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Wendt, Frank R.; Garcia-Argibay, Miguel; Cabrera-Mendoza, Brenda; Nivard, Michel G.; Polimanti, Renato; Mattheisen, Manuel; Meier, Sandra M.; Post-Traumatic Stress Disorder Working Group of the Psychiatric Genomics Consortium

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The Relationship of Attention-Deficit/Hyperactivity Disorder With Posttraumatic Stress Disorder: A Two-Sample Mendelian Randomization and Population-Based Sibling Comparison Study

Frank R. Wendt, Miguel Garcia-Argibay, Brenda Cabrera-Mendoza, Unnur A. Valdimarsdóttir, Joel Gelernter, Murray B. Stein, Michel G. Nivard, Adam X. Maihofer, Post-Traumatic Stress Disorder Working Group of the Psychiatric Genomics Consortium, Caroline M. Nievergelt, Henrik Larsson, Manuel Mattheisen, Renato Polimanti, and Sandra M. Meier

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and posttraumatic stress disorder (PTSD) are associated, but it is unclear if this is a causal relationship or confounding. We used genetic analyses and sibling comparisons to clarify the direction of this relationship.

METHODS: Linkage disequilibrium score regression and 2-sample Mendelian randomization were used to test for genetic correlation (r_g) and bidirectional causal effects using European ancestry genome-wide association studies of ADHD (20,183 cases and 35,191 controls) and 6 PTSD definitions (up to 320,369 individuals). Several additional variables were included in the analysis to verify the independence of the ADHD-PTSD relationship. In a population-based sibling comparison (N = 2,082,118 individuals), Cox regression models were fitted to account for time at risk, a range of sociodemographic factors, and unmeasured familial confounders (via sibling comparisons).

RESULTS: ADHD and PTSD had consistent r_g (r_g range, 0.43–0.52; $p < .001$). ADHD genetic liability was causally linked with increased risk for PTSD ($\beta = 0.367$; 95% CI, 0.186–0.552; $p = 7.68 \times 10^{-5}$). This result was not affected by heterogeneity, horizontal pleiotropy (Mendelian randomization Egger intercept = 4.34×10^{-4}, p = .961), or other phenotypes and was consistent across PTSD datasets. However, we found no consistent associations between PTSD genetic liability and ADHD risk. Individuals diagnosed with ADHD were at a higher risk for developing PTSD than their undiagnosed sibling (hazard ratio = 2.37; 95% CI, 1.98–3.53).

CONCLUSIONS: Our findings add novel evidence supporting the need for early and effective treatment of ADHD, as patients with this diagnosis are at significantly higher risk to develop PTSD later in life.

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Although 50% to 85% of individuals experience traumatic events over a lifetime, lifetime posttraumatic stress disorder (PTSD) prevalence is approximately 7% (1,2), suggesting differential resilience to stress and vulnerability to the disorder (2). Attention-deficit/hyperactivity disorder (ADHD) has been suggested to be a putative risk factor for PTSD (3) due to its association with risk-taking behavior (RTB) and impulsivity resulting in higher likelihood of experiencing traumatic events (4). Stimulant medication for ADHD has been suggested to increase the risk of developing PTSD (5), although associations with PTSD have also been observed for unmedicated ADHD (6). While cross-sectional studies suggested an association between ADHD and PTSD (3), few prospective studies examined this link. A family study including 402 children diagnosed with ADHD and their siblings found a significant association between ADHD and increased risk of PTSD at 10-year follow-up (odds ratio = 2.23) (7). Similarly, an analysis examining 4612 U.S. soldiers found that the presence of ADHD before deployment was associated with a higher risk of after-deployment PTSD (6). Other well-powered studies failed to observe such an association (3,8). As these prior results were mainly based on either military or clinical samples as well as self-reported data, it remains unclear whether the co-occurrence of clinically diagnosed ADHD and PTSD is present in the general population.

Mendelian randomization (MR) and sibling comparisons are powerful research designs that can allow causal inference from observational data (9–11). To elucidate the nature of the relationship between ADHD and PTSD, we examined the potential causal role of ADHD for subsequent PTSD 1) using a 2-sample

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MR approach based on data from the largest available meta-analyses of genome-wide association studies (GWASs) for these traits (12–14) and 2) a population-based sibling comparison design. We also tested for influence of other variables on the pathway from ADHD to PTSD.

METHODS AND MATERIALS

Primary GWASs

We leveraged large nonoverlapping ADHD and PTSD GWASs from individuals of European descent. The ADHD data consisted of 55,374 individuals (20,183 cases defined by ICD-10 code F90.0 or structured or semistructured clinical interviews and 35,191 controls) (12). In contrast to ADHD, for PTSD there were multiple adequately powered GWAS datasets available including different PTSD phenotype definitions (case-control status but also PTSD subdomains and/or symptom severity). Specifically, the PTSD case-control GWAS from the Million Veteran Program (MVP) analyzed 36,301 cases and 178,107 controls algorithmically defined using the U.S. Veterans Administration Healthcare electronic health records (14). The PTSD quantitative GWASs were 1) Psychiatric Genomics Consortium (PGC) for PTSD v2.5 excluding Yale-Penn and iPSYCH cohorts that were included in the ADHD study (N = 173,709) (13); 2–4) MVP avoidance, hyperarousal, and reexperiencing symptom subdomains (N = 168,689) (14); and 5) MVP PTSD Checklist 17-item questionnaire total score (PCL-17) of 168,689 individuals (14). In our analyses we included all these PTSD GWASs to ensure the generalizability of results across phenotype definitions and demographic characteristics (military/nonmilitary) used in individual studies. All GWASs considered in this study included principal components of ancestry as covariates together with age and sex. Note that prior work has investigated whether cohort-specific details related to PTSD (e.g., military vs. civilian cohorts) contribute to different genetic architectures (14). Notably, the genetic correlation between MVP PTSD traits and PGC PTSD traits is extremely high (14).

Linkage Disequilibrium Score Regression Analysis and Polygenic Scoring

We used linkage disequilibrium score regression to assess the genetic correlations of ADHD and PTSD phenotypes (15) using the European ancestry linkage disequilibrium reference panel from the 1000 Genomes Project (16). Polygenic score (PGS) analysis was performed using genome-wide association statistics and the gtx R package incorporated in PRSice (17). Both directions for possible causality were investigated in the PGS analysis: 1) ADHD as the base and PTSD phenotypes as the target and 2) ADHD as the target and PTSD phenotypes as the base (Supplement 1).

Mendelian Randomization

The R package TwoSampleMR (18) was used to estimate bidirectional causal effects between traits. In the Supplemental Methods in Supplement 1, we describe details for genetic instrument selection. Briefly, all genetic instruments consisted of linkage disequilibrium–independent single nucleotide polymorphisms (SNPs) associated with the exposure at some p value defined by the best-fit PGS between base and target phenotypes. As this relaxed genetic instrument selection threshold potentially violates the above MR assumptions, we applied the MR–Robust Adjusted Profile Score, which is a method designed to identify and estimate confounded associations using weak genetic instrument variables (19). If effect size of a variant was estimated from meta-analysis, we verified where possible the consistency of SNP-phenotype association across meta-analyzed cohorts. SNP I^2 estimates indicated a lack of variability due to between-study heterogeneity (ADHD I^2 adjusted p value $>$ .780). MR-heterogeneity testing was used to evaluate possible violation of the MR assumptions. Leave-one-out testing was used to detect outlier SNPs. Causal estimates were reported after removing SNPs underlying significant heterogeneity and/or leave-one-out results (20–22). Unless otherwise noted, we report inverse variance weighted (IVW) effect estimates.

Multivariable MR

To investigate further whether other factors might be underlying or mediating the ADHD→PTSD relationship, we conducted a multivariable MR (MVMR) considering 1) household income and educational attainment (EA) as covariates and 2) RTB and lifetime trauma as mediators [details of GWASs (12,14) are given in the Supplemental Methods in Supplement 1]. Note that RTB was used here instead of individual risky behaviors (e.g., number of sexual partners or automobile speeding propensity) to avoid reduction in MVMR power through inclusion of many highly correlated traits. MVMR was performed for the ADHD→PTSD relationship using only MVP PCL-17 as the outcome phenotype of interest due to the strong statistical power and the lack of sample overlap with the GWASs for all selected potentially confounding exposures. For each variable, we tested the 2-sample MR effect on PCL-17 in the absence of heterogeneity and horizontal pleiotropy using a genetic instrument defined by the best-fit PGS. After estimating the univariable MR effect of each variable on PCL-17, we tested their effect with respect to the ADHD→PTSD relationship using the MVMR approach implemented in the MendelianRandomization R package (23). All mediators and covariate traits were included in a single MVMR analysis.

Swedish Population-Based Sibling Comparison Cohort

Using the Swedish Total Population Register and the Swedish Cause of Death Register, we identified 2,082,087 individuals born between 1987 and 2007 who were alive and living in Sweden at age 6 with information on their biological relatives. Individuals were followed up from the age of 6 until PTSD diagnosis, death, emigration, or December 31, 2013, whichever occurred first. Parents and full siblings were identified using the Swedish Multi-generation Register (24), and we created a family identification variable using the unique personal identity number (PIN) from each biological parent (25). Individuals with ADHD were identified using the National Patient Register (26) based on a registered diagnosis (ICD-10 code F90) or any record of a prescribed ADHD medication (methylphenidate hydrochloride [Anatomical Therapeutic Chemical [ATC] code N06BA04], amphetamine [ATC code

N06BA01], dextroamphetamine sulfate [N06BA02], atomoxetine hydrochloride [ATC code N06BA09], and lisdexamfetamine [ATC code N06BA12]) in the Prescription Drug Register (26). Previous research has indicated high specificity for this register-based ADHD definition in Sweden (27) and shown that patterns of etiological influences remain similar whether people with ADHD are identified through diagnoses or ADHD medication prescriptions (28). Only physicians who specialize in psychiatry or neurology responsible for ADHD treatment are authorized to prescribe the medication in Sweden, which supports that prescription of ADHD medication is a valid indicator of ADHD diagnoses (29). PTSD was defined as the presence of an ICD-10 diagnosis code for PTSD (F43.1) in the National Patient Register. Information about the covariates sex, highest parental EA, and household income were obtained from the Swedish Total Population Register and Longitudinal Integration Database for Health Insurance and Labor Market Studies (30). The mediator traumatic events during the study period were defined as the cumulative sum of the number of ICD-10 codes for sexual abuse, fire or explosion, transportation accident, exposure to a toxic substance, traumatic brain injury, physical assault, assault with a weapon, or death of a parent. Finally, based on the National Crime Register, we defined the mediator RTB as any criminal conviction until the end of follow-up, marriage before age 18, divorce before age 20, or pregnancy before age 18 by using data from civil status and the Multi-generation Register (24) (Supplement 1).

Longitudinal Analyses in Population-Based Sibling Comparison Cohort

A time-varying Cox regression model with age as the underlying time scale was fitted to determine the ADHD→PTSD relationship at the population level. Estimates were presented as hazard ratio (HR) with 95% confidence intervals. First, a crude model adjusted for sex and year was fitted followed by a model adjusted with 1) ADHD, cumulative traumatic events, and RTB allowed to vary over time and 2) sex, birth year, household income, and parental EA defined as time-fixed covariates. To examine unmeasured familial confounding, we performed a Cox model with separated strata for each cluster of siblings (i.e., individuals with the same family identification number). Proportionality assumption was tested using scaled Schoenfeld residuals. Data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc.) and R version 4.1.0 (R Foundation for Statistical Computing). We were not able to evaluate the PTSD→ADHD relationship, as the onset of PTSD occurred before the ADHD diagnosis in only 31 individuals (0.001%), consistent with current literature (31). Furthermore, we were not able to evaluate several specific RTBs of interest, such as the number of sexual partners (data not available) and drinking/smoking behaviors (lack of validated registry data). The Regional Ethical Review Board in Stockholm, Sweden, approved this study. Requirement for informed consent was waived for the current study because it was a secondary analysis of existing data. Analyses followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines (https://www.strobe-statement.org/).

RESULTS

Genetic Correlation

Among PTSD phenotypes, PCL-17 had the highest genetic correlation with ADHD (r_g = 0.52, SE = 0.037, $p = 1.83 \times 10^{-37}$). There were no significant differences in r_g when using other phenotype definitions of PTSD or its symptom domains (p difference [p_{diff}] between .122 and .399) (Figure S1 in Supplement 1; Tables S1 and S2 in Supplement 2). Furthermore, RTB, household income, EA, and lifetime trauma were genetically correlated with ADHD and PTSD (ADHD: $|r_g|$ = 0.3–0.52, $p < 1.02 \times 10^{-19}$; PTSD: $|r_g|$ = 0.24–0.67, $p < 8.88 \times 10^{-9}$).

Association of ADHD PGS With PTSD

$ADHD_{PGS}$ was associated with all PTSD phenotypes (Figure S2 in Supplement 1; Table S3 in Supplement 2). The strongest association was between $ADHD_{PGS}$ and MVP PCL-17 (r^2 = 0.076%, $p = 9.61 \times 10^{-30}$, p-value threshold (p_T) = .001). All significant MR estimates comparing genetic instruments from ADHD and PTSD phenotypes support a positive causal effect of ADHD on PTSD (Figure 1; Tables S1 and S2 in Supplement 2). Using a subset of 482 SNPs associated with ADHD ($p_T < .001$), the strongest association was observed between ADHD→PCL-17 (IVW β = 0.367; 95% CI, 0.186–0.552; $p = 7.68 \times 10^{-5}$). This result was not affected by heterogeneity (Q_{481} = 384.0, p = .99) or horizontal pleiotropy (MR Egger intercept = 4.34×10^{-4}, p = .96). Consistencies with PTSD phenotypes, all association estimates, and results of tests for heterogeneity and horizontal pleiotropy are reported in Table S4 in Supplement 2 and Table S5 in Supplement 1.

Association of PTSD PGS With ADHD

All $PTSD_{PGS}$ from the primary polygenic score analysis were associated with ADHD after multiple testing correction (5% false discovery rate) (Figure S2 in Supplement 1; Table S3 in Supplement 2). The strongest association was using PGS derived from PCL-17 (r^2 = 0.195%, $p = 2.47 \times 10^{-23}$, p_T = .001). Associations between genetic instruments associated with PTSD phenotypes and ADHD were heterogeneous across PTSD definitions and MR methods. After removal of outliers contributing to heterogeneity and horizontal pleiotropy, the association of PTSD with ADHD was significant only with respect to certain phenotype definitions, and some of these significant associations were very small (Figure 1; Table S3 in Supplement 2): PGC PTSD v2.5→ADHD (IVW β = 0.456; 95% CI, 0.205–0.708; $p = 3.72 \times 10^{-4}$); MVP PCL-17→ADHD (IVW β = 0.005; 95% CI, 0.002–0.008; $p = 8.13 \times 10^{-4}$); MVP PTSD Case/Control→ADHD (IVW β = 0.024; 95% CI, 0.011–0.038; $p = 4.51 \times 10^{-4}$). Results of additional MR analyses are described in Supplemental Results in Supplement 1.

MVMR Analysis of ADHD Effect on PTSD

RTB, household income, EA, and lifetime trauma were evaluated for a 2-sample univariable association on PTSD as measured by the PCL-17. Table S6 in Supplement 2 describes the PGS analysis defining each genetic instrument for univariable 2-sample MR between covariate traits and PCL-17. RTB, household income, EA, and lifetime trauma all exhibited significant associations with PCL-17 (Table S5 in Supplement

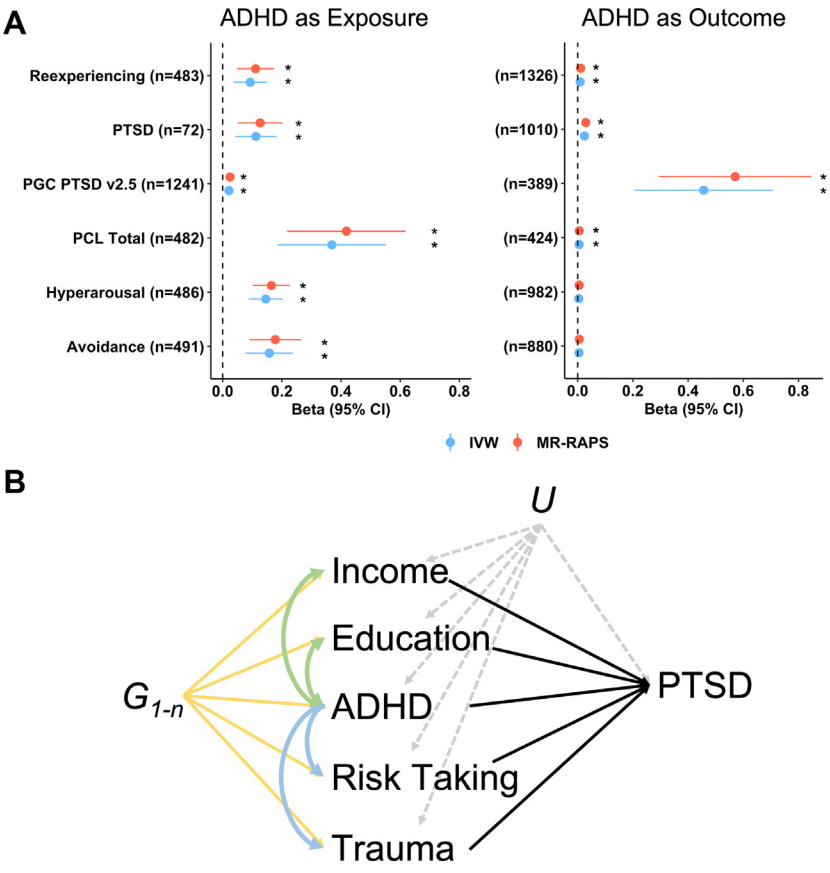

Figure 1. Attention-deficit/hyperactivity disorder (ADHD) and posttraumatic stress disorder (PTSD) Mendelian randomization (MR) results. **(A)** Causal effect of ADHD on PTSD phenotypes (left) and PTSD phenotypes on ADHD (right). All estimates lack evidence of heterogeneity and horizontal pleiotropy among the genetic instruments. For clarity, inverse variance weighted (IVW) and MR–Robust Adjusted Profile Score (MR-RAPS) (which accounts for weak genetic instruments) estimates are shown graphically, and estimates across MR methods are provided in Table S4 in Supplement 2. Odds ratios and 95% confidence interval (CI) are reported for each MR test. The number of single nucleotide polymorphisms contributing to each genetic instrument is shown in parentheses for each PTSD trait on the y-axis. Asterisks indicate significance after multiple testing correction accounting for all trait pairs and all MR causal inference methods applied (6 PTSD traits × 2 directions tested × 6 MR methods = 72 tests). **(B)** Directed acyclic diagram of multivariable MR results for ADHD and PTSD including bidirectional paths to covariates (green arrows) and direct causal paths to mediators (blue arrows) of the ADHD→PTSD relationship. All mediators and covariate traits were included in a single multivariable MR analysis. *G* indicates subsets of single nucleotide polymorphisms associated with one or more of the exposures. *U* indicates the effect of an unobserved confounder. PCL, PTSD Checklist; PGC, Psychiatric Genomics Consortium.

1). In the MVMR analysis simultaneously considering all confounders and mediators, the effect of ADHD on PCL-17 (IVW $\beta = 0.372$; 95% CI, 0.191–0.524; $p = .001$) was independent of other variables tested with no difference in effect size magnitude relative to the univariable estimate ($p_{diff} = 0.62$) (Table S5 in Supplement 1; Table S7 in Supplement 2). The multivariable did not nullify the associations of any other phenotype, but significantly reduced the association of RTB ($p_{diff} = 9.32 \times 10^{-30}$) and household income ($p_{diff} = 5.99 \times 10^{-12}$) on PCL-17 (Table S7 in Supplement 2).

Association of ADHD With PTSD Based on a Population-Based Sibling Comparison Design

Among 2,082,118 individuals (1,518,115 individuals nested within 665,342 families with at least 2 siblings [mean = 2.28, range 2–15]), 79,006 (3.79%) were diagnosed with ADHD (Table 1). Individuals with ADHD had a higher prevalence of PTSD (prevalence = 15.02; 95% CI, 14.19–15.9) compared with individuals without ADHD (prevalence = 1.62; 95% CI, 1.56–1.67; prevalence ratio = 9.30; 95% CI, 8.70–9.93). As the proportionality assumption was not met for the variable sex, we stratified the analyses on sex to accommodate a distinct baseline hazard function for each stratum level. In the crude model, individuals diagnosed with ADHD showed an increased rate of PTSD compared with individuals with no diagnosis of ADHD (HR = 6.92; 95% CI, 6.34–7.56). The association between ADHD and PTSD attenuated after adjustment for demographic factors, cumulative traumatic events, and RTB (HR = 4.32; 95% CI, 3.93–4.75). This association was similar between males and females (HR_{males} = 4.44; 95% CI, 3.98–4.96; $HR_{females}$ = 3.79; 95% CI, 3.16–4.55), with no statistically significant differences between them ($p = .154$). Results from the sibling comparison showed an increased risk for developing PTSD in individuals diagnosed with ADHD compared with their undiagnosed full siblings (HR = 2.37; 95% CI, 1.58–3.55) after adjustments (Figure 2; Table 2).

DISCUSSION

Most of the data suggesting an association between ADHD and PTSD risk are from observational studies (3). While statistical associations do not imply causality, the hypothesis that ADHD is an antecedent risk factor for PTSD is supported by findings that ADHD onset was consistently observed earlier than PTSD onset (31). With 2-sample MR and population-based sibling comparisons, we found consistent evidence for an association between ADHD genetic liability and an increased risk of PTSD. Importantly, we demonstrate that the

Table 1. Descriptive Statistics for Population-Based Sibling Study

Characteristic	Without ADHD, *n* = 2,003,112	With ADHD, *n* = 79,006
Person-Years	21,436,933	912,035
Sex		
Female	985,912 (49.22%)	25,505 (32.28%)
Male	1,017,200 (50.78%)	53,501 (67.72%)
Parental Education		
High	464,991 (23.21%)	10,555 (13.36%)
Low	290,567 (14.51%)	16,632 (21.05%)
Medium	1,208,479 (60.33%)	49,605 (62.79%)
No information	39,075 (1.95%)	2214 (2.80%)
Disposable Parental Income (SEK)	2119 (1669, 2634)	1924 (1441, 2396)
No information	39,075 (1.95%)	2214 (2.80%)
Traumatic Events		
Sexual abuse	4508 (0.23%)	889 (1.13%)
Fire or explosion	20,409 (1.02%)	1336 (1.69%)
Transportation accident	153,933 (7.68%)	10,271 (13.00%)
Exposure to toxic substance	181,797 (9.08%)	15,082 (19.09%)
Traumatic brain injury	107,552 (5.37%)	7260 (9.19%)
Physical assault	13,043 (0.65%)	1734 (2.19%)
Assault with a weapon	2403 (0.12%)	391 (0.49%)
Death of a family member <18 years old	45,758 (2.28%)	3312 (4.19%)
Risk-Taking Behaviors		
Criminal conviction	114,875 (5.73%)	15,053 (19.05%)
Pregnancy before age 18	2201 (0.11%)	332 (0.42%)
Divorce before age 20	201 (0.01%)	22 (0.03%)
Marriage before age 18	612 (0.03%)	27 (0.03%)
PTSD		
Without PTSD	1,999,875 (99.84%)	77,819 (98.50%)
With PTSD	3237 (0.16%)	1187 (1.50%)

Values are presented as *n*, *n* (%), or median (IQR).

ADHD, attention-deficit/hyperactivity disorder; IQR, interquartile range; PTSD, posttraumatic stress disorder; SEK, Swedish krona.

positive relationship between ADHD and PTSD is concordant across several MR methods that apply various adjustments to account for different pleiotropic scenarios that may affect the instrumental variables. In line with these findings, studies of trauma-exposed cohorts found a significantly increased risk of PTSD in individuals with ADHD (3). This indicates that the increased risk for PTSD in individuals with ADHD cannot be explained solely by an increased rate of trauma exposure in this population or RTB tendencies, household income, or EA in individuals with ADHD (32) or PTSD (33). While we observed support for mediation by these factors, more research is needed to identify the role of plausible mediators. This is important as it may lead to new secondary prevention targets.

Conversely, our findings regarding the association with PTSD on ADHD were highly inconsistent. In most of the cases, the associations observed are null or very small. This could be explained by the genetic effects shared across the psychopathology spectrum and is potentially in line with the controversy around the idea that ADHD could arise de novo in adulthood. Population-based studies suggested that ADHD in adulthood may be idiopathic and that the adult-onset form of the disorder is categorically different from the childhood-onset form (34–36). However, adult-onset ADHD is rare and usually arises in the context of a complex psychiatric history and not on its own (37). Thus, our findings might reflect these differences by observing an increased risk of ADHD in individuals with PTSD depending on ADHD age of onset and psychiatric comorbidity. In other words, our results indicate that individuals diagnosed with ADHD are clearly at a higher risk to develop PTSD later in life, while the risk of individuals diagnosed with PTSD to subsequently develop ADHD seems much more rare and likely to be negligible. The most common scenario underlying the comorbidity of ADHD and PTSD can accordingly be estimated as an initial ADHD diagnosis followed by a PTSD diagnosis. Preventive efforts should therefore primarily focus on this directionality.

Although causal factors underlying the association between ADHD and PTSD remain unclear, several possibilities can be considered. Preclinical work in rodents indicated that prenatal nicotine exposure resulted in an ADHD-like phenotype (38) in mice as well as impairment in fear extinction learning (39), traits strongly resembling the fear extinction deficiencies of patients (40). In humans, abnormalities in fear circuits during extinction learning and extinction recall (41) similar to those documented in PTSD have been observed in individuals with ADHD (42). A long-lasting effect of methylphenidate on fear extinction has been described (43), suggesting that adequate treatment of ADHD might lower the subsequent risk of developing PTSD in individuals with ADHD; however, the permissive effects of ADHD medications have also been described (5). Preliminary data also suggest a therapeutic benefit of methylphenidate in treatment of PTSD (44). Further research is needed to better understand the neurobiological underpinnings that are common to ADHD and PTSD. Such research could more accurately describe vulnerable neural circuitry that may be helpful in the development of targeted prevention and treatment strategies for PTSD in individuals with ADHD.

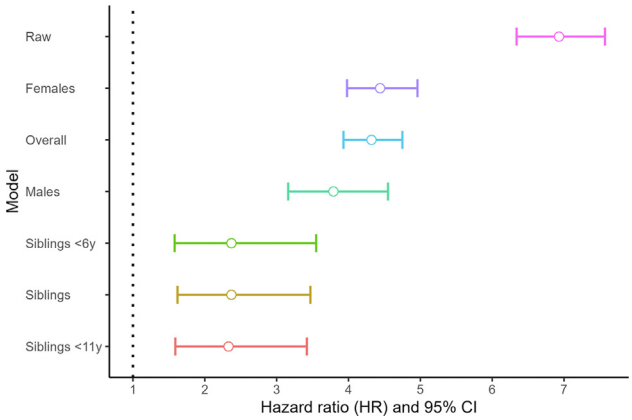

Figure 2. Effect of attention-deficit/hyperactivity disorder on posttraumatic stress disorder based on a population-based sibling comparison design. Hazard ratio and 95% confidence interval (CI) for the association between attention-deficit/hyperactivity disorder and posttraumatic stress disorder.

Table 2. Summary of Results From the Cox Proportional Hazards Model

	Overall	Females	Males	Sibling Analysis	Siblings, Age Difference <11 Years	Siblings, Age Difference <6 Years
Unadjusted[a]	6.92 (6.34–7.56)	7.57 (6.83–8.39)	5.51 (4.64–6.55)	–	–	–
Confounders[b]	6.72 (6.14–7.36)	7.39 (6.65–8.20)	5.20 (4.35–6.22)	2.81 (1.94–4.05)	2.75 (1.90–3.97)	2.78 (1.89–4.09)
Fully adjusted[c]	4.32 (3.93–4.75)	3.79 (3.16–4.55)	4.44 (3.98–4.96)	2.37 (1.62–3.47)	2.33 (1.59–3.42)	2.37 (1.58–3.55)

Values are presented as hazard ratio (95% confidence interval).
[a]Model adjusted for year and sex.
[b]Model adjusted for year, sex, disposable parental income, and parental education.
[c]Model adjusted for year, disposable parental income, cumulative count traumatic events, parental education, early marriage, early divorce, early pregnancy, and criminal conviction.

Our findings could have an important clinical impact by encouraging clinicians to screen for PTSD in individuals with ADHD and/or monitor its symptoms more closely. By underlining the increased risk for PTSD in ADHD, our results might help guide the development of screening and preventive efforts, potentially reaching individuals at high risk. This relationship was independent of several covariates and mediating variables, of which the most notable was the large causal effect of RTB on PCL-17. While RTB is one major behavioral source of exposure to traumatic experiences, it also strongly correlates with the externalizing behaviors commonly observed in individuals diagnosed with ADHD. This might be of particular interest considering the recent traumatic event of the COVID-19 pandemic. The extent to which the presence of ADHD may define a PTSD subtype that might benefit from different treatments needs to be explored in future research.

Our study investigating the relationship between ADHD and PTSD has several strengths. We conducted a causal inference analysis using the largest available GWASs that showed a consistent causal association between ADHD and PTSD assessed in cohorts developed using different study designs (12,14). We also used complementary 2-sample MR methods for sensitivity analysis (45). The MVMR analysis enabled us to establish that the association of ADHD with PTSD could not be accounted for by many potential confounding factors (RTB, household income, EA, and lifetime trauma). Additionally, the sibling comparison analyses permitted us to rule out any potential familial confounding effects. Finally, the population-based cohort design provided additional context to the ADHD→PTSD findings by extending the associations from military and clinical samples (who were primarily included in the GWASs) to the general population.

There are also limitations to this study. Different measures were used to define ADHD, PTSD, and confounding factors across analyses. The population-based study ADHD diagnoses relied on register-based records, and an overestimation of the association between ADHD and PTSD is possible, as more severely affected individuals are more likely to seek treatment. Similarly, the population-based sibling comparison cohort was significantly younger than the individuals included in the GWAS samples. However, despite this age discrepancy, we observed a remarkable consistency in our findings. Future studies could benefit from longitudinal cohort studies involving a deeper clinical phenotyping to supplement register-based records. While we were able to examine specific symptom dimensions of PTSD in our MR analyses, we could not assess the impact of specific symptom dimensions of ADHD or age of onset because no well-powered GWASs were available for these phenotypes, to our knowledge (46). Large differences in the effect magnitude of ADHD symptom dimensions on PTSD may attenuate the overall estimates for the unstratified analysis. Although our different sensitivity analyses did not indicate the presence of relevant biases, our MR and sibling comparison findings could still be affected by unmeasured confounders. Therefore, our findings, while largely consistent across methods, cannot definitively establish a causal relationship of ADHD with subsequent PTSD. Finally, the analyses were conducted using GWAS data of European ancestry and the Swedish population, and thus the generalizability of our results to other populations might be limited.

This MR and population-based sibling comparison study found robust evidence for an association between ADHD and increased risk for PTSD. The findings are clinically relevant because they may help identify individuals who are at high risk of developing PTSD and may benefit from preventive efforts.

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ARTICLE INFORMATION

From the Division of Human Genetics, Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (FRW, BC-M, JG, RP); Department of Psychiatry, Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut (FRW, BC-M, JG, RP); Department of Anthropology, University of Toronto, Toronto, Ontario, Canada (FRW); School of Medical Sciences, Örebro University, Örebro, Sweden (MG-A, HLar); Center of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland (UAV); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (UAV); Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts (UAV); Department of Psychiatry, UC San Diego School of Medicine, University of California, San Diego, La Jolla, California (MBS, AXM, CMN); Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, California (MBS); Veterans Affairs San Diego Healthcare System, San Diego, California (MBS, AXM, CMN); Department of Biological Psychology, Faculty of Behaviour and Movement Sciences, VU University, Amsterdam, The Netherlands (MGN); Center of Excellence for Stress and Mental Health, Veterans Affairs San Diego Healthcare System, San Diego, California (AXM, CMN); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (HL); Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada (MM, SM); Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada (MM, SMM); Institute of Psychiatric Phenomics and Genomics, University Hospital, Ludwig-Maximilians-University Munich, Munich, Germany (MM); and Faculty of Computer Science, Dalhousie University, Halifax, Nova Scotia, Canada (MM, SMM).

List of PGC-PTSD Consortium authors: Adam X. Maihofer, Karmel W. Choi, Jonathan R.I. Coleman, Nikolaos P. Daskalakis, Christy A. Denckla, Elizabeth Ketema, Rajendra A. Morey, Renato Polimanti, Andrew Ratanatharathorn, Katy Torres, Aliza P. Wingo, Clement C. Zai, Allison E. Aiello, Lynn M. Almli, Ananda B. Amstadter, Soren B. Andersen, Ole A. Andreassen, Paul A. Arbisi, Allison E. Ashley-Koch, S. Bryn Austin, Esmina Avdibegovic, Anders D. Borglum, Dragan Babic, Marie Bækvad-Hansen, Dewleen G. Baker, Jean C. Beckham, Laura J. Bierut, Jonathan I. Bisson, Marco P. Boks, Elizabeth A. Bolger, Bekh Bradley, Meghan Brashear, Gerome Breen, Richard A. Bryant, Angela C. Bustamante, Jonas Bybjerg-Grauholm, Joseph R. Calabrese, Jose Miguel Caldas-de-Almeida, Chia-Yen Chen, Anders M. Dale, Shareefa Dalvie, Jürgen Deckert, Douglas L. Delahanty, Michelle F. Dennis, Seth G. Disner, Katharina Domschke, Laramie E. Duncan, Alma Dzubur Kulenovic, Christopher R. Erbes, Alexandra Evans, Lindsay A. Farrer, Norah C. Feeny, Janine D. Flory, David Forbes, Carol E. Franz, Sandro Galea, Melanie E. Garrett, Aarti Gautam, Bizu Gelaye, Joel Gelernter, Elbert Geuze, Charles F. Gillespie, Aferdita Goci Uka, Scott D. Gordon, Guia Guffanti, Rasha Hammamieh, Michael A. Hauser, Andrew C. Heath, Sian M.J. Hemmings, David Michael Hougaard, Miro Jakovljevic, Marti Jett, Eric Otto Johnson, Ian Jones, Tanja Jovanovic, Xue-Jun Qin, Karen-Inge Karstoft, Milissa L. Kaufman, Ronald C. Kessler, Alaptagin Khan, Nathan A. Kimbrel, Anthony P. King, Nastassja Koen, Henry R. Kranzler, William S. Kremen, Bruce R. Lawford, Lauren A.M. Lebois, Catrin Lewis, Israel Liberzon, Sarah D. Linnstaedt, Mark W. Logue, Adriana Lori, Bozo Lugonja, Jurjen J. Luykx, Michael J. Lyons, Jessica L. Maples-Keller, Charles Marmar, Nicholas G. Martin, Douglas Maurer, Matig R. Mavissakalian, Alexander McFarlane, Regina E. McGlinchey, Katie A. McLaughlin, Samuel A. McLean, Divya Mehta, Rebecca Mellor, Vasiliki Michopoulos, William Milberg, Mark W. Miller, Charles Phillip Morris, Ole Mors, Preben Bo Mortensen, Elliot C. Nelson, Merete Nordentoft, Sonya B. Norman, Meaghan O'Donnell, Holly K. Orcutt, Matthew S. Panizzon, Edward S. Peters, Alan L. Peterson, Matthew Peverill, Robert H. Pietrzak, Melissa A. Polusny, John P. Rice, Victoria B. Risbrough, Andrea L. Roberts, Alex O. Rothbaum, Barbara O. Rothbaum, Peter Roy-Byrne, Kenneth J. Ruggiero, Ariane Rung, Bart P.F. Rutten, Nancy L. Saccone, Sixto E. Sanchez, Dick Schijven, Soraya Seedat, Antonia V. Seligowski, Julia S. Seng, Christina M. Sheerin, Derrick Silove, Alicia K. Smith, Jordan W. Smoller, Scott R. Sponheim, Dan J. Stein, Jennifer S. Stevens, Martin H. Teicher, Wesley K. Thompson, Edward Trapido, Monica Uddin, Robert J. Ursano, Leigh Luella van den Heuvel, Miranda Van Hooff, Eric Vermetten, Christiaan Vinkers, Joanne Voisey, Yunpeng Wang, Zhewu Wang, Thomas Werge, Michelle A. Williams, Douglas E. Williamson, Sherry Winternitz, Christiane Wolf, Erika J. Wolf, Rachel Yehuda, Keith A. Young, Ross McD. Young, Hongyu Zhao, Lori A. Zoellner, Magali Haas, Heather Lasseter, Allison C. Provost, Rany M. Salem, Jonathan Sebat, Richard Shaffer, Tianying Wu, Stephan Ripke, Mark J. Daly, Kerry J. Ressler, Karestan C. Koenen, Murray B. Stein, and Caroline M. Nievergelt.

FRW and MG-A contributed equally to this work as joint first authors.

HLar, MM, RP, and SMM contributed equally to this work as joint senior authors.

Address correspondence to Renato Polimanti, Ph.D., at renato.polimanti@yale.edu, and Sandra M. Meier, Ph.D., at sandra.meier@iwk.nshealth.ca.

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