



# A Gene-Environment Interaction Study of Polygenic Scores and Maltreatment on Childhood ADHD

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## Abstract

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 low ADHD PGS may confer a protective effect from maltreatment in the development of ADHD. Data were from participants with phenotypic and genotypic data in the National Longitudinal Study of Adolescent to Adult Health (Add Health;  $n = 4,722$ ). 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. ADHD PGS and maltreatment were positively associated with ADHD symptoms, as expected. However, no interaction between ADHD PGS and maltreatment on ADHD symptoms was detected. 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 PGS studies that have also failed to detect PGS-environment interplay in mental disorders. We discuss possible reasons for this pattern of results and offer alternative methods for future research in understanding gene-environment interactions.

**Keywords** Polygenic scores · ADHD · Gene-environment interaction · Maltreatment · Add Health

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects 5–10% of children and young adults globally (Danielson et al., 2018). Maltreatment is associated with a broad range of mental disorders, such as internalizing disorders, PTSD, externalizing behaviors, and substance use (Copeland et al., 2018; Proctor et al., 2017; Warrier et al., 2021; Yoon, 2017). In particular, maltreatment is also a potent risk factor in the development of ADHD (González et al., 2019), though as with most negative outcomes, not all maltreated individuals go on to develop ADHD (Tabone et al., 2011; Yoon, 2018). 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 (i.e., heritability) that are consistent across the lifespan (Faraone & Larsson, 2019). 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 individual SNPs themselves only contribute a small to negligible amount of the variance in ADHD (Demontis et al., 2019; Pettersson et al., 2019). While the most recent GWAS on ADHD identified novel genes such as the *FOXP2* (Demontis et al., 2019), which is also linked to speech and language problems, many previously examined candidate genes for ADHD did not emerge in GWAS, such as *DRD4*, *DAT1* and *MAOA* (Brookes et al., 2006; Gizer et al., 2009). As GWAS has shown ADHD to be a

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highly polygenic disorder, researchers are increasingly using approaches that aggregate the effects of common genetic variants (i.e., polygenic scores; PGS) to characterize one's genetic risk for the disorder. Traditionally, PGS represent each person's genetic liability based on the weighted sum of their alleles across the variants that contribute to the 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 & He, 2021). Importantly, the primary use of PGS is not to identify relevant genes or to reveal biological mechanisms, but rather, to better predict the heritable phenotype in question.

Crucially, 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 (2019b) found that individuals at the lowest end of the ADHD PGS distribution (i.e., in the bottom 20<sup>th</sup> 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., 21<sup>st</sup> to 79<sup>th</sup> percentiles) and highest ends of the ADHD PGS distribution (i.e., top 80<sup>th</sup> percentile). These results suggest that a low burden of genetic risk for ADHD may have beneficial or possibly protective effects on various functional outcomes (Li, 2019b). This finding also leads to a 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, which is understudied for ADHD using contemporary genetic frameworks (Gould et al., 2018; Palladino et al., 2019).

In addition to genetic risk factors, maltreatment is also associated with the development of ADHD (Briscoe-Smith & Hinshaw, 2006; Sanderud et al., 2016). The association of maltreatment and ADHD is consistently observed across the types of maltreatment experienced (e.g., neglect, abuse), sex of participants, sampling methods (e.g., nationally-representative sample, community sample, online survey), and retrospective versus prospective studies (Clayton et al., 2018; González et al., 2019; Stern et al., 2018). 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 and their interactive effects on various adverse childhood environments (e.g., childhood trauma, and negative parenting behavior) (Li & Lee, 2012; Nigg et al., 2010; Park et al., 2017). However, candidate gene-environment interaction studies are now 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 (Dick et al., 2015). 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 (Gould et al., 2018; Palladino et al., 2019).

The current study used data from Add Health to examine whether 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 PGS (Li, 2019b), 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 began as a prospective longitudinal 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). Written consent was acquired from parents or legal guardians and participants themselves when they were younger than 18, and only from participants after they were 18 years of age or older (see Add Health study design for additional details: <https://addhealth.cpc.unc.edu/documentation/study-design/>). 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 populations (Duncan et al., 2019), 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 on their own childhood 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

**Table 1** Descriptive statistics comparing high, medium, and low ADHD PGS groups

	ADHD PGS Groups (low, medium and high)			F or Chi-square	p-value
	Low(n=1,181)	Medium(n=2,360)	High(n=1,181)		
ADHD symptoms (M, SD)	2.78(sd=3.38)	3.22(sd=3.62)	3.45(sd=3.89)	F(2, 4719)= 10.39	< .001
Emotional neglect (%)	83(7.52%)	187(8.37%)	77(6.87%)	$\chi^2=2.50$	.287
Physical neglect (%)	48(4.21%)	123(5.39%)	75(6.56%)	$\chi^2=6.19$	.045
Physical abuse (%)	135(11.89%)	328(14.37%)	180(15.73%)	$\chi^2=7.22$	.027
Sexual abuse (%)	44(3.83%)	90(3.91%)	60(5.19%)	$\chi^2=3.66$	.160
Psychological abuse (%)	123(10.46%)	324(13.90%)	167(14.29%)	$\chi^2=9.93$	.007
Parental education (0–9)	6.010(sd=2.12)	5.810(sd=2.12)	5.670(sd=2.14)	F(2,4260)=6.91	.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 thousands)	53.90(sd=48.42)	53.06(sd=56.17)	49.93(sd=48.17)	F(2,4230)=.23	.797
Age	15.99(sd=1.39)	16.04(sd=1.38)	15.97(sd=1.40)	F(2,4719)=.65	.520
# Female (%)	628(53.17%)	1276(54.07%)	660(55.88%)	$\chi^2=1.85$	.397

F-statistics were computed from a one-way ANOVA for continuous outcomes; Pearson Chi-squared tests (df=2) were conducted for binary outcomes

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* (American Psychiatric Association, 2013). 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 study (Brumley et al., 2019). 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 precedent (Brumley et al., 2019), 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 0.90 and RMSEA values less than 0.06 generally indicate “acceptable” model fit (Hu & Bentler, 1999). A one-factor model fit the data well (CFI=0.94, TLI=0.87, RMSEA=0.05,  $\chi^2(5)=169.81$ ). Individuals whose maltreatment factor score was 1 standard deviation higher than the mean had 1.13 times more ADHD symptoms (OR = 1.13, se = 0.03, 95%CI = [1.07, 1.19],  $\chi^2(1)=20.62$ ,  $p < 0.001$ ). 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 (Brumley et al., 2019). 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 0.02, Hardy–Weinberg Equilibrium of 0.0001, and minor allele frequency of 0.01, 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](https://www.cpc.unc.edu/projects/addhealth/documentation/guides/AH_GWAS_QC.pdf)).

### Polygenic Scores (PGS) for ADHD

Per convention (International Schizophrenia Consortium et al., 2009), 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 (Demontis et al., 2019). 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) (Demontis et al., 2019).

ADHD PGS were computed in *PRSice2* software in *R* (Choi & O’Reilly, 2019). 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 (Li & He, 2021). “Low”, “medium” and “high” ADHD PGS were derived in the following way. Following prior studies (Fang et al., 2019; Li, 2019b), 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*<sup>2</sup>. 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 25<sup>th</sup>, middle 26<sup>th</sup>–75<sup>th</sup>, and highest 75<sup>th</sup> percentiles. As expected, dummy-coded ADHD PGS were significantly associated with ADHD symptoms (LRT(2) = 9.58, *p* = 0.008;  $\chi^2(2) = 8.95$ , *p* = 0.011; *r*<sup>2</sup> = 0.084). In *post-hoc* group comparison by PGS percentile groups, where the lowest 25<sup>th</sup> PGS percentile served as the reference group, individuals in the medium (26<sup>th</sup>–75<sup>th</sup>) percentile group exhibited higher log of expected number of symptoms (*b* = 0.19, 95%CI = [0.06, 0.31]; OR = 1.21, 95%CI = [1.06, 1.37], *p* = 0.008), and individuals in the high (top 75<sup>th</sup>) percentile group also exhibited higher log of expected number of

**Table 2** ADHD PGS cut-point model fit statistics

Percentile	LRT(df=2)	<i>p</i>	Wald(df=2)	<i>p</i>	AIC	BIC	R <sup>2</sup>
5%	3.79	.151	5.94	.051	20,518.22	20,678.43	.09
10%	.38	.827	.40	.820	20,539.27	20,699.48	.08
15%	1.62	.445	1.58	.454	20,532.16	20,692.37	.08
20%	5.25	.072	4.97	.083	20,525.59	20,685.80	.09
25%	9.58	.008	8.95	.011	20,512.97	20,673.17	.08

*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; *R*<sup>2</sup> R-squared statistics based on the correlation between predicted and observed ADHD symptom count

symptoms by ( $b = 0.21$ , 95%CI = [0.04, 0.37]; OR = 1.23, 95%CI = [1.04, 1.44],  $p = 0.013$ ).

## 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 ADHD (Russell et al., 2016). 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. All models were adjusted for sample weights, region stratification, and treated schools as the cluster variable for multi-level modeling. To account for Type I error, we also controlled for false discovery rate (FDR) in our hypothesis testing. Finally, we conducted secondary analyses using a continuous ADHD PGS to check the robustness of our results that utilized a categorical ADHD PGS (in the event that categorizing PGS may have limited the variance in this variable).

## 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 ( $F(2, 4719) = 10.39$ ,  $p < 0.001$ ). Individuals in the high PGS group had more ADHD symptoms relative to low PGS group ( $\Delta$  symptoms = 0.67, 95% CI = [0.37, 0.96],  $p < 0.001$ ). Group differences in the maltreatment score were significant as well ( $F(2, 4291) = 3.08$ ,  $p = 0.046$ ); the high PGS group had higher maltreatment scores relative to the low PGS group ( $\Delta$  maltreatment = 0.09, 95%CI = [0.01, 0.18],  $p = 0.033$ ). 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 = 1.60, 95%CI = [1.11, 2.34],  $p = 0.028$ ), physical abuse (OR = 1.38, 95%CI = [1.09, 1.77],  $p = 0.016$ ), and psychological abuse (OR = 1.43, 95%CI = [1.12, 1.84],  $p = 0.005$ ). Parental education level also differed across the three PGS groups ( $F(2, 4260) = 6.91$ ,  $p = 0.001$ ) 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 ( $\chi^2(1) = 11.34$ ,  $p = 0.003$ ). As expected, those in the high PGS group had 1.29 time more ADHD symptoms than those in the low PGS group (OR = 1.29, s.e. = 0.10, 95%CI = [1.10, 1.51],  $p = 0.004$ ). The standardized maltreatment score was also positively associated with ADHD symptoms (OR = 1.14, s.e. = 0.03,  $\chi^2(1) = 24.90$ ,  $p < 0.001$ ). The main effects model provided a significantly better fit to the data than a model with just the covariates alone (LRT(3) = 34.859,  $p < 0.001$ ; Table 3). However, the interaction between ADHD PGS and maltreatment did not predict ADHD symptoms ( $\chi^2(2) = 1.38$ ,  $p = 0.502$ ) (see Fig. 1). The full model with the interaction of ADHD PGS and maltreatment score provided no improvement to model fit ( $\Delta$ LRT(2) = 1.35,  $\Delta$ AIC = 2.65,  $\Delta$ BIC = 15.89,  $\Delta$ R<sup>2</sup> = 0.001; Table 3). Critically, these results remain similar after we statistically account for the significant association between ADHD PGS and maltreatment factor score (by regressing maltreatment on ADHD PGS and covariates and using the residuals in downstream analyses; results available upon request).

### 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, the standardized continuous ADHD PGS were positively associated with ADHD symptoms (OR = 1.08, s.e. = 0.03,  $\chi^2(2) = 8.58$ ,  $p = 0.003$ ). The standardized maltreatment score was also positively associated with ADHD symptoms (OR = 1.13, s.e. = 0.03,  $\chi^2(1) = 21.45$ ,  $p < 0.001$ ). The full model with the interaction term provided minimal improvement in model fit

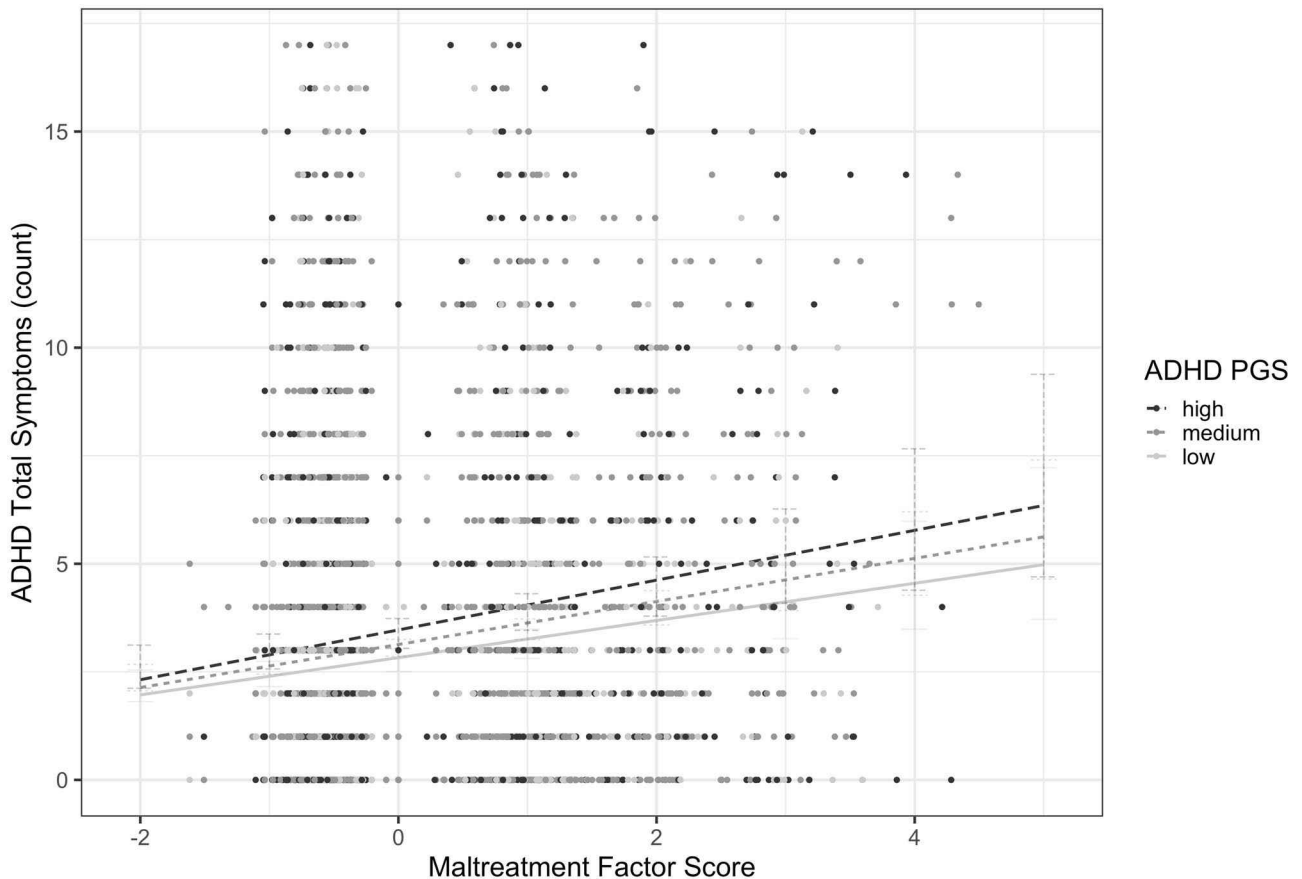
**Table 3** Model statistics for the interaction between ADHD PGS and maltreatment in predicting ADHD symptoms

Model	Model Term	OR(s.e.)	Wald(df)	<i>p</i>	LRT(df)	<i>p</i>	AIC	BIC	R <sup>2</sup>
Main	ADHD PGS		11.34(2)	.003	34.86(3)	<.001	15,076.95	15,278.84	.14
	medium	1.21(.08)							
	high	1.29(.10)							
Full	MaltFS	1.14(.03)	24.90(1)	<.001	36.21(5)	<.001	15,079.60	15,293.73	.14
	ADHD PGS		12.05(2)	.002					
	medium	1.23(.09)							
	high	1.28(.11)							
	MaltFS * ADHD PGS		1.38(2)	.502					
	medium	.10(.05)							
	high	1.01(.05)							

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

( $\Delta LRT(1) = 0.16$ ,  $\Delta AIC = 1.84$ ,  $\Delta BIC = 7.96$ ,  $\Delta R^2 < 0.001$ ; Table 4) over the main effects only model. The interaction between ADHD PGS and the maltreatment score was not significant (OR = 1.01, s.e. = 0.02,  $\chi^2(2) = 0.16$ ,  $p = 0.691$ ).

Statistically accounting for the association between ADHD PGS and maltreatment only led to minimal changes in the results (available upon request).



**Fig. 1** Non-significant interaction between ADHD PGS and maltreatment on ADHD symptoms

**Table 4** Model statistics for the interaction between ADHD PGS (continuous) and maltreatment factor score

Model	Model Term	OR(s.e.)	Wald	p	LRT(df)	p	AIC	BIC	R <sup>2</sup>
Main					41.29(4)	<.001	15,078.74	15,243.33	.13
	ADHD PGS	1.08(.03)	8.58	.003					
	MaltFS	1.13(.03)	21.45	<.001					
Full					41.44(5)	<.001	15,079.98	15,251.29	.13
	ADHD PGS	1.08(.03)	8.00	.005					
	MaltFS	1.13(.03)	21.24	<.001					
	ADHD PGS * MaltFS	1.01(.02)	.16	.691					

All models controlled for age, sex, parental education and parental income at Wave I; ADHD PGS and MaltFS were standardized before model fitting

*MaltFS* maltreatment factor score; *LRT* Likelihood ratio test, comparing a model with the predictors and a model with only covariates

## Discussion

Following on prior findings (Li, 2019b) 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 mental disorder history, education, working status and income in ADHD in a large case-control sample in Denmark (Østergaard et al., 2020). Other researchers have also reported either null or generally inconsistent findings between PGS and environmental risk factors on mental disorders more broadly (Lewis & Vassos, 2020). For example, a meta-analysis of major depressive disorder (MDD) found no interaction involving childhood trauma and MDD PGS (Peyrot et al., 2018), while another study found a negative interaction between MDD PGS and childhood trauma (Mullins et al., 2016) (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 (Trotta et al., 2016). 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 mental disorders as previously expected (Dick et al., 2015).

We use our findings to advance alternative considerations for gene-environment interaction studies of ADHD and mental

disorders 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 mental disorders per se (Gottesman & Gould, 2003). 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 inhibition (Nigg et al., 2007). Similarly, in a sample enriched with children with ADHD, slower response inhibition increased the negative associations of low social preference and high relational aggression in childhood with future exposure to intimate partner violence, compared to faster response inhibition (Youn et al., 2019). As neuropsychological endophenotypes like response inhibition are also quite heritable (Crosbie et al., 2013), 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 abuse (Groman et al., 2009), bipolar disorder (Roberts et al., 2013), and autism spectrum disorder (Geurts et al., 2014). Future studies might benefit from investigating PGS for endophenotypes in gene-environment interaction models of related mental disorders.

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 inherited from 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-inherited genotypes from both parents as well (Kong et al., 2018; Young et al., 2019). This is referred to as “genetic nurture” because uninherited parental genotypes can impact one's phenotype indirectly through the

effects of the home environment. Thus, conventional PGS for mental disorders 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 genotypes (de Zeeuw et al., 2020). Future PGS-environment interaction studies should separately compute the direct and the indirect effects of mental disorder 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 al., 2020). Both direct and indirect effect PGS could be promising variables to examine in gene-environment interactions. Although the indirect effect PGS did not exhibit a significant main effect in de Zeeuw et al. (2020), it remains unclear if additional exogenous, non-familial exposures could moderate its effect on behavior. Additionally, unraveling the mechanisms that explain direct and indirect PGS effects is critical to understanding etiology and intergenerational transmission of ADHD (Branje et al., 2020). Potential mechanisms that explain direct and indirect PGS pathways include specific neural pathways (e.g., ventral striatum) or psychosocial factors such as parenting behaviors (Li & Lee, 2012; Thorell et al., 2012; Tibu et al., 2016). This work has yet to emerge, which is sensible given how recently direct and indirect effect PGS were described (Kong et al., 2018).

A few study limitations are also noteworthy. First, we limited our analyses to individuals of European ancestry. Some scholars suggest that trans-ancestral PGS predictions may misrepresent the true association between genetic risk and a wide range of phenotypes given that non-European discovery sample sizes are comparatively small and underpowered relative to European sample sizes (e.g., Duncan et al., 2019). We await more diverse and larger genotyped samples in non-European ancestry 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., Carbonneau et al., 2020), and while Martin et al. (2018) recently showed no differences in mean ADHD PGS between males and female cases, there may be sex-specific ADHD PGS x environment interactions for ADHD. Third, maltreatment was retrospectively self-reported by participants. Retrospective self-reports of maltreatment may be influenced by recall bias or inaccurate reporting, which

could contribute to null or false findings (Osborn & Widom, 2020; von Wirth et al., 2020). On the other hand, while substantiated records of maltreatment may offer additional validity, these records come at the cost of likely underreporting (i.e., many instances of maltreatment go unreported), detection bias, and relatively low concordance with self-reports (Finkelhor et al., 2014; Osborn & Widom, 2020; Swahn et al., 2006; Widom et al., 2015). Therefore, our results should be interpreted with caution given the challenges in measuring maltreatment. Fourth, childhood ADHD was also retrospectively self-reported when the respondents were young adults. Retrospective reporting of childhood ADHD could be influenced by concurrent (adult) symptoms of ADHD, in addition to other recall biases (Gomez et al., 2020; Miller et al., 2010). Therefore, the PGS-ADHD association we found could be reflective of unique (e.g., persistent) forms of ADHD during adulthood (Agnew-Blais et al., 2021). Finally, we note that Add Health only assessed ADHD at a single time point, thus precluding our ability to examine trajectories of ADHD development over time. Developmental considerations in gene-environment interaction studies are important, yet understudied in this literature (Li, 2019a).

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 into adulthood. Despite the increase in predictive power that PGS approaches afford, our findings highlight the continued complexity of studying gene-environment interactions for mental disorders, 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 work in understanding gene-environment interplay.

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## Compliance with Ethical Standards

**Ethics Approval** This study has been approved by the University of Wisconsin-Madison Education and Social/Behavioral Science IRB (Protocol #2015–1189, Title: Add Health Study).

**Consent to Participate** Add Health participants provided written informed consent for participation in all aspects of Add Health in accordance with the University of North Carolina School of Public Health Institutional Review Board guidelines that are based on the Code of Federal Regulations on the Protection of Human Subjects 45CFR46: <https://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>. Additional information can be found on Add Health's webpage under FAQs: (<https://addhealth.cpc.unc.edu/documentation/frequently-asked-questions/>).

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