PREPRINT
STUDY CURRENTLY UNDER REVIEW

Do Low Polygenic Scores Buffer the Effects of Maltreatment? A Polygene-Environment
Interaction Study of ADHD

Quanfa He, B.A.¹ and James J. Li, Ph.D.^{1,2,3}

¹ Department of Psychology, University of Wisconsin-Madison

² Waisman Center, University of Wisconsin-Madison

³ Center for Demography of Health and Aging, University of Wisconsin-Madison

Corresponding author

James J. Li, Ph.D., Department of Psychology, University of Wisconsin-Madison, 1202 West
Johnson Street, Madison, WI, 53706, USA, Email: james.li@wisc.edu, Tel: 1-608-265-1091

Acknowledgements

J.J.L. was supported in part by a core grant to the Waisman Center from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (U54 HD090256) and the Wisconsin Alumni Research Foundation. J.J.L. and Q.H. were also supported by the UW-Madison Center for Human Genomics and Precision Medicine. This research uses data from Add

Health, a program project directed by Kathleen Mullan Harris and designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris at the University of North Carolina at Chapel Hill and funded by grant P01-HD31921 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, with cooperative funding from 23 other federal agencies and foundations. Special acknowledgment is due Ronald R. Rindfuss and Barbara Entwisle for assistance in the original design. Information on how to obtain the Add Health data files is available on the Add Health website (<http://www.cpc.unc.edu/addhealth>). No direct support was received from grant P01-HD31921 for this analysis.

Keywords

Polygenic scores, ADHD, gene-environment interaction, maltreatment, Add Health

Abstract

Objective: This study explored whether maltreatment moderates the association of polygenic risk for ADHD. Because individuals with low polygenic scores (PGS) for ADHD were previously shown to have better than expected functional outcomes (i.e., cognitive, mental health, social-emotional) than individuals with middle or high ADHD PGS, we hypothesized that low ADHD PGS may possible confer a protective effect against maltreatment in the development of ADHD. **Method:** Data were from participants with phenotypic and genotypic data in the National Longitudinal Study of Adolescent to Adult Health (Add Health; $n=4,722$), which was used to examine the effects of ADHD PGS, maltreatment, and their interaction on childhood ADHD symptoms. ADHD PGS were generated from the most recent genome-wide association study on ADHD and categorized into three groups (i.e., low, medium, high) using empirically determined cut-points. A maltreatment factor score was derived from five forms of self-reported maltreatment experiences prior to age 18. **Results:** ADHD PGS and maltreatment were positively associated with ADHD symptoms, as expected. However, we did not detect an interaction between ADHD PGS and maltreatment on ADHD symptoms. **Conclusion:** Despite the increase in predictive power afforded by PGS, the lack of an interaction between ADHD PGS and maltreatment on ADHD symptoms converges with an emerging body of psychiatric PGS studies that have also failed to detect polygenic-environment interplay on psychiatric outcomes. We discuss possible reasons for this pattern of results and offer alternative methods for future research in revealing important polygenic-environment interactions for ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects 5-10% of youths and young adults globally ¹. Although maltreatment is a potent risk factor in the development of ADHD ², not all maltreated individuals go on to develop ADHD ^{3,4}. The current study leverages powerful genetic methods using genome-wide information to test the hypothesis that polygenic liability for ADHD might moderate the negative effects of maltreatment in the development of ADHD in a large, population-based dataset.

Genes play a substantial role in the origins of ADHD. Twin studies suggest that approximately 70-80% of the variance in ADHD can be attributed to broad-band genetic differences among individuals ⁵. Genome-wide association studies (GWAS) have shown that common genetic variants via single nucleotide polymorphisms (SNPs) account for a substantial part of this heritability, although the individual SNPs themselves may only contribute a small to negligible amount of the variance in ADHD ^{6,7}. Researchers are increasingly using approaches that aggregate the effects of common genetic variants (i.e., polygenic scores, PGS), which represent each person's genetic liability based on the weighted sum of the alleles across the variants that contribute to a trait in question. Higher ADHD PGS are consistently and robustly associated with ADHD symptoms and diagnosis across a wide range of populations, including clinical as well as population-based samples (see meta-analysis by Li and He ⁸).

However, ADHD PGS may reflect more than simply one's genetic risk for ADHD. Using data from the National Longitudinal Study of Adolescent to Adult Health (Add Health), Li ⁹ found that individuals at the lowest end of the ADHD PGS distribution (i.e., in the bottom 20th percentile) had a 17-19% lower risk for ADHD, but they also had significantly higher IQ and educational attainment, and lower risks for other mental (e.g., fewer depressive symptoms) and

physical health outcomes (e.g., lower BMI) compared to individuals in the middle (i.e., 21st to 79th percentiles) and highest ends of the ADHD PGS distribution (i.e., top 80th percentile). These results suggest that a low burden of genetic risk for ADHD may have beneficial or possibly protective effects on various functional outcomes ⁹. This finding also highlights an important follow-up inquiry as it pertains to gene-environment interplay – can having a low ADHD PGS also protect against the negative effects of adverse environments, such as maltreatment, in the development of ADHD? The current study addresses this question.

Maltreatment confers a significant risk in the development of ADHD ^{10,11}. The negative effect of maltreatment on child ADHD is consistently observed across the types of maltreatment (e.g., neglect, abuse), sex of participants, sampling methods (e.g., nationally-representative sample, community sample, online survey), and retrospective and prospective studies ^{2,12,13}. However, less known is the extent to which ADHD PGS may moderate the negative effects of maltreatment on ADHD. Prior ADHD studies on gene-environment interactions have focused on candidate genes (e.g., *COMT*, *DRD4*, *MAOA*) and their interactive effects on various adverse childhood environments (e.g., childhood trauma, and negative parenting behavior) related to ADHD and antisocial outcomes in children ^{14–16}. However, candidate gene-environment interaction studies are currently viewed with skepticism due to their focus on only a single or a few candidate genes that likely have small to null effects on complex phenotypes ^{17,18}. There remains a critical lack of gene-environment interaction studies that have utilized contemporary and more powerful genetic methods (i.e., PGS) in ADHD research.

The current study used data from Add Health to test the hypothesis that ADHD PGS moderates the association between maltreatment and ADHD symptoms. Based on prior work showing that individuals with low ADHD PGS may not only have lower rates of ADHD, but also

have better cognitive performance and mental and physical health outcomes compared to individuals with medium and high ADHD PGS⁹, we hypothesized that individuals with low ADHD PGS would be protected from the negative effects of maltreatment (as it pertains to their ADHD symptoms) relative to those with medium and high ADHD PGS.

Method

Participants

Add Health is sample of adolescents from grades 7-12 who were recruited from high schools across the United States. Data were collected from adolescents, their caregivers, peers at school, school administrators, siblings, and romantic partners across five Waves: Wave I (1994–1995, grades 7–12, N=20,745), Wave II (1995–1996, grades 8–12, N = 14,738), Wave III (2001–2002, ages 18–26, N = 15,197), Wave IV (2007–2008, ages 24–32, N = 15,701) and Wave V (2016-2018, ages 34-43, N=12,000). To account for potential population stratification effects, as well as to reduce concerns regarding the poorer predictive performance of health-related PGS when applied to non-European ancestry populations¹⁹, the current analysis focused on Add Health individuals of European ancestry for whom phenotypic and genetic data were available ($n=4,722$). See Table 1 for descriptive statistics of key demographic variables and other study variables.

Measures

ADHD Symptoms. Participants retrospectively self-reported their ADHD symptoms at Wave III. Participants responded to 17 items on a 4-point Likert scale, describing how often a symptom “best describes your behavior when you were (between 5 and 12)”. Responses are dichotomized as presence (i.e., ‘*sometimes*’, ‘*often*’, ‘*very often*’), or absence (i.e., ‘*never*’) of that symptom. The symptoms were keyed to the *Diagnostic and Statistical Manual of Mental*

*Disorders*²⁰. ADHD total symptoms were computed by summing the number of positively endorsed symptoms.

Maltreatment. Maltreatment was retrospectively self-reported by participants at Wave III and Wave IV. Participants rated on a 6-point Likert scale regarding the frequency of five types of maltreatment experiences during childhood (i.e., prior to age 18), including physical abuse (“being slapped, hit or kicked by parents or other adult caregivers”), sexual abuse (“parents or adult caregivers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations”), emotional abuse (“a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved”), physical neglect (“parents or other adult caregivers not taken care of your basic needs, such as keeping you clean or providing food or clothing”), and emotional neglect (“parents or other adult caregivers left you home alone when an adult should have been with you”). Possible responses range from 1 (i.e., *one time*) to 5 (i.e., *over ten times*), and 6 represents “never happened”. A response of 6 was recoded to 0. Each maltreatment item was then dichotomized into presence or absence using a cut-off score for each item as established in a previous study²¹. Specifically, each type of maltreatment was present (versus absent) if its reported frequency was three or more times for physical abuse, one or more times for sexual abuse, ten or more times for emotional abuse, two or more times for physical neglect, and ten or more times for emotional neglect. Per empirical precedent²¹, a latent factor score for maltreatment was computed (see Dimension Reduction section for details).

Dimension Reduction

We computed a latent factor score for maltreatment based on a confirmatory factor analysis of the frequencies of the five types of maltreatment. Maximum likelihood estimation

was used for the CFA. Model fit was evaluated by comparative fit index (CFI), Tucker-Lewis index (TLI), and the root mean squared error of approximation (RMSEA). CFI and TLI values greater than .90 and RMSEA values less than .06 generally indicate “acceptable” model fit ²². A one-factor model fit the data well (CFI=.936, TLI=.872, RMSEA=.054, $\chi^2(5)=169.806$).

Individuals whose maltreatment factor score was 1 standard deviation higher than the mean had 1.133 times more ADHD symptoms ($b=.125$, $se=.028$, 95% CI= [.07, .18], $\chi^2(1)=20.621$, $p<.001$). The maltreatment latent factor score had higher explanatory power compared to the cumulative composite of maltreatment in a separate study using the same Add Health data ²¹. In the current study, the maltreatment factor score explained 4.78% of the variance in ADHD symptoms, whereas the cumulative composite explained 4% of the variance, after accounting for covariates (see Statistical Analyses section for details of the covariates).

Genotyping and Quality Control

Saliva samples were collected from consenting participants at Wave IV (96% of all Wave IV participants). Genotyping was done on two Illumina platforms (i.e., Omni-Quad BeadChip and Omni2.5-Quad BeadChip), and quality control (QC) procedures were carried out. Filtering by missing call rate of .02, Hardy-Weinberg Equilibrium of .0001, and minor allele frequency of .01, 346,754 single nucleotide polymorphisms (SNPs) carried through to imputation.

European genetic samples were imputed on Release 1 of the Human Reference Consortium (HRS r1.1). Additional details of the quality control are available online

(https://www.cpc.unc.edu/projects/addhealth/documentation/guides/AH_GWAS_QC.pdf)

Polygenic Scores (PGS) for ADHD

Per convention ²³, ADHD PGS for each Add Health individual were computed as the sum of the number of alleles weighted by their GWAS effect sizes. We employed the most recent and

largest ADHD GWAS to date, a case-control meta-analysis that consisted of 55,374 children and adults (20,183 cases and 35,191 controls) from 12 studies of mixed (but predominantly European) ancestries ⁶. The largest cohort among these 12 studies is a population-based case-control cohort in Denmark (iPSYCH; 14,584 cases and 22,492 controls). The other 11 case-control or trio samples were collected in Europe, Canada, United States and China, and aggregated by the Psychiatric Genomic Consortium (PGC). ADHD case status was determined based on International Classification of Diseases, tenth revision (ICD-10) in iPSYCH, and semi-structured clinical interviews (e.g., Schedule for Affective Disorders and Schizophrenia for School-Age Children, K-SADS) in the other 11 cohorts. As mentioned previously, because we focused on the European-ancestry subset of Add Health, we computed ADHD PGS based on the European-ancestry subset of the GWAS (totaling 19,099 cases and 34,194 controls) ⁶.

ADHD PGS was computed in *PRSice2* software in *R* ²⁴. We applied a *p*-value threshold of 1.0, as this included all available genetic information while downweighing SNPs with null or marginal effect sizes. Furthermore, this threshold specifically avoids “cherry picking” via biased model selection and arbitrary *p*-value threshold cutoffs based on variances explained ⁸. “Low”, “medium” and “high” ADHD PGS were derived in the following way. Following prior studies ^{9,25}, we compared five pairs of percentile cut-points (i.e., lowest group being 5%, 10%, 15%, 20%, and 25%). ADHD PGS were dummy coded according to each pair of cut-points (e.g., 0-5% was low group and coded as 0, 6-94% was medium group and coded as 1, 95%-100% was high group and coded as 2). ADHD symptom counts were regressed on the dummy coded PGS variable, covarying out the effects of sex, age and 10 genetic PCs. The pairs of cut-points that provided the best model fit (by percent of variance explained in ADHD symptoms) were chosen as the optimal cut-points for “low”, “medium” and “high” PGS. Model fit statistics that we

considered included AIC, BIC and r^2 . Statistical significance was evaluated by Wald Chi-square test, and Likelihood Ratio Test (LRT). Omnibus test statistics as well as model fit indices are presented in Table 2, where the best-fitting PGS cut-points were at the lowest 25th, middle 26th-75th, and highest 75th percentiles. As expected, dummy-coded ADHD PGS were significantly associated with ADHD symptoms ($\chi^2=8.953$, $p=.011$; $LRT(2)=9.576$, $p=.008$; $r^2=.084$). In *post-hoc* group comparison by PGS percentile groups, where the lowest 25th PGS percentile served as the reference group, being in the medium (26th-75th) percentile group increased the log of expected number of symptoms by .187 (95%CI=[.059, .314]), and being in the high (top 75th) percentile group increased the log of expected number of symptoms by .205 (95%CI=[.043, .366]).

Statistical Analyses

First, ADHD symptom counts were regressed on ADHD PGS (i.e., low, medium and high groups derived as described in the previous section) and the maltreatment latent factor score (i.e., henceforth referred to as the maltreatment score), covarying out effects of sex, and age, parental education and parental income at Wave I. We also covaried the first 10 genetic principal components (PCs) in our models to further account for the possibility of population stratification within the Add Health European-ancestry subsample. We controlled for parental education and parental income because they have been shown to associate with offspring ADHD²⁶. After testing the main effects model, we added a term for the interaction between ADHD PGS and the maltreatment score. A Wald chi-square test was used to determine the statistical significance of each of predictor. For ADHD PGS and the interaction term, significant chi-square statistics were followed with *post-hoc* analyses of between-group comparisons. To account for overdispersion and zero-inflation in the outcome variable (i.e., ADHD symptoms), zero-inflated negative

binomial models were fit for all analyses. The models also adjusted for sample weights, region stratification, and treated schools as the cluster variable for multi-level modeling. Finally, we conducted secondary analyses using a continuous ADHD PGS to check the robustness of our results that utilized a categorical ADHD PGS.

Results

Descriptive Statistics

Descriptive statistics (by PGS categories) are provided in Table 1. As expected, there were significant differences among the three PGS groups in ADHD symptoms ($F(2, 4719)=10.39, p<.001$). Individuals in the high PGS group had more ADHD symptoms relative to low PGS group (Δ symptoms=.667, 95% CI=[.37, .96], $p<.001$). Group differences in the maltreatment score were significant as well ($F(2,4291)=3.213, p=.040$); the high PGS group had higher maltreatment scores relative to the low PGS group (Δ maltreatment=.090, 95%CI=[.01, .17], $p=.034$). Significant group differences were also detected in physical neglect, physical abuse, and psychological abuse, but not for psychological neglect or sexual abuse. That is, individuals with high PGS were more likely to report physical neglect (OR=1.598, 95%CI=[1.11, 2.34], $p=.014$), physical abuse (OR=1.383, 95%CI=[1.09, 1.77], $p=.008$), and psychological abuse (OR=1.426, 95%CI=[1.12, 1.84], $p=.005$). Parental education level also differed across the three PGS groups ($F(2,4260)=6.906, p=.001$) such that those in the low PGS group had parents with higher educational levels compared to those with higher PGS. Household income, age and biological sex did not differ by PGS groups.

Interaction of ADHD PGS and Maltreatment Score on ADHD Symptoms

In the main effects only model, ADHD PGS were positively associated with ADHD symptoms ($\chi^2=11.337, p=.009$). The maltreatment score was also positively associated with ADHD symptoms ($\chi^2=24.896, p<.001$). The main effects model provided a significantly better fit

to the data than a model with just the covariates alone ($LRT(3)=34.859, p<.001$; Table 3).

However, the interaction between ADHD PGS and maltreatment did not predict ADHD symptoms ($\chi^2=1.377, p=.502$) (see Figure 1). The full model with the interaction of ADHD PGS and maltreatment score provided no improvement to model fit ($\Delta LRT(2)=1.354, \Delta AIC=2.65, \Delta BIC=15.89, \Delta R^2=.001$; Table 3).

Secondary Analysis with a Continuous ADHD PGS

To account for the possible loss of variance with a categorical ADHD PGS (i.e., low, medium and high groups) in our prior models, we tested parallel analytic models using a more conventional continuous ADHD PGS instead. The results from these models were entirely consistent with the models that used the categorical ADHD PGS.

In the main effects only model, continuous ADHD PGS were positively associated with ADHD symptoms ($b=.074, s.e.=.025, \chi^2=8.493, p=.004$). The maltreatment score was also positively associated with ADHD symptoms ($b=.130, s.e.=.027, \chi^2=23.489, p<.001$). The full model with the interaction term provided minimal improvement in model fit ($\Delta LRT(1)=.315, \Delta AIC=1.69, \Delta BIC=7.81, \Delta R^2<.001$; Table 4) over the main effects only model. The interaction between ADHD PGS and the maltreatment score was not significant ($b=.010, s.e.=.018, \chi^2=.315, p=.575$).

Discussion

Following on prior findings⁹ using Add Health data, the current study tested the hypothesis that individuals with low ADHD PGS may be protected from the negative effects of maltreatment (as it pertains to their ADHD symptoms) relative to those with medium and high ADHD PGS. While we found positive associations of ADHD PGS and maltreatment on ADHD symptoms, no interaction between the two were detected.

Despite the drastic increase in predictive power afforded by the PGS approach (relative to the candidate gene approach), we did not find evidence to support our hypothesis that ADHD PGS moderates one's sensitivity to maltreatment in relation to ADHD symptoms. This finding is consistent with another recent study that also found no significant interaction between ADHD PGS and a range of environmental risk factors including parental psychiatric history, education, working status and income in ADHD in a large case-control sample in Denmark ²⁷. Other researchers have also reported either null or generally inconsistent findings between PGS and environmental risk factors on psychiatric outcomes more broadly ²⁸. For example, a meta-analysis of major depressive disorder (MDD) found no interaction involving childhood trauma and MDD PGS ²⁹, while another study found a negative interaction between MDD PGS and childhood trauma ³⁰ (i.e., lower MDD PGS associated with *enhanced* negative effects of childhood adversity on MDD). Yet another recent study found no interaction between schizophrenia PGS and childhood adversity in other psychotic disorders ³¹. Our finding adds to a growing body of psychiatric genetics literature that even the use of more powerful PGS approaches may not reliably detect gene-environment interaction effects for psychiatric outcomes as previously expected ¹⁷.

We use our findings to advance alternative considerations for gene-environment interaction studies of ADHD and psychiatric outcomes more broadly. For example, gene-environment interactions may be better elucidated if we focused on endophenotypes, which are more proximal to the etiology of ADHD and possibly even more susceptible to environmental influences than psychiatric outcomes *per se* ^{32,33}. In ADHD research, studies have shown that response inhibition moderated psychosocial risks, such that individuals with faster response inhibition are less likely to develop ADHD and ODD in the presence of family adversity

compared to those with slower response inhibition³⁴. Similarly, in a sample enriched for children with ADHD, slower response inhibition increased the negative effects of low social preference and high relational aggression in childhood on future exposure to intimate partner violence, compared to faster response inhibition³⁵. Another recent study found that slow response inhibition exacerbated the effect of sleep problem on hyperactivity symptoms in a longitudinal sample of children, compared to faster response inhibition³⁶. As neuropsychological endophenotypes like response inhibition are also quite heritable³⁷, it stands to reason that genetic factors underlying response inhibition may also help to shed light on how environmental influences can impact the expression of downstream consequences of poor response inhibition, which not only include ADHD, but also substance abuse³⁸, bipolar disorder³⁹, and autism spectrum disorder⁴⁰. Future studies might benefit from investigating PGS for endophenotypes in gene-environment interaction models of related psychiatric outcomes.

Additionally, conventional PGS may not represent “pure” genetic risks for psychopathology in the first place, making them a challenge to interpret in gene-environment models. Genetic variants identified in GWAS are variants that were directly transmitted from the parents that convey a direct (i.e., biologically mediated) role on the offspring’s phenotype. However, emerging evidence from family-based studies indicate that GWAS estimates also incorporate the effects of non-transmitted genotypes from both parents as well^{41,42}. This is referred to as “genetic nurture” because the uninherited parental genotypes can impact one’s phenotype indirectly through the effects of the home environment. Thus, conventional PGS for psychiatric outcomes may have already incorporated critical environmental signals via indirect effects from non-transmitted parental genotypes, which may confound or possibly attenuate potential gene-environment interaction effects. For example, a recent study found that only a

direct effect ADHD PGS was associated with ADHD (and not the indirect effect PGS), suggesting that genetic risk in ADHD is mainly (although not entirely) accounted for by the transmitted genotypes from parents rather than non-transmitted parental genotypes⁴³. Future PGS-environment interaction studies should separately compute the direct and the indirect effects of psychiatric PGS. Although large-scale and genetically informed family-based datasets are still relatively rare, new statistical methods are becoming available for disentangling direct and indirect genetic effects in GWAS (e.g., Wu et al⁴⁴). We predict that these applications will be forthcoming in the gene-environment literature for psychiatric outcomes.

A few study limitations are also noteworthy. First, we focused our analysis to individuals of European ancestry. Some studies suggest that trans-ethnic PGS predictions are likely inaccurate and misrepresent the true association between genetic risk and a wide range of phenotypes (e.g., Duncan et al¹⁹). Thus, we await more diverse and larger genotyped samples to better address the growing racial-ethnic disparity in psychiatric genetics research. Second, we did not test for sex differences in the interactive effects of ADHD PGS and maltreatment given that our investigation was likely underpowered to do so. There are clear sex differences in the prevalence of ADHD (e.g., Carboneau et al⁴⁵), and while Martin et al⁴⁶ recently showed no differences in mean ADHD PGS between males and female cases in the PGC, iPSYCH, as well as a registry-based Swedish sample, it remains unknown whether there may be sex-specific ADHD PGS x environment interactions for ADHD. Third, both ADHD symptoms and maltreatment were retrospectively reported when individuals were young adults. Retrospective reports may be influenced by recall bias or inaccurate reporting, which could contribute to null or false findings^{47,48}. However, while objective records of maltreatment (e.g., social service involvement) may have increased the validity of our measure, these records are not without

limitations given that underreporting, detection bias and their low concordance with self-reports make them a challenge to interpret in population-based studies like Add Health^{47,49}. Finally, ADHD was only examined retrospectively at Wave III, thus precluding our ability to examine trajectories of ADHD development over time. Developmental considerations in gene-environment interaction studies of psychopathology are important, yet understudied in the literature⁵⁰.

In summary, our study found no evidence of an interaction between ADHD PGS and maltreatment in ADHD symptoms in a sample of nationally representative adolescents followed longitudinally. Despite the increase in predictive power that PGS approaches afford, our finding highlights the continued complexity of studying gene-environment interactions for psychiatric outcomes, including ADHD. We are optimistic that approaches that leverage existing theories with new methods, including a focus on endophenotypes and disentangling genetic nurture from GWAS effects, will aid future studies.

References

1. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. *J Clin Child Adolesc Psychol.* 2018;47(2):199-212. doi:10.1080/15374416.2017.1417860
2. González RA, Vélez-Pastrana MC, McCrory E, et al. Evidence of concurrent and prospective associations between early maltreatment and ADHD through childhood and adolescence. *Soc Psychiatry Psychiatr Epidemiol.* 2019;54(6):671-682. doi:10.1007/s00127-019-01659-0
3. Tabone JK, Guterman NB, Litrownik AJ, et al. Developmental Trajectories of Behavior Problems Among Children Who Have Experienced Maltreatment: Heterogeneity During Early Childhood and Ecological Predictors. *J Emot Behav Disord.* 2011;19(4):204-216. doi:10.1177/1063426610383861
4. Yoon S. Fostering Resilient Development: Protective Factors Underlying Externalizing Trajectories of Maltreated Children. *J Child Fam Stud.* 2018;27(2):443-452. doi:10.1007/s10826-017-0904-4
5. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry.* 2019;24(4):562-575. doi:10.1038/s41380-018-0070-0
6. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet.* 2019;51(1):63-75. doi:10.1038/s41588-018-0269-7
7. Pettersson E, Lichtenstein P, Larsson H, et al. Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls. *Psychol Med.* 2019;49(7):1166-1173. doi:10.1017/S0033291718002039
8. Li JJ, He Q. Polygenic Scores for ADHD: A Meta-Analysis. *Res Child Adolesc Psychopathol.* Published online January 25, 2021. doi:10.1007/s10802-021-00774-4
9. Li JJ. The positive end of the polygenic score distribution for ADHD: a low risk or a protective factor? *Psychol Med.* Published online October 29, 2019:1-10. doi:10.1017/S0033291719003039
10. Briscoe-Smith AM, Hinshaw SP. Linkages Between Child Abuse and Attention-Deficit/Hyperactivity Disorder in Girls: Behavioral and Social Correlates. *Child Abuse Negl.* 2006;30(11):1239-1255. doi:10.1016/j.chiabu.2006.04.008
11. Sanderud K, Murphy S, Elklit A. Child maltreatment and ADHD symptoms in a sample of young adults. *Eur J Psychotraumatology.* 2016;7. doi:10.3402/ejpt.v7.32061
12. Clayton K, Lee JB, Cheung K, Theule J, Henrikson B. Quantifying the Relationship

- between Attention-Deficit/Hyperactivity Disorder and Experiences of Child Maltreatment: A Meta-Analysis. *Child Abuse Rev.* 2018;27(5):361-377. doi:10.1002/car.2530
13. Stern A, Agnew-Blais J, Danese A, et al. Associations between abuse/neglect and ADHD from childhood to young adulthood: A prospective nationally-representative twin study. *Child Abuse Negl.* 2018;81:274-285. doi:10.1016/j.chiabu.2018.04.025
 14. Li JJ, Lee SS. Association of Positive and Negative Parenting Behavior with Childhood ADHD: Interactions with Offspring Monoamine Oxidase A (MAO-A) Genotype. *J Abnorm Child Psychol.* 2012;40(2):165-175. doi:10.1007/s10802-011-9553-z
 15. Nigg J, Nikolas M, Burt SA. Measured Gene by Environment Interaction in Relation to Attention-Deficit/Hyperactivity Disorder (ADHD). *J Am Acad Child Adolesc Psychiatry.* 2010;49(9):863-873. doi:10.1016/j.jaac.2010.01.025
 16. Park S, Kim B-N, Kim J-W, Shin M-S, Yoo HJ, Cho S-C. Interactions Between Early Trauma and Catechol-O-Methyltransferase Genes on Inhibitory Deficits in Children With ADHD. *J Atten Disord.* 2017;21(3):183-189. doi:10.1177/1087054714543650
 17. Dick DM, Agrawal A, Keller MC, et al. Candidate Gene–Environment Interaction Research: Reflections and Recommendations. *Perspect Psychol Sci.* 2015;10(1):37-59. doi:10.1177/1745691614556682
 18. Duncan LE, Ostacher M, Ballon J. How genome-wide association studies (GWAS) made traditional candidate gene studies obsolete. *Neuropsychopharmacology.* 2019;44(9):1518-1523. doi:10.1038/s41386-019-0389-5
 19. Duncan L, Shen H, Gelaye B, et al. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat Commun.* 2019;10(1):1-9. doi:10.1038/s41467-019-11112-0
 20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th Ed.)*. Arlington, VA: Author; 2013. Accessed September 11, 2019. <https://www.psychiatry.org/psychiatrists/practice/dsm>
 21. Brumley LD, Brumley BP, Jaffee SR. Comparing cumulative index and factor analytic approaches to measuring maltreatment in the National Longitudinal Study of Adolescent to Adult Health. *Child Abuse Negl.* 2019;87:65-76. doi:10.1016/j.chiabu.2018.08.014
 22. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Struct Equ Model Multidiscip J.* 1999;6(1):1-55. doi:10.1080/10705519909540118
 23. International Schizophrenia Consortium, Purcell SM, Wray NR, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature.* 2009;460(7256):748-752. doi:10.1038/nature08185
 24. Choi SW, O'Reilly PF. PRSice-2: Polygenic Risk Score software for biobank-scale data.

- GigaScience*. 2019;8(7). doi:10.1093/gigascience/giz082
25. Fang Y, Scott L, Song P, Burmeister M, Sen S. Genomic prediction of depression risk and resilience under stress. *Nat Hum Behav*. Published online October 28, 2019. doi:10.1038/s41562-019-0759-3
 26. Russell AE, Ford T, Williams R, Russell G. The Association Between Socioeconomic Disadvantage and Attention Deficit/Hyperactivity Disorder (ADHD): A Systematic Review. *Child Psychiatry Hum Dev*. 2016;47(3):440-458. doi:10.1007/s10578-015-0578-3
 27. Østergaard SD, Trabjerg BB, Als TD, et al. Polygenic risk score, psychosocial environment and the risk of attention-deficit/hyperactivity disorder. *Transl Psychiatry*. 2020;10(1):1-11. doi:10.1038/s41398-020-01019-6
 28. Lewis CM, Vassos E. Polygenic risk scores: from research tools to clinical instruments. *Genome Med*. 2020;12(1):44. doi:10.1186/s13073-020-00742-5
 29. Peyrot WJ, Van der Auwera S, Milaneschi Y, et al. Does Childhood Trauma Moderate Polygenic Risk for Depression? A Meta-analysis of 5765 Subjects From the Psychiatric Genomics Consortium. *Biol Psychiatry*. 2018;84(2):138-147. doi:10.1016/j.biopsych.2017.09.009
 30. Mullins N, Power RA, Fisher HL, et al. Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. *Psychol Med*. 2016;46(4):759-770. doi:10.1017/S0033291715002172
 31. Trotta A, Iyegbe C, Di Forti M, et al. Interplay between schizophrenia polygenic risk score and childhood adversity in first-presentation psychotic disorder: A pilot study. *PLoS ONE*. 2016;11(9). Accessed February 7, 2020. <http://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,uid&db=psyh&AN=2016-47244-001&site=ehost-live&scope=site>
 32. Gottesman II, Gould TD. The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *Am J Psychiatry*. 2003;160(4):636-645. doi:10.1176/appi.ajp.160.4.636
 33. Rose EJ, Donohoe G. Brain vs Behavior: An Effect Size Comparison of Neuroimaging and Cognitive Studies of Genetic Risk for Schizophrenia. *Schizophr Bull*. 2013;39(3):518-526. doi:10.1093/schbul/sbs056
 34. Nigg J, Nikolas M, Friderici K, Park L, Zucker RA. Genotype and Neuropsychological Response Inhibition as Resilience Promoters for ADHD, ODD, and CD under Conditions of Psychosocial Adversity. *Dev Psychopathol*. 2007;19(3):767-786. doi:10.1017/S0954579407000387
 35. Youn C, Meza JI, Hinshaw SP. Childhood Social Functioning and Young Adult Intimate Partner Violence in Girls With and Without ADHD: Response Inhibition as a Moderator. *J Atten Disord*. 2019;23(12):1486-1496. doi:10.1177/1087054718778119

36. Kidwell KM, Hankey M, Nelson JM, Espy KA, Nelson TD. Child Executive Control as a Moderator of the Longitudinal Association Between Sleep Problems and Subsequent Attention-Deficit/Hyperactivity Disorder Symptoms. *J Pediatr Psychol*. 2017;42(10):1144-1155. doi:10.1093/jpepsy/jsx071
37. Crosbie J, Arnold P, Paterson A, et al. Response Inhibition and ADHD Traits: Correlates and Heritability in a Community Sample. *J Abnorm Child Psychol*. 2013;41(3):497-507. doi:10.1007/s10802-012-9693-9
38. Groman SM, James AS, Jentsch JD. Poor response inhibition: At the nexus between substance abuse and attention deficit/hyperactivity disorder. *Neurosci Biobehav Rev*. 2009;33(5):690-698. doi:10.1016/j.neubiorev.2008.08.008
39. Roberts G, Green MJ, Breakspear M, et al. Reduced Inferior Frontal Gyrus Activation During Response Inhibition to Emotional Stimuli in Youth at High Risk of Bipolar Disorder. *Biol Psychiatry*. 2013;74(1):55-61. doi:10.1016/j.biopsych.2012.11.004
40. Geurts HM, Bergh SFWM van den, Ruzzano L. Prepotent Response Inhibition and Interference Control in Autism Spectrum Disorders: Two Meta-Analyses. *Autism Res*. 2014;7(4):407-420. doi:https://doi.org/10.1002/aur.1369
41. Kong A, Thorleifsson G, Frigge ML, et al. The nature of nurture: Effects of parental genotypes. *Science*. 2018;359(6374):424-428. doi:10.1126/science.aan6877
42. Young AI, Benonisdottir S, Przeworski M, Kong A. Deconstructing the sources of genotype-phenotype associations in humans. *Science*. 2019;365(6460):1396-1400. doi:10.1126/science.aax3710
43. de Zeeuw EL, Hottenga J-J, Ouwens KG, et al. Intergenerational Transmission of Education and ADHD: Effects of Parental Genotypes. *Behav Genet*. Published online February 6, 2020. doi:10.1007/s10519-020-09992-w
44. Wu Y, Zhong X, Lin Y, et al. Estimating genetic nurture with summary statistics of multi-generational genome-wide association studies. *bioRxiv*. Published online January 1, 2020:2020.10.06.328724. doi:10.1101/2020.10.06.328724
45. Carbonneau M, Demers M, Bigras M, Guay M-C. Meta-Analysis of Sex Differences in ADHD Symptoms and Associated Cognitive Deficits. *J Atten Disord*. Published online June 4, 2020:1087054720923736. doi:10.1177/1087054720923736
46. Martin J, Walters RK, Demontis D, et al. A Genetic Investigation of Sex Bias in the Prevalence of Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry*. 2018;83(12):1044-1053. doi:10.1016/j.biopsych.2017.11.026
47. Osborn M, Widom CS. Do documented records and retrospective reports of childhood maltreatment similarly predict chronic inflammation? *Psychol Med*. 2020;50(14):2406-2415. doi:10.1017/S0033291719002575

48. von Wirth E, Mandler J, Breuer D, Döpfner M. The Accuracy of Retrospective Recall of Childhood ADHD: Results from a Longitudinal Study. *J Psychopathol Behav Assess*. Published online December 7, 2020. doi:10.1007/s10862-020-09852-1
49. Widom CS, Czaja SJ, DuMont KA. Intergenerational transmission of child abuse and neglect: Real or detection bias? *Science*. 2015;347(6229):1480-1485. doi:10.1126/science.1259917
50. Li JJ. Assessing phenotypic and polygenic models of ADHD to identify mechanisms of risk for longitudinal trajectories of externalizing behaviors. *J Child Psychol Psychiatry*. 2019;60(11):1191-1199. doi:10.1111/jcpp.13071

Table 1.

Descriptive statistics comparing high, medium, and low ADHD PGS groups

	ADHD PGS Groups (high, medium, and low)			F or Chi-square	<i>p</i> -value
	Low (<i>n</i> =1,181)	Medium (<i>n</i> =2,360)	High (<i>n</i> =1,181)		
ADHD symptoms (M, SD)	2.78 (<i>sd</i> =3.38)	3.22 (<i>sd</i> =3.62)	3.45 (<i>sd</i> =3.89)	F(2, 4719)=10.39	<.001
Psychological neglect (%)	83 (7.52%)	187 (8.37%)	77 (6.87%)	$\chi^2=2.495$	.287
Physical neglect (%)	48 (4.21%)	123 (5.39%)	75 (6.56%)	$\chi^2=6.188$	.045
Physical abuse (%)	135 (11.89%)	328 (14.37%)	180 (15.73%)	$\chi^2=7.218$	.027
Sexual abuse (%)	44 (3.83%)	90 (3.91%)	60 (5.19%)	$\chi^2=3.659$	.160
Psychological abuse (%)	123 (10.46%)	324 (13.90%)	167 (14.29%)	$\chi^2=9.934$	.007
Parental education (0-9)	6.010 (<i>sd</i> =2.12)	5.810 (<i>sd</i> =2.12)	5.670 (<i>sd</i> =2.14)	F(2,4260)=6.906	.001
Less than HS (0-3)	90 (7.62%)	208 (8.81%)	120 (10.16%)	-	-
HS (4-5)	319 (27.01%)	684 (28.98%)	371 (31.41%)	-	-
Some college (6-7)	338 (28.62%)	698 (29.58%)	331 (28.03%)	-	-
College + (8-9)	325 (27.52%)	522 (22.12%)	257 (21.76%)	-	-
Household income (in	53.90 (<i>sd</i> =48.42)	53.06 (<i>sd</i> =56.17)	49.93 (<i>sd</i> =48.17)	F(2,4230)=.227	.797

thousands)					
Age	15.99 (<i>sd</i> =1.39)	16.04 (<i>sd</i> =1.38)	15.97 (<i>sd</i> =1.40)	F(2,4719)=.654	.520
# Female (%)	628 (53.17%)	1276 (54.07%)	660 (55.88%)	$\chi^2=1.849$	.397

Note. F-statistics were computed from a one-way ANOVA for continuous outcomes; Pearson Chi-squared tests were conducted for binary outcomes

Table 2.

ADHD PGS cut-point model fit statistics

Percentile	LRT (df)	<i>p</i>	Wald (2)	<i>p</i>	AIC	BIC	R2
5%	3.785 (2)	.151	5.940	.051	20518.221	20678.428	.092
10%	.381 (2)	.827	.397	.820	20539.272	20699.479	.079
15%	1.619 (2)	.445	1.578	.454	20532.158	20692.365	.081
20%	5.250 (2)	.072	4.973	.083	20525.593	20685.800	.087
25%	9.576 (2)	.008	8.953	.011	20512.966	20673.173	.084

Note: LRT: Likelihood ratio test, comparing the model with dummy coded PGS and a model with only covariates; Wald: Wald Chi-squared test comparing the model with the dummy coded PGS and a model without the PGS; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; R2: R-squared statistics based on the correlation between predicted and observed ADHD symptom count

Table 3.

Model statistics for the interaction between ADHD PGS and maltreatment in predicting ADHD symptoms

Model	Model Term	b (s.e.)	Wald (df)	<i>p</i>	LRT (df)	<i>p</i>	AIC	BIC	R2
Main					34.859 (3)	<.001	15076.95	15278.84	.137
	ADHD PGS		11.337 (2)	.003					
	medium	.189 (.068)							
	high	.255 (.081)							
	MaltFS	.129 (.026)	24.896 (1)	<.001					
Full					36.213 (5)	<.001	15079.60	15293.73	.138
	ADHD PGS		12.046 (2)	.002					
	medium	.210 (.069)							
	high	.245 (.082)							
	MaltFS	.145 (.042)	11.988 (1)	<.001					
	ADHD PGS * MaltFS		1.377 (2)	.502					
	medium	-.041 (.049)							
	high	.008 (.054)							

Note. All models controlled for age, sex, parental education and parental income at Wave I; MaltFS: maltreatment factor score; LRT: Likelihood ratio test, comparing a model with the predictors and a model with only covariates

Table 4.

Model statistics for the interaction between ADHD PGS (continuous) and maltreatment factor score

Model	Model Term	b (s.e.)	Wald	p	LRT (df)	p	AIC	BIC	R2
Main					43.762(5)	<.001	15105.63	15270.81	.131
	ADHD PGS	.074 (.025)	8.493	.004					
	MaltFS	.130(.027)	23.489	<.001					
Full					44.077(6)	<.001	15107.32	15278.62	.131
	ADHD PGS	.071 (.026)	7.752	.005					
	MaltFS	.129 (.027)	22.661	<.001					
	ADHD PGS * MaltFS	.010 (.018)	.315	.575					

Note. All models controlled for age, sex, parental education and parental income at Wave I; MaltFS: maltreatment factor score; LRT:

Likelihood ratio test, comparing a model with the predictors and a model with only covariates

Figure 1.

Non-significant interaction between ADHD PGS and maltreatment on ADHD symptoms

[See Attachment]