP moderation models

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remained underpowered to detect SNP-level interaction effects because of our multiple testing burden, the possibility of using clumped GWAS results to target and preserve power in the genomic search for SNP–exposure interactions may be worth further exploration. Further, the only significant interaction effect we observed in the model was an xPGS – based on SNPs accounting for most of the polygenic signal for ADHD, neuroticism, and PTSD – moderated the extent to which maternal drinking was associated with child emotional problems at 3 years. Given the isolated nature of this result and the potential for some degree of overfitting in these models (despite using a separate training sample to parameterize the xPGS), we do not interpret it as robust evidence of a G × E mechanism operating in this context.

The absence of evidence for G × E in our study should not be taken as evidence of absence. The small magnitude of the adjusted exposure effect of maternal at-risk drinking hampers our ability to say anything general about the likelihood of SNPs linked to traits plausibly indexing sensitivity to the environment being involved in the moderation of risk. As the average exposure effect approaches zero, the likelihood of observing a significant interaction effect decreases unless that interaction is either: (a) a crossover interaction, meaning – quite implausibly, in our case – that exposure to maternal at-risk drinking would have to have a beneficial effect on emotional or behavioral problems among children with low genetic liability to, for example, neuroticism; or (b) nonlinear in form, such that the effect only appears when genetic liability is high. This latter possibility is more plausible but not trivial to model. We would likely be underpowered to do so here. In line with these observations, it is notable that one of the largest absolute exposure effects we estimated on behavioral problems at 1.5 years old in the ADHD-PGS-moderator model coincided with the strongest interaction effect estimate in the expected direction. Simply put, there is more 'space' above the overall null to see an interaction without it requiring a reversal of the effect at low-PGS values. Nonetheless, it is important to emphasize that this effect did not pass multiple testing corrections. We observed no consistent effect for the main effect on behavioral problems in the same model at 5 years.

Methodological considerations

Major strengths of the study include that it is based on a prospective population-based cohort study with many related individuals. This allowed us to explore the role of genetics and environment in the intergenerational transmission of risk and familial confounding in associations between maternal at-risk drinking and offspring emotional and behavioral problems (Corfield et al., 2022). The methodological robustness is a particular strength, including PGS for children, mothers, and fathers.

The study also has several limitations. The MoBa study has a participation rate of 41%, which may have resulted in selection bias. Indeed, some groups are underrepresented, including young mothers, mothers with more than two previous births, smokers, women living alone, and women with low education. Further, those who continue to participate are healthier and more educated than those who discontinue MoBa participation; this selection bias may contribute to biased results. Regarding maternal at-risk drinking, it is likely that the MoBa sample does not represent as adverse an environment as the population at large. For a G × E mechanism to operate within an intergenerational exposure, greater variability in the severity of the exposure may be necessary. Importantly, we cannot say for sure – based on these results – whether the lack of such variability in our sample was the reason for the lack of an effect or whether the effect would also have been absent with a more adverse environmental exposure.

Second, though the structure of MoBa is longitudinal, associations are examined cross-sectionally in this study in order to be able to detect evidence of any G × E. Cross-sectional observations maximize our chances of capturing any exposure-based effects of maternal drinking on offspring outcomes, which may plausibly be short-lived and not persist across MoBa data collection waves. We could afford to do this at the cost of the observed associations being inflated by confounding because of the implementation of the multilevel modeling, which parcel out such confounding at the analysis stage. Longitudinal analyses of these data would be advantageous in future work, especially where the goal is to triangulate evidence about the extent to which the association between maternal at-risk drinking and child behavioral and emotional problems is causal across different research designs. Moreover, a significantly longer-term follow-up would be required to ascertain whether maternal at-risk drinking during childhood affects offspring development and functioning later in life, whether moderated by genetic sensitivities or otherwise.

Finally, most previous studies on associations between maternal at-risk drinking and offspring emotional and behavior outcomes have focused on clinical-level maternal drinking, measured using diagnostic interviews or registry records indicative of alcohol-use disorder diagnosis (e.g. Kendler et al., 2015; Knopik et al., 2006; Marmorstein et al., 2012; Oro et al., 2021; Waldron et al., 2009; Wolfe, 2017). We used maternal self-report of drinking frequency and amount; different exposures are possible explanations for differing findings (Hicks et al., 2013; Kendler et al., 2015; Kim & Sin, 2020). In the same vein, many emotional and behavioral outcomes measured in the adult samples, e.g. substance use disorder and crime, differ from emotional and behavioral outcomes measured in studies of preschool children; further, genetic and environmental factors may influence offspring outcomes differently at different ages (Knopik, Neiderhiser, DeFries, & Plomin, 2013). It would have been ideal to include information from the complete alcohol-use disorders identification test (AUDIT) on alcohol consumption. However, the full AUDIT was not included in the MoBa questionnaires administered at children ages 1.5, 3, and 5. We were therefore limited to using maternal alcohol consumption to identify maternal at-risk drinking. The mothers reported on their own alcohol consumption and offspring outcomes; this is not ideal and may have resulted in common method bias. It would have been preferable to have information about the offspring's emotional and behavioral outcomes from sources besides maternal reports, e.g. kindergarten teachers. Further, paternal drinking may also be associated with offspring outcomes. However, as fathers were not invited to respond to the 1.5-, 3- and 5-year questionnaires, we could not examine this. The study does not control for unmeasured factors specific to the individual, such as stressful life events that may influence maternal drinking and offspring's emotional and behavioral problems.

Conclusion

Our findings suggest that genetic sensitivities to unfavorable environmental influences do not moderate the small exposure effect of maternal at-risk drinking on offspring behavior and emotional problems that remains after controlling for genetic

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confounding in our sample. The findings are consistent with substantial inflation of observational effects by GE correlation. However, we found no robust support for G × E in this context.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003057.

Data availability statement. Data from the Norwegian Mother, Father, and Child Cohort Study and the Medical Birth Registry of Norway used in this study are managed by the national health register holders in Norway (Norwegian Institute of Public Health) and can be made available to researchers, provided approval from the Regional Committees for Medical and Health Research Ethics (REK), compliance with the EU General Data Protection Regulation (GDPR) and approval from the data owners. The consent given by the participants does not allow for data storage on an individual level in repositories or journals. Researchers who want access to data sets for replication should apply through helsedata.no. Access to data sets requires approval from The Regional Committee for Medical and Health Research Ethics in Norway and an agreement with MoBa.

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Competing interests. None.

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