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Do Polygenic Indices Capture "Direct" Effects on Child Externalizing Behavior Problems? Within-Family Analyses in Two Longitudinal Birth Cohorts

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Abstract

Failures of self-control can manifest as externalizing behaviors (e.g., aggression, rule-breaking) that have far-reaching negative consequences. Researchers have long been interested in measuring children's genetic risk for externalizing behaviors to inform efforts at early identification and intervention. Drawing on data from the Environmental Risk Longitudinal Twin Study (N = 862 twins) and the Millennium Cohort Study (N = 2,824 parent–child trios), two longitudinal cohorts from the United Kingdom, we leveraged molecular genetic data and within-family designs to test for genetic associations with externalizing behavior that are not affected by common sources of environmental influence. We found that a polygenic index (PGI) calculated from genetic variants discovered in previous studies of self-controlled behavior in adults captures direct genetic effects on externalizing problems in children and adolescents when evaluated with rigorous within-family designs (βs = 0.13–0.19 across development). The PGI for externalizing behavior can usefully augment psychological studies of the development of self-control.

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From very young ages, children are required to delay gratification, regulate their emotions, and control their impulses, and their success or failure in developing self-control has lifelong consequences. Difficulty with self-control is a central feature of the externalizing spectrum, a constellation of behaviors such as aggression, hyperactivity, and rule-breaking; the clinical manifestations of externalizing behavior include conduct disorder, attention-deficit/hyperactivity disorder (ADHD), and substance use disorders (Kotov et al., 2017). Looking beyond clinical diagnoses, self-control measured in childhood predicts illness, impecunity, and victimization well into adulthood (Moffitt et al., 2011; Tanksley et al., 2020). Likewise, externalizing problems in adolescence have been linked with life-course number of emergency room visits, prescription fills, and injury claims, as well as reliance on social welfare and interaction with the criminal justice system (Rivenbark et al., 2018). Overall, a young person's difficulty with self-control has profound personal and societal costs, making early detection and intervention a public-health priority (Moffitt et al., 2011).

Research with twins and adoptees has long hinted that genetic differences contribute to variation in self-control problems (Barr & Dick, 2020), but researchers have previously been unable to measure that risk directly. Recently, a large-scale genome-wide association study (GWAS) attempted to study the genetic underpinnings of self-control by examining its manifestations in the form of adult externalizing behaviors. Specifically, data on seven traits relevant to self-control (i.e., ADHD, problematic alcohol use, cannabis use, number of sexual partners, age at first sexual intercourse, smoking initiation, and general risk tolerance) were pooled from 1.5 million people of European genetic ancestry (Karlsson Linnér et al., 2021) to identify genetic variants associated with shared variation across all seven traits. A follow-up analysis in independent data sets found that these genetic variants, when aggregated in a polygenic index (referred to as the "externalizing PGI"), were associated with an array of adult behaviors that reflect difficulties with self-control, including opioid and other substance use, employment histories, and contact with the criminal justice system. The externalizing PGI also explained 9% to 10% of the variance in a latent factor of phenotypic externalizing that matched the behaviors included in the discovery GWAS. Given that these adult behaviors are often rooted in difficulties with self-control that emerge early in development, these results suggest that the externalizing PGI has potential utility for research aiming to understand, and ultimately to intervene on, the development of self-control problems in childhood.

However, associations between a child's PGI and their behavior must be interpreted carefully (Pingault et al., 2022; Raffington et al., 2020). First, PGI associations may be driven by the measured genetic variants included in the index or by other genetic variants that are correlated with these variants across the genome (i.e., in linkage disequilibrium). Second, the genetic variants discovered to be associated with a given phenotype or set of phenotypes are unlikely to be uniquely associated with only that phenotype (Belsky & Harden, 2019). Although the externalizing PGI might be useful for researchers focused on self-control problems, it might also be widely associated with any number of other social, behavioral, neurobiological, and physiological phenotypes.

Third, PGI associations may operate not only through biological processes happening within the body and brain of the individual whose genotype is being measured but also through social and environmental transactions in which the individual's initial genetically influenced characteristics leads them to select or evoke particular environmental exposures that affect the subsequent development of the phenotype ("nature via nurture"; Lynch, 2017; Plomin et al., 1977). Such active and evocative gene–environment correlations are undoubtedly critical for the development of externalizing behavior (Burt, 2022).

Fourth, and of particular concern in the current article, PGI associations might be driven by demographic and environmental processes that do not originate with the child whose genotype is being measured but instead vary between nuclear families; such processes include population stratification, assortative mating, and indirect genetic effects (also known as "genetic nurture"; Friedman et al., 2021; Young et al., 2019). These processes have been found to contribute heavily to PGI associations with some social and behavioral phenotypes, most notably educational outcomes (Okbay et al., 2022). Indirect genetic effects, in particular, might be particularly important for the development of self-control because these effects operate through environments provided by biological

relatives, including parents (Gottfredson & Hirschi, 1990). For example, if a genetic variant increases the likelihood of maternal alcohol abuse, and parenting by a substance-abusing mother increases a child's risk for conduct problems, then that genetic variant might come to be correlated with child conduct problems, but its effect is mediated through an environmental exposure that occurs regardless of the child's own genetic inheritance. Before PGIs are further integrated into the study of the development of self-control problems, additional information regarding the extent to which the externalizing PGI is tapping environmental differences between families rather than processes originating in the child's own genetics is necessary.

One approach for better understanding the sources of PGI-phenotype associations is to focus on genetic differences that arise within nuclear families (Selzam et al., 2019; Young et al., 2019). Within-family designs leverage the natural experiment of segregation of genotypes occurring during reproduction: Every parent has two copies of every gene, and which one a child inherits is random. Accordingly, a within-family association between externalizing behavior and a PGI can be interpreted in terms of a "direct" causal effect of children's genetics on within-family variation in behavior, an effect that might be substantially mediated by children's interactions with their social environment but that cannot be attributed to environmental stratification between families. Within-family genetic studies are thus critical for building knowledge about processes by which children's genotypes come to be correlated with their life-course outcomes (Raffington et al., 2020).

Here, we estimated associations between the externalizing PGI and children's self-control problems. More specifically, we tested whether a PGI trained on a latent factor of adult externalizing behavior is associated with observed symptoms of inattention, hyperactivity, and conduct problems. To identify direct genetic effects of the externalizing PGI (i.e., no environmental influence), we used two within-family designs. First, the dizygotic twin comparison leverages genetic differences between full siblings, effectively adjusting for genetic effects from parental genotypes and shared environmental factors with which parental genotypes may be correlated. Second, the parent–child trio design directly models parental genetic associations with offspring outcomes by including their genotypes in the model, thus making the offspring's own genotype associations independent of their parents' genotypes (and the family environment; Kong et al., 2018). We used two longitudinal cohorts from the United Kingdom: the Environmental Risk Longitudinal Twin Study (E-Risk; $N = 862$ same-sex dizygotic twins) and the Millennium Cohort Study (MCS; $N = 2{,}824$ parent–child trios). Our analysis focuses on childhood through adolescence, the period when problems with self-control first manifest and the period of most interest for early detection and intervention (Moffitt et al., 2011).

Transparency and Openness

This analysis was preregistered on the OSF at https://osf.io/nhtw2. Code for the analysis is available from the corresponding authors on request. Sensitive health information (genetic data) was included in the analysis data; thus, these data are not publicly accessible. Information on data access for qualified researchers may be accessed at https://cls.ucl.ac.uk/data-access-training/data-access for the MCS and https://eriskstudy.com/data-access for the E-Risk.

Method

Data sources

Data for this study come from two cohorts based in the United Kingdom. The E-Risk is a prospective birth cohort of 2,232 twins (44% dizygotic) born between 1994 and 1995 in England and Wales. The sample was assessed at the ages of 5, 7, 10, 12, and 18 years and has been shown to reflect the full range of socioeconomic conditions in the United Kingdom (Moffitt & Team, 2002; Odgers et al., 2012). The analytic sample included only dizygotic twin pairs (50% female) with complete data and who self-identified as White British ($N = 862$ twins). Zygosity was confirmed with identity-by-descent estimates ($\hat{\pi}$) derived from array data (Hannon et al., 2018). The MCS is a nationally representative prospective birth cohort of 18,827 children (18,552 families) born in the United Kingdom at the turn of the new century. The sample was observed at the ages of 9 months and 3, 5, 7, 11, 14, and 17 years and was designed to capture the full scope of sociodemographic composition in the United Kingdom through the oversampling of disadvantaged families (Connelly & Platt, 2014). The analytic sample included complete genotyped parent–child trios (children were 50% female) whose genotypes most closely resembled genomic reference panels sampled from Europe compared with elsewhere in the world ($N = 2{,}824$). Further details about each cohort are provided in the Supplemental Material available online. (Additional cohorts were considered in our original analysis plan on the OSF. We updated our analysis plan to limit cohorts to only those with at least 200 unique families to preserve adequate statistical power.)

Polygenic scoring

We computed PGIs on the basis of the summary statistics from a multivariate GWAS of traits and behaviors related to self-control in adulthood (Karlsson Linnér et al., 2021). No significance threshold was applied to select single-nucleotide polymorphisms (SNPs) for inclusion in PGI analyses (i.e., all matched SNPs were included). Linkage disequilibrium adjustment was accomplished in the MCS cohort using LDpred2 (Privé et al., 2020) and in the E-Risk cohort using PRSice-2 (Choi & O'Reilly, 2019). Full details about genotyping and PGI construction are provided in the Supplemental Material.

Measures

Externalizing behavior problems. Externalizing behavior problems were assessed using two behavioral instruments: the Child Behavioral Checklist (CBCL; Achenbach & Edelbrock, 1991) in the E-Risk and the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) in the MCS. Following prior research, a measure of externalizing behavior problems was derived by combining information from two subscales from each instrument: the aggressive behavior/rule-breaking subscales from the CBCL and the conduct problems and hyperactivity/inattention SDQ subscales. Because both cohorts are population-based (i.e., nonclinical), they demonstrated similar prevalence rates of clinically significant cases for externalizing disorders/symptoms. For instance, by the age of 12 years (the last wave of data used in the current study), 11.9% and 15.6% of twins in the E-Risk met the diagnostic criteria from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 1994) for ADHD and conduct disorder, respectively. Likewise, by the age of 17 years (the last wave used), 9% and 12.4% of youths in the full MCS cohort demonstrated clinically significant levels of hyperactivity and conduct problems (as reported by parents), respectively.

In the E-Risk cohort, the externalizing behavior problems measure was constructed by averaging each CBCL subscale across all reporters (i.e., parent, teacher) for a specific observation and then summing the two averages together. The resulting scores were right-skewed, so we added a positive constant of 1 and log-transformed the scale to achieve normality. For the MCS, the SDQ subscales were averaged across reporters (i.e., parent, teacher, self-report) for each event, and then scores across all events were entered into a principal component (PC) analysis, and the first PC was extracted. The resulting externalizing scores for both cohorts were then residualized for age, sex, and their interaction and then averaged across events such that every participant in a cohort had a single age- and sex-independent externalizing score. For developmentally sensitive (i.e., within-epoch) analyses, externalizing scores were residualized and averaged within each developmental period, producing externalizing scores that were age- and sex-independent but specific to developmental periods.

Family-level variables. We tested the impact of two family-level mediators through which genetic indirect effects might operate: parental externalizing and parental socioeconomic status (SES).

Parental externalizing problems. In the E-Risk cohort, parental externalizing was measured using mothers' reports for themselves and the twins' biological fathers when the children were 5 years old using the Adult Behavioral Checklist (Achenbach, 1997) and supplemented with questions from the Diagnostic Interview Schedule (Robins et al., 1995) asking about the lifetime presence of *DSM-IV* symptoms of antisocial personality disorder (for more details, see Caspi et al., 2001; see also the Supplemental Material). In the MCS cohort, parental externalizing was measured by entering three variables that were measured when the children were 14 years old into a PC analysis and extracting the first PC: an index of alcohol problems (Alcohol Use Disorders Identification Test; Piccinelli et al., 1997) and the agreeableness and conscientiousness subscales (reverse-coded) from the Big Five personality inventory (Costa & McCrae, 1992). In both cohorts, standardized externalizing composite variables were averaged across parents to produce the final parental externalizing measures.

Parental SES. In the E-Risk, we measured parental SES using a standardized composite index of income, education, and social class assessed at the age of 5 years (M = 0, SD = 1). In the MCS, parental SES was operationalized as a composite of average family income (log) between the ages of 9 months and 7 years and average parental educational attainment (highest earned degree). Both income and educational-attainment variables were standardized (M = 0, SD = 1) and then averaged across parents to produce the final time-stable parental SES.

Covariates. We adjusted for the first 10 ancestry PCs to account for population stratification. Both cohorts processed their genotypes in single batches, so no technical covariates were included. We adjusted for age, sex, and their interaction; however, these covariates were residualized out of the outcome rather than included in the model alongside other covariates (for a description, see above). Additionally, the E-Risk sample did not include ancestry PCs in analytic models, but instead they were residualized out of the externalizing PGI (see Supplemental Methods section in the Supplemental Material).

Analytic plan

Genetic effects. In the current study, we identified two distinct genetic effects: the population and direct genetic effects. The population effect includes the direct genetic effects as well as other sources of environment influence (e.g., population stratification, assortative mating, indirect genetic effects) and is estimated as follows:

$$EXT_{ij} = \beta_{population}(PGI_{ij}),$$

where phenotypic externalizing behavior problems, EXT, of individual i in family j is regressed on their externalizing PGI. Because of the presence of genetic effects other than the direct effects, the $\beta_{population}$ is often inflated beyond the true direct genetic effect (i.e., genetic correlations between the genes of others in the environment and the outcome are absorbed into the population estimate; Young et al., 2019).

Next, we identified the direct genetic effect of the externalizing PGI by leveraging within-family methods developed for the two types of family structures in the current study: full siblings and parent–child trios. Following prior research (Demange et al., 2022), we identified the direct genetic effects for full siblings (or dizygotic twins) by estimating a linear model that partitions genetic effects into within- and between-pair genetic effects:

$$EXT_{ij} = \beta_{within}(PGI_{ij} - \overline{PGI}_j) + \beta_{between}(\overline{PGI}_j),$$

where PGI_{ij} is the externalizing PGI value for individual i in family j and $\overline{PGI}_j$ is the family-specific average externalizing PGI value within family j. This approach decomposes the PGI association into a within-family component, β_{within}, representing the direct genetic effect, versus a between-family component, $\beta_{between}$, representing the residual genetic effects. Finally, we identified direct genetic effects for parent–child trios using a linear model of the following form:

$$EXT_{ij} = \beta(PGI\_Child_{ij}) + \beta(PGI\_Mother_j) + \beta(PGI\_Father_j),$$

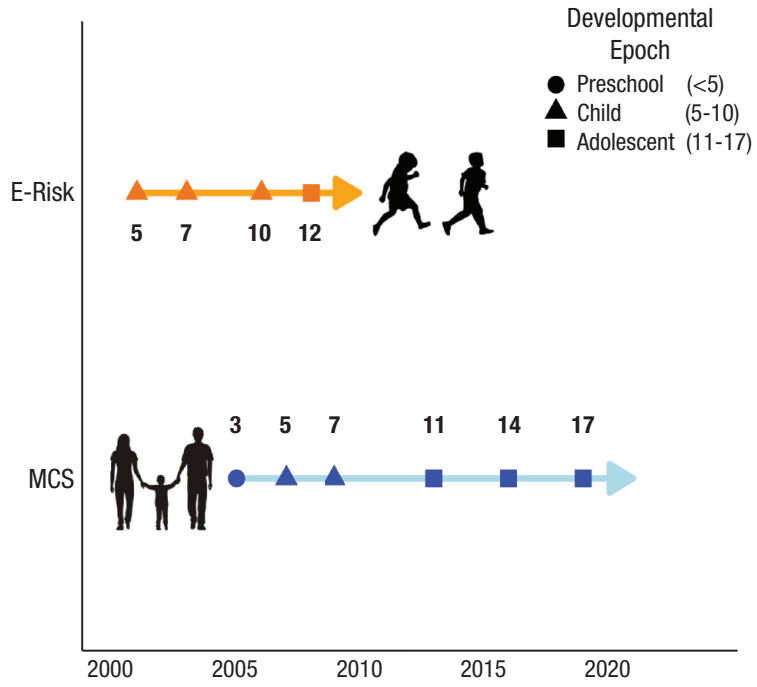
where $\beta(PGI\_Child_{ij})$ captures the direct genetic effect for the child, the residual genetic effects having been adjusted for by the inclusion of both parents' PGI. All models were estimated as linear models that include the first 10 genetic PCs to adjust for population stratification (note that population stratification was adjusted for in the E-Risk by residualizing the externalizing PGI before the analysis). Bias-adjusted confidence intervals (CIs) were estimated using 1,000 bootstrapped samples of each model.

Developmental analysis. Using the above methods to identify the population and direct genetic effects, we estimated a series of models to investigate the dynamic nature of externalizing behavior across development. The cohorts in the current study observed their participants at different ages throughout development. To maximize comparability across cohorts, we binned observations within three developmentally informed epochs: preschool (< 5 years), childhood (5–10 years), and adolescence (11–17 years; for a breakdown of the timing of each cohort's observations relative to developmental epochs, see Fig. 1).

Supplemental analyses. We concluded by investigating three possible sources of influence on the results of our main analysis. First, we investigated the influence of parental behaviors in the forms of assortative mating and family-level variables. In the E-Risk, we examined assortative mating by estimating the co-twin correlation of the externalizing PGI (i.e., a correlation with a CI that did not include an indicated assortment of 0.5). In the MCS, we examined assortative mating related to externalizing genetics by comparing the parents of each trio on their externalizing PGI. Under phenotypic assortment, mate-pair genetics will be independent after adjusting for mate-pair phenotypes (Bulmer, 1980). Thus, mate-pair PGI correlations should be equal to the product of (a) maternal PGI-phenotype correlation, (b) paternal PGI-phenotype correlation, and (c) maternal- and paternal-phenotype correlation (Okbay et al., 2022). (These analyses were not preregistered.) We also tested two family-level variables (i.e., parental externalizing behavior and SES) as possible mechanisms contributing to shared environmental influence in population genetic effects. Second, we explored the possibility of parent-specific effects by adjusting for only one parent at a time and seeing which adjustment brought the estimate of the population genetic effect closest to the estimate for the direct genetic effect (these models were estimated only in the MCS). We calculated the percentage change in effect size attributable to each parent as follows:

$$\text{Parental control (\%)} = \frac{\text{Partial direct genetic effect} - \text{direct genetic effect}}{\text{Population genetic effect} - \text{direct genetic effect}} \times 100,$$

where "partial direct genetic effect" is the estimate for an offspring's externalizing PGI on their externalizing behavior adjusting for the externalizing PGI of a single parent. These analyses allowed us to examine which parent made larger contributions to the population genetic effect. Third, and finally, we tested for possible sex differences across development by reestimating our main models while including main and multiplicative interaction terms with sex.



	E-Risk	MCS
Sample Size	862	2,824
Design	Full sibling (dizygotic twins)	Parent-child trios
Cohort Members		
Sex	50% Female	50% Female
Externalizing Behavior Problems	**Child Behavior Checklist** • Aggressive Behavior subscale • Delinquent Behavior subscale	**Strengths & Difficulties Questionnaire** • Conduct Problems subscale • Hyperactivity/Inattention subscale
Parents		
Externalizing Behavior Problems	**Adult Behavior Checklist** • Aggressive Behavior subscale • Delinquent Behavior subscale **Diagnostic Interview Schedule** • (Lifetime) ASPD symptoms	**Alcohol Use Disorders Identification Test–Primary Care** • Alcohol problems **"Big Five" Personality Inventory** • Agreeableness (reverse) • Extraversion (reverse)
Socioeconomic Status	• Family income • Educational attainment • Occupational prestige	• Family income • Educational attainment

Fig. 1. Data-collection timeline and key study variables. E-Risk = Environmental Risk Longitudinal Twin Study; MCS = Millennium Cohort Study; ASPD = antisocial personality disorder.

Results

Young people with higher externalizing PGIs showed more externalizing behavior problems even when comparing within families

Across cohorts, young people who had higher EXT-PGI values showed more externalizing behavior problems with zero-order correlations (r) ranging from 0.17 to 0.20 for the E-Risk and MCS cohorts, respectively (Fig. 2a). We next estimated between- and within-family linear models, pooling all available data within each cohort (Table 1). Across the E-Risk dizygotic twin sample, children with higher EXT-PGI values also exhibited more externalizing behavior problems, $\beta_{population} = 0.17$, 95% CI = [0.10, 0.24], false discovery rate (FDR)-adjusted p value (p_{FDR}) < .001. When comparing siblings within the same family to one another, we found the twins with the higher EXT-PGI values again had more externalizing behavior problems, on average, than their cotwins, $\beta_{direct} = 0.13$, 95% CI = [−0.002, 0.25], $p_{FDR} = .077$ ("all youths" model in Fig. 2b). We note that the estimate from the within-family model was not statistically

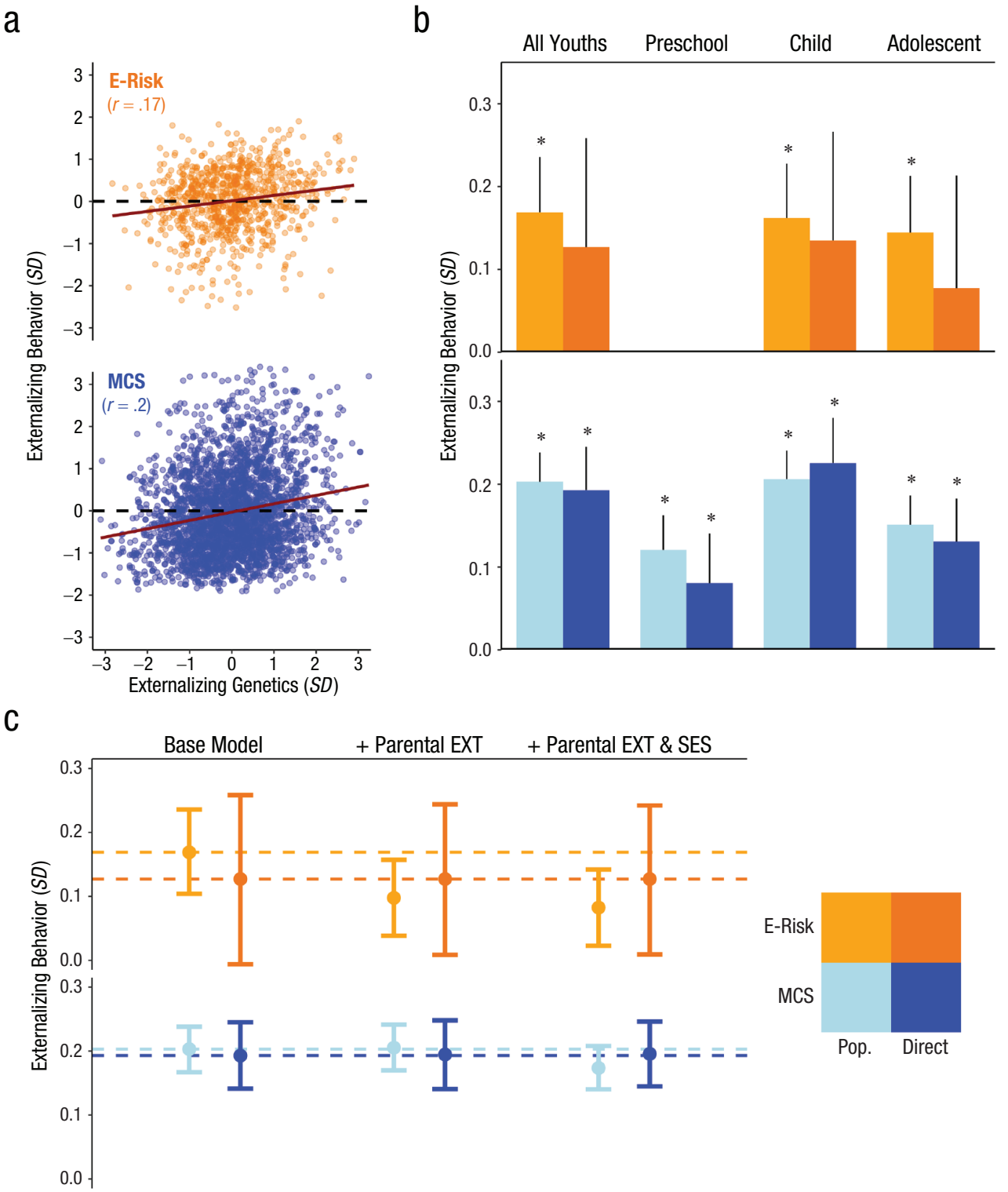


Fig. 2. Associations between EXT genetics and behavior. Scatter plots (a) show the association between genotypic and phenotypic EXT measures in the E-Risk (orange) and MCS (blue) cohorts (trendline = slope of correlation). Bar plot (b) show the degree of attenuation of effect sizes between the population (lighter orange/blue) and direct genetic effects (darker orange/blue) for the E-Risk and MCS cohorts across development. Columns include bias-adjusted bootstrapped 95% CIs (1,000 repetitions). *$p < .05$ (null: $\beta = 0$). Point estimates and bias-adjusted bootstrapped 95% CIs (1,000 repetitions) (c) demonstrate genotype-phenotype associations across three models of progressive covariate adjustment in the E-Risk and MCS cohorts. The first ("base") model includes no additional covariates, the second model includes parental EXT, and the third model includes parental EXT and parental SES. The EXT measure was derived by pooling observations across all epochs. Dashed horizontal lines provide references for the effect sizes observed in the base model. EXT = externalizing behavior problems; E-Risk = Environmental Risk Longitudinal Twin Study; MCS = Millennium Cohort Study; CI = confidence interval; SES = socioeconomic status.

Table 1. Population and Direct Genetic Effects of Externalizing PGI in the E-Risk and MCS Cohorts

	E-Risk cohort											
	All youths			Preschool (< 5 years)			Childhood (5–10 years)			Adolescence (11–17 years)		
Effect	β	*SE*	95% CI	β	*SE*	95% CI	β	*SE*	95% CI	β	*SE*	95% CI
Pop.	0.169	0.034***	[0.104, 0.236]	—	—	—	0.162	0.033***	[0.098, 0.228]	0.144	0.035***	[0.077, 0.213]
Direct	0.127	0.067	[–0.006, 0.258]	—	—	—	0.135	0.068	[0.001, 0.266]	0.077	0.069	[–0.06, 0.213]
Ratio		0.752			—			0.833			0.535	
STD_{DIFF}		–0.943			—			–0.581			–1.501	
N		862			—			862			862	
	MCS cohort											
	All youths			Preschool (< 5 years)			Childhood (5–10 years)			Adolescence (11–17 years)		
Effect	β	*SE*	95% CI	β	*SE*	95% CI	β	*SE*	95% CI	β	*SE*	95% CI
Pop.	0.203	0.018***	[0.167, 0.238]	0.121	0.021***	[0.079, 0.162]	0.206	0.018***	[0.172, 0.241]	0.151	0.018***	[0.114, 0.186]
Direct	0.193	0.026***	[0.141, 0.245]	0.08	0.030**	[0.022, 0.14]	0.226	0.027***	[0.173, 0.28]	0.131	0.027***	[0.078, 0.183]
Ratio		0.950			0.667			1.094			0.859	
STD_{DIFF}		–0.531			–1.906			1.093			–1.052	
N		2,824			2,690			2,822			2,813	

Note: All *p* values were FDR-adjusted. PGI = polygenic index; E-Risk = Environmental Risk Longitudinal Twin Study; MCS = Millennium Cohort Study; CI = confidence interval; Pop. = population genetic effect of the externalizing PGI on externalizing behavior; Direct = within-family coefficient as estimated by full-sibling (E-Risk) and parent–child trio (MCS) designs; Ratio = direct genetic effect divided by the population effect; STD_{DIFF} = standardized difference; FDR = false discovery rate.

*$p < .05$. **$p < 0.01$. ***$p < .001$.

significant, largely because of the increase in uncertainty typical of sibling fixed-effects model (Kaufman, 2008). We observed similar patterns for the children in the MCS cohort, with children with higher EXT-PGI values also demonstrating more externalizing problems across development, $\beta_{population}$ = 0.2, 95% CI = [0.17, 0.24], $p_{FDR} < .001$. After adjusting for their parents' genotypes, we found nearly identical associations that remained statistically significant, β_{direct} = 0.19, 95% CI = [0.14, 0.25], $p_{FDR} < .001$.

To formally test for attenuation among the between- and within-family estimates, we evaluated the standardized difference (STD_{DIFF}) between $\beta_{population}$ and β_{direct}, that is, a *z*-statistic assumed to be normally distributed (Fig. S1 in the Supplemental Material; Karlsson Linnér et al., 2021). In the models that pooled data across development, we failed to find evidence of attenuation in the E-Risk (STD_{DIFF} = −0.94) or the MCS (STD_{DIFF} = −0.53) when comparing the between- and within-family models (both two-sided *p*s > .05).

These results are consistent with the conclusion that the association between the EXT-PGI and externalizing behavior in young people is primarily explained by direct genetic effects rather than by other environmentally contingent processes, such as population stratification, assortative mating, or indirect genetic effects. However, by pooling data across development, these results could be masking heterogeneity in the effects of the EXT-PGI within specific developmental epochs. We examined this possibility next.

Genetic associations with externalizing behavior problems differ across development

We found evidence for a moderate degree of heterogeneity in PGI associations across developmental epochs. We again estimated between- and within-family models but pooled data within discrete developmental epochs instead of across all observations. These epochs were preschool (< 5 years), childhood (5–10 years), and adolescence (11–17 years; for a depiction of how observations from each cohort fall into each epoch, see Fig. 1).

Only the MCS provided data on externalizing behavior problems (as reported by parents) within the preschool epoch. We found that children younger than 5 years who had higher EXT-PGI values were also reported to have more externalizing behavior problems, $\beta_{population}$ = 0.12, 95% CI = [0.08, 0.16], $p_{FDR} < .001$. After adjusting for parental genotypes, this association reduced somewhat, β_{direct} = 0.08, 95% CI = [0.02, 0.14], p_{FDR} = .008, although we failed to find evidence of a substantive attenuation in effect size using conventional statistical thresholds (STD_{DIFF} = −1.91, two-sided *p* = .057; Fig. 2b and Table 1).

The childhood epoch contained the largest epoch-specific effect sizes for both cohorts. The dizygotic twins in the E-Risk cohort demonstrated the expected pattern of associations, with larger between-family estimates, $\beta_{population}$ = 0.16, 95% CI = [0.1, 0.23], $p_{FDR} < .001$, than within-family estimates, β_{direct} = 0.13, 95% CI = [0.00, 0.26], p_{FDR} = .077, but we again failed to find evidence of a statistical difference between effect sizes (STD_{DIFF} = −0.58, two-sided *p* = .561). The MCS cohort exhibited the opposite trend. Children with higher EXT-PGI values were predicted to have slightly higher levels of externalizing behavior problems after adjusting for their parents' genotypes, β_{direct} = 0.23, 95% CI = [0.17, 0.28], $p_{FDR} < .001$, rather than before, $\beta_{population}$ = 0.21, 95% CI = [0.17, 0.24], $p_{FDR} < .001$. However, we again failed to find evidence that these differences were substantive (STD_{DIFF} = 1.09, two-sided *p* = .275).

When moving from the childhood to adolescent epoch, we observed a decline in effect sizes for both cohorts. Comparing across all twins in the E-Risk cohort, we found that twins' EXT-PGI was associated with their externalizing behavior at a level like that of the childhood epoch, $\beta_{population}$ = 0.14, 95% CI = [0.08, 0.21], $p_{FDR} < .001$. Compared with the childhood epoch, a change in effect size was observed when comparing between- versus within-family associations, ($\beta_{population}$ = 0.14 vs. β_{direct} = 0.08), but we again did not find statistical support for attenuation (STD_{DIFF} = −1.50, two-sided *p* = .133). In contrast, in the MCS cohort there was a decline in the association between adolescents' EXT-PGI and their externalizing behavior compared with childhood, $\beta_{population}$ = 0.15, 95% CI = [0.11, 0.19], $p_{FDR} < .001$, and a smaller reduction in effect size after accounting for their parents' genotypes, β_{direct} = 0.13, 95% CI = [0.08, 0.18], p_{FDR} = .237 (STD_{DIFF} = −1.05, two-sided *p* = .293).

Overall, a moderate amount of heterogeneity in effect sizes was uncovered when the models were disaggregated by developmental epochs ($\beta_{population}$ values from 0.12 to 0.21), with the largest effect sizes observed in the childhood epoch (5–10 years). Despite this, both cohorts demonstrated small attenuations in their effect sizes when switching to a within-family model, and all attenuations were statistically indistinguishable from zero, with the largest attenuation occurring in the MCS cohort during the childhood epoch.

Parental effects do not explain the association between polygenic predictors and externalizing behavior problems

Next, we investigated two potential contributors to the between-family PGI association: assortative mating and parent-specific genetic effects. Assortative mating occurs when people are more likely to mate with

people who are genotypically and/or phenotypically similar. Assortment increases the variance of a trait in the population and fosters Gene-environment correlation (rGE), thus inflating the population genetic effect of a PGI.

We found little support for the substantive influence of assortment in either cohort. In the E-Risk cohort, the correlation (r) between twins' externalizing PGI was .5, 95% CI = [.43, .57], giving no indication of assortative mating (Table S1 in the Supplemental Material). In the MCS, the parental mate-pair correlation of the EXT-PGI was larger than expected under an assumption of phenotypic assortment ($r_{\text{mate-pair}}$ = .032 vs. r_{expected} = .00003); however, the mate-pair correlation was not distinguishable from zero, 95% CI = −.004, .067, p = .08, leading us to conclude that negligible assortment on EXT genetics was present in the MCS (Table S1).

We also compared the relative importance of maternal and paternal genotypes on child externalizing behavior (MCS only). By accounting for one parent at a time (i.e., partially identifying the direct genetic effect), we were able to identify which parental genotypes contributed more to the indirect genetic pathways inflating the population genetic effect. When pooling data across epochs, we found that the genotypes of fathers accounted for more of the difference between the population and direct genetic effects (85% vs. 47% for mothers). To contextualize this finding, however, we note that the overall amount of change in effect size was very small ($\beta_{\text{population}}$ = 0.203 vs. β_{direct} = 0.198), making even trivial variation in the differences between parents' estimates appear large. When assessing models within epochs, we found that the greatest distance between estimates of parental control was in the childhood epoch, with genotypes of mothers and fathers accounting for 90% and 40%, respectively, of the difference between population and direct genetic effects (Table S2).

Overall, these results reinforce the possibility that the EXT-PGI may be driven primarily by direct genetic effects because there is little evidence for assortment and little difference in the effect size between fully and partially adjusted genetic effects.

Genetic associations with externalizing cannot be accounted for by measures of parental SES or parental externalizing behaviors

We examined the robustness of our results by considering family-level phenotypes that are known to be associated with the intergenerational transmission of externalizing behavior: parental SES and parental externalizing behavior. Including family-level covariates should attenuate estimates of only the population genetic effect because the within-family model accounts for shared environmental variance by design. We observed no change in either cohort in the effect sizes of the direct genetic effects but a small change of the population effect (e.g., largest difference was 0.08 SDs) when including family-level phenotypes, consistent with this prediction (Table S3 and Fig. 2c).

Sex differences in genetic associations with externalizing were detected only in within-family models

The expression and timing of externalizing behavior across development is different for boys and girls. It is possible that developmental sex differences in externalizing account for some of the above results. We examined this possibility by testing for moderation of the population and direct genetic effects by the sex of the participants.

We recalculated our measure of externalizing behavior in both cohorts by residualizing for age only and averaging between and within developmental epochs. Next, we reestimated the previous population and within-family models and included terms for *Sex* and *PGI* × *Sex* (Table S4). The E-Risk cohort contains only same-sex twin pairs, meaning that only between-pair sex differences could be estimated because sex varied only at the family level. Thus, we report results for the E-Risk cohort in the Supplemental Material and focus on results from the MCS here. Linear models were used to test for sex differences in the MCS. Effect coding was used for *Sex* to facilitate interpretation. Thus, the intercepts represent the model grand mean of externalizing behavior across the categories in the model (i.e., male, female) for someone of average PGI. The main effects are interpretable as true main effects and not marginal effects. The interaction terms are directly interpretable as the difference in the association (i.e., slope) between the externalizing PGI and phenotypic externalizing for the effect group (i.e., males). Bias-adjusted 95% CIs were produced using 1,000 sex-stratified bootstrapped samples to ensure stable interaction estimates.

Pooling data across epochs or examining epochs individually did not reveal any statistically significant interactions with sex in the between-family models (Table S4 and Fig. S2). The within-family models identified statistically significant sex differences in all models except the childhood epoch. Across all within-family models except the childhood model, the interaction term was positive (βs from 0.13 to 0.14; all $p_{\text{FDRs}} < .05$), indicating that boys had stronger associations between the externalizing PGI and externalizing behaviors than

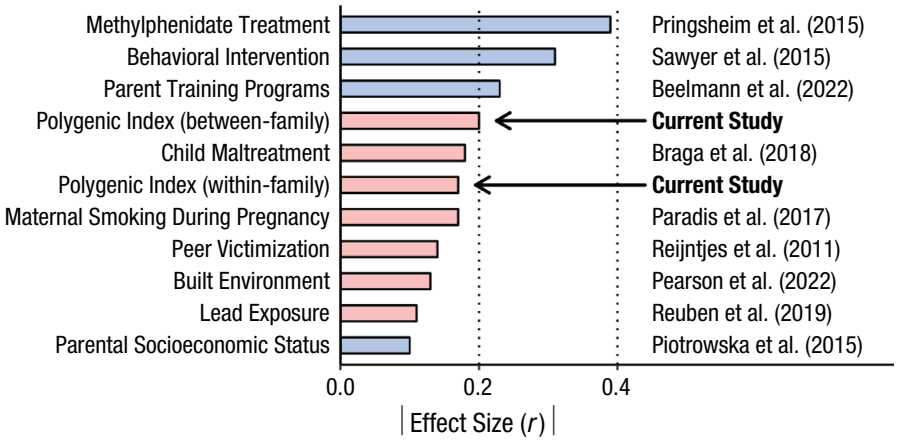


Fig. 3. Comparison of effect sizes (interpretable on the correlation scale) of predictors observed in the current study, and those from the literature, on conduct problems. Colors represent the polarity of the effect size reported in the original article, with negative values (blue) representing reductions in externalizing behavior problems and positive values (red) representing increases. Between- and within-family estimates for the externalizing PGI were taken from the MCS models with data pooled across epochs. PGI = polygenic index; MCS = Millennium Cohort Study.

girls in the MCS. Interestingly, it was the childhood model that also identified the largest main effect of the externalizing PGI across the within-family models, β_{direct} = 0.24, 95% CI = [0.19, 0.29], $p_{FDR} < .001$. The large main effect of the externalizing PGI during the childhood period may help explain the above finding, wherein the direct effect was larger than the population effect during the childhood epoch, because both boys and girls were experiencing similarly high levels of direct genetic effects.

Discussion

When failures in self-control manifest as externalizing behavior problems, there can be long-lasting consequences across many life domains. Given the high heritability of externalizing behaviors, researchers have been interested in incorporating direct measurements of genetic risk alongside other known risk factors to improve efforts at early identification/intervention. Following a preregistered analytic plan, we used data from two longitudinal cohorts from the United Kingdom, leveraging molecular genetic data and within-family designs to identify direct genetic effects on externalizing behavior problems in childhood and adolescence. Results are consistent with the conclusion that the externalizing PGI captures genetic effects that are causally related to difficulties with self-control in early life.

The externalizing PGI effect size that we observed here is comparable to many established environmental risk factors and clinical interventions for externalizing (Fig. 3; Beelmann et al., 2022; Braga et al., 2018; Paradis et al., 2017; Pearson et al., 2022; Piotrowska et al., 2015; Pringsheim et al., 2015; Reijntjes et al., 2011; Reuben et al., 2019; Sawyer et al., 2015). For instance, the effect sizes observed in the current work are similar in magnitude to correlations observed between externalizing problems and childhood maltreatment (Braga et al., 2018) and maternal smoking during pregnancy (Paradis et al., 2017). Note, however, that we present correlations with single dimensions of environmental risk and clinical interventions; a "poly-environmental index" that aggregated many environmental exposures would likely be more strongly correlated with externalizing behavior.

We highlight four key findings. First, we failed to find evidence of attenuation when comparing population and direct genetic effects of the externalizing PGI across cohorts. Our result accords with recent findings in which no indirect genetic effects of the externalizing PGI (i.e., residual parental genetic effects after accounting for offspring genotypes) were detected in a Dutch sample of adolescents (Kretschmer et al., 2022) and small indirect effects were detected in a sample of American families ascertained for involvement in alcohol treatment programs (Kuo et al., 2022). Despite the lack of statistical evidence for attenuation, the observed differences between the population and direct genetic effects was larger in the E-Risk cohort than in the MCS cohort. This variation across cohorts might be due to differences in the type of family design used (parent-child trio vs. sibling comparison). Estimates from sibling-comparison models can be biased downward by sibling-to-sibling interaction effects (Trejo & Domingue, 2019). However, other recent simulation studies have

demonstrated similar performance of the sibling-comparison and parent–child trio designs in the presence of a variety of environmental influences (Demange et al., 2022), suggesting the role of other factors, such as differences in measurements or sampling strategies.

Second, we observed heterogeneity in effect sizes when data were disaggregated by developmental epochs. This result emphasizes the dynamic nature of externalizing behavior and highlights the importance of genetic factors early in development. The early peak in effect sizes during childhood and decline in adolescence may be attributable to the increasing heritability of specific forms of externalizing behavior problems (e.g., alcohol use) above and beyond latent externalizing risk that has been observed later in development (Kendler et al., 2011; Meyers et al., 2014). Despite the variation in epoch-specific levels of genetic associations, the differences between population and direct genetic effects were consistently small within epochs, suggesting that the level of nondirect genetic influence remains low regardless of age.

Third, statistical adjustment for family-level variables (i.e., parental SES and externalizing behavior problems) had little impact on population genetic effects, suggesting that the externalizing PGI is not redundant with common social-science variables. Moreover, we observed limited evidence for genetic assortment among parents. Overall, we observed a small role of the shared family-level environment in measured genetic associations with externalizing behavior, a result that supports twin-based estimates of the shared environment (approximately 15%; Burt, 2009). Other phenotypes of interest to social and clinical scientists do not always follow this pattern. Educational attainment, for instance, has larger shared environmental variances (approximately 30% in twin studies; Silventoinen et al., 2020) and correspondingly larger attenuations in the population genetic effect size (approximately 50%; Okbay et al., 2022) when estimated using genomic data and within-family designs as done here.

Fourth, sex differences (i.e., MCS only) in polygenic associations were dependent on the model used. The between-family models did not detect any sex differences, whereas results from the within-family models indicated larger direct genetic effects for boys compared with girls. We emphasize this last finding because it offers a potential explanation for the general dearth of sex differences observed in research on PGIs (Zhu et al., 2023). Although results will vary depending on the nature of the PGI of interest, it may be that the environmental effects inherent in population genetic associations are sufficient to obfuscate sex differences and that within-family designs are needed to identify these differences.

This study has several limitations. First, we maximized comparability across epochs by using measures of conduct problems assessed consistently over time; however, we know that the expression of behaviors in the externalizing spectrum can be highly varied in early life. It is likely that our approach was not able to capture the full scope of conduct behaviors as they began to be expressed in the study samples (i.e., because of heterotypic continuity). Likewise, our measurements of parental externalizing behavior and SES were not comprehensive. We might have observed a greater change in the population genetic effect when including parental covariates if our study included more comprehensive and reliable measures of these parental phenotypes (Westfall & Yarkoni, 2016).

Another limitation concerns the possibility of differential attrition in our samples resulting from being restricted to only those participants who had complete data on key study variables, as well as having a complete family structure (i.e., both siblings in the E-Risk and offspring with both parents in the MCS). This concern is less relevant for the E-Risk sample, in which retention rates were high (93% of the original sample participated in the most recent wave of data collection). Comparing the analytic sample from the MCS (N = 2,824) to the participants with partial data from the relevant waves (N = 5,377; Table S5 in the Supplemental Material), we found that the analytic sample was higher on measures of parental externalizing and SES and lower on genotypic and phenotypic externalizing, and these differences were statistically significant (all ps < .001). However, effect sizes (Cohen's d) of these differences were small (i.e., ranging from 0.29 to 0.38), except for parental SES, which was a medium-sized effect ($|d|$ = 0.62; Fig. S3). Considering these differences, we cannot rule out the possibility that selection may have influenced some of the results reported here.

Third, we relied on a PGI that was developed in adults and used phenotypes that are rare in pediatric samples (e.g., problematic alcohol use). A PGI based on genetic discovery studies in children might capture more of the genetic signal relevant to child and adolescent externalizing problems. However, previous research has suggested that the genetic factors contributing to latent externalizing are highly stable across development and into adulthood. That is, the specific genetic basis for childhood externalizing behavior problems remains stable as children become adults, although its expression (through specific behaviors) will change (Barr & Dick, 2020; Hatoum et al., 2018). These results support our use of the externalizing PGI in a pediatric sample.

Fourth, our analysis relied solely on British families whose genotypes are most similar to reference panels of people sampled from Europe versus other places in the world, and thus our findings are not expected to be broadly generalizable to children with different genomic ancestry patterns. Focusing on European-ancestry children was appropriate for the current analysis because the GWAS of externalizing behavior was conducted in European-ancestry individuals, and PGIs (particularly those for complex behavioral traits) have low portability across ancestry groups (Martin et al., 2019; Privé et al., 2022). For instance, it has been observed that the PGI for externalizing behavior is less predictive for African- than European-ancestry individuals in an American cohort (Kuo et al., 2021, 2022). Without a PGI that performs comparably in non-European ancestries, application of the current externalizing PGI to other ancestry groups is unwarranted.

Despite these limitations, we believe that DNA-based measures may be useful for efforts aimed at identifying and supporting at-risk youths before low self-control develops into externalizing behaviors. This line of research would benefit from further replication in better powered samples, especially those outside of the United Kingdom, which would also be informative regarding the cultural specificity of our results. It would also benefit from work that more comprehensively examines emotional and behavioral problems across development because the genetic variants included in the externalizing PGI are likely not specifically associated with only self-control problems. Nonetheless, we have provided preliminary evidence that a PGI trained on adult externalizing behaviors could predict childhood-onset externalizing behavior problems in two nonclinical samples, even when using a rigorous design-based control for between-family environmental stratification. Because our analysis identified effect sizes comparable to established risk factors such as family SES or lead exposure, we believe that DNA-based measures may provide incremental value to current risk-assessment tools.

Transparency

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Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Supplemental Material

Additional supporting information can be found at http://journals.sagepub.com/doi/suppl/10.1177/21677026241260260

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