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Gene-Environment Correlation Across Trauma Subtypes and Developmental Timing: Evidence From the EU-GEI and ALSPAC

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ABSTRACT

BACKGROUND: Childhood trauma is a well-known environmental risk factor for psychiatric disorders, yet genetic influences may also shape exposure to adversity via gene-environment correlation (rGE).

METHODS: We examined rGE between polygenic risk scores (PRSs) for psychiatric and behavioral traits and trauma subtypes across development in 2 large cohorts: the EU-GEI (European Network of National Schizophrenia Networks Studying Gene-Environment Interactions) case-control study (n = 1191) and the ALSPAC (Avon Longitudinal Study of Parents and Children) birth cohort (N = 8141). Trauma was assessed retrospectively in EU-GEI and both prospectively and retrospectively in ALSPAC. Multinomial logistic regressions tested associations between PRSs and timing of exposure (early: 0–11 years vs. late: 12–17 years) to 5 trauma types (emotional abuse, physical abuse, sexual abuse, bullying, and household discord).

RESULTS: In EU-GEI, 20 PRS-trauma associations survived false discovery rate correction. The posttraumatic stress disorder PRS showed strong associations with early emotional abuse (odds ratio [OR] = 3.37), sexual abuse (OR = 3.08), physical abuse (OR = 2.90), and bullying (OR = 2.19). Attention-deficit/hyperactivity disorder (ADHD) PRS was linked to early sexual abuse (OR = 1.49), emotional abuse (OR = 1.33), household discord (OR = 1.27), and bullying (OR = 1.24). Schizophrenia (SCZ) PRS was associated with early emotional abuse (OR = 1.90) and late bullying (OR = 1.46). In ALSPAC, 20 PRS-trauma associations were replicated, including ADHD, depression, bipolar disorder, SCZ, and cannabis use disorder with early traumas. Variance explained was small in both cohorts. Sensitivity analyses restricted to control participants in EU-GEI confirmed results.

CONCLUSIONS: These findings provide novel and robust evidence for rGE between psychiatric PRSs and specific trauma exposures, particularly in early development, underscoring the importance of incorporating genetic liability in trauma research.

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Childhood trauma is a widely recognized environmental risk factor for various psychiatric outcomes, including psychosis, depression, and affective dysregulation (1,2). Meta-analytic evidence confirms that individuals exposed to childhood adversities—such as abuse and bullying—are at greater risk of developing psychosis (3). However, the nature of this association remains complex. Recent work suggests that part of the link between trauma and psychopathology may be due to gene-environment correlation (rGE), in which an individual's genetic liability contributes up to 40% of the likelihood of experiencing certain environmental exposures, with stronger evidence for bullying as compared with maltreatment (4,5). rGE refers to nonrandom exposure to environments as a function of genetic liability. In the context of childhood trauma, this does not imply that victimization is genetically determined or that responsibility lies with the child. Rather, it reflects that the risks for maltreatment and bullying cluster within families and social contexts and that children differ in behavioral, emotional, and cognitive traits that can shape how they are treated by caregivers and peers. Because these characteristics are partly heritable, genetic vulnerability can be linked to exposure to adversity, via both the family context in which children are raised and the ways in which children's behaviors and emotions affect how they are treated by others.

In psychiatric genetics, rGE is increasingly explored using polygenic risk scores (PRSs), which reflect inherited liability for psychiatric and cognitive traits (6). PRSs capture only a fraction of the total genetic liability for a trait and should be interpreted as probabilistic indices rather than comprehensive measures of genetic influence. Emerging findings indicate that

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individuals with higher PRSs for schizophrenia (SCZ), depression, and other conditions are modestly more likely to report childhood adversity (7–9). These correlations can arise via passive rGE (parents' genetically influenced traits shape the home environment), evocative rGE (children's traits elicit responses from others), and active rGE (individuals select environments consistent with their traits), although the current study is not designed to disentangle these mechanisms (4,5).

Despite growing interest, prior studies have primarily examined cumulative or undifferentiated trauma exposure, often relying on retrospective self-report measures (7). However, less is known about whether polygenic liability is differentially associated with specific trauma subtypes (e.g., emotional vs. sexual abuse) or whether rGE varies by developmental timing of exposure (e.g., early or late childhood) (10). Moreover, few studies have tested rGE across multiple traits and psychiatric domains in diverse samples, considering its link with a broad range of adversities (11–13).

The developmental period may shape the extent to which genetic liability influences trauma exposure. Early childhood adversities, often embedded in the family environment, may reflect inherited risk, whereas traumas arising during adolescence—especially those outside the household—may be more contingent on peer or situational factors. To test these hypotheses, we examined rGE across multiple psychiatric and behavioral PRSs and specific trauma subtypes (i.e., emotional abuse, physical abuse, sexual abuse, bullying, and household discord) in the EU-GEI (European Network of National Schizophrenia Networks Studying Gene-Environment Interactions) case-control sample, distinguishing between early (0–11 years) and late (12–17 years) exposures. Then we evaluated replicability and generalizability in the ALSPAC (Avon Longitudinal Study of Parents and Children) birth cohort, which provides both prospective and retrospective trauma assessments across developmental windows. This 2-cohort design provides a robust test of rGE effects across different population types, measurement strategies, and stages of development.

METHODS AND MATERIALS

Study Design and Participants

This study used data from the EU-GEI project, a large multicenter case-control study investigating genetic and environmental risk factors for psychosis (14). Data were drawn from Work Package 2 of the EU-GEI study, focusing on first-episode psychosis (FEP). Participants were recruited across 16 catchment sites in 6 countries in Europe (England, the Netherlands, Spain, France, and Italy) and Brazil. FEP cases were of ages 18 to 64 years and were included if they presented with their first episode of a psychotic disorder, diagnosed according to the ICD-10 (F20–33), and confirmed using the Operational Criteria Checklist for Psychotic and Affective Illness (15). Exclusion criteria for cases included prior treatment for psychosis, diagnosis of organic psychotic disorders (ICD-10: F09), and psychotic episodes secondary to acute intoxication (ICD-10: F1X.5). Control participants were recruited from the same geographic areas as cases using a combination of random and quota population sampling strategies and were screened to ensure the lifetime absence of psychotic disorders (14). All participants provided written informed consent. Ethical approval was obtained from local and national research ethics committees in each participating site.

Replication analyses were conducted using data from ALSPAC, a U.K.-based population birth cohort study. ALSPAC initially recruited 14,541 pregnancies with expected delivery dates between April 1, 1991, and December 31, 1992 (phase 1 enrollment), resulting in 13,988 children alive at age 1 year. Subsequent recruitment phases (phases 2–4) increased the total sample to 15,447 pregnancies and 14,901 children alive at 1 year for analyses after age 7 years (16,17). The cohort provides detailed prospective and retrospective measures of environmental exposures and mental health outcomes. For the current analysis, ALSPAC participants were included if they had available genome-wide genotyping data and completed trauma exposure assessments, collected prospectively throughout childhood and adolescence and retrospectively at approximately age 22 years. Study data were collected and managed using REDCap (Research Electronic Data Capture) tool hosted at the University of Bristol (18). REDCap is a secure, web-based software platform designed to support data capture for research studies. Ethical approval for ALSPAC was obtained from the ALSPAC ethics and law committee and the local research ethics committees. Consent for biological samples was obtained in accordance with the Human Tissue Act (2004), and informed consent for questionnaire and clinic data was obtained in accordance with committee recommendations. Further information about the cohort is available at http://www.bristol.ac.uk/alspac/. The study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool.

Measures of Childhood Trauma

In the EU-GEI sample, childhood trauma exposure was assessed retrospectively using 2 instruments: 1) the Childhood Experience of Care and Abuse Interview, capturing emotional abuse, physical abuse, sexual abuse, and household discord; and 2) a dedicated bullying questionnaire, assessing peer victimization (19). For each trauma subtype, exposure timing was categorized as no exposure, early exposure (0–11 years), or late-only exposure (12–17 years), based on the reported age at first occurrence. When a trauma was reported in both developmental periods, it was coded as early exposure. Trauma subtypes were modeled separately in multinomial regression models.

The ALSPAC measures of childhood trauma are described in detail elsewhere (20). Briefly, childhood trauma was measured using an integrated approach, combining prospective assessments (collected from birth to age 17) with retrospective self-reports obtained at age 22. Trauma domains included emotional abuse, physical abuse, sexual abuse, bullying, and parental domestic violence (used as a proxy for household discord). Exposure was assessed across 3 developmental windows: early childhood (0–5 years), middle childhood (6–11 years), and adolescence (12–17 years). Binary exposure variables (present/absent) were created for each trauma subtype within each window. For comparability with EU-GEI, early trauma in ALSPAC analyses was defined as any exposure occurring before age 12 (i.e., between 0–11 years)

and late trauma as exposure occurring during adolescence (12–17 years).

Genotyping and Polygenic Risk Calculations

In EU-GEI, DNA samples were genotyped at the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University (United Kingdom), using the Illumina HumanCoreExome-24 BeadChip.

Standard quality control procedures included 1) exclusion of single nucleotide polymorphisms (SNPs) with call rates < 98%, minor allele frequency < 1%, or Hardy-Weinberg equilibrium p values $< 1 \times 10^{-6}$ in control participants; and 2) assessment of population stratification via genetic principal component analysis (PCA) (21).

PRSs were calculated separately by ancestry groups to account for differences in linkage disequilibrium (LD) patterns and allele frequencies. For participants of European (EUR) ancestry, PRSs were generated using PRS–continuous shrinkage (PRS-CS), a Bayesian regression framework applying continuous shrinkage priors and leveraging an EUR ancestry LD reference panel (1000 Genomes phase 3) (22). Unlike clumping-thresholding approaches, PRS-CS does not rely on selecting variants based on genome-wide association study (GWAS) p-value thresholds; instead, posterior SNP effect sizes are inferred genome-wide using continuous shrinkage. For participants of other ancestries, PRSs were generated using PRS-CSx, a multiancestry extension of PRS-CS that integrates summary statistics across diverse populations to improve predictive accuracy (23,24). Due to the predominance of EUR ancestry participants in EU-GEI, the main analyses were restricted to individuals of EUR ancestry to optimize PRS performance and comparability with the discovery GWASs. Additional multiancestry PRS analyses, including African and admixed ancestry participants from the EU-GEI cohort, were conducted separately and are reported in the Supplement. The most recent and largest publicly available GWAS summary statistics were used for each phenotype; further details are provided in the Supplement (25–33). To minimize bias from discovery/target overlap, we used GWAS summary statistics excluding EU-GEI and/or ALSPAC participants.

In ALSPAC, participants were genotyped using Illumina arrays, and genotype imputation was conducted using the Haplotype Reference Consortium panel. Data for 8346 participants of genetically defined EUR ancestry were provided. PRSs were calculated using PRS-CS and PLINK, following the same pipeline used for EUR participants in EU-GEI (22,34). PCs were derived separately and used to adjust for population structure.

Across both cohorts, PRSs were calculated for the following traits: 1) main PRSs–SCZ, bipolar disorder (BD), major depressive disorder (MDD), posttraumatic stress disorder (PTSD), neuroticism, and attention-deficit/hyperactivity disorder (ADHD); and 2) sensitivity PRSs–cannabis use disorder (CUD), short sleep duration, long sleep duration, and autism spectrum disorder (25–33). Main PRSs were selected as the most widely reported in prior literature examining rGE, while sensitivity PRSs are less extensively studied but potentially relevant to trauma exposure. All PRSs were standardized to z scores (mean = 0, standard deviation [SD] = 1) and adjusted for the first 10 PCs in all analyses (24).

Statistical Analyses

All statistical analyses were conducted using R Studio (version 4.3.1). We examined rGE between PRSs and trauma exposure using multinomial logistic regression models. Analyses were conducted separately for the EU-GEI and ALSPAC cohorts. Models were fitted for each trauma subtype and stratified by timing. The dependent variable was coded as a 3-level factor: no trauma, early trauma, and late trauma. Each model included the following covariates: study site, age (EU-GEI only), gender, and 10 ancestry PCs to adjust for population stratification. To quantify variance explained, we computed Nagelkerke R^2 for each model, comparing the full model (PRS+covariates) against a null model with covariates only. Nagelkerke R^2 values were interpreted as a relative measure of the contribution of PRSs to the prediction of trauma exposure. We applied false discovery rate (FDR) correction (Benjamini-Hochberg) to all PRS-trauma subtype tests within each cohort (35). Results were considered statistically significant at FDR-adjusted $p_{FDR} < .05$. In ALSPAC, identical multinomial models used trauma timing (early vs. none, late vs. none), paralleling the EU-GEI analysis. In EU-GEI, additional analyses were restricted to control participants only. In both cohorts, we conducted sensitivity analyses to assess the robustness of the findings. These included models adjusting for family history of psychiatric disorders (in EU-GEI, this referred to parental history of psychosis-specific for SCZ, BD, and MDD PRSs, and any mental illness for other PRSs; in ALSPAC, only parental history of SCZ was available), models adjusting for cannabis use frequency (categorical: non/infrequent, weekly, daily use—harmonized across cohorts), and extended multiancestry PRS analyses (EU-GEI only). To further examine developmental timing effects, overall trauma exposure was additionally modeled using a 4-category outcome (no trauma, early-only, late-only, and both early and late exposure). In ALSPAC, analyses were repeated using only retrospectively reported trauma. Finally, robustness of modeling assumptions was assessed using PRS quintile models and mutually adjusted PRS models, including all PRSs simultaneously. Full sensitivity analyses are reported in the Supplement.

RESULTS

EU-GEI Sample Characteristics

The primary analytic sample for the EU-GEI cohort comprised 1191 individuals of EUR ancestry, selected based on genetic PCA (Table 1). This subsample comprised 567 female (48%) and 624 male (52%) participants, with a mean age of 35 years (SD = 13). The distribution of trauma exposure varied significantly by age and country ($p = .011$ and $p < .001$, respectively) but not by gender ($p = .5$). Individuals reporting no trauma were on average older than those reporting early or late trauma. Early trauma was reported by 684 participants (57%) and late trauma by 128 participants (11%).

Table 1. Demographic Characteristics of the EU-GEI Sample Stratified by Trauma Timing

Characteristic	Overall, *n* = 1191	No Trauma, *n* = 379	Early Trauma, *n* = 684	Late Trauma, *n* = 128	*p* Value
Gender					
Female	567 (48%)	172 (45%)	331 (48%)	64 (50%)	.5
Male	624 (52%)	207 (55%)	353 (52%)	64 (50%)	
Age, Years	35 (13)	37 (14)	34 (13)	34 (12)	.11
Country					
Brazil	299 (25%)	115 (30%)	163 (24%)	21 (16%)	<.001
France	122 (10%)	48 (13%)	59 (8.6%)	15 (12%)	
Holland	262 (22%)	75 (20%)	160 (23%)	27 (21%)	
Italy	135 (11%)	40 (11%)	69 (10%)	26 (20%)	
Spain	102 (8.6%)	50 (13%)	45 (6.6%)	7 (5.5%)	
United Kingdom	271 (23%)	51 (13%)	188 (27%)	32 (25%)	

Values are presented as mean (SD) or *n* (%).

PRS-Trauma Associations in the EU-GEI Sample

Across the 110 models tested in the EUR ancestry subsample, 20 PRS-trauma associations survived FDR correction ($p_{FDR} < .05$). These results are illustrated in Figure 1, with complete model estimates, including odds ratios (ORs), confidence intervals (CIs), and FDR-adjusted *p* values, presented in Table S2A, B. The strongest effects were observed for the PTSD PRS, which was strongly associated with a range of early trauma exposures. PTSD genetic liability was associated with early emotional abuse (OR = 3.37, 95% CI [1.66–6.84]), early sexual abuse (OR = 3.08, 95% CI [1.33–7.12]), early physical abuse (OR = 2.90, 95% CI [1.74–4.83]), and early bullying (OR = 2.19, 95% CI [1.31–3.66]). Other psychiatric PRSs also showed consistent associations. The BD PRS was associated with early household discord (OR = 1.60, 95% CI [1.23–2.07]), early emotional abuse (OR = 1.94, 95% CI [1.27–2.98]), and late bullying (OR = 1.64, 95% CI [1.10–2.44]). The SCZ PRS was linked to early emotional abuse (OR = 1.90, 95% CI [1.35–2.66]), early household discord (OR = 1.44, 95% CI [1.18–1.76]), and late bullying (OR = 1.36, 95% CI [1.12–1.64]). The ADHD PRS was associated with multiple early traumas, including sexual abuse (OR = 1.53, 95% CI [1.11–2.11]), emotional abuse (OR = 1.50, 95% CI [1.16–1.95]), physical abuse (OR = 1.34, 95% CI [1.14–1.58]), household discord (OR = 1.40, 95% CI [1.14–1.73]), and bullying (OR = 1.36, 95% CI [1.12–1.64]). For the depression PRS, significant associations were observed with early sexual abuse (OR = 1.49, 95% CI [1.12–1.98]), early emotional abuse (OR = 1.33, 95% CI [1.06–1.68]), early household discord (OR = 1.27, 95% CI [1.10–1.46]), and early bullying (OR = 1.24, 95% CI [1.06–1.46]). Among sensitivity PRSs, the CUD PRS emerged as a significant correlate of early household discord (OR = 1.70, 95% CI [1.31–2.20]).

Variance Explained by PRSs in the EU-GEI Sample

To quantify variance explained beyond covariates, we computed incremental Nagelkerke R^2 (ΔR^2) comparing each model to a covariate-only baseline. As shown in Figure 2, ΔR^2 values were modest across trauma types, with family history typically accounting for more variance than PRS alone and combined PRS+family history yielding the largest increments. The highest ΔR^2 was observed for household discord with the CUD PRS+family history ($\Delta R^2 = 0.07$). For emotional abuse, the ADHD PRS+family history model reached $\Delta R^2 = 0.04$. PRS-only increments were generally <0.02 across subtypes.

Sensitivity Analysis: Control Participants–Only Subset

To reduce the likelihood of reverse causation or diagnostic confounding, we conducted sensitivity analyses restricted to control participants (*n* = 731). As illustrated in Figure 3, 7 PRS-trauma associations remained significant after FDR correction ($p_{FDR} < .05$). The PTSD PRS showed the strongest associations with early physical abuse (OR = 4.08, 95% CI [2.04–8.18]) and early bullying (OR = 2.81, 95% CI [1.38–5.71]). The SCZ PRS was associated with early emotional abuse (OR = 2.24, 95% CI [1.33–3.76]), while the BD PRS was associated with early household discord (OR = 1.66, 95% CI [1.18–2.36]). Among other traits, the ADHD and depression PRSs were associated with early bullying (OR = 1.55, 95% CI [1.20–2.02] and OR = 1.40, 95% CI [1.12–1.76], respectively) and the CUD PRS with early household discord (OR = 1.85, 95% CI [1.29–2.65]).

Replication Analyses in ALSPAC

In the ALSPAC cohort, 20 significant PRS-trauma associations emerged, as shown in Figure 4. These included associations across a broad range of psychiatric traits and trauma subtypes, with effects detected for both early and late exposures. Consistent with EU-GEI, most associations were observed for early trauma. Notable associations included ADHD PRS with early sexual abuse (OR = 1.33, 95% CI [1.12–1.59]), early physical abuse (OR = 1.11, 95% CI [1.03–1.20]), early bullying (OR = 1.15, 95% CI [1.09–1.26]), and early domestic violence (OR = 1.09, 95% CI [1.03–1.16]); depression PRS with early emotional abuse (OR = 1.21, 95% CI [1.14–1.28]), early sexual abuse (OR = 1.16, 95% CI [1.08–1.26]), early bullying (OR = 1.16, 95% CI [1.09–1.28]), early physical abuse (OR = 1.15, 95% CI [1.06–1.25]), early domestic violence (OR = 1.21, 95% CI [1.14–1.28]), and late domestic violence (OR = 1.36, 95% CI [1.10–1.67]); BD PRS with early emotional abuse (OR = 1.15, 95% CI [1.08–1.23]), early physical abuse (OR = 1.16, 95% CI [1.07–1.26]), early domestic violence (OR = 1.09, 95% CI

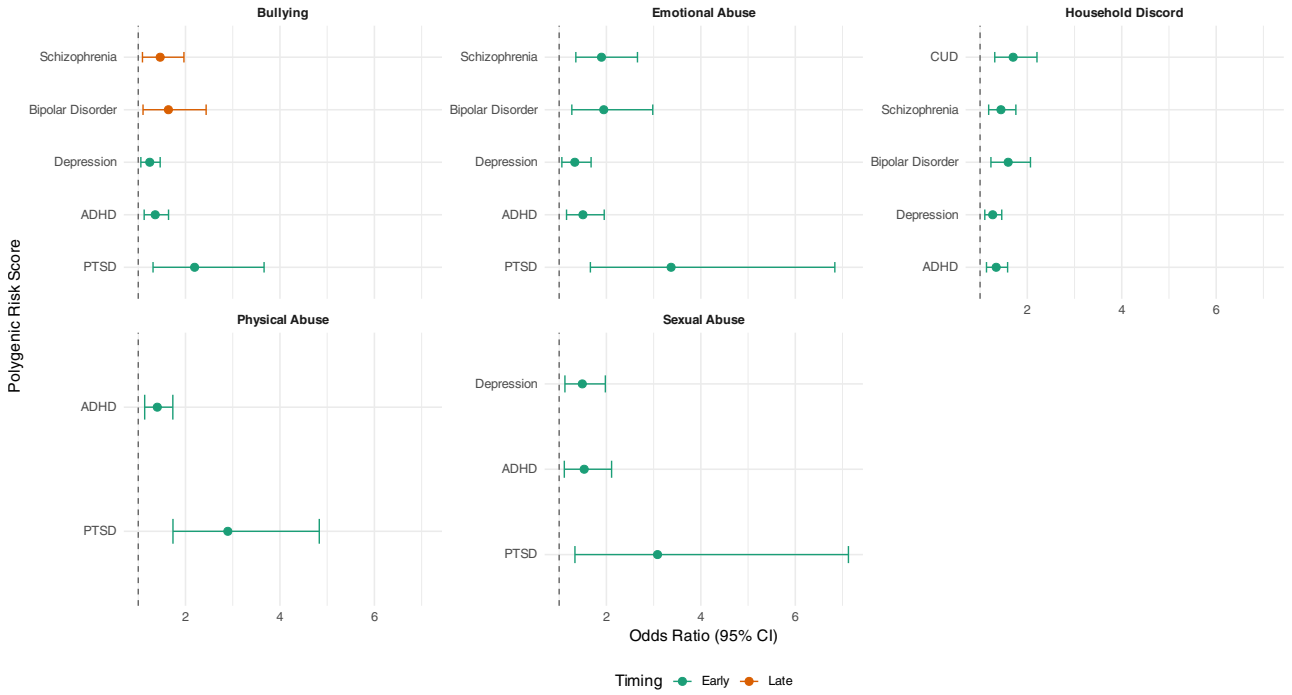

Figure 1. Forest plot of significant PRS-trauma associations (FDR < .05) in the EU-GEI sample. Odds ratios and 95% CIs from the multinomial logistic regression models examining associations between PRSs for psychiatric and behavioral traits and trauma exposure, stratified by timing (early vs. late). Forest plots are faceted by trauma subtypes (i.e., emotional abuse, physical abuse, sexual abuse, bullying, and household discord). All models are adjusted for age, gender, study site, and the first 10 genetic principal components. Green markers indicate associations with early trauma, and orange markers indicate late trauma. Only associations that survived FDR correction ($q < .05$) are shown. ADHD, attention-deficit/hyperactivity disorder; CUD, cannabis use disorder; EU-GEI, European Network of National Schizophrenia Networks Studying Gene-Environment Interactions; FDR, false discovery rate; PRS, polygenic risk score; PTSD, posttraumatic stress disorder.

[1.03–1.16]), and late sexual abuse (OR = 1.23, 95% CI [1.08–1.39]); SCZ PRS with early domestic violence (OR = 1.10, 95% CI [1.03–1.17]) and early emotional abuse (OR = 1.10, 95% CI [1.02–1.17]); CUD PRS with early domestic violence (OR = 1.13, 95% CI [1.07–1.20]); neuroticism PRS with both early and late domestic violence (OR = 1.11, 95% CI [1.05–1.18] and OR = 1.36, 95% CI [1.10–1.67], respectively); and short sleep PRS with early domestic violence (OR = 1.14, 95% CI [1.08–1.21]). Although several PRS-trauma associations were statistically significant, the variance explained beyond covariates was small (ΔR^2 generally <1%) in PRS-only models (Figure 5).

DISCUSSION

To our knowledge, this is the first study to provide comprehensive evidence for rGE between polygenic liability across several psychiatric and behavioral traits and exposure to specific types and timings of childhood trauma. Using a large, ancestrally homogeneous subsample from the EU-GEI case-control cohort, we identified 20 PRS-trauma associations after FDR correction and further explored replication and generalization in the ALSPAC birth cohort.

Our findings highlight the developmental specificity of rGE. Associations were most consistently observed for early-life trauma (i.e., before age 12 years), including emotional abuse, bullying, and household discord.

This pattern is congruent with theoretical models of passive and evocative rGE, in which inherited genetic risks shape early caregiving environments or elicit adverse reactions from adults and peers during developmental periods (4,36). Importantly, because trauma timing was coded based on first occurrence, exposures beginning early are more likely to be captured than those beginning later, which may partly explain why early associations were stronger due to greater statistical power.

The strongest and most consistent effects emerged for the PTSD PRS, which was associated with multiple trauma types, including emotional, physical, and sexual abuse, as well as bullying. The ADHD PRS also showed broad associations with emotional and interpersonal traumas, such as household discord and bullying. These patterns suggest that genetic predisposition to stress sensitivity or behavioral dysregulation may increase exposure to adverse environments. Notably, the SCZ PRS was linked to both emotional abuse and late bullying, while BD and depression PRSs showed specific associations with household discord and bullying, respectively. The CUD PRS, examined as a sensitivity trait, was significantly associated with household discord, highlighting the role of externalizing liability in conflict-prone environments.

Variance explained by PRSs was modest, consistent with expectations in polygenic models (36). However, combining PRSs with family history improved the model fit, particularly for household discord (6%–7%). This indicates that family

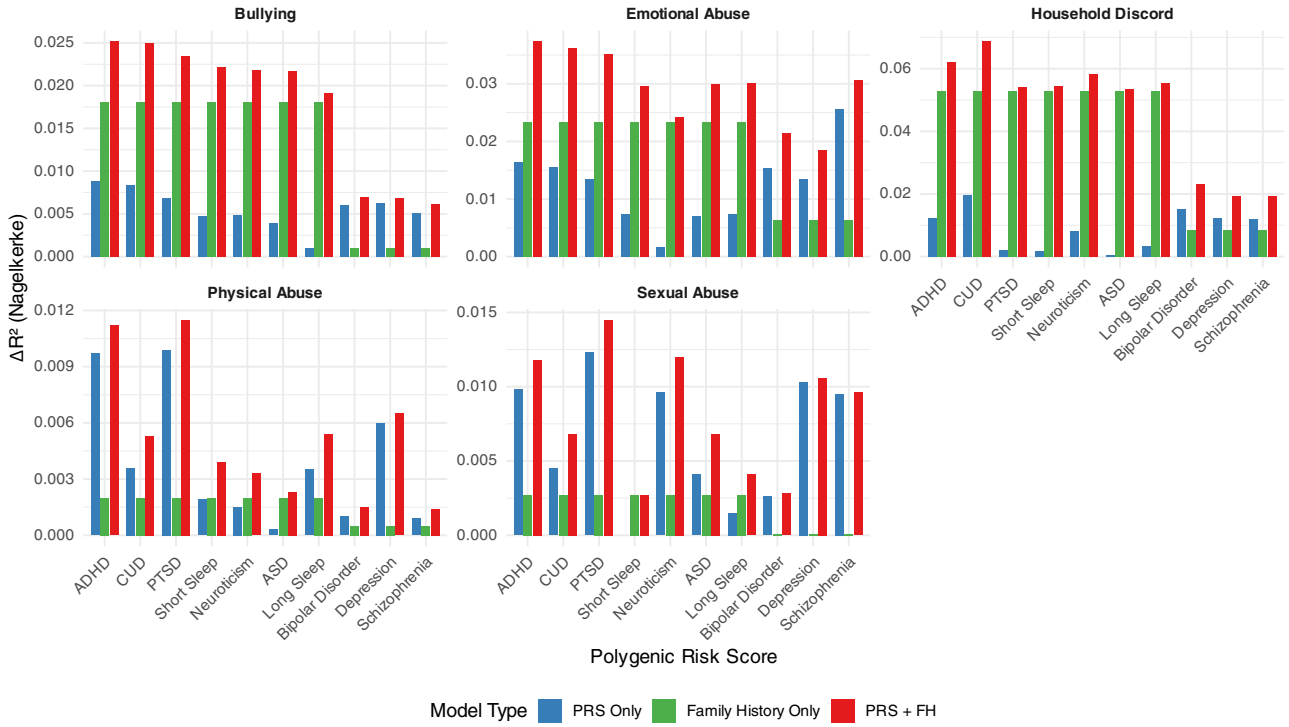

Figure 2. Variance explained by PRSs, FH, and combined models beyond covariates in the EU-GEI sample. Bar plots showing Nagelkerke R^2 values from binomial logistic regression models estimating the variance in trauma exposure explained by different predictors. Separate models were fit for each trauma subtype, comparing individuals with early trauma or late trauma to those with no trauma. Models were adjusted for sociodemographic covariates and 10 principal components. Each facet represents a trauma subtype. Within each panel, bars are grouped by PRS trait. Blue bars indicate models including only the PRS, green bars indicate models including only FH, and red bars indicate combined PRS+FH models. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CUD, cannabis use disorder; FH, family history; PRS, polygenic risk score; PTSD, posttraumatic stress disorder.

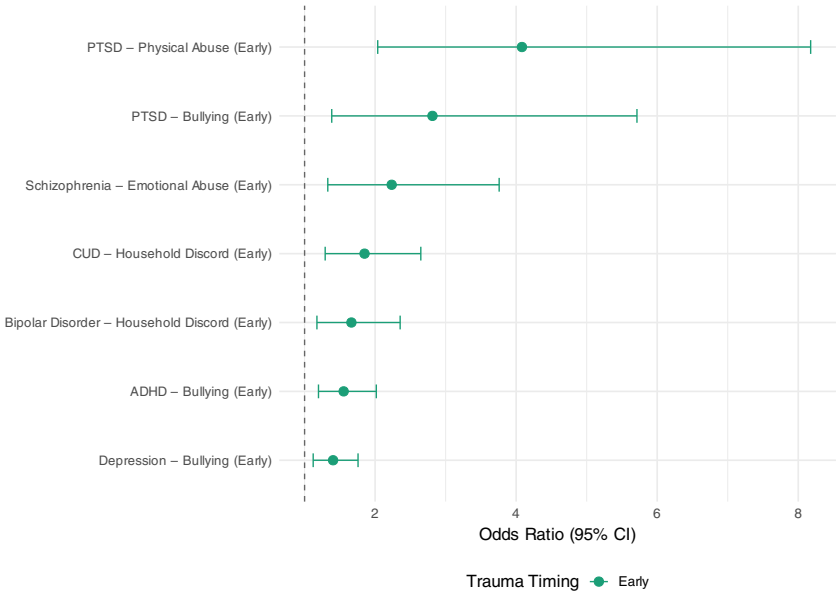

Figure 3. Forest plot of significant PRS-trauma associations (controls only). ORs and 95% CIs from multinomial logistic regression models examining associations between PRSs for psychiatric and behavioral traits and trauma exposure, stratified by timing (early vs. late). All models are adjusted for age, gender, study site, and the first 10 genetic principal components. Only associations that survived FDR correction ($q < .05$) are shown. The vertical dashed line indicates the null value (OR = 1). ADHD, attention-deficit/hyperactivity disorder; CUD, cannabis use disorder; FDR, false discovery rate; OR, odds ratio; PRS, polygenic risk score; PTSD, posttraumatic stress disorder.

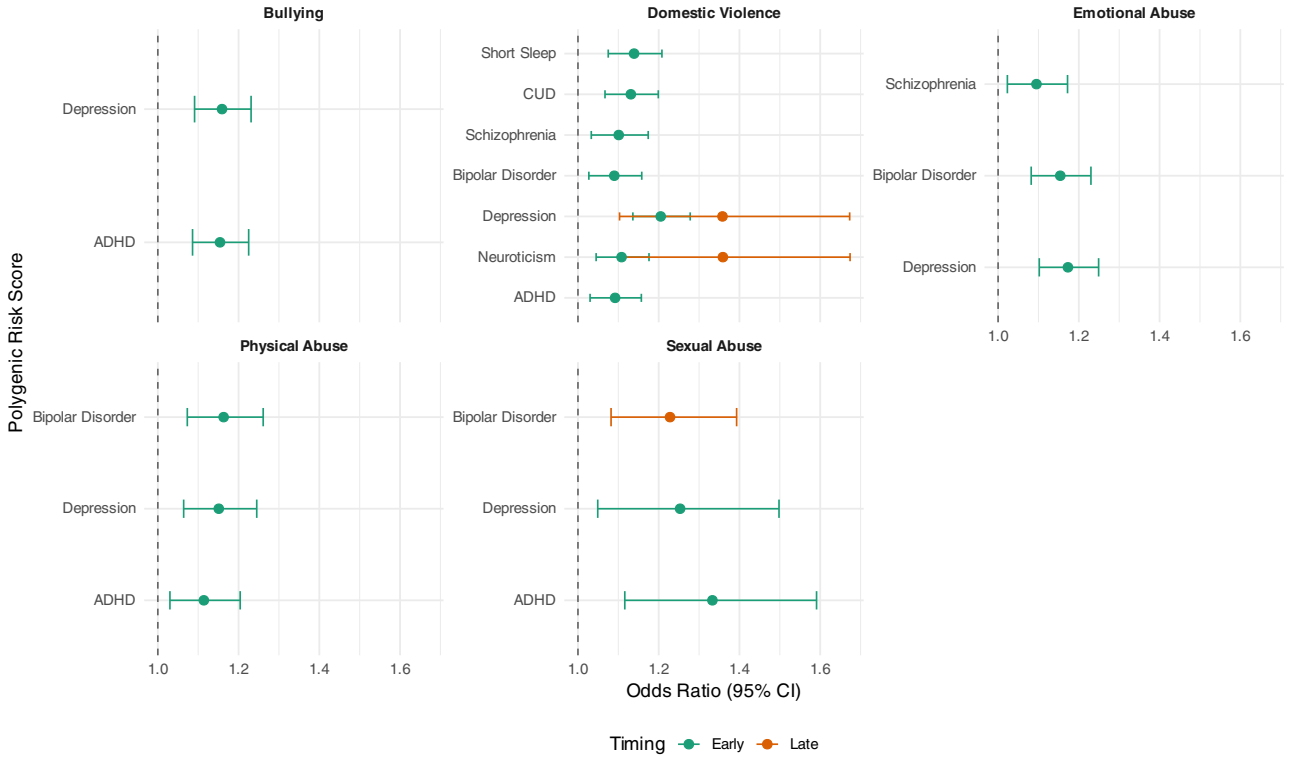

Figure 4. Forest plot of significant PRS-trauma associations (FDR < .05) in the ALSPAC cohort. Odds ratios and 95% CIs from multinomial logistic regression models examining associations between PRSs for psychiatric and behavioral traits and trauma exposure, stratified by timing (early vs. late). Forest plots are faceted by trauma subtypes (i.e., emotional abuse, physical abuse, sexual abuse, bullying, and domestic violence). All models are adjusted for gender and the first 10 genetic principal components. Green markers indicate associations with early trauma, and orange markers indicate late trauma. Only associations that survived FDR correction ($q < .05$) are shown. ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; CUD, cannabis use disorder; FDR, false discovery rate; PRS, polygenic risk score.

history captures additional variance not explained by PRSs, reflecting shared genetic and environmental pathways.

Sensitivity analyses confirmed the robustness of these findings. Restricting analyses to the control participants confirmed several key associations, reducing the risk that observed effects were driven by diagnostic status or case-control sampling.

Replication analyses in ALSPAC provided further support for these patterns, with 20 PRS-trauma associations surviving FDR correction, spanning a wide range of traits and trauma subtypes. The pattern of associations—stronger for early interpersonal trauma and clustered within traits characterized by affective or behavioral dysregulation—closely mirrored EU-GEI. However, the variance explained in ALSPAC was consistently lower even for the strongest associations. Notably, we did not replicate the PTSD PRS findings observed in EU-GEI. In sensitivity analyses restricting ALSPAC to retrospectively reported trauma, the overall pattern of associations remained comparable to primary analyses, and PTSD PRS effects remained weaker than in EU-GEI. These findings suggest that differences between cohorts are unlikely to be driven solely by prospective versus retrospective measurement. Instead, the discrepancy may reflect differences in sample characteristics, trauma severity, or other cohort-specific features.

These findings have several implications. First, they reinforce that polygenic liability is not only a marker of psychiatric risk but also a marker of increased exposure to adverse environments, especially in childhood (37). Second, they suggest that rGE may manifest most strongly in early development, when children have less autonomy to shape or escape their environment. Finally, they underscore the need to consider genetic liability in trauma research to better understand its complex origins and inform prevention.

This cross-cohort consistency highlights the generalizability and replicability of PRS-trauma associations, while also underlining important cohort differences. Retrospective trauma reporting in EU-GEI versus prospective assessments in ALSPAC may account for discrepancies in effect magnitude. Furthermore, ALSPAC's population-based design and younger age distribution contrast with the case-control sampling and broader age range of EU-GEI.

The current study was designed to test whether polygenic liability for psychiatric and behavioral traits is correlated with exposure to specific trauma subtypes at different developmental stages. Although we discussed rGE in terms of passive, evocative, and active pathways, our data structure and analytical approach did not allow us to distinguish between these mechanisms, and we therefore interpreted the findings as evidence of rGE being broadly defined rather than evidence for any specific pathway.

Despite the strengths of this study—including large, deeply phenotyped samples, harmonized trauma constructs, and

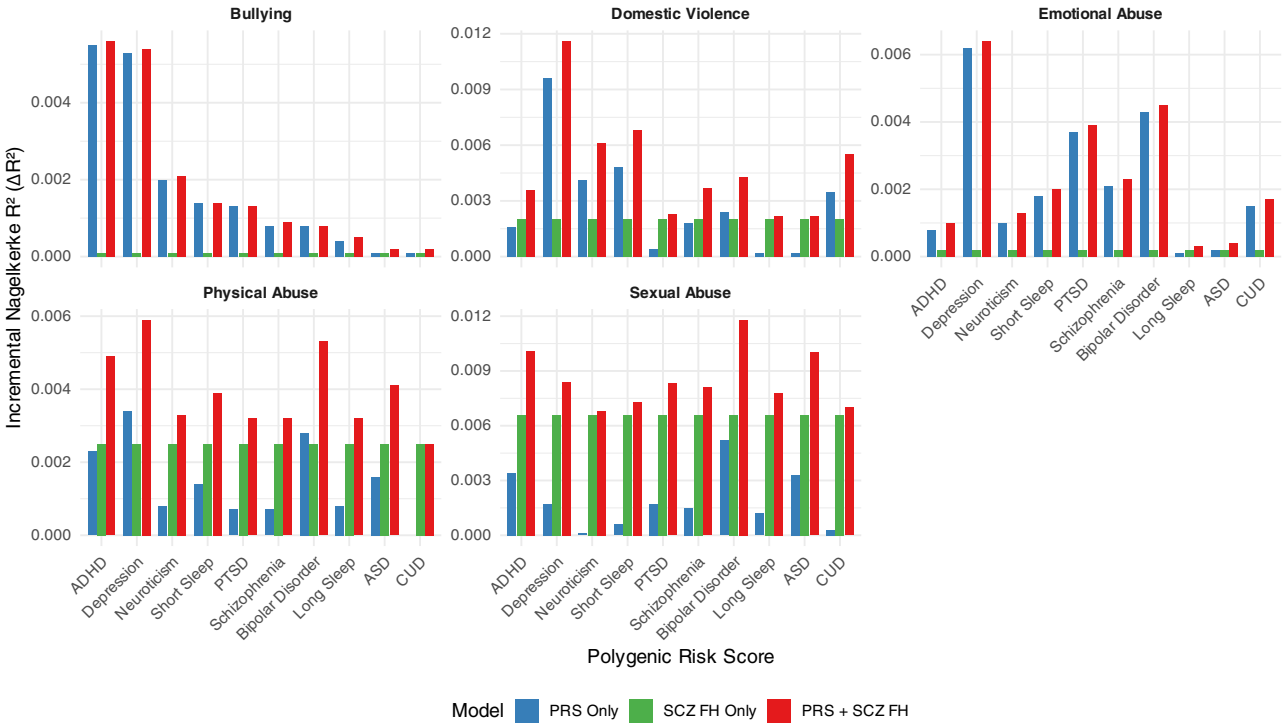

Figure 5. Variance explained by PRSs, FH, and combined models beyond covariates in the ALSPAC sample. Bar plots showing Nagelkerke R^2 values from binomial logistic regression models estimating the variance in trauma exposure explained by different predictors. Separate models were fit for each trauma subtype, comparing individuals with early trauma or late trauma to those with no trauma. Models were adjusted for sociodemographic covariates and 10 principal components. Each facet represents a trauma subtype. Within each panel, bars are grouped by PRS trait. Blue bars indicate models including only the PRS, green bars indicate models including only SCZ FH, and red bars indicate combined PRS+SCZ FH models. ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorder; CUD, cannabis use disorder; FH, family history; PRS, polygenic risk score; PTSD, posttraumatic stress disorder; SCZ, schizophrenia.

replication in an independent birth cohort—some limitations should be noted. First, trauma exposure in the EU-GEI sample was assessed retrospectively, introducing potential recall bias, particularly for early-life events (38). In cohorts relying on retrospective assessment, PRS-trauma associations may partially reflect genetically influenced differences in recall, appraisal, or interpretation of adverse experiences, rather than exposure alone. However, the subjective recall of trauma may itself be clinically meaningful; what individuals remember can have as much impact as what objectively occurred (39). From this perspective, retrospective reporting may not undermine validity and could capture the psychological consequences of trauma more effectively. Second, the trauma timing categories (early vs. late) were constrained to predefined age brackets and did not capture chronicity, severity, or cumulative burden. They also measured the age of the first exposure, not excluding that patients exposed early may also have been exposed late. More granular longitudinal data would enhance the developmental resolution of rGE effects, also exploring experiences involving neglect and deprivation, which were not available in our datasets and which remain an important type of adversity affecting mental health outcomes. Third, although PRSs were derived from large GWAS consortia, they reflect only common SNP-based liability and may miss rare or structural variants that also influence environmental risk. PRS predictive power remains limited, particularly outside EUR ancestry groups, and replication in ancestrally diverse populations is needed to test the generalizability of these findings. Fourth, the modest variance explained highlights that many other genetic and nongenetic factors likely contribute to trauma exposure, and the current models should not be interpreted deterministically. Finally, although the ALSPAC cohort provided valuable replication, differences in study design, age at assessment, and trauma detection limit direct comparability with EU-GEI.

Disentangling passive from evocative/active rGE is an important next step. Future work incorporating parental genotypes could help quantify the extent to which associations reflect familial genetic liability shaping early environments (passive rGE) versus child characteristics that evoke or select environments (evocative/active rGE).

Future research should expand beyond rGE to examine gene-by-environment interaction, testing whether genetic liability not only correlates with trauma exposure but also moderates its psychological impact. Such models may help identify subgroups of individuals who are particularly vulnerable to adverse environments due to underlying genetic sensitivity. In parallel, integrating biologically informed polygenic scores—such as pathway-specific PRSs—may enhance mechanistic interpretation and predictive utility. Together, these approaches can improve etiological models of psychopathology and contribute to the development of more tailored prevention and intervention strategies.

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