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Archival Report

Does Childhood Trauma Moderate Polygenic Risk for Depression? A Meta-analysis of 5765 Subjects From the Psychiatric Genomics Consortium

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ABSTRACT

BACKGROUND: The heterogeneity of genetic effects on major depressive disorder (MDD) may be partly attributable to moderation of genetic effects by environment, such as exposure to childhood trauma (CT). Indeed, previous findings in two independent cohorts showed evidence for interaction between polygenic risk scores (PRSs) and CT, albeit in opposing directions. This study aims to meta-analyze MDD-PRS × CT interaction results across these two and other cohorts, while applying more accurate PRSs based on a larger discovery sample.

METHODS: Data were combined from 3024 MDD cases and 2741 control subjects from nine cohorts contributing to the MDD Working Group of the Psychiatric Genomics Consortium. MDD-PRS were based on a discovery sample of ~110,000 independent individuals. CT was assessed as exposure to sexual or physical abuse during childhood. In a subset of 1957 cases and 2002 control subjects, a more detailed five-domain measure additionally included emotional abuse, physical neglect, and emotional neglect.

RESULTS: MDD was associated with the MDD-PRS (odds ratio [OR] = 1.24, $p = 3.6 \times 10^{-5}$, $R^2 = 1.18\%$) and with CT (OR = 2.63, $p = 3.5 \times 10^{-18}$ and OR = 2.62, $p = 1.4 \times 10^{-5}$ for the two- and five-domain measures, respectively). No interaction was found between MDD-PRS and the two-domain and five-domain CT measure (OR = 1.00, $p = .89$ and OR = 1.05, $p = .66$).

CONCLUSIONS: No meta-analytic evidence for interaction between MDD-PRS and CT was found. This suggests that the previously reported interaction effects, although both statistically significant, can best be interpreted as chance findings. Further research is required, but this study suggests that the genetic heterogeneity of MDD is not attributable to genome-wide moderation of genetic effects by CT.

Keywords: Childhood trauma, Depression, Genetics, Interaction, Meta-analysis, Polygenic risk

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Recent studies have found the first associated genetic variants for major depressive disorder (MDD) and depressive complaints (1–3), but research on MDD still has not met the success of research on schizophrenia, for which 108 genetic variants were found in 2014 (4). This discrepancy is attributable to several factors, including the higher population prevalence of MDD (so that the difference in liability between cases and control subjects is smaller than in schizophrenia cases) (5,6), the lower heritability of MDD (assuming the same degree of polygenicity in terms of number of risk loci) (5), and the greater genetic and phenotypic heterogeneity of MDD (7). To illustrate the possible consequence of heterogeneity, Wray and Maier (8) showed that the power to detect a causal single nucleotide polymorphism (SNP) decreases dramatically when a disorder is caused by two distinct pathways, while Milaneschi *et al.* (9,10) found that genetic effects in those with typical MDD might partially differ from genetic effects in those with atypical MDD.

Another source of genetic heterogeneity may arise from gene-by-environment (G × E) interaction: the moderation of genetic effects on MDD by specific environmental factors. Much research concerning G × E interaction has been

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conducted with candidate genes, in particular the interaction between the serotonin transporter gene *5-HTTLPR* and childhood trauma (CT) (11), but this research has produced contradictory findings (12–15) that have been attributed, at least in part, to publication bias (16). Recently, Culverhouse *et al.* published results from a collaborative meta-analysis showing no evidence for interaction between *5-HTTLPR* and CT (17) based on a previously published protocol for analyses (18). Nevertheless, in the last couple of years, methods have been developed to assess the combined impact of all genotyped SNPs, such as polygenic risk score (PRS) analyses (19). Kendler (20) proposed that a confirmed main effect is a desirable condition for G × E interaction testing. This suggests that PRSs may be preferable over candidate genes to test for G × E interaction, because PRSs have a confirmed significant effect on MDD (21,22) contrasting the nonreplicated and nonconsistent effects of candidate genes (23,24).

In G × E interaction research, numerous environmental factors can be tested, which may have catalyzed publication bias in the candidate gene literature (16) and may also present as a challenge for G × E interaction tests with PRSs. Nevertheless, a plausible environmental factor to test in the context of G × E interaction is CT, which is one of the strongest risk factors with a lifelong impact on MDD risk (25) and may perhaps be more uniformly defined than stress later in life. Moreover, exposure to CT has been hypothesized to distinguish a clinically and neurobiologically distinct subtype of MDD, because MDD patients exposed to CT have an earlier onset, more chronic course, higher severity with more neurovegetative and psychotic symptoms, more comorbidities, more suicide attempts, and poorer treatment outcome than MDD patients that did not experience CT (26).

Following this reasoning, Peyrot *et al.* (27) tested for G × E interaction between PRS and CT in the NESDA (Netherlands Study of Depression and Anxiety) and found a significantly stronger impact of PRS on MDD risk in individuals exposed to CT compared with that on individuals not exposed to CT. In a replication study, Mullins *et al.* (28) found a significant but opposing interaction effect in the RADIANT-UK sample with a stronger impact of PRS on MDD risk in those unexposed to CT. These opposing findings, both of which were significant, are not well understood, and it remains unclear whether these reflect actual differences between cultures, differences between recruitment of participants into cohorts, or chance findings. The aim of the current study is 1) to reanalyze NESDA and RADIANT-UK with more accurate PRSs based on discovery results from ~110,000 individuals (compared with ~15,000 applied previously) and 2) to place the NESDA and RADIANT-UK findings in a broader perspective by meta-analyzing their results with seven additional cohorts from the Psychiatric Genomics Consortium (PGC) MDD wave 2 (29). Secondary analyses used PRS calculated from discovery genome-wide association study (GWAS) results for schizophrenia and bipolar disorder, as these are genetically related to MDD (7,30).

METHODS AND MATERIALS

Subjects

Subjects were recruited from the PGC wave 2, which combines genotype and phenotype data of individuals of European ancestry in 29 different cohorts (29). The combined samples include data of 16,823 MDD cases and 25,632 control subjects. Of these 29 cohorts, nine cohorts included a measure of CT: Cognition and Function in Mood Disorders Study (COFAMS) from Australia (31); Depression Gene Network (DGN) from the U.S. (32); the NESDA (33); the Queensland Institute of Medical Research (QIMR in three different cohorts defined by genotyping platform) from Australia (23); RADIANT-UK (34); and SHIP (Study of Health in Pomerania) (both SHIP-0 and SHIP-TREND) from Germany (see Supplemental Table S1 for more detailed information) (35). Briefly, SHIP-O, SHIP-T, and QIMR are community studies with MDD cases and screened control subjects defined from responses to self-report questionnaires, while the other studies recruit MDD cases from inpatient or outpatient clinics and recruit screened control subjects, with both cases and control subjects completing the same CT questionnaires. The definition of MDD in all studies was based on structured psychiatric interviews following DSM-IV criteria.

Childhood Trauma Questionnaire

The Childhood Trauma Questionnaire (CTQ) was applied to assess CT, defined as trauma before the age of 16, in five of the nine cohorts (COFAMS, NESDA/Netherlands Twin Register (NTR), RADIANT-UK, SHIP-0, and SHIP-TREND). The CTQ covers the five domains of sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. Each domain is assessed by five questions (scored 1 to 5) resulting in a domain score ranging from 5 to 25, and an overall CTQ continuous score ranging from 25 to 125 (36). Per domain, cutoffs were applied to define a narrow definition of CT separating no or mild trauma from moderate or severe trauma (Supplemental Methods). From this, an overall dichotomous CTQ indicator was constructed to separate trauma in any of the five domains (indicator = 1) from trauma in none of the domains (indicator = 0). The analyses were based on the continuous and dichotomous five-domain CT scores. The five domains were highly correlated: all pairwise correlation coefficients were larger than 0.4 except for sexual abuse, which was slightly less connected (Supplemental Table S2), as has previously also been reported by Spinhoven *et al.* (37).

Other CT Instruments

In addition to the five cohorts that assessed CT with the CTQ instrument, four additional PGC cohorts (DGN and the three subcohorts of QIMR) assessed CT with other instruments (before the age of 18 in QIMR). To obtain the largest possible dataset, CT information was matched across all nine cohorts for sexual abuse and physical abuse (Supplemental Methods). A broad definition (no abuse vs. mild, moderate, or severe abuse) was applied to create a CT indicator separating those with trauma (exposed to sexual and/or physical abuse) from those not exposed to CT (neither exposed to sexual nor physical abuse). The correlation (Spearman's rho) between the two-domain dichotomous CT indicator and the five-domain continuous CT score equaled .50 ($p < 2 \times 10^{-16}$).

Genotyping, Quality Control, and Imputation

The cohorts were genotyped following their local protocols, after which quality control and imputation against the reference panel of the 1000 Genomes Project (38) were performed centrally in the PGC per cohort (29). The SNP probabilities were converted to best-guess data with a genotype call probability cutoff of 0.8, after which individuals were removed with a missing rate >2%. A total of 1,171,526 HapMap 3 SNPs passed postimputation quality control in at least two of nine batches (missing rate <2%, minor allele frequency >0.01, and imputation INFO score >0.6). These 1,171,526 SNPs were used to calculate the genetic relatedness matrix (GRM) with PLINK 2.0 (39), which was thus based on a different set of SNPs for individuals from each cohort and between each pair of cohorts (Supplemental Table S3), in this way providing genome-wide coverage of well-described HapMap 3 SNPs. From the GRM, unrelated individuals were selected with relatedness <0.05, and ancestry informative principal components were calculated with GCTA (40).

Polygenic Risk Scores

PRSs for MDD (MDD-PRS) were based on meta-analysis of the GWAS results from the 20 PGC MDD wave 2 cohorts with no CT information available (10,409 cases, 18,640 control subjects) (29), deCODE (1980 cases, 9536 control subjects) (29), Generation Scotland (997 cases, 6358 control subjects) (41,42), GERA (Genetic Epidemiology Research on Adult Health and Aging) (7162 cases, 38,307 control subjects) (43), The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPsych) (16,242 cases, 15,847 control subjects) (29), and UK Biobank (8248 cases, 16,089 control subjects) (44,45). This discovery sample comprised 45,038 cases and 104,777 control subjects yielding a power similar to a sample of 56,134 cases and 56,134 control subjects ($n_{effective}$ = 56,134 + 56,134 = 112,268). Additional PRSs were based on GWAS results from schizophrenia (SCZ-PRS) (4) and bipolar disorder (BIP-PRS) (46), because these disorders are genetically related to MDD (7,30). PRSs were calculated using 463,215 SNPs shared between the discovery sample results and passing quality control in all cohorts (missing rate <2%, minor allele frequency >0.01, and imputation INFO score >0.6). Thus, PRSs were based on the same set of SNPs in all analyses to increase comparability of results across cohorts. These SNPs were clumped with PLINK (—clump-p1 1—clump-p2 1—clump-r2 0.25—clump-kb 500) and provided 73,576 lowly correlated SNPs for MDD, 73,559 for SCZ, and 73,656 for BIP. The MDD-PRS were based on five different thresholds of GWAS significance for SNP inclusion (p < .01, .05, .1, .5, and 1, respectively). The SCZ-PRS was based on a threshold of p < .05, which provided optimal predictive power on SCZ (4). The BIP-PRS was based on a threshold of p < .5 with best predictive performance on BIP (46). The PRS were calculated by summing the number of risk alleles weighted by their effect size (score command in PLINK) (39).

Statistical Analyses

The prevalences at the population level of the five- and two-domain dichotomous CT indicators were approximated from this study assuming a population lifetime risk of MDD of 15%, with a lifetime risk of 20% in women and 10% in men (5,47). The impact of the PRS, CT, and PRS × CT was first estimated in the individual cohorts, and the effects in the total sample were subsequently assessed with random-effect meta-analysis. Within each cohort, the impact of CT on MDD was assessed with logistic regression including sex as covariate. The tests for the main effects of the PRS on MDD included sex and the first three ancestry informative principal components as covariates. Interaction analyses were conducted with the 5-domain continuous CT measure and with the 2-domain dichotomous CT indicator. Interaction analyses of PRS × CT were corrected for sex, three principal components, PRS, CT, and the interaction terms of PRS and CT with sex and the principal components in line with Keller's recommendation (48). With logistic regression, interaction is tested as departure from multiplicativity (combined impact different from the product of the individual effects), but it has been argued that interaction as departure from additivity (combined impact different from the sum of the individual effects) is more meaningful biologically (49). For testing interaction as departure from additivity, the relative excess risks due to interaction were estimated with the coefficients from logistic regression as $e^{\widehat{\beta_{PRS}}+\widehat{\beta_{CT}}+\widehat{\beta_{PRSxCT}}}-e^{\widehat{\beta_{PRS}}}-e^{\widehat{\beta_{CT}}}+1$, and their 95% confidence intervals (CIs) by means of bootstrapping with 10,000 iterations. The impact of the PRS on MDD was further expressed as variation explained on the liability scale, R^2 (50). The PRS and continuous five-domain CT measure were standardized (i.e., mean of 0 and variance of 1), and the presented odds ratios (ORs) can thus be interpreted as increased MDD risk per standard deviation increase in PRS or CT. The analyses were conducted in R (51).

GRM-Based Analyses

The variance in MDD liability and CT explained by genotyped SNPs (SNP heritability) was assessed with cross-product Haseman-Elston regression (52). These analyses were corrected for covariates by calculating the residuals of linear regression of MDD and CT on sex, genotyping batch, and 20 ancestry-informative principal components. We included 20 principal components, because GRM-based analyses are more sensitive to population stratification than PRS analyses are (7). To test for interaction between CT and genome-wide genetic effects in MDD, the genetic correlation between MDD in unexposed individuals and MDD in exposed individuals can give information about differences in genetic effects (53). Unfortunately, the current data did not allow for the latter analyses because of limited sample size (e.g., only 389 exposed control subjects), while analyses had to be corrected for nine cohorts.

RESULTS

Phenotypic Association Between MDD and CT

The five-domain continuous and dichotomous CT measures were available for 1957 cases and 2002 control subjects, and the two-domain dichotomous indicator was available for 3024 cases and 2741 control subjects. The prevalence of CT was estimated at 0.25 based on the five-domain indicator (Table 1), and at 0.17 for the two-domain indicator. As expected, the

Table 1. Number of Depression Cases and Control Subjects and the 5-Domain CT Measure

			Dichotomous CT Indicator				Continuous CT Measure		
	n		Proportion of CT				Mean (SD)		
Cohort	Case	Control	Case	Control	Pop	OR (*p* Value)	Case	Control	OR (*p* Value)
Male and Female									
COFAMS	56	22	0.70	0.23	0.30	7.22 (8.6×10^{-4})	54.7 (21.4)	33.2 (11.6)	5.60 (1.2×10^{-3})
NESDA	1143	272	0.53	0.21	0.26	4.18 (6.9×10^{-19})	43.0 (14.6)	33.6 (9.1)	3.29 (3.4×10^{-21})
RADIANT-UK	269	267	0.62	0.18	0.24	7.60 (1.1×10^{-22})	46.4 (16.2)	32.7 (8.8)	4.08 (7.4×10^{-21})
SHIP-0	340	993	0.36	0.23	0.25	1.94 (1.1×10^{-6})	37.4 (12.3)	33.0 (8.4)	1.52 (7.4×10^{-11})
SHIP-TREND	149	448	0.28	0.15	0.17	2.43 (1.5×10^{-4})	36.9 (14.2)	31.6 (7.3)	1.72 (2.4×10^{-7})
Total	1957	2002	0.50	0.21	0.25	3.80 (3.0×10^{-6})	42.4 (15.1)	32.7 (8.4)	2.62 (1.4×10^{-5})
Male Only									
COFAMS	20	12	0.55	0.25	0.28	3.67 (1.1×10^{-1})	50.2 (19.9)	34.8 (14.5)	2.94 (4.4×10^{-2})
NESDA	357	111	0.53	0.19	0.22	4.70 (5.4×10^{-9})	42.0 (13.5)	33.4 (9.1)	3.17 (3.4×10^{-9})
RADIANT-UK	73	109	0.62	0.18	0.23	7.42 (7.8×10^{-9})	45.5 (14.5)	33.2 (9.1)	3.43 (4.4×10^{-8})
SHIP-0	112	562	0.39	0.25	0.26	1.95 (1.8×10^{-3})	37.0 (9.1)	33.2 (7.8)	1.48 (1.8×10^{-5})
SHIP-TREND	44	246	0.27	0.18	0.19	1.71 (1.5×10^{-1})	35.7 (10.9)	32.3 (7.5)	1.42 (1.3×10^{-2})
Total	606	1040	0.49	0.22	0.25	3.30 (8.7×10^{-5})	41.3 (13.4)	33.0 (8.2)	2.18 (1.1×10^{-4})
Female Only									
COFAMS	36	10	0.78	0.20	0.32	14.0 (2.9×10^{-3})	57.2 (22.0)	31.4 (7.0)	18.44 (2.2×10^{-2})
NESDA	786	161	0.53	0.23	0.29	3.90 (2.1×10^{-11})	43.5 (15.1)	33.7 (9.0)	3.30 (1.5×10^{-13})
RADIANT-UK	196	158	0.61	0.17	0.26	7.70 (2.4×10^{-15})	46.8 (16.8)	32.3 (8.6)	4.41 (3.0×10^{-14})
SHIP-0	228	431	0.35	0.22	0.24	1.94 (1.7×10^{-4})	37.5 (13.6)	32.6 (9.0)	1.57 (5.5×10^{-7})
SHIP-TREND	105	202	0.29	0.11	0.15	3.10 (2.6×10^{-4})	37.4 (15.4)	30.7 (6.9)	2.04 (1.2×10^{-5})
Total	1351	962	0.50	0.19	0.25	4.03 (2.5×10^{-6})	42.8 (15.8)	32.3 (8.6)	2.74 (3.6×10^{-5})

Information is displayed for the cohorts that assessed childhood trauma (CT) with the Childhood Trauma Questionnaire covering the five domains of sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglect in a dichotomous five-domain indicator (exposed vs. unexposed) and continuous measure (ranging from 25 to 125). For the dichotomous CT measure, the proportion of exposed individuals is presented in cases, control subjects, and in terms of the full population (Pop) assuming a population prevalence of major depressive disorder of 15% with twice the prevalence in female subjects (20%) as in male subjects (10%), as well as the odds ratio (OR) of exposed versus unexposed to develop major depressive disorder. For the continuous CT measure, the means are displayed in the original scale, and the OR for major depressive disorder was assessed for the Childhood Trauma Questionnaire measure scaled to variance 1 and can thus be interpreted as increased odds per SD increase in childhood trauma. The ORs were estimated with logistic regression including sex as covariate. The ORs in the Total sample were estimated with random effect meta-analysis.

COFAMS, Cognition and Function in Mood Disorders Study; NESDA, Netherlands Study of Depression and Anxiety; SHIP, Study of Health in Pomerania.

prevalence was considerably larger in cases than control subjects (0.50 vs. 0.21 for the five-domain measure and 0.35 vs. 0.14 for the two-domain measure). This was reflected in an OR for MDD of 3.80 ($p = 3.0 \times 10^{-6}$) for the five-domain dichotomous measure, and an OR of 2.63 ($p = 3.5 \times 10^{-18}$) for the two-domain measure. For the five-domain continuous CT measure, an OR for MDD of 2.62 ($p = 1.4 \times 10^{-5}$) per standard deviation increase in CT was found (Table 1, Figure 1). The impact of CT on MDD was comparable in men and women, with ORs of 2.18 (male subjects, $p = 1.1 \times 10^{-4}$) and 2.74 (female subjects, $p = 3.6 \times 10^{-5}$) per standard deviation increase in the continuous five-domain CT measures (Table 1). CT had an impact on MDD risk in all cohorts (Table 1), and the five CTQ domains all had an impact on MDD risk (Supplemental Table S4).

PRS Analyses

The MDD-PRS based on all SNPs (inclusion threshold of $p < 1$) had the greatest predictive power, with an OR of 1.34 ($p = 5.1 \times 10^{-11}$, $R^2 = 1.71\%$) in the 1957 cases and 2002 control subjects with availability of the five-domain CT measures (Table 2). The SCZ-PRS and BIP-PRS also predicted MDD but to a lesser extent than the MDD-PRS (Table 2), reflecting the well-described genetic correlation among MDD, BIP, and SCZ (7). Because gene-environment correlation can lead to spurious G × E results (54), we tested for an association between the MDD-PRS and CT. The MDD-PRS did predict the five-domain continuous CT measure ($\beta = .76$, $p = .004$ in linear regression), but this was approximated to reflect only a small correlation in terms of the full population of ~0.04 (Supplemental Table S5). No interaction between the PRS and the five-domain continuous CTQ measure was found, with an impact of MDD-PRS × CT on MDD with an OR of 1.05 ($p = .52$) (Table 2). In addition, no evidence was found for interaction as departure from additivity (relative excess risks due to interaction = 0.83, 95% CI = −0.62 to 18.03). The BIP-PRS and SCZ-PRS showed no evidence for interaction with the five-domain CT measure.

Applying the two-domain dichotomous CT indicator of sexual or physical abuse allowed inclusion of four additional cohorts in the analyses (Table 3): DGN and three QIMR cohorts

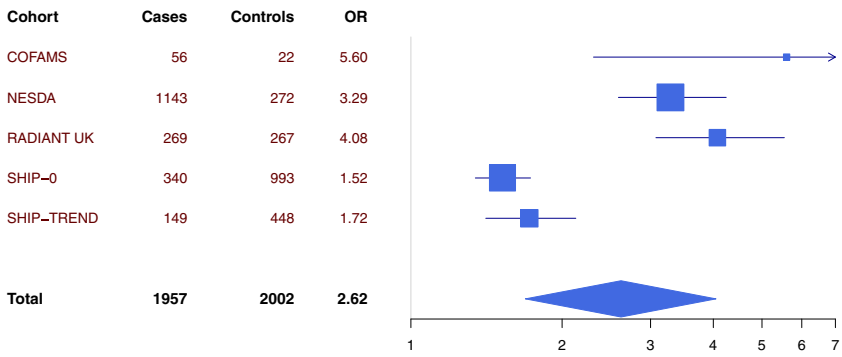

Figure 1. Forest plot of impact on major depressive disorder of the continuous childhood trauma score covering the five domains of sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. The odds ratio (OR) represents one standard deviation increased in childhood trauma. COFAMS, Cognition and Function in Mood Disorders Study; NESDA, Netherlands Study of Depression and Anxiety; SHIP, Study of Health in Pomerania.

(one of the QIMR cohorts was split in two to acknowledge different instruments applied to assess CT). The total sample size thus increased to 3024 cases and 2741 control subjects, in which the MDD-PRS had an impact on MDD with an OR of 1.24 ($p = 3.6 \times 10^{-5}$, $R^2 = 1.18\%$). The PRS did predict MDD in DGN, but not in all QIMR cohorts, which is attributable to the relatively small number of QIMR subjects with CT information available compared with the full QIMR sample (in which PRS predict MDD as expected). No interaction was found between the PRS and two-domain dichotomous CT indicator (Table 3).

An alternative method sometimes applied to test for interaction as departure from additivity is linear regression with the disease trait as outcome (28). We suggest caution in interpreting findings from this approach because this method has, to the best of our knowledge, not been formally described. Nevertheless, for reasons of completeness, this approach was applied and also showed no evidence for interaction with the five-domain CT measure ($\beta = -.004$, $p = .67$) and the two-domain CT measure ($\beta = -.005$, $p = .45$).

GRM-Based Analyses

The SNP heritability of MDD was estimated at 0.14 (SE = 0.03; $p = 3.7 \times 10^{-8}$) based on the 6348 cases and 6751 control subjects across the nine cohorts (Supplemental Table S1; these analyses included additional individuals with no CT information available). The SNP heritability of CT was estimated at 0.00 (SE = 0.07; $p < 1$; $n = 3959$) for the five-domain continuous measure, and at 0.09 (SE = 0.08; $p = .27$; $n = 5765$) for the two-domain dichotomous indicator.

DISCUSSION

This study was conducted to test for interaction between polygenic risk for MDD and CT in 5765 individuals from nine cohorts contributing to the PGC that had a CT assessment available. CT occurred in 25% of individuals based on an indicator of five domains (sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect) and in 17% based on broad definition of two domains (sexual and/or physical abuse). As expected, the prevalence was considerably higher in cases than control subjects (0.50 vs. 0.21 for the five-domain measure and 0.35 vs. 0.14 for the two-domain measure). The five-domain measure was more detailed and uniformly assessed in 1957 cases and 2002 control subjects; the two-domain indicator was assessed heterogeneously across cohorts, but available for a larger sample comprising 3024 cases and 2741 control subjects. The PRSs explained 1.18% to 1.71% of variation in MDD risk. No evidence for interaction between PRS and CT was found with the five-domain CT measure (Table 2) and the two-domain CT indicator (Table 3). Secondary analyses also showed no evidence for interaction in analyses with PRS based on discovery results from schizophrenia and bipolar disorder, in tests for interaction as departure from additivity, in analyses in male and female subjects separately (Supplemental Table S6), and in analysis in the five separate domains of CT (Supplemental Table S7; significance threshold 0.01 = 0.05/5). Analyses excluding NESDA and RADIANT-UK showed no evidence for interaction between the MDD-PRS (p value threshold 1) and five-domain CT measure (OR = 1.06, $p = .67$) and two-domain CT measure (OR = 0.98, $p = .61$) in the remainder of the cohorts.

Remarkably, no interaction effects were found in NESDA (OR = 1.08, 95% CI = 0.83–1.39, $p = .56$) and RADIANT-UK (OR = 0.93, 95% CI = 0.66–1.31, $p = .67$) with the five-domain CT measure (Table 2), which contrasts previous findings in these respective cohorts by Peyrot *et al.* (27) (OR = 1.12, $p = .018$, discovery sample $n_{effective} = 15{,}295$) and Mullins *et al.* (28) (OR = 0.96 based on differently scaled PRS and CT, $p = .002$, discovery sample $n_{effective} = 15{,}540$). Aiming to clarify these discrepancies, we analyzed PRS based on discovery results from PGC MDD wave 2 with an effective sample size of ~37,000 (Supplemental Table S8) and confirmed the previously reported interaction effects in NESDA (OR = 1.38, 95% CI = 1.07–1.76, $p = .011$) and RADIANT-UK (OR = 0.67, 95% CI = 0.51–0.90, $p = .006$). Therefore, it appears that the ORs of the interaction effects are reduced by adding deCODE (29), Generation Scotland (41,42), GERA (43), iPsych (29), and UK Biobank (44,45) to the PRS discovery sample. These discrepancies in interaction results may reflect different study designs in the discovery datasets with application of self-reported depression status in UK Biobank and clinical records in iPsych and GERA, contrasting the semistructured interviews (such as the Structured Clinical Interview for DSM, Composite International Diagnostic Interview, and Mini International Neuropsychiatric Interview) applied in most PGC cohorts (29). However, these discrepancies may also reflect random variation in effects with discovery sample size increasing from ~37,000 to ~110,000. The latter possibility seems more likely since 1) we observe an increase in the variance explained by the PRS from 0.66% ($p = 2.8 \times 10^{-5}$) to

Table 2. Impact on MDD of PRS and Their Interaction With the Five-Domain CT Continuous Measure of Sexual Abuse, Physical Abuse, Emotional Abuse, Physical Neglect, and Emotional Neglect

			Impact on MDD					
	n		PRS			PRS × CT		
Discovery	Case	Control	OR (95% CI)	*p* Value	R^2 (SE, %)	OR (95% CI)	*p* Value	RERI (95% CI)
COFAMS								
MDD $p < 1$	56	22	1.41 (0.82:2.49)	.212	3.13 (4.61)	0.38 (0.08:1.74)	.201	−2.07 (NA:NA)
SCZ $p < .05$	56	22	1.18 (0.59:2.33)	.623	0.54 (1.95)	0.01 (0.00:0.37)	.030	−62.80 (NA:NA)
BIP $p < .5$	56	22	0.85 (0.44:1.58)	.612	0.44 (1.77)	0.13 (0.01:0.96)	.076	−2.46 (NA:NA)
NESDA								
MDD $p < 1$	1143	272	1.24 (1.08:1.42)	.002	1.33 (0.84)	1.08 (0.83:1.39)	.556	1.06 (−1.07:10.48)
SCZ $p < .05$	1143	272	1.25 (1.07:1.46)	.006	1.02 (0.74)	0.91 (0.68:1.22)	.510	0.39 (–1.18:8.78)
BIP $p < .5$	1143	272	1.14 (1.00:1.31)	.049	0.53 (0.53)	1.19 (0.92:1.52)	.182	1.97 (–0.28:17.61)
RADIANT-UK								
MDD $p < 1$	269	267	1.64 (1.35:2.00)	6.8×10^{-7}	5.90 (2.19)	0.93 (0.66:1.31)	.670	4.42 (−1.78:178.22)
SCZ $p < .05$	269	267	1.61 (1.31:2.01)	1.3×10^{-5}	4.44 (1.92)	0.90 (0.62:1.30)	.581	9.87 (−0.43:275.79)
BIP $p < .5$	269	267	1.19 (1.00:1.43)	.053	0.85 (0.86)	1.02 (0.75:1.38)	.920	4.25 (−0.95:137.22)
SHIP-0								
MDD $p < 1$	340	993	1.30 (1.14:1.48)	1.0×10^{-4}	1.81 (0.91)	1.02 (0.89:1.18)	.737	0.52 (−0.18:2.86)
SCZ $p < .05$	340	993	1.05 (0.91:1.22)	.470	0.06 (0.17)	0.95 (0.83:1.10)	.497	−0.22 (−0.97:0.60)
BIP $p < .5$	340	993	0.95 (0.84:1.09)	.477	0.06 (0.16)	0.92 (0.81:1.05)	.230	−0.12 (−0.89:0.96)
SHIP-TREND								
MDD $p < 1$	149	448	1.33 (1.09:1.63)	.005	2.10 (1.47)	1.28 (0.96:1.72)	.103	0.22 (−0.50:1.43)
SCZ $p < .05$	149	448	1.10 (0.89:1.37)	.379	0.20 (0.46)	0.90 (0.71:1.15)	.404	−0.09 (−1.09:1.62)
BIP $p < .5$	149	448	1.20 (0.99:1.46)	.071	0.86 (0.95)	1.05 (0.85:1.32)	.659	0.07 (−0.75:1.51)
Total								
MDD $p < .01$	1957	2002	1.22 (1.08:1.37)	.001	0.58 (0.26)	1.02 (0.89:1.17)	.790	−0.17 (−2.86:10.25)
MDD $p < .05$	1957	2002	1.29 (1.14:1.45)	4.0×10^{-5}	1.08 (0.36)	0.98 (0.79:1.22)	.846	0.27 (−2.46:15.37)
MDD $p < .1$	1957	2002	1.34 (1.18:1.53)	1.0×10^{-5}	1.49 (0.42)	1.01 (0.84:1.22)	.910	0.51 (−2.02:15.72)
MDD $p < .5$	1957	2002	1.35 (1.22:1.48)	2.2×10^{-9}	1.70 (0.45)	1.03 (0.86:1.23)	.755	0.84 (−0.52:22.18)
MDD $p < 1$	1957	2002	1.34 (1.23:1.47)	5.1×10^{-11}	1.71 (0.45)	1.05 (0.91:1.20)	.519	0.83 (−0.62:18.03)
SCZ $p < .05$	1957	2002	1.22 (1.04:1.43)	.013	0.57 (0.26)	0.91 (0.79:1.04)	.172	−0.15 (−2.87:11.06)
BIP $p < .5$	1957	2002	1.10 (0.98:1.23)	.114	0.16 (0.14)	1.00 (0.85:1.18)	.997	0.39 (−1.13:20.78)

The impact on major depressive disorder (MDD) is displayed for polygenic risk scores (PRSs) and their interaction with the five-domain continuous childhood trauma (CT) measure including sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglect. The impact of the PRS is presented as the odds ratio (OR) from logistic regression corrected for sex and three principal components, as well as with the variance explained by the PRS on the liability scale. Interaction of PRS with CT (PRS × CT) was assessed as departure from multiplicativity with logistic regression while additionally correcting for the main effects of PRS and CT. Interaction as departure from additivity was expressed as the relative excess risks due to interaction (RERI) estimated as described in the main text, and their 95% confidence intervals (CIs) were estimated with bootstrapping with 10,000 iterations. The PRSs were based on discovery genome-wide association results from MDD, schizophrenia (SCZ), and bipolar disorder (BIP). Results in the Total sample were based on random-effect meta-analysis of the effects in the individual cohorts.

COFAMS, Cognition and Function in Mood Disorders Study; NA, not available; NESDA, Netherlands Study of Depression and Anxiety; SHIP, Study of Health in Pomerania.

1.71% ($p = 5.1 \times 10^{-11}$) (Supplemental Table S8), which corresponds with the increase predicted from theory given the increased sample size (55); 2) a genetic correlation of 0.91 to 0.96 between the PGC wave 2 discovery results and the extended discovery results as estimated with LD-score regression (30); and 3) an overlap of the 95% CI of the interaction effects based on the PGC discovery sample and the larger discovery sample applied in this article (Supplemental Table S8). In other words, our results suggest that the additional discovery cohorts (deCODE, Generation Scotland, GERA, iPsych, and UK Biobank) capture the same genetic information that the PGC cohorts do. Therefore, we hypothesize that the previously reported interaction results in NESDA (27) and RADIANT-UK (28) were both chance findings. The fact that these findings were both significant in an opposite direction may reflect the statistical vulnerability of interaction testing (48,54,56).

A source of spurious interaction effects can be found in GE correlation as explained for twin analyses by Purcell (54). Notably, the PRS based on the PGC wave 2 discovery results were slightly more correlated with CT in the full population (with ∼−0.09 in NESDA and 0.13 in RADIANT-UK) than the PRS based on the extended sample was (∼0.02 and ∼0.06, respectively). A simulation study suggested that the type I error rate can indeed be inflated in the context of GE correlation, but to a modest extent of 0.075

Table 3. Proportion Exposed to CT Measured as Either Sexual or Physical Abuse, and Its Interaction With PRSs (With SNP Threshold $p < 1$) in Predicting MDD

	n		Proportion Exposed to CT			Impact on MDD						
						CT		PRS			PRS × CT	
Cohorts	Case	Control	Case	Control	Pop	OR	*p* Value	OR (95% CI)	*p* Value	R^2 (SE, %)	OR (95% CI)	*p* Value
COFAMS	56	22	0.43	0.27	0.30	1.85	.268	1.41 (0.82:2.49)	.212	3.13 (4.61)	0.51 (0.21:1.05)	.088
DGN	461	458	0.40	0.20	0.22	2.49	1.9×10^{-9}	1.30 (1.13:1.50)	2.5×10^{-4}	1.77 (0.94)	1.06 (0.91:1.22)	.465
NESDA	1133	271	0.32	0.11	0.14	3.83	8.3×10^{-11}	1.24 (1.09:1.43)	.002	1.36 (0.85)	1.06 (0.87:1.28)	.587
QIMR_3	186	55	0.44	0.18	0.22	3.66	7.0×10^{-4}	1.07 (0.79:1.46)	.670	0.13 (0.60)	0.82 (0.52:1.25)	.355
QIMR_3_M7	126	29	0.48	0.31	0.34	2.10	.092	1.16 (0.75:1.80)	.494	0.66 (1.80)	0.83 (0.49:1.40)	.496
QIMR_6	121	107	0.38	0.23	0.29	2.05	.016	0.90 (0.67:1.19)	.452	0.30 (0.78)	0.87 (0.61:1.22)	.418
QIMR_C	180	46	0.40	0.33	0.33	1.36	.387	0.83 (0.58:1.17)	.297	0.92 (1.70)	0.89 (0.60:1.30)	.564
RADIANT-UK	262	263	0.42	0.15	0.19	4.33	1.5×10^{-11}	1.61 (1.33:1.97)	2.1×10^{-6}	5.46 (2.14)	1.04 (0.83:1.30)	.761
SHIP_0	352	1042	0.22	0.12	0.14	2.10	6.0×10^{-6}	1.31 (1.15:1.49)	4.2×10^{-5}	1.95 (0.93)	0.97 (0.86:1.10)	.606
SHIP-TREND	147	448	0.20	0.08	0.10	2.77	2.0×10^{-4}	1.34 (1.09:1.64)	.005	2.14 (1.50)	1.08 (0.88:1.35)	.460
Total	3024	2741	0.35	0.14	0.17	2.63	3.5×10^{-18}	1.24 (1.12:1.37)	3.6×10^{-5}	1.18 (0.31)	1.00 (0.93:1.07)	.894

The impact on major depressive disorder (MDD) is displayed for polygenic risk scores (PRSs) and their interaction with the childhood trauma (CT) dichotomous indicator covering sexual abuse and physical abuse. The prevalence of CT is presented in MDD cases, control subjects, and in terms of the full population (Pop), assuming a population prevalence of MDD of 15% with twice the prevalence in female subjects (20%) as in male subjects (10%). The impact of the PRS and CT is presented as the odds ratio (OR) from logistic regression corrected for sex and three principal components, as well as with the variance explained by the PRS on the liability scale. Interaction of PRS with CT (PRS × CT) was assessed as departure from multiplicativity with logistic regression while additionally correcting for the main effects of PRS and CT. The PRSs were based on discovery genome-wide association results from MDD including all single nucleotide polymorphisms (SNPs), that is, with significance threshold $p < 1$.

COFAMS, Cognition and Function in Mood Disorders Study; DGN, Depression Gene Network; NESDA, Netherlands Study of Depression and Anxiety; QIMR, Queensland Institute of Medical Research (subdivided in four batches: _3, _3_M7, _6, and _C); SHIP, Study of Health in Pomerania.

(with α set at 0.05) for a strong correlation of 0.3 between G and E (Supplemental Methods). It is therefore unlikely that the G × E interactions previously found would be attributable to GE correlation.

The current study has both strengths and limitations. First, this study is the largest to date to test for interaction between PRSs and CT in MDD risk. Second, PRSs were based on a powerful discovery GWAS with ~110,000 individuals. Third, diagnoses were DSM based, aiming to select clinically relevant cases of MDD. A limitation of our study is that CT was not assessed uniformly across cohorts for the two-domain measure, but analyses restricted to cohorts assessed uniformly with the five-domain CTQ instrument showed similar results. Although this study is the largest to date, power to detect an interaction effect between PRS and CT was still limited (power ≥ 0.8 for interaction effects with OR ≤ 0.83 or OR ≥ 1.21 for analyses with the two-domain CT measure in 5765 individuals, based on power analyses with QUANTO software) (57). Of note, tests of interaction with PRS do not rule out interaction with individual SNPs; the PRSs were based on many SNPs, some but not all of which may be involved in interaction. The current study tested for interaction with CT because CT has been hypothesized to define a distinct type of MDD (26), but other environmental factors could have also been tested. Nevertheless, testing too many environmental conditions assessed with a variety of instruments may increase risk of publication bias when significant findings would be published selectively (16,58).

Lastly, we would like to emphasize the complex nature of interaction testing with PRS based on genome-wide SNPs. For analyses with twin data, Purcell (54) described the distinction between qualitative interaction (different genes have an effect across different environments) and quantitative interactions (the same genes have an effect but they explain a different proportion of variance). In an attempt to elucidate some of the characteristics of interaction testing with PRS, we conducted a second simulation study constructing PRS from simulated SNP-level data for different underlying genetic architectures (Supplemental Methods and Supplemental Table S9). First, we note that the discovery results are typically based on a discovery sample with an unknown mixture of individuals unexposed (CT = 0) and individuals exposed to CT (CT = 1). When assuming qualitative genome-wide interaction with different directions of SNP effects in exposed and unexposed individuals (explaining the same proportion of variance in both groups), the discovery GWAS would mainly tag the effects in unexposed individuals that form the majority of the discovery sample. Consequently, negative interaction between PRS and CT would be detected under this scenario. Second and contrary, for quantitative interaction, a positive interaction effect may be expected when SNPs would explain more variance in exposed individuals.

To conclude, no overall evidence was found for interaction between PRS and CT. Previously found interaction effects (27,28) were no longer significant when applying more powerful discovery results. This study provides a cautionary tale for interaction analyses with PRS: it emphasizes the need to perform meta-analyses on results across different cohorts to obtain external validity. The quest continues to clarify the nature of the heterogeneity of MDD, but the present study has shown that the heterogeneity is unlikely to be attributable to moderation of genome-wide genetic effects by CT. Future

research may focus on interaction effects between CT and individual SNPs. We hereby call for large GWAS cohorts to assess CT in a uniform manner to facilitate such research in the years to come.

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