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Mapping relationships between ADHD genetic liability, stressful life events, and ADHD symptoms in healthy adults

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) symptoms are continuously distributed in the general population, where both genetic and environmental factors play roles. Stressful life events (SLEs) have been associated with ADHD diagnosis, but the relationship between ADHD genetic liability, SLEs, and ADHD symptoms in healthy individuals is less clear. Using a sample of 1,531 healthy adults (average age 26.9 years; 55.8% female), we investigated relationships between ADHD polygenic risk scores (ADHD-PRSs), SLEs, and ADHD symptoms in a general population sample. Confirming earlier findings in an overlapping sample, all SLE-measures assessed (lifetime SLEs, recent SLEs, and childhood trauma (CT)) were significantly correlated with total ADHD, inattention (IA), and hyperactivity-impulsivity (HI) scores (r^2 range = .08–.15; all $p < .005$). ADHD-PRSs was associated with HI ($R^2_{best-fit}$ = .37%), lifetime SLEs ($R^2_{best-fit}$ = .56%), and CT ($R^2_{best-fit}$ = .40%). Mediation analyses showed that lifetime SLEs partially mediated the association between ADHD-PRSs and HI (indirect effect: β = 68.6, bias corrected accelerated 95% confident interval (BCa95%CI) [11.9, 131.0], p = .016, proportion mediated (P_M) =19.5%), with strongest effects contributed by CT (β = 34.4, BCa95%CI [0.4, 76.5], p = .040, P_M = 9.8%). On the other hand, HI partially mediated the association between the ADHD-PRSs and lifetime SLEs (β = 42.9, BCa95%CI [7.3, 83.9], p = .014, P_M = 18.8%). Our study observed a complex relationship of genetic and environmental risk factors contributing to ADHD symptoms in the healthy adult population.

KEYWORDS
ADHD scores, ADHD-polygenic risk scores (ADHD-PRSs), childhood trauma (CT), mediation analysis, stressful life events (SLEs)

1 | INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in children, and in over 60% of patients, symptoms persist into adulthood (Faraone et al., 2015). ADHD is characterized by the two symptom dimensions of inattention (IA) and hyperactivity and impulsivity (HI). A growing number of studies has shown that the clinical diagnosis and classification of ADHD may represent the extreme end of a continuum of traits in the population (Larsson, Anckarsater, Rastam, Chang, & Lichtenstein, 2012; McLennan, 2016). Nearly 60% of the general population have sub-threshold symptoms (Arcos-Burgos & Acosta, 2007), and our own recent study showed that 28.5% of a general population sample (average age 56.1 years) have at least one IA symptom and 46.1% have at least one HI symptom (Li et al., 2019).

ADHD has a substantial genetic background, with estimated heritability ranging between 70 and 80% based on family and twin studies (Faraone & Larsson, 2019). Population-based studies also showed that ADHD traits are heritable (Arias-Vasquez et al., 2019; Crosbie et al., 2013; Middeldorp et al., 2016), and several studies showed substantial sharing of genetic influences between the population ADHD symptoms and the clinical ADHD diagnosis, with genetic correlations ranging between 0.94 and 0.96 (Demontis et al., 2019; Middeldorp et al., 2016; Rovira et al., 2020; Stergiakouli et al., 2015).

Besides genetic factors, environmental risk factors are known to contribute to ADHD etiology (Froehlich et al., 2011). Stressful life events (SLEs) are among those environmental risk factors for ADHD; the exposure to SLEs increases the risk of ADHD (Biederman, 2005; Sugaya et al., 2012), as well as its severity and persistence (Biederman et al., 1995; Fairchild, 2012; Grizenko, Shayan, Polotskaia, Ter-Stepanian, & Joober, 2008). Among SLEs, childhood adversity is a robust predictor of ADHD (Bjorkenstam, Bjorkenstam, Jablonska, & Kosidou, 2018). On the other hand, ADHD seems to predispose to SLEs. Compared to community controls, ADHD patients were shown to be at increased risk of SLEs (Friedrichs, Igl, Larsson, & Larsson, 2012). For example, children with ADHD experienced more adversity than their peers without ADHD (Humphreys & Zeanah, 2015), and adults with ADHD have more long-term negative outcomes compared with healthy controls in terms of occupation as well as marital and financial problems (Faraone et al., 2015; Franke et al., 2018).

The association between SLEs and ADHD symptoms has also been reported in the general population. Prenatal maternal stress has been associated with ADHD symptoms in early childhood (Ronald, Pennell, & Whitehouse, 2010). Studies on adopted children indicated a link between early deprivation and ADHD symptoms (Roskam et al., 2014), and numbers of SLEs have been associated with ADHD symptoms in childhood with small to moderate effect sizes (Humphreys et al., 2019). For healthy adults, we also found SLEs to be positively correlated with ADHD scores (Vrijsen et al., 2018), and childhood trauma (emotional and/or physical neglect, physical and/or sexual abuse) have been associated with increased risk of ADHD symptom (Capusan et al., 2016).

Although there is a clear link of both genetic and environmental factors with ADHD symptoms in the population, the specific relationships among those factors are less clear. In this study, we expand on our earlier work on SLEs and ADHD symptoms (Vrijsen et al., 2018) further adding information on ADHD polygenic risk scores (ADHD-PRSs) in an extended sample of self-reported healthy adults. We hypothesized that the genetic liability for ADHD is associated with ADHD symptoms and/or an increased risk for SLEs in the general population. In order to test this, we (a) sought to confirm the earlier association between SLEs and ADHD symptoms, (b) tested whether ADHD-PRSs, estimated from the largest ADHD GWAS study (Demontis et al., 2019), were associated with ADHD total score, IA and/or HI score and/or SLEs, and (c) tested if mediational associations exist among ADHD-PRSs, SLEs and ADHD scores.

2 | METHODS

2.1 | Participants

This study was performed in participants from the Cognomics Initiative Resource, the brain imaging genetics (BIG) project (http://www.cognomics.nl). The BIG project was initiated in 2007 and composed of brain imaging data and genetic data of over 2,500 self-reported healthy adults, who were recruited in Nijmegen, The Netherlands. The exclusion criteria were a history of neurological or psychiatric diseases. Cognitive data on the BIG participants were collected through internet-based questionnaires and tests. More information about the BIG cohort can be found in https://www.ru.nl/donders/vm-site/collaborations/projects/cognomics-0/big-project/big-database/. A total of 1901 completed the ADHD symptoms and SLEs questionnaires (described below). Among those, 1,531 unrelated participants of European descent had genome-wide genotype data available after appropriate quality control (see below). The study was approved by the local ethics committee (CMO Region Arnhem-Nijmegen, The Netherlands). All participants gave written informed consent and were financially compensated for participation.

2.2 | ADHD scores

The Dutch version of the ADHD DSM-IV Rating Scale was used to measure self-reported current ADHD symptoms (Kooij et al., 2005). This instrument assesses ADHD symptoms in the last 6 months on a four-point scale (1="rarely or never"; 2 = "sometimes"; 3 = "often"; 4 = "very often"). The questionnaire consists of 23 items in total; 11 items are related to the IA symptom domain and 12 to the HI symptom domain. In the analyses, the 23 items were re-calculated to the original 18 DSM-IV ADHD diagnostic criteria items (APA, 2000). The variables "Total ADHD score" (possible range 0–72), "IA score" and "HI score" (possible range 0–36 each) were then derived from the questionnaire by summing up the responses that participants filled in. Only individuals without missing data were included.

2.3 | Stressful life events

SLEs were assessed using an adapted version of the List of Threatening Life Events (Brugha & Cragg, 1990). The questionnaire consists of 21 binary (yes/no) questions about life events, which are likely to occur frequently and have significant long-term impact. Participants were asked to indicate whether they had experienced an event before the age of 16 years, after the age of 16, and/or within the last year. Three variables were calculated, as described in (Vrijsen et al., 2018): "lifetime-SLEs" indicated the total number of experienced life events across the whole life span; "childhood trauma (CT)" reflected the number of traumatic events that participants experienced (aggression, physical and/or sexual abuse) within or outside the family before 16 years old; "recent-SLEs" indicated the number

of stressful events (e.g., health problems, death of a family member, problems in the romantic relationship, divorce, conflicts in work, financial problems, or legal issues) that participants had within the last year.

2.4 | Genotyping and quality control

DNA was isolated from saliva collected using Oragene containers (DNA Genotek, Ottawa, ON, Canada) according to standard protocols. Genome-wide genotyping of single nucleotide polymorphisms (SNPs) was performed for the 1,531 unrelated individuals on three genotyping platforms: for 678 participants, genotyping was performed using Affymetrix GeneChip (Affymetrix Inc., Santa Clara, CA), for 634 participants, genotyping was performed using Infinium OmniExpress BeadChip (Illumina Inc., San Diego, CA), and 219 participants were genotyped using Infinium PsychArray BeadChip (Illumina Inc.). Using the Rapid Imputation Consortium Pipeline (RICOPILI) (Lam et al., 2019), quality control was carried with default parameters and ungenotyped SNPs were imputed using 1,000 genomes Phase I version 2 as a reference and IMPUTE2 software (Howie, Donnelly, & Marchini, 2009). RICOPILI was also used to carry out principal component analysis (PCA) to generate ancestry-informative components (Lam et al., 2019). After imputation, SNPs were filtered in order to keep only those with imputation quality scores (INFO) ≥0.8 and minor allele frequency (MAF) higher than 1%. Of the 6,889,427 SNPs on Affymetrix chip, 7,459,572 SNPs on OmniExpress, and 6,203,209 SNPs on PsychArray Chip remaining after postimputation quality control, only those present on all three platforms (n = 5,532,978 SNPs) were used for following analyses.

2.5 | ADHD-PRSs

ADHD-PRSs were calculated based on the results from the ADHD GWAS meta-analysis, conducted by the Psychiatric Genomics Consortium (PGC) and the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), on 19,099 ADHD patients and 34,194 controls from European-ancestry (Demontis et al., 2019). The summary statistics were downloaded from the PGC website (https://www.med.unc.edu/pgc/results-anddownloads).

2.6 | Statistical analyses

Partial correlation analyses were carried out to test relationships between SLE-based variables and ADHD scores, with age and sex as covariates (in linear regression). Prior to analyses, log-transformation was performed for non-normally distributed variables. Two outliers that are more than 4.5 SD in lifetime SLEs were excluded from analyses. Additional sensitivity analyses were run, including the two outliers for lifetime SLEs. The results are reported in the supplement. Bonferroni correction for multiple testing was implemented for the

number of comparisons (correlation analysis), resulting in a significance level of $p < .0056$ (nine comparisons).

Polygenic risk scores were created using PRSice2 software (Choi & O'Reilly, 2019). Independent index SNPs for each linkage disequilibrium (LD) block in the genome were selected based on significance levels in the reference data set and form clumps of all other SNPs that are within 250 kb window and in LD ($r^2 > .1$). The ADHD meta-analysis results for SNPs up to eight p-value thresholds ($p_T = .001$, $p_T = .05$, $p_T = .1$, $p_T = .2$, $p_T = .3$, $p_T = .4$, $p_T = .5$, and $p_T = 1.0$) were selected to generate ADHD-PRSs in our targeted sample. PRSs for the other major mental disorders (autism spectrum disorder (ASD), major depressive disorder (MDD), bipolar disorder (BP), and schizophrenia (SCZ)) were also generated, based on the largest available GWAS meta-analysis results (Grove et al., 2019; Ripke et al., 2014; Ruderfer et al., 2018; Wray et al., 2018).

Regression models were built to detect whether ADHD-PRSs were associated with ADHD scores and SLEs variables, with age, sex, genotyping array, and 10 PCAs as covariates. Given that ADHD-PRSs were calculated at different p-value thresholds, permutation was used to adjust the best fit p-values. Empirical p-values were obtained by comparing the uncorrected p-values from regression models with p-values from a null distribution generated by permuting the phenotypes 10,000 times. These analyses were performed in PRSice2 software (Choi & O'Reilly, 2019). We also examined the association between PRSs for the other four major mental disorders, ADHD scores, and SLEs variables.

Mediation analyses were applied to test whether (a) SLEs variables with significant effects on ADHD scores were tested as mediators in the association between ADHD-PRSs and ADHD scores and (b) ADHD scores may mediate the association between ADHD-PRSs and SLEs variables. As mediation analyses require the independent variable to be a significant predictor for both dependent variable and mediator, ADHD-PRSs including SNPs at a threshold $p_T = .001$ was utilized in the mediation model, given that the ADHD-PRSs at the p-value threshold was significantly associated with HI score, lifetime SLEs, and CT, respectively. Age, sex, genotyping array, and 10 PCAs were included as covariates. Mediation analyses were performed in IBM SPSS Statistics 22, with using the PROCESS macro for SPSS (Hayes, 2013; Sales, 2016). A bootstrapping method was applied to assess the indirect effects based on 5,000 bootstrapped samples using 95% bias corrected accelerated confidence intervals (BCa 95% CI). The P_M (proportion mediated) value outputted by the program provides an effect size measure, which is referred to as the ratio of the indirect effect to the total effect.

3 | RESULTS

3.1 | Participant characteristics

A total of 1,531 individuals was included. The mean age of the study sample was 26.9 years (SD: 11.6, range 18–77 years), and 55.8% of the sample were females. Demographic characteristics of the sample are presented in Table 1 and Figure S1. Age was significantly negative correlated with total ADHD score ($r^2 = -.12$, $p < .001$), IA score ($r^2 = -.09$,

TABLE 1 Characteristics of the BIG sample, including means (*SD*) or percentage and range

Variable	Total sample (*N* = 1,531)	Males (*n* = 678)		Females (*n* = 853)	
	Mean (*SD*)/%	Mean (*SD*)/%	Range	Mean (*SD*)/%	Range
Age (years)	26.9 (11.6)	28.0 (13.2)	18–77	25.9 (9.9)	18–73
Total ADHD score	31.1 (6.6)	31.3 (6.6)	18–57	31.0 (6.5)	18–68
IA score	15.5 (4.0)	16.0 (4.0)	9–30.5	15.2 (4.0)	9–34
HI score	15.6 (3.5)	15.3 (3.5)	9–30.5	15.8 (3.5)	9–34
Experience lifetime SLEs	98.8%	98.2%		99.3%	
Lifetime SLEs	4.6 (2.6)	4.7 (2.8)	0–17	4.5 (2.5)	0–15
Experienced CT	21.6%	22.9%		20.6%	
Number of CT	0.28 (0.6)	0.29 (0.6)	0–4	0.27 (0.6)	0–4
0	1,200	523		677	
1	250	119		131	
2	68	30		38	
3	9	5		4	
4	4	1		3	
Experienced recent SLEs	32.6%	31.6%		33.4%	
Number of recent SLEs	0.46 (0.8)	0.45 (0.8)	0–4	0.46 (0.8)	0–4
0	1,032	464		568	
1	341	143		198	
2	122	53		69	
3	30	15		15	
4	6	3		3	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CT, childhood trauma; HI score, hyperactivity-impulsivity score; IA score, inattention score; SLEs, stressful life events.

$p < .001$), and HI score ($r^2 = -.13$, $p < .001$), and positively correlated with lifetime SLEs ($r^2 = .43$, $p < .001$). There was no sex difference in the total ADHD score ($t = 0.67$, $p = .050$), but males had higher IA score ($t = 3.47$; $p < .001$) and lower HI score than females ($t = -2.75$, $p = .006$).

3.2 | Correlation between SLE variables and ADHD scores

Consistent with our earlier publication on 675 participants of BIG (Vrijsen et al., 2018), SLE variables were positively correlated with total ADHD score (lifetime SLEs: $r^2 = .20$, $p < .001$; recent SLEs: $r^2 = .15$, $p < .001$; CT: $r^2 = .10$, $p < .001$). Both IA (lifetime SLEs: $r^2 = .16$, $p < .001$; recent SLEs: $r^2 = .12$, $p < .001$; CT: $r^2 = .08$, $p = .002$) and HI (lifetime SLEs: $r^2 = .19$, $p = .001$; recent SLEs: $r^2 = .15$, $p < .001$; CT: $r^2 = .11$, $p < .001$) scores contributed to the correlation.

3.3 | Association of ADHD-PRSs with ADHD scores and with SLE variables

After correcting for multiple *p*-value thresholds tested, ADHD-PRSs were associated with HI score in the BIG healthy adults (best-fit $p_T = .001$: $R^2 = .37\%$, $p = .016$, $p_{empirical} = .046$), with individuals

carrying higher ADHD-PRSs reporting higher HI score. No significant association was observed with total ADHD score (best-fit $p_T = .001$: $R^2 = .16\%$, $p = .118$, $p_{empirical} = .288$) or IA score (best-fit $p_T = .2$: $R^2 = .05\%$, $p = .375$, $p_{empirical} = .718$) (Figure 1). We also observed significant associations (corrected for multiple testing) between ADHD-PRSs and lifetime SLEs (best-fit $p_T = .4$: $R^2 = .56\%$, $p = .001$, $p_{empirical} = .002$) in healthy adults, with higher ADHD-PRSs were linked to more lifetime SLEs. This effect seemed to be contributed mainly by CT (best-fit $p_T = .4$: $R^2 = .40\%$, $p = .014$, $p_{empirical} = .039$); no associations were found with recent SLEs (best-fit $p_T = .001$: $R^2 = .04\%$, $p = .438$, $p_{empirical} = .797$) (Figure 1).

3.4 | Mediation analyses for ADHD-PRSs, ADHD scores, and SLE variables

Using mediation analyses, we found that lifetime SLEs mediated the association between ADHD-PRSs and HI score (Figures 2a and S2A). In detail, the total effect of ADHD-PRSs on HI score was $\beta = 352.1$ (BCa 95%CI [55.8, 643.2], $p = .018$). Dissecting the total effect, the direct effect was $\beta = 283.5$ (BCa 95%CI [−3.2, 570.2], $p = .053$), and the indirect effect through lifetime SLEs was $\beta = 68.6$ (BCa 95%CI [11.9, 131.0], $p = .016$). The latter indirect contribution accounted for 19.5% of the total effect ($P_M = 0.195$).
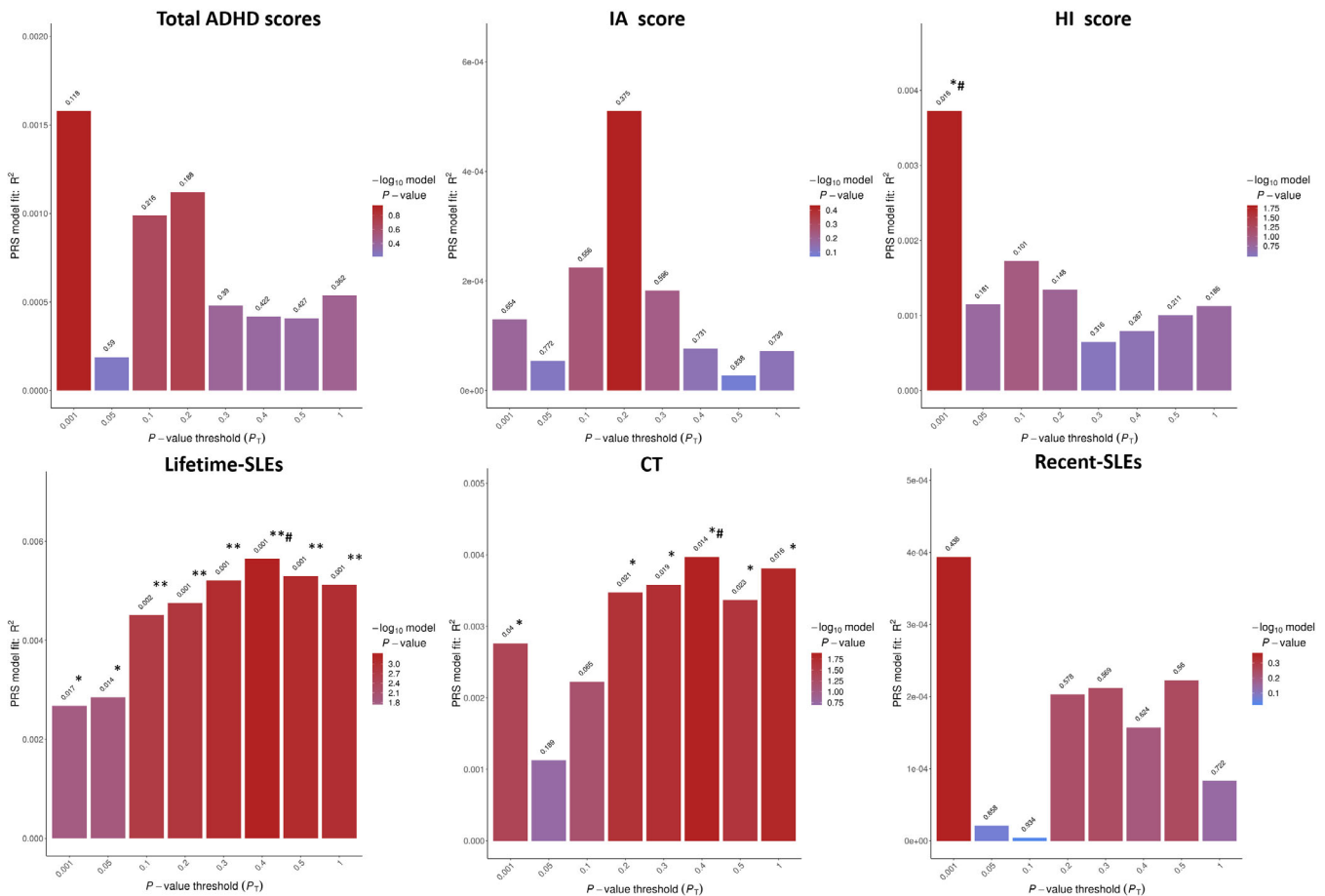
FIGURE 1 Bar plot from PRSice 2 showing results at eight broad p-value thresholds (P_T) for ADHD-PRSs associations with ADHD scores and SLE variables. *p < .05, **p < .01; #empirical p < .05. ADHD, attention-deficit/hyperactivity disorder; IA score, inattention score; HI score, hyperactivity-impulsivity score; SLEs, stressful life events; CT, childhood trauma [Color figure can be viewed at wileyonlinelibrary.com]

We further examined whether this mediation effect could be recapitulated by CT (Figure 2b). The results showed that the direct effect of ADHD-PRSs on HI score was β = 318.4 (BCa 95%CI [28.7, 608.1], p = .031). The indirect effect via CT was β = 34.8, which also reached significance (BCa 95%CI [0.4, 76.5], p = .040). Of the total effect of ADHD-PRSs on HI score, 9.8% seemed to operate indirectly through CT (P_M = 0.098).

Using an alternative mediation model, we also examined whether HI score played a role as mediator between ADHD-PRSs and lifetime SLEs (Figures 2c and S2B). The results indicated the direct effect of ADHD-PRSs on lifetime SLEs was β = 185.1 (BCa 95%CI [2.6, 367.5], p = .047). The indirect effect, operating through HI score, was β = 42.9, which reached statistical significance (BCa 95%CI [7.3, 83.9], p = .014). This indirect effect accounted for 18.8% (P_M = 0.188) of the total effect.

3.5 | The association between PRS for the other major mental disorders, ADHD scores, and SLE variables

To investigate whether our findings were specific for the ADHD-PRSs, we also carried out association analyses for PRS of other major

mental disorders. We found that the PRS for MDD was associated with HI score and CT at PT = .05 (Table S1). The PRS for BP was associated with lifetime SLEs and CT in adult general population. The PRS for SCZ was associated with CT. Although we found a trend that the PRS for ASD was associated with total ADHD score, IA score, lifetime SLEs, and Recent SLEs, the association did not survived after 10,000 permutation correction.

Given the association findings for both ADHD scores and SLEs, we further modeled mediation to examine whether CT acted as a mediator between MDD-PRS and HI symptoms (Figure S3). The direct effect of PRS for MDD on HI symptoms was β = 3,307.3 (BCa 95%CI [912.5, 5,643.2], p = .008). The indirect effect, operating through CT, was β = 421.7, which reached statistical significance (BCa 95%CI [119.5, 796.2], p = .002). This indirect effect accounted for 12.8% (P_M = 0.128) of the total effect.

4 | DISCUSSION

In the current study, we focused on determining the relationships among ADHD genetic liability, SLE variables, and ADHD scores in an adult, healthy population sample. Firstly, we confirmed the earlier
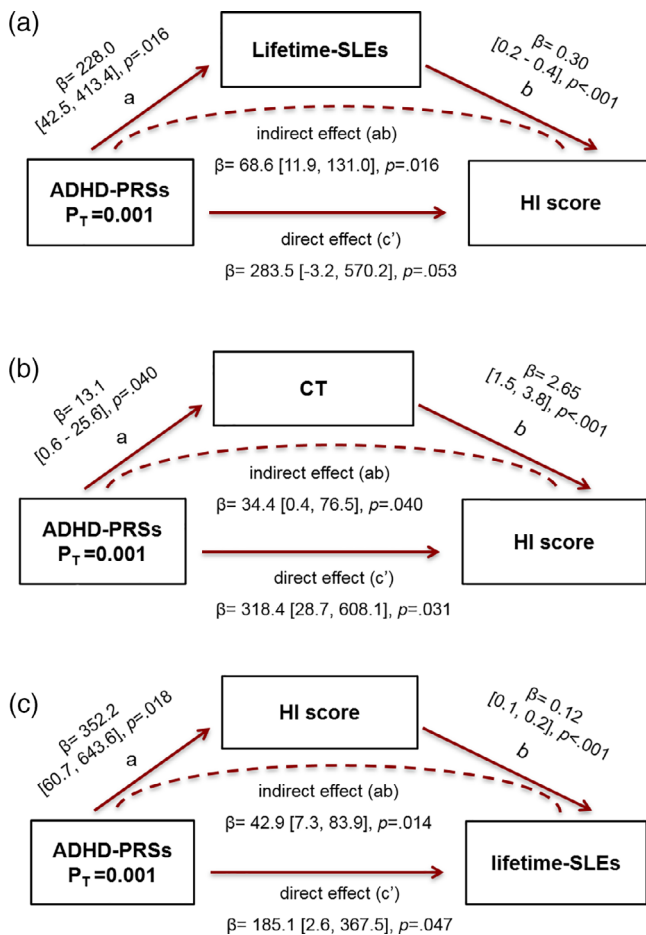
FIGURE 2 Mediation results of ADHD-PRSs (at p_T = .001), SLE variables, and HI score. The indirect effect is the product of the pathway from a and b. The direct effect (c′) refers to the regression of ADHD-PRSs on HI score/lifetime SLEs after taking mediators into account. (a) The effect of ADHD-PRSs on HI score was mediated by lifetime SLEs; (b) the effect of ADHD-PRSs on HI score was mediated by CT; and (c) the effect of ADHD-PRSs on lifetime SLEs was mediated by HI score [Color figure can be viewed at wileyonlinelibrary.com]

finding that the number of SLEs was associated with ADHD scores and second, we found a significant association between ADHD-PRSs with HI score and SLEs. Lifetime SLEs, especially through CT, partly mediated the association between the ADHD-PRSs and HI score. In addition, HI score also mediated the association between the ADHD-PRSs and lifetime-SLEs. Investigating the specificity of our findings for ADHD-PRSs, we found that the PRS for MDD was associated with both HI score and CT, and CT also mediated between MDD-PRS and HI score.

Using ADHD-PRSs derived from the results of the largest ADHD GWAS meta-analysis to date (Demontis et al., 2019), our findings suggest that ADHD genetic liability was specifically associated with HI symptom domain scores in the healthy adult population. This is consistent with findings from several earlier studies. Brikell et al. reported unique associations between ADHD-PRSs and HI symptoms in children from the general population, while there were no associations

between ADHD-PRSs and IA symptoms (Brikell et al., 2018). A study in 544 participants (mean age: 21 years, 212 [39%] with ADHD diagnosis) also reported ADHD-PRSs to be significantly associated with HI symptoms, but not with IA symptoms (Sudre et al., 2019). Our work further extends those findings to the adult general population. In twin study designs the genetic correlation between IA and HI symptoms was estimated at 0.6 (Faraone et al., 2015; Larsson et al., 2013); the apparent differential association of ADHD-PRSs with HI but not IA symptoms may therefore be explained by the differential contribution of genetic variation to the two symptom domains. Additionally, several studies have suggested that with the currently available data, more genetic variance can be explained for HI symptoms than for IA symptoms (Bidwell et al., 2017; McLoughlin, Ronald, Kuntsi, Asherson, & Plomin, 2007; Nikolas & Burt, 2010). We might therefore have had more power to observe associations of ADHD-PRSs with HI symptoms. Other possible factors, such as the age structure and sex ratio of participants in ADHD GWAS meta-analysis and the sample size of the current study may also have influenced the statistical power and findings of our study.

We also found associations between ADHD-PRSs and self-reported SLEs in the adult general population. Individuals with higher ADHD-PRSs were likely to report more SLEs across their lifespan. Among SLEs, the subgroup of CT events seemed to contribute the most to the observed association. This is in line with previous studies, which demonstrated that individuals with ADHD report higher self-perceived stress and stressors than typically developing individuals (Hirvikoski, Lindholm, Nordenstrom, Nordstrom, & Lajic, 2009) and that ADHD symptoms are associated with perceived stress (Combs, Canu, Broman-Fulks, Rocheleau, & Nieman, 2015). Our work extends these earlier studies by showing associations between ADHD genetic liability and SLEs in the adult population.

The mediation analyses showed that lifetime SLEs and CT partially mediated the link between ADHD-PRSs and HI symptoms in the healthy adult population (19.5 and 9.8% of total effect, respectively). Reversely, HI symptoms mediated the association between ADHD-PRSs and lifetime SLEs (18.8% of total effect). Previous studies have reported that genetic and environmental factors may contribute to ADHD in a nonindependent way (Ficks & Waldman, 2009; Schuch, Utsumi, Costa, Kulikowski, & Muszkat, 2015; van der Meer et al., 2017). In the current study, we observed genetic and environmental interplay in ADHD traits in the adult population. In line with previous studies, individuals with higher ADHD genetic liability appeared more prone to stress in daily life, with childhood trauma contributing most to the (persistence of) ADHD symptoms. In addition, individuals with more ADHD risk alleles appear to be at increased risk for SLEs due to their higher impulsivity and hyperactivity.

Investigating the specificity of our results for the ADHD-PRSs, we also studied PRSs for four other psychiatric disorders. Associations with measures of SLEs were seen with several of the disorders. These results are in line with a previous study reporting that the PRSs for five major psychiatric disorders are associated with mental health-related traits in adult life in the general population; more specifically,

the PRSs for ADHD, MDD, and SCZ have been found associated with trauma-related phenotypes (Leppert et al., 2020). MDD was the only disorder, which was related both to ADHD symptoms and to SLEs. While the PRSs for MDD has been associated with self-rated ADHD symptoms in adulthood in the general population previously (Riglin et al., 2020), this previous study did not link to a specific ADHD symptom domain. Here, we found that the PRSs for MDD is specifically associated with HI symptoms. The PRSs for MDD also has been associated with physical abuse in childhood (Leppert et al., 2020) and with SLEs (Clarke et al., 2019). In the current study, we found that the PRSs for MDD is associated with CT, which includes trauma from experienced aggression, and physical and/or sexual abuse. While we found that CT also partly mediated the association between the MDD-PRSs and HI symptoms, ADHD genetic risk factors strongly overlap with those for MDD; in recent cross-disorder analyses, the genetic correlation of ADHD and MDD was found to be 0.42–0.44 (Demontis et al., 2019; Lee et al., 2019). Considering such genetic correlation and pleiotropy, we would like to argue that we cannot distinguish whether the effects we see are driven more strongly by factors specific to the ADHD-PRSs or the MDD-PRSs. This subject is in need of further research in the future.

Our study should be interpreted in the context of strengths and limitations. A particular strength of the study is that we investigated the entire continuum of ADHD symptoms in the adult population, a group for which limited information is currently available. Our study examined the complex relationships between ADHD genetic loadings, environmental risk factors, and ADHD symptoms, which expanded our knowledge of ADHD symptomatology in the healthy population. In terms of study limitations, it is worth pointing out that ADHD symptoms and SLEs were assessed by self-report questionnaires, which may be subjected to biases. The questionnaire concerning SLEs were binary (yes/no) questions, which did not measure the severity of SLEs. As a subtype of SLEs, CT only assessed whether participants had traumatic events before 16 years old, like aggression, sexual, and/or physical abuse; therefore, the variance of CT was limited in this healthy population sample. Lastly, CT was a non-normally distributed variable and, by performing log-transformation, we cannot exclude transformation-related biases. As an additional potential limitation, we did not control for the presence of symptoms of other conditions, which are known to be (genetically) linked to ADHD. Genetic studies have demonstrated genetic overlap of ADHD and a broad range of psychiatric conditions in the general population. For example, Du Rietz et al. reported ADHD-PRSs to be associated with neuroticism, depression, and anxiety in adults from the UK Biobank population sample (Du Rietz et al., 2018). These psychiatric traits and conditions have been associated with the number of SLEs in individuals with ADHD (Francis, Moitra, Dyck, & Keller, 2012; Jeronimus, Ormel, Aleman, Penninx, & Riese, 2013; Jonker, Rosmalen, & Schoevers, 2017; Shapero et al., 2014). In that sense, since we did not control for the presence of symptoms of these conditions, we cannot exclude that these (also) play a role in observed associations.

In conclusion, our study observed a complex relationships of genetic and environmental risk factors to ADHD symptoms in healthy adults. ADHD genetic liability exerts both direct and indirect effects on HI symptoms, while no effect was observed in IA or total ADHD symptom scores. SLEs, especially though traumatic events in childhood, partially mediated the effect on HI symptoms; reciprocally, HI symptoms also partially mediated the effect of ADHD genetic liability on SLEs.

CONFLICT OF INTEREST

Barbara Franke has received educational speaking fees from Medice. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Ting Li was involved in study design, the conduction of statistical analysis, interpretation, and preparation of the article. Barbara Franke contributed interpretation and revision of the article critically for important intellectual content. Alejandro Arias Vasquez provided critical comment which enhanced significantly the final draft. Nina Roth Mota contributed to data analysis, interpretation the result. All authors approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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