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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 UK, 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 (β's = 0.13–0.19 across development). The externalizing behavior PGI can usefully augment psychological studies of the development of self-control.

Keywords

Self-control; Externalizing; Polygenic Index; Direct Genetic Effects; Development

Introduction

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 life-long 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/hyper-activity 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). Similarly, 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, general risk tolerance) were pooled from 1.5 million people of European genetic ancestry (Karlsson Linnér et al., 2021), in order to identify genetic variants associated with shared variation across all

seven traits. Follow-up analysis in independent datasets found 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 9–10% 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). While 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 through biological processes happening within the body and brain of the individual whose genotype is being measured, but also through social and environmental transactions whereby 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 paper, 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 the child'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 estimate associations between the externalizing PGI and children's self-control problems. More specifically, we test if 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 use two longitudinal cohorts from the United Kingdom (UK): the Environmental Risk (E-Risk) Longitudinal Twin Study (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

The following analysis was preregistered on the Open Science Framework (OSF; https://osf.io/nhtw2/). Code for analysis is available from the corresponding authors upon request. Sensitive health information (genetic data) was included in analysis data; thus it is 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.

Materials and Methods

Data sources

Data for this study come from two UK-based cohorts. The Environmental Risk (E-Risk) Longitudinal Twin Study is a prospective birth cohort of 2,232 twins (44% dizygotic) born in 1994–1995 in England and Wales. The sample was assessed at ages 5, 7, 10, 12, and 18, and has been shown to reflect the full range of socioeconomic conditions in the UK (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 Millennium Cohort Study (MCS) is a nationally-representative prospective birth cohort of 18,827 children (18,552 families) born in the UK at the turn of the new century. The sample was observed at ages 9m, 3, 5, 7, 11, 14, and 17 years of age and was designed to capture the full scope of sociodemographic composition in the UK 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 to sampled from elsewhere in the world (N = 2,824). Further details about each cohort are provided in the Supplement. (Additional cohorts were considered in our original analysis plan on OSF. We updated our analysis plan to limit cohorts to only those with at least N = 200 unique families to preserve adequate statistical power.)

Polygenic scoring

We computed polygenic indices (PGI) based on 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 SNPs for inclusion in PGI analyses (i.e., all matched SNPs were included). LD-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 Supplement.

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 the prior literature, 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. As both cohorts are population-based (i.e., non-clinical), they demonstrated similar prevalence rates of clinically significant cases for externalizing disorders/symptoms. For instance, by age 12 (the last wave of data used in the current study), 11.9% and 15.6% of twins in the E-risk study met the DSM-IV diagnostic criteria for ADHD and conduct disorder, respectively. Similarly, by age 17 (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).

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 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, SDQ subscales were averaged across reporters (i.e., parent, teacher, self-report) for each event, and then scores across all events were be entered into a principal component analysis and the first principal component (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 has 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 are age-/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 age 5 years using the Adult Behavioral Checklist (Achenbach, 1997) and supplemented with questions from the Diagnostic Interview Schedule (Robins et al., 1995) asking about lifetime presence of DSM-IV symptoms of antisocial personality disorder (for more details, see Supplement and Caspi et al., 2001). In the MCS cohort, parental externalizing was measured by entering three variables, measured when the children were age 14 years, into a principal components analysis and extracting the first principal component (PC): an index of alcohol problems (Alcohol Use Disorders Identification Test–Primary Care) (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 socioeconomic status.: In the E-Risk study, we measured parental socioeconomic status (SES) using a standardized composite index of income, education, and social class assessed at age 5 (M = 0, SD = 1). In the MCS, parental SES was operationalized as a composite of average family income (log) between ages 9m-7yrs 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 ten ancestry PCs to account for population stratification. Both cohorts processed their genotypes in single batches, so no technical covariates were included. We adjust 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).

Analytic plan

Genetic effects.—In the current study, we identify 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 in regressed on their externalizing PGI. Due to 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:

$$EXT_{ij} = \beta_{Within}\left(PGI_{ij} - \overline{PGI}_{j}\right) + \beta_{Between}\left(\overline{PGI}_{j}\right)$$

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 ten genetic principal components to adjust for population stratification (note: population stratification was adjusted for in the E-Risk by residualizing the externalizing PGI prior to the analysis). Bias-adjusted confidence intervals were estimated using $N = 1000$ bootstrapped samples of each model.

Developmental analysis.—Using the above methods to identify the population and direct genetic effects, we estimate a series of models to investigate the dynamic nature 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 (<5yrs), childhood (5–10yrs), and adolescence (11–17yrs) (see Figure 1 for a breakdown of the timing of each cohort's observations relative to developmental epochs).

Supplemental analyses.—We conclude by investigating three possible sources of influence on the results of our main analysis. First, we investigate influence of parental

behaviors in the forms of assortative mating and family-level variables. In the E-Risk, we examined the assortative mating by estimating the co-twin correlation of the externalizing PGI (i.e., a correlation with a confidence interval that did not include 0.5 indicates assortment). In the MCS, we examined assortative mating related to externalizing genetics by comparing the parents of each trio on their EXT-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 (1) maternal PGI-phenotype correlation, (2) paternal PGI-phenotype correlation, and (3) maternal-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 socioeconomic position) 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 brings the estimate of the population genetic effect closest to the estimate for the direct genetic effect (these models were only estimated in the MCS). We calculated the percent change in effect size attributable to each parent as:

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

where “partial direct genetic effect” is the estimate for an offspring’s EXT-PGI on their externalizing behavior adjusting for the EXT-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 re-estimating our main models while including main and multiplicative interaction terms with sex.

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-PGIs showed more externalizing behavior problems with zero-order correlations ranging from $r = 0.17–0.20$ for the E-Risk and MCS cohorts, respectively (Figure 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 values on the EXT-PGI also exhibited more externalizing behavior problems ($\beta_{Population} = 0.17$, 95%CI [0.10, 0.24], $P_{FDR} < 0.001$). When comparing siblings within the same family to one another, we found the twins with the higher EXT-PGI again had more externalizing behavior problems, on average, than their co-twins ($\beta_{Direct} = 0.13$, 95%CI [−0.002, 0.25], $P_{FDR} = 0.077$) (Figure 2B, “all youths” model). We note that the estimate from the within-family model was not statistically significant, largely due to 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 who were higher on the EXT-PGI also demonstrating more externalizing problems across development ($\beta_{Population} = 0.2$, 95% CI [0.17, 0.24], $P_{FDR} <$

0.001). After adjusting for their parents' genotypes, we found nearly identical associations, which remained statistically significant (β_{Direct} = 0.19, 95%CI [0.14, 0.25], P_{FDR} < 0.001).

To formally test for attenuation amongst the between-/within-family estimates, we evaluated the standardized difference (STD_{DIFF}) between $\beta_{Population}$ and β_{Direct} (i.e., a z-statistic assumed to be normally distributed [Figure S1]; Supplement provides materials on the derivation of standard errors) (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-/within-family models (both two-sided P > 0.05).

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 examine 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-/within-family models, but pooled data within discrete developmental epochs instead of across all observations. These epochs were preschool (<5y), childhood (5–10y), and adolescence (11–17y) (see Figure 1 for a depiction of how observations from each cohort fall into each epoch).

Only the MCS provided data on externalizing behavior problems within the preschool epoch, which were reported by parents. We found that children younger than five years who had higher values on the EXT-PGI were also reported to have more externalizing behavior problems ($\beta_{Population}$ = 0.12, 95%CI [0.08, 0.16], P_{FDR} < 0.001). After adjusting for parental genotypes, this association reduced somewhat (β_{Direct} = 0.08, 95%CI [0.02, 0.14], P_{FDR} = 0.008), although we failed to find evidence of a substantive attenuation in effect size using conventional statistical thresholds (STD_{DIFF} = −1.91, two-sided P = 0.057) (Figure 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} < 0.001) than within-family estimates (β_{Direct} = 0.13, 95%CI [0.00, 0.26], P_{FDR} = 0.077), but we again failed to find evidence of a statistical difference between effect sizes (STD_{DIFF} = −0.58, two-sided P = 0.561). The MCS cohort exhibited the opposite trend. Children with higher values on the EXT-PGI 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} < 0.001) rather than before ($\beta_{Population}$ = 0.21, 95%CI [0.17, 0.24], P_{FDR} < 0.001). However, we again failed to find evidence that these differences were substantive as indicated by a STD_{DIFF} of 1.09 (two-sided P = 0.275).

When moving from the childhood to the 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} < 0.001). Compared to the childhood epoch, we observed a change in effect size when comparing associations between- versus within-families ($\beta_{Population}$ = 0.14 vs. β_{Direct} = 0.08) but we again did not find statistical support for attenuation (STD_{DIFF} = −1.50, two-sided P = 0.133). In contrast, adolescents in the MCS cohort saw a decline in the association between the EXT-PGI and their externalizing behavior compared to childhood ($\beta_{Population}$ = 0.15, 95%CI [0.11, 0.19], P_{FDR} < 0.001) 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} = 0.237; STD_{DIFF} = −1.05, two-sided P = 0.293).

Overall, a moderate amount of heterogeneity in effect sizes was uncovered when the models were disaggregated by developmental epochs ($\beta_{Population}$'s ranged from 0.12–0.21), with the largest effect sizes observed in the childhood epoch (5–10y). 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-families 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 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 between twins' externalizing PGI was r = 0.5 (95%CI [0.43, 0.57]), giving no indication of assortative mating (Table S1). In the MCS, the parental mate-pair correlation of the EXT-PGI was larger than was expected under an assumption of phenotypic assortment ($r_{mate\text{-}pair}$ = 0.032 vs. $r_{Expected}$ = 0.00003); however, the mate-pair correlation was not distinguishable from zero (95% CI [−0.004, 0.067], P = 0.08) 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/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 ($\beta_{Population}$ = 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 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, as there is little evidence for assortment and little difference in effect size between fully and partially adjusted genetic effects.

Genetic associations with externalizing cannot be accounted for by measures of parental socioeconomic status 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 externalizing behavior and family socioeconomic status (SES). Including family-level covariates should attenuate estimates of only the population genetic effect, as the within-family model accounts for shared environmental variance by design. Consistent with this prediction, for both cohorts, we observed no change 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 (Table S3 and Figure 2C).

Sex differences in genetic associations with externalizing were detected only in withinfamily 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/within developmental epoch. Next, we re-estimated 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, as sex only varied at the family level. Because of this, we report results for the E-Risk cohort in the Supplement 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% confidence intervals were produced using $N = 1000$ sex-stratified bootstrapped samples to ensure stable interaction estimates.

Pooling data across epochs or examining epochs individually, the between-family model did not identify any statistically significant interactions with sex (Table S4 and Figure S2). The within-family models identified statistically significant sex difference in all models, save for the childhood epoch. Across all within-family models, excepting the childhood model, the interaction term was positive (β's ranged from 0.13–0.14; all $P_{FDR} < 0.05$) indicating that boys had stronger associations between the externalizing PGI and externalizing behaviors

than 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} < 0.001). 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, as 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 (https://osf.io/nhtw2/), we used data from two longitudinal cohorts from the UK, 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 PGI-externalizing effect size that we observe here is comparable to many established environmental risk factors and clinical interventions for externalizing (Figure 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 present 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 fail to find evidence of attenuation when comparing population and direct genetic effects of the externalizing PGI across cohorts. Our result accords with recent findings where 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. This variation across cohorts might be due to differences in the type of family design used (parent-child trio versus 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 non-direct genetic influence remains low regardless of age.

Third, statistical adjustment for family-level socioeconomic status and parental 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 (~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 (~30% in twin studies) ((Silventoinen et al., 2020) and correspondingly larger attenuations in the population genetic effect size (~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 upon the model used. The between-family models did not detect any sex differences, whereas results from the within-family models found larger direct genetic effects for boys compared to girls. We emphasize this last finding as it offers a potential explanation for the general dearth of sex differences observed in research on PGIs (Zhu et al., 2022). 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., due to heterotypic continuity). Similarly, our measurements of parental externalizing behavior and parental socioeconomic status 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 due to 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 where

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), we found that the analytic sample was higher on measures of parental externalizing and SES, lower on genotypic and phenotypic externalizing, and these differences were statistically significant (all $P < 0.001$). However, effect sizes (Cohen's d) of these differences were "small" (i.e., ranging from 0.29–0.38), except for parental SES, which was a medium sized effect ($|d| = 0.62$) (Figure 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, using 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., 2022; Kuo et al., 2021). 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 have utility 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 UK, 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, as 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 non-clinical samples, even when using a rigorous design-based control for between-family environmental stratification. As our analysis identified effect sizes comparable to established risk factors such a family socioeconomic status or lead exposure, we believe that DNA-based measures may provide incremental value to current risk assessment tools.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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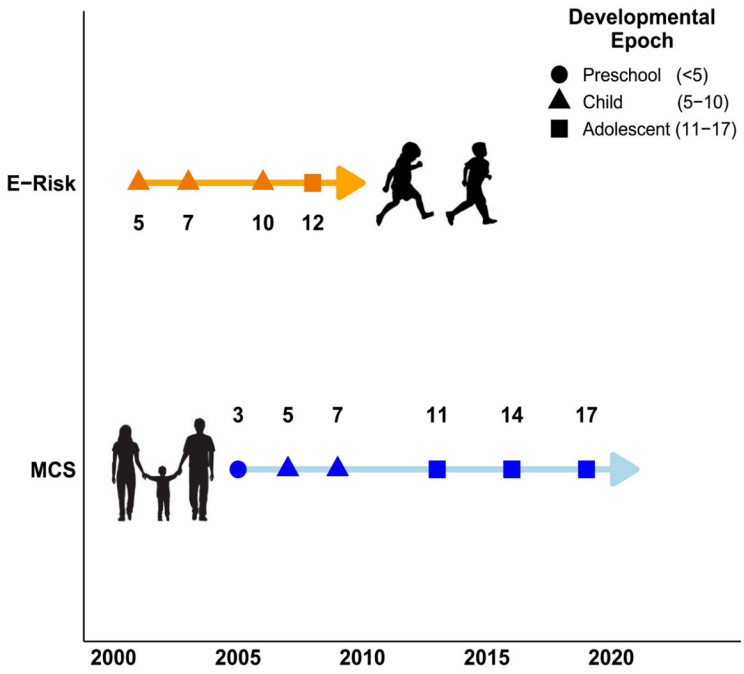

	E-Risk	MCS
Sample Size	862	2,824
Design	Full sibling (dizygotic twins)	Parent-child trios
Cohort Members		
Sex	50% Female	50% Female
Externalizing Behavior Problems	**Child Behavior Checklist** • Aggressive Behavior subscale • Delinquent Behavior subscale	**Strengths & Difficulties Questionnaire** • 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

Figure 1.
Data collection timeline and key study variables.

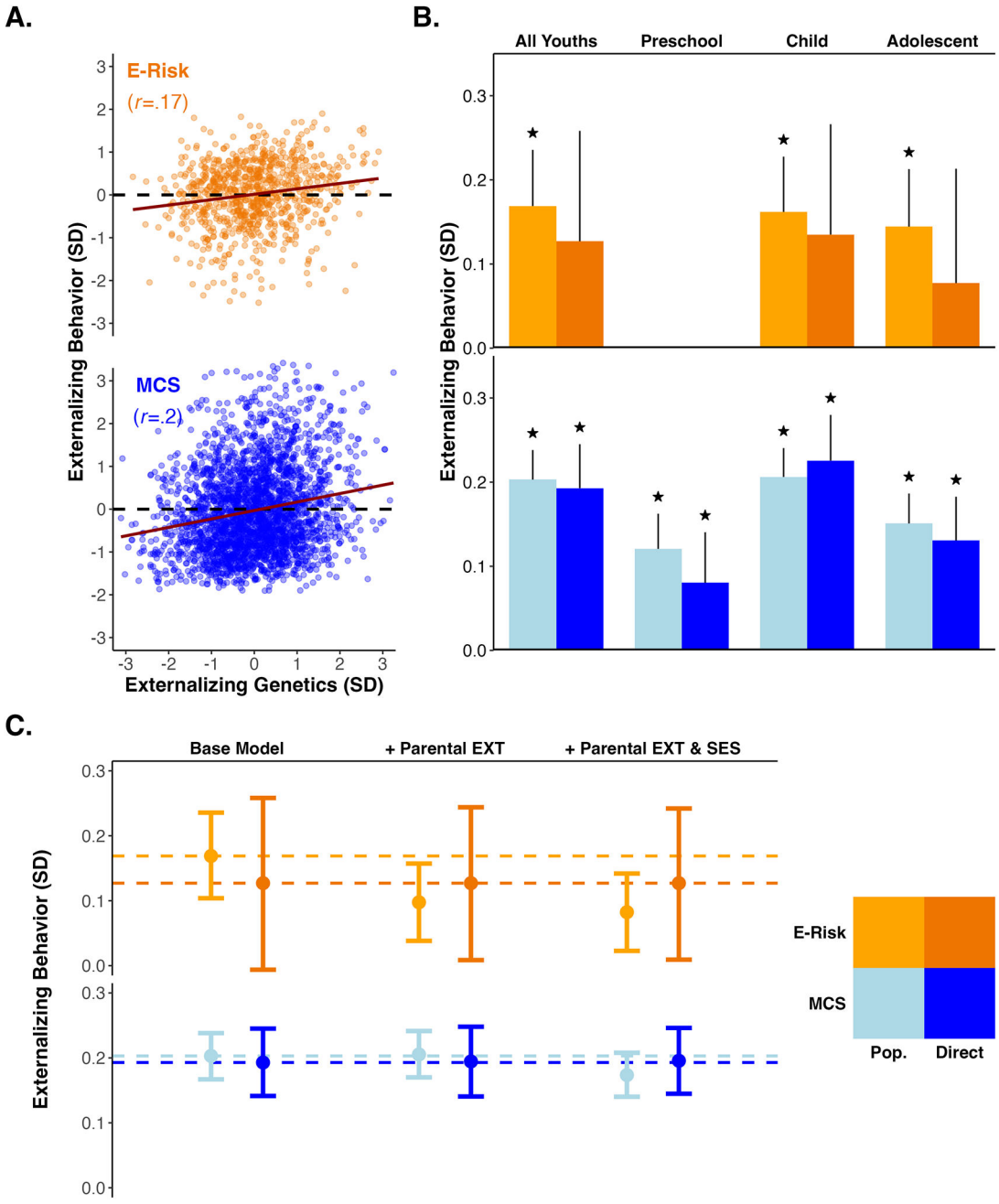

Figure 2.

Panel A. Scatter plots of the genotypic and phenotypic externalizing behavior problems measures in the E-Risk (orange) and MCS (blue) cohorts (trendline = slope of correlation). **Panel B**. Bar plot of the population (lighter orange/blue) and direct genetic effects (darker orange/blue) for the E-Risk and MCS cohorts. Columns include bias-adjusted bootstrapped 95% confidence intervals (reps = 1000); $*P < 0.05$ (null: $\beta = 0$). **Panel C**. Point estimates and bias adjusted bootstrapped 95% confidence intervals (reps = 1000) across three models of progressive covariate adjustment in the E-Risk and MCS cohorts. The "Base Model" includes no additional covariates, the next model includes parental externalizing behavior

problems, and the final model includes parental externalizing behavior problems and parental socioeconomic status. The measure of externalizing behavior problems was derived by pooling observations across all epochs. Dashed horizontal lines provide references for the effect sizes observed in the “Base Model”.

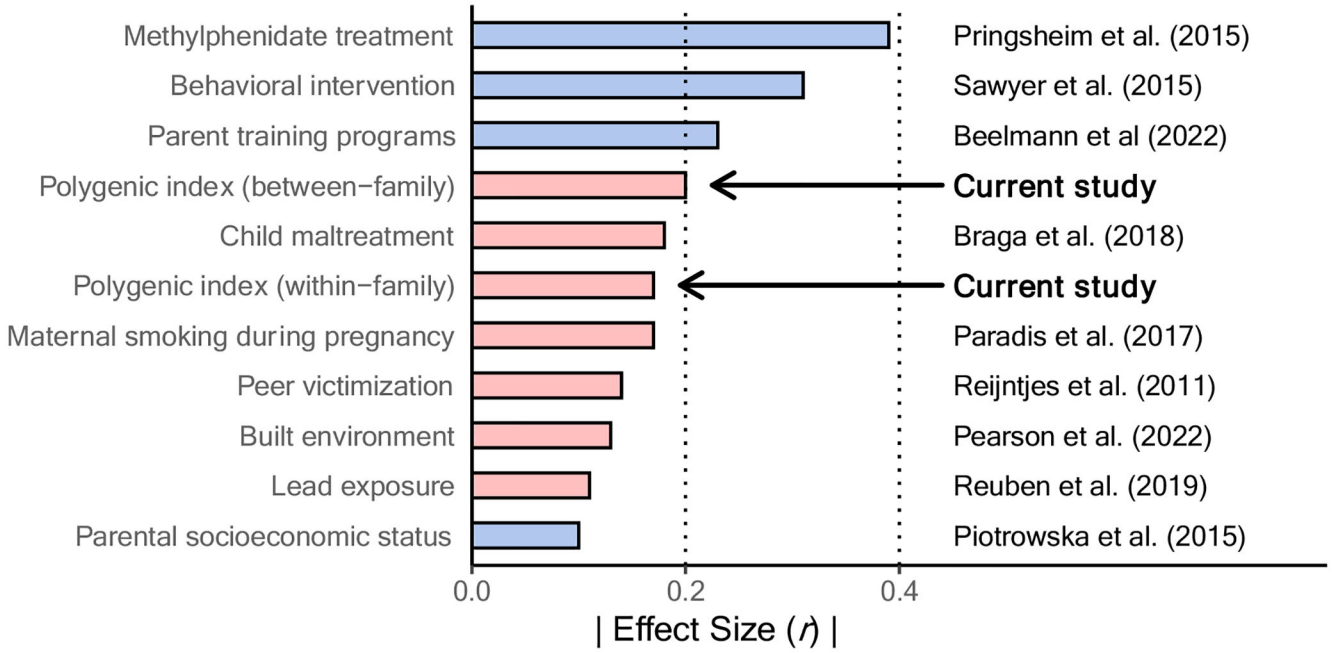

Figure 3.

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-/within-family estimates for the externalizing PGI were taken from the MCS models with data pooled across epochs.

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)			Child (5–10 years)			Adolescent (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)			Child (5–10 years)			Adolescent (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	

* $p<0.05$,

** $p<0.01$,

*** $p<0.001$. *P*-values are FDR-adjusted. Pop. = population genetic effect of the externalizing PGI on externalizing behavior. Direct = within-family coefficient as estimated by a full-sibling (E-Risk) and parent-child trio (MCS) designs. Ratio = direct genetic effect divided by the population effect. STD_{DIFF}= standardized difference.