Biological Psychiatry

Archival Report

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

Wouter J. Peyrot, Sandra Van der Auwera, Yuri Milaneschi, Conor V. Dolan, Pamela A.F. Madden, Patrick F. Sullivan, Jana Strohmaier, Stephan Ripke, Marcella Rietschel, Michel G. Nivard, Niamh Mullins, Grant W. Montgomery, Anjali K. Henders, Andrew C. Heat, Helen L. Fisher, Erin C. Dunn, Enda M. Byrne, Tracy A. Air, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Bernhard T. Baune, Gerome Breen, Douglas F. Levinson, Cathryn M. Lewis, Nick G. Martin, Elliot N. Nelson, Dorret I. Boomsma, Hans J. Grabe, Naomi R. Wray, and Brenda W.J.H. Penninx

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

https://doi.org/10.1016/j.biopsych.2017.09.009

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

SEE COMMENTARY ON PAGE 82

 ISSN: 0006-3223

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

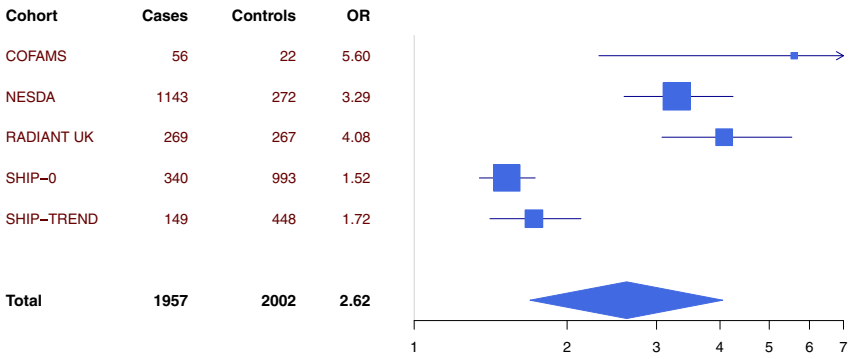

Figure 1. Forest plot of impact on major depressive disorder of the continuous childhood trauma score covering the five domains of sexual abuse, physical abuse, emotional abuse, emotional neglect, and physical neglect. The odds ratio (OR) represents one standard deviation increased in childhood trauma. 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.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was funded by the Australian National Health and Medical Research Council Grant Nos. 1078901 and 1087889 (to NRW) and Fellowship No. 1053639 (to EMB). The NESDA was funded by the Netherlands Organization for Scientific Research (MagW/ZonMW Grant Nos. 904-61-090, 985-10-002, 904-61-193, 480-04-004, 400-05-717, 912-100-20; Spinozapremie Grant No. 56-464-14192; Geestkracht program Grant No. 10-000-1002); the Center for Medical Systems Biology (NWO Genomics), Biobanking and Biomolecular Resources Research Infrastructure, VU Institutes for Health and Care Research and Neuroscience Campus Amsterdam, Netherlands Bioinformatics Centre/BioAssist/RK (Grant No. 2008.024); the European Science Foundation (Grant No. EU/QLRT-2001-01254); the European Community's Seventh Framework Program (Grant No. FP7/2007-2013); European Network for Genetic and Genomic Epidemiology (ENGAGE) (Grant No. HEALTH-F4-2007-201413); and the European Science Council (European Research Council Grant No. 230374). Genotyping was funded in part by the Genetic Association Information Network of the Foundation for the US National Institutes of Health, and analysis was supported by grants from Genetic Association Information Network and the National Institute of Mental Health (Grant No. MH081802). COFAMS was supported by a grant from the National Health and Medical Research Council (Grant No. APP 1060524 to BTB). SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (Grant Nos. 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs, and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Genome-wide data analyses in SHIP have been supported by a joint grant from Siemens Healthineers, Erlangen, Germany, and the Federal State of Mecklenburg-West Pomerania. Genome-wide genotyping in SHIP-TREND-0 was supported by the Federal Ministry of Education and Research (Grant No. 03ZIK012). This work was also funded by the German Research Foundation (Grant No. GR 1912/5-1). In addition, this work was supported by the German Federal Ministry of Education and Research within the framework of the e:Med research and funding concept (Integrament; Grant No. 01ZX1314E). DIB received Royal Netherlands Academy of Science Professor Award PAH/6635. MR received funding from the German Federal Ministry of Education and Research within the context of the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders; Grant No. 01ZX1314G). The German Research Foundation within the context of Forschergruppe 2107 awarded Grant Nos. RI908/11-1 (to MR) and WI 3439/3-1 (to SHW). This report represents independent research partially funded by the National Institute for Health Research Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust and King's College London. The RADIANT studies were funded by a joint grant from the UK Medical Research Council (Grant No. G0701420) and GlaxoSmithKline and by the National Institute for Health Research Biomedical Research Centre for Mental Health at South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry, Psychology, and Neuroscience, King's College London. The European Community's Seventh Framework Programme under the Marie Curie Industry-Academia Partnership and Pathways awarded Grant No. 286213 (to NM and CML). The National Institute of Mental Health provided Grant No. 1K01MH102403 (to ECD). Macquarie University provided Fellows Award No. MQ14F40 (to HLF).

We thank all individuals who participated in the RADIANT study and all those involved with data collection and management.

The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry (WJP, YM, BWJHP), VU University Medical Center and GGZ inGeest, and the Department of Biological Psychology (CVD, MGN, DIB), VU University Medical Center, Amsterdam, the Netherlands; the Department of Psychiatry and Psychotherapy (SVdA, HJG), University Medicine Greifswald, Greifswald, the Department of Genetic Epidemiology in Psychiatry (JS, MR), Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, and the Department of Psychiatry and Psychotherapy (SR), Charité–Universitätsmedizin, Berlin, Germany; the Department of Psychiatry (PAFM, ACH, ENN), Washington University Medical School, St. Louis, Missouri; Department of Psychiatry (PFS), University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Analytic and Translational Genetics Unit (SR), Massachusetts General Hospital, and the Department of Psychiatry (ECD), Harvard Medical School, Boston, Massachusetts; Department of Psychiatry and Behavioral Sciences (DFL), Stanford University, Stanford, California; the Institute of Psychiatry (NM, HLF, GB, CML), Psychology and Neuroscience, King's College London, UK; the Queensland Brain Institute (GWM, AKH, EMB, NRW), the Institute for Molecular Bioscience (GWM, AKH, EMB, NRW), University of Queensland, and the Queensland Institute of Medical Research Berghofer Medical Research Institute (NGM), Brisbane, and the Discipline of Psychiatry (TAA, BTB), University of Adelaide, Adelaide, Australia.

The Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium is a collaborative co-author for this article. The individual authors are (affiliations are listed in the Supplement) Naomi R. Wray, Stephan Ripke, Manuel Mattheisen, Maciej Trzaskowski, Enda M. Byrne, Abdel Abdellaoui, Mark J. Adams, Esben Agerbo, Tracy M. Air, Till F. M. Andlauer, Silviu-Alin Bacanu, Marie Bækvad-Hansen, Aartjan T. F. Beekman, Tim B. Bigdeli, Elisabeth B. Binder, Douglas H. R. Blackwood, Julien Bryois, Henriette N. Buttenschøn, Jonas Bybjerg-Grauholm, Na Cai, Enrique Castelao, Jane Hvarregaard Christensen, Toni-Kim Clarke, Jonathan R. I. Coleman, Lucía Colodro-Conde, Baptiste Couvy-Duchesne, Nick Craddock, Gregory E. Crawford, Gail Davies, Ian J. Deary, Franziska Degenhardt, Eske M. Derks, Nese Direk, Conor V. Dolan, Erin C. Dunn, Thalia C. Eley, Valentina Escott-Price, Farnush, Farhadi Hassan Kiadeh, Hilary K. Finucane, Andreas J. Forstner, Josef Frank, Héléna A. Gaspar, Michael Gill, Fernando S. Goes, Scott D. Gordon, Jakob Grove, Lynsey S. Hall, Christine Søholm Hansen, Thomas F. Hansen, Stefan Herms, Ian B. Hicki, Per Hoffmann, Georg Homuth, Carsten Horn, Jouke-Jan Hottenga, David M. Hougaard, Marcus Ising, Rick Jansen, Eric Jorgenson, James A. Knowles, Isaac S. Kohane, Julia Kraft, Warren W. Kretzschmar, Jesper Krogh, Zoltán Kutalik, Yihan Li, Penelope A. Lind, Donald J. MacIntyre, Dean F. MacKinnon, Robert M. Maier, Wolfgang Maier, Jonathan Marchini, Hamdi Mbarek, Patrick McGrath, Peter McGuffin, Sarah E. Medland, Divya Mehta, Christel M. Middeldorp, Evelin Mihailov, Yuri Milaneschi, Lili Milani, Francis M. Mondimore, Grant W. Montgomery, Sara Mostafavi, Niamh Mullins, Matthias Nauck, Bernard Ng, Michel G. Nivard, Dale R. Nyholt, Paul F. O'Reilly, Hogni Oskarsson, Michael J. Owen, Jodie N. Painter, Carsten Bøcker Pedersen, Marianne Giørtz Pedersen, Roseann E. Peterson, Erik Pettersson, Wouter J. Peyrot, Giorgio Pistis, Danielle Posthuma, Jorge A. Quiroz, Per Qvist, John P. Rice, Brien P. Riley, Margarita Rivera, Saira Saeed Mirza, Robert Schoevers, Eva C. Schulte, Ling Shen, Jianxin Shi, Stanley I. Shyn, Engilbert Sigurdsson, Grant C. B. Sinnamon, Johannes H. Smit, Daniel J. Smith, Hreinn Stefansson, Stacy Steinberg, Fabian Streit, Jana Strohmaier, Katherine E. Tansey, Henning Teismann, Alexander Teumer, Wesley Thompson, Pippa A. Thomson, Thorgeir E. Thorgeirsson, Matthew Traylor, Jens Treutlein, Vassily Trubetskoy, André G. Uitterlinden, Daniel Umbricht, Sandra Van der Auwera, Albert M van Hemert, Alexander Viktorin, Peter M. Visscher, Yunpeng Wang, Bradley T. Webb, Shantel Marie Weinsheimer, Jürgen Wellmann, Gonneke Willemsen, Stephanie H. Witt, Yang Wu, Hualin S. Xi, Jian Yang, Futao Zhang, Volker Arolt, Bernhard T. Baune, Klaus Berger, Dorret I. Boomsma, Sven Cichon, Udo Dannlowski, E. J. C. de Geus, J. Raymond DePaulo, Enrico Domenici, Katharina Domschke, Tõnu Esko, Hans J. Grabe, Steven P. Hamilton, Caroline Hayward, Andrew C. Heath, Kenneth S. Kendler, Stefan Kloiber, Glyn Lewis, Qingqin S. Li, Susanne Lucae, Pamela A. F. Madden, Patrik K. Magnusson, Nicholas G. Martin, Andrew M. McIntosh, Andres Metspalu, Ole Mors, Preben Bo Mortensen, Bertram Müller-Myhsok, Merete Nordentoft, Markus M. Nöthen, Michael C. O'Donovan, Sara A.

Paciga, Nancy L. Pedersen, Brenda W. J. H. Penninx, Roy H. Perlis, David J. Porteous, James B. Potash, Martin Preisig, Marcella Rietschel, Catherine Schaefer, Thomas G. Schulze, Jordan W. Smoller, Kari Stefansson, Henning Tiemeier, Rudolf Uher, Henry Völzke, Myrna M. Weissman, Thomas Werge, Cathryn M. Lewis, Douglas F. Levinson, Gerome Breen, Anders D. Børglum, and Patrick F. Sullivan.

HJG, NRW, and BWJHP contributed equally to this work.

Address correspondence to Wouter J. Peyrot, M.D., VU University Medical Center and GGZ inGeest, Department of Psychiatry, AJ Ernststraat 1187, Amsterdam 1081 HL, Netherlands; E-mail: peyrot.w@gmail.com.

Received May 21, 2017; revised and accepted Sep 1, 2017.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2017.09.009.

REFERENCES

1. Cai N, Bigdeli TB, Kretzschmar W, Li Y, Liang J, Song L, *et al.* (2015): Sparse whole-genome sequencing identifies two loci for major depressive disorder. Nature 523:588–591.
2. Okbay A, Baselmans BML, De Neve J-E, Turley P, Nivard MG, Fontana MA, *et al.* (2016): Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet 48:624–633.
3. Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, *et al.* (2016): Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. Nat Genet 48:1031–1036.
4. Ripke S, Neale BM, Corvin A, Walters JTR, Farh K-H, Holmans PA, *et al.* (2014): Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427.
5. Sullivan PF, Daly MJ, O'Donovan M (2012): Genetic architectures of psychiatric disorders: The emerging picture and its implications. Nat Rev Genet 13:537–551.
6. Peyrot WJ, Boomsma DI, Penninx BWJH, Wray NR (2016): Disease and polygenic architecture: Avoid trio design and appropriately account for unscreened control subjects for common disease. Am J Hum Genet 98:382–391.
7. Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, *et al.* (2013): Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet 45:984–994.
8. Wray NR, Maier R (2014): Genetic basis of complex genetic disease: The contribution of disease heterogeneity to missing heritability. Curr Epidemiol Reports 1:220–227.
9. Milaneschi Y, Lamers F, Mbarek H, Hottenga J-J, Boomsma DI, Penninx BWJH (2014): The effect of FTO rs9939609 on major depression differs across MDD subtypes. Mol Psychiatry 19:960–962.
10. Milaneschi Y, Lamers F, Peyrot WJ, Abdellaoui A, Willemsen G, Hottenga J-J, *et al.* (2015): Polygenic dissection of major depression clinical heterogeneity. Mol Psychiatry 21:516–522.
11. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, *et al.* (2003): Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389.
12. Fergusson DM, Horwood LJ, Miller AL, Kennedy MA (2011): Life stress, 5-HTTLPR and mental disorder: Findings from a 30-year longitudinal study. Br J Psychiatry 198:129–135.
13. Munafò MR, Durrant C, Lewis G, Flint J (2009): Gene X environment interactions at the serotonin transporter locus. Biol Psychiatry 65:211–219.
14. Karg K, Burmeister M, Shedden K, Sen S (2011): The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. Arch Gen Psychiatry 68:444–454.
15. Risch N, Herrell R, Lehner T, Liang K-Y, Eaves L, Hoh J, *et al.* (2009): Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. JAMA 301:2462–2471.
16. Duncan LE, Keller MC (2011): A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. Am J Psychiatry 168:1041–1049.
17. Culverhouse RC, Saccone NL, Horton AC, Ma Y, Anstey KJ, Banaschewski T, *et al.* (2018): Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. Mol Psychiatry 23:133–142.
18. Culverhouse RC, Bowes L, Breslau N, Nurnberger JI, Burmeister M, Fergusson DM, *et al.* (2013): Protocol for a collaborative meta-analysis of 5-HTTLPR, stress, and depression. BMC Psychiatry 13:304.
19. Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P (2009): Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460:748–752.
20. Kendler KS, Gardner CO (2010): Interpretation of interactions: Guide for the perplexed. Br J Psychiatry 197:170–171.
21. Demirkan A, Penninx BWJH, Hek K, Wray NR, Amin N, Aulchenko YS, *et al.* (2011): Genetic risk profiles for depression and anxiety in adult and elderly cohorts. Mol Psychiatry 16:773–783.
22. Peyrot WJ, Lee SH, Milaneschi Y, Abdellaoui A, Byrne EM, Esko T, *et al.* (2015): The association between lower educational attainment and depression owing to shared genetic effects? Results in ~25 000 subjects. Mol Psychiatry 20:735–743.
23. Wray NR, Pergadia ML, Blackwood DHR, Penninx BWJH, Gordon SD, Nyholt DR, *et al.* (2012): Genome-wide association study of major depressive disorder: New results, meta-analysis, and lessons learned. Mol Psychiatry 17:36–48.
24. Clarke H, Flint J, Attwood AS, Munafò MR (2010): Association of the 5-HTTLPR genotype and unipolar depression: A meta-analysis. Psychol Med 40:1767–1778.
25. Hovens JGFM, Wiersma JE, Giltay EJ, van Oppen P, Spinhoven P, Penninx BWJH, Zitman FG (2010): Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. Acta Psychiatr Scand 122:66–74.
26. Teicher MH, Samson JA (2013): Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. Am J Psychiatry 170:1114–1133.
27. Peyrot WJ, Milaneschi Y, Abdellaoui A, Sullivan PF, Hottenga JJ, Boomsma DI, Penninx BWJH (2014): Effect of polygenic risk scores on depression in childhood trauma. Br J Psychiatry 205:113–119.
28. Mullins N, Power RA, Fisher HL, Hanscombe KB, Euesden J, Iniesta R, *et al.* (2015): Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. Psychol Med 46:759–770.
29. Major Depressive Disorder Working Group of the PGC (2017): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depressive disorder. bioRxiv. Available at: https://www.biorxiv.org/content/early/2017/07/24/167577. Accessed July 24, 2017.
30. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh P-R, *et al.* (2015): An atlas of genetic correlations across human diseases and traits. Nat Genet 47:1236–1241.
31. Baune BT, Air T (2016): Clinical, functional, and biological correlates of cognitive dimensions in major depressive disorder: Rationale, design, and characteristics of the Cognitive Function and Mood Study (CoFaM-Study). Front Psychiatry 7:150.
32. Mostafavi S, Battle A, Zhu X, Potash JB, Weissman MM, Shi J, *et al.* (2014): Type I interferon signaling genes in recurrent major depression: Increased expression detected by whole-blood RNA sequencing. Mol Psychiatry 19:1267–1274.
33. Penninx BWJH, Beekman ATF, Smit JH, Zitman FG, Nolen WA, Spinhoven P, *et al.* (2008): The Netherlands Study of Depression and Anxiety (NESDA): Rationale, objectives and methods. Int J Methods Psychiatr Res 17:121–140.
34. Lewis CM, Ng MY, Butler AW, Cohen-Woods S, Uher R, Pirlo K, *et al.* (2010): Genome-wide association study of major recurrent depression in the U.K. population. Am J Psychiatry 167:949–957.
35. Völzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N, *et al.* (2011): Cohort profile: The study of health in Pomerania. Int J Epidemiol 40:294–307.
36. Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, *et al.* (2003): Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl 27:169–190.

37. Spinhoven P, Penninx BW, Hickendorff M, van Hemert AM, Bernstein DP, Elzinga BM (2014): Childhood Trauma Questionnaire: Factor structure, measurement invariance, and validity across emotional disorders. Psychol Assess 26:717–729.
38. Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, *et al.* (2010): A map of human genome variation from population-scale sequencing. Nature 467:1061–1073.
39. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ (2015): Second-generation PLINK: Rising to the challenge of larger and richer datasets. Gigascience 4:7.
40. Yang J, Lee SH, Goddard ME, Visscher PM (2011): GCTA: A tool for genome-wide complex trait analysis. Am J Hum Genet 88:76–82.
41. Fernandez-Pujals AM, Adams MJ, Thomson P, McKechanie AG, Blackwood DHR, Smith BH, *et al.* (2015): Epidemiology and heritability of major depressive disorder, stratified by age of onset, sex, and illness course in Generation Scotland: Scottish Family Health Study (GS: SFHS). PLoS One 10:e0142197.
42. Smith BH, Campbell A, Linksted P, Fitzpatrick B, Jackson C, Kerr SM, *et al.* (2013): Cohort profile: Generation Scotland: Scottish Family Health Study (GS: SFHS). The study, its participants and their potential for genetic research on health and illness. Int J Epidemiol 42:689–700.
43. Banda Y, Kvale MN, Hoffmann TJ, Hesselson SE, Ranatunga D, Tang H, *et al.* (2015): Characterizing race/ethnicity and genetic ancestry for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort. Genetics 200:1285–1295.
44. Smith DJ, Nicholl BI, Cullen B, Martin D, Ul-Haq Z, Evans J, *et al.* (2013): Prevalence and characteristics of probable major depression and bipolar disorder within UK biobank: Cross-sectional study of 172, 751 participants. PLoS One 8:e75362.
45. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, *et al.* (2015): UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 12:e1001779.
46. Sklar P, Ripke S, Scott LJ, Andreassen OA, Cichon S, Craddock N, *et al.* (2011): Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet 43:977–983.
47. Graaf R de, Have M ten, Gool C van, Dorsselaer S van. (2012): Prevalence of mental disorders and trends from 1996 to 2009: Results from the Netherlands Mental Health Survey and Incidence Study-2. Soc Psychiatry Psychiatr Epidemiol 47:203–213.
48. Keller MC (2014): Gene × environment interaction studies have not properly controlled for potential confounders: The problem and the (simple) solution. Biol Psychiatry 75:18–24.
49. Knol MJ, van der Tweel I, Grobbee DE, Numans ME, Geerlings MI (2007): Estimating interaction on an additive scale between continuous determinants in a logistic regression model. Int J Epidemiol 36:1111–1118.
50. Lee SH, Goddard ME, Wray NR, Visscher PM (2012): A better coefficient of determination for genetic profile analysis. Genet Epidemiol 36:214–224.
51. R Core Team (2015): R: A language and environment for statistical computing (version 3.2.2). Available at: http://www.r-project.org. Accessed August 14, 2015.
52. Golan D, Lander ES, Rosset S (2014): Measuring missing heritability: Inferring the contribution of common variants. Proc Natl Acad Sci U S A 111:E5272–E5281.
53. Falconer D (1952): The problem of environment and selection. *Am Nat*. Available at: http://www.jstor.org/stable/2457811. Accessed April 18, 2016.
54. Purcell S (2002): Variance components models for gene-environment interaction in twin analysis. Twin Res 5:554–571.
55. Palla L, Dudbridge F (2015): A fast method that uses polygenic scores to estimate the variance explained by genome-wide marker panels and the proportion of variants affecting a trait. Am J Hum Genet 97:250–259.
56. Eaves LJ (2006): Genotype x Environment interaction in psychopathology: Fact or artifact? Twin Res Hum Genet 9:1–8.
57. Kraft P, Yen Y, Stram O, Morrison J (2007): Exploiting gene-environment interaction. Hum Hered 63:111–119.
58. Sullivan PF (2007): Spurious genetic associations. Biol Psychiatry 61:1121–1126.

Does Childhood Trauma Moderate Polygenic Risk for Depression? A Meta-analysis of 5,765 Subjects From the Psychiatric Genomics Consortium

Supplemental Information

Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium

Naomi R Wray* 1, 2
Stephan Ripke* 3, 4, 5
Manuel Mattheisen* 6, 7, 8, 9
Maciej Trzaskowski* 1
Enda M Byrne 1
Abdel Abdellaoui 10
Mark J Adams 11
Esben Agerbo 9, 12, 13
Tracy M Air 14
Till F M Andlauer 15, 16
Silviu-Alin Bacanu 17
Marie Bækvad-Hansen 9, 18
Aartjan T F Beekman 19
Tim B Bigdeli 17, 20
Elisabeth B Binder 15, 21
Douglas H R Blackwood 11
Julien Bryois 22
Henriette N Buttenschøn 8, 9, 23
Jonas Bybjerg-Grauholm 9, 18
Na Cai 24, 25
Enrique Castelao 26
Jane Hvarregaard Christensen 7, 8, 9
Toni-Kim Clarke 11
Jonathan R I Coleman 27
Lucía Colodro-Conde 28
Baptiste Couvy-Duchesne 29, 30
Nick Craddock 31
Gregory E Crawford 32, 33
Gail Davies 34
Ian J Deary 34
Franziska Degenhardt 35, 36
Eske M Derks 28
Nese Direk 37, 38
Conor V Dolan 10
Erin C Dunn 39, 40, 41
Thalia C Eley 27
Valentina Escott-Price 42
Farnush Farhadi Hassan Kiadeh 43
Hilary K Finucane 44, 45
Andreas J Forstner 35, 36, 46, 47
Josef Frank 48
Héléna A Gaspar 27
Michael Gill 49
Fernando S Goes 50
Scott D Gordon 51
Jakob Grove 7, 8, 9, 52
Lynsey S Hall 11, 53
Christine Søholm Hansen 9, 18
Thomas F Hansen 54, 55, 56
Stefan Herms 35, 36, 47
Ian B Hickie 57
Per Hoffmann 35, 36, 47
Georg Homuth 58
Carsten Horn 59
Jouke-Jan Hottenga 10
David M Hougaard 9, 18
Marcus Ising 60
Rick Jansen 19, 19
Eric Jorgenson 61
James A Knowles 62
Isaac S Kohane 63, 64, 65
Julia Kraft 4
Warren W. Kretzschmar 66
Jesper Krogh 67
Zoltán Kutalik 68, 69
Yihan Li 66
Penelope A Lind 28
Donald J MacIntyre 70, 71
Dean F MacKinnon 50
Robert M Maier 2
Wolfgang Maier 72
Jonathan Marchini 73
Hamdi Mbarek 10
Patrick McGrath 74
Peter McGuffin 27
Sarah E Medland 28
Divya Mehta 2, 75
Christel M Middeldorp 10, 76, 77
Evelin Mihailov 78
Yuri Milaneschi 19, 19
Lili Milani 78
Francis M Mondimore 50
Grant W Montgomery 1
Sara Mostafavi 79, 80
Niamh Mullins 27
Matthias Nauck 81, 82
Bernard Ng 80
Michel G Nivard 10
Dale R Nyholt 83
Paul F O'Reilly 27
Hogni Oskarsson 84
Michael J Owen 85
Jodie N Painter 28
Carsten Bøcker Pedersen 9, 12, 13
Marianne Giørtz Pedersen 9, 12, 13
Roseann E. Peterson 17, 86
Erik Pettersson 22
Wouter J Peyrot 19
Giorgio Pistis 26
Danielle Posthuma 87, 88
Jorge A Quiroz 89
Per Qvist 7, 8, 9
John P Rice 90
Brien P. Riley 17
Margarita Rivera 27, 91
Saira Saeed Mirza 37
Robert Schoevers 92
Eva C Schulte 93, 94
Ling Shen 61
Jianxin Shi 95
Stanley I Shyn 96
Engilbert Sigurdsson 97

1, Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU
2, Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU
3, Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, US
4, Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, DE
5, Medical and Population Genetics, Broad Institute, Cambridge, MA, US
6, Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, SE
7, Department of Biomedicine, Aarhus University, Aarhus, DK
8, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK
9, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK
10, Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL
11, Division of Psychiatry, University of Edinburgh, Edinburgh, GB
12, Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK
13, National Centre for Register-Based Research, Aarhus University, Aarhus, DK
14, Discipline of Psychiatry, University of Adelaide, Adelaide, SA, AU
15, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE
16, Munich Cluster for Systems Neurology (SyNergy), Munich, DE
17, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US
18, Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK
19, Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, NL
20, Virginia Institute for Psychiatric and Behavior Genetics, Richmond, VA, US
21, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, US
22, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE
23, Department of Clinical Medicine, Translational Neuropsychiatry Unit, Aarhus University, Aarhus, DK
24, Human Genetics, Wellcome Trust Sanger Institute, Cambridge, GB
25, Statistical genomics and systems genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, GB
26, Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, CH
27, MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB
28, Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, AU
29, Centre for Advanced Imaging, The University of Queensland, Saint Lucia, QLD, AU
30, Queensland Brain Institute, The University of Queensland, Saint Lucia, QLD, AU
31, Psychological Medicine, Cardiff University, Cardiff, GB
32, Center for Genomic and Computational Biology, Duke University, Durham, NC, US
33, Department of Pediatrics, Division of Medical Genetics, Duke University, Durham, NC, US
34, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB
35, Institute of Human Genetics, University of Bonn, Bonn, DE
36, Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE
37, Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, NL
38, Psychiatry, Dokuz Eylul University School Of Medicine, Izmir, TR
39, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US
40, Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US
41, Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US

42, Neuroscience and Mental Health, Cardiff University, Cardiff, GB
43, Bioinformatics, University of British Columbia, Vancouver, BC, CA
44, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, US
45, Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, US
46, Department of Psychiatry (UPK), University of Basel, Basel, CH
47, Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH
48, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE
49, Department of Psychiatry, Trinity College Dublin, Dublin, IE
50, Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US
51, Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU
52, Bioinformatics Research Centre, Aarhus University, Aarhus, DK
53, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, GB
54, Danish Headache Centre, Department of Neurology, Rigshospitalet, Glostrup, DK
55, Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, DK
56, iPSYCH, The Lundbeck Foundation Initiative for Psychiatric Research, Copenhagen, DK
57, Brain and Mind Centre, University of Sydney, Sydney, NSW, AU
58, Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
59, Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH
60, Max Planck Institute of Psychiatry, Munich, DE
61, Division of Research, Kaiser Permanente Northern California, Oakland, CA, US
62, Psychiatry & The Behavioral Sciences, University of Southern California, Los Angeles, CA, US
63, Department of Biomedical Informatics, Harvard Medical School, Boston, MA, US
64, Department of Medicine, Brigham and Women's Hospital, Boston, MA, US
65, Informatics Program, Boston Children's Hospital, Boston, MA, US
66, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, GB
67, Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, DK
68, Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, VD, CH
69, Swiss Institute of Bioinformatics, Lausanne, VD, CH
70, Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, GB
71, Mental Health, NHS 24, Glasgow, GB
72, Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, DE
73, Statistics, University of Oxford, Oxford, GB
74, Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, US
75, School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, AU
76, Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, AU
77, Child Health Research Centre, University of Queensland, Brisbane, QLD, AU
78, Estonian Genome Center, University of Tartu, Tartu, EE
79, Medical Genetics, University of British Columbia, Vancouver, BC, CA
80, Statistics, University of British Columbia, Vancouver, BC, CA
81, DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE

82, Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
83, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, AU
84, Humus, Reykjavik, IS
85, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, GB
86, Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US
87, Clinical Genetics, Vrije Universiteit Medical Center, Amsterdam, NL
88, Complex Trait Genetics, Vrije Universiteit Amsterdam, Amsterdam, NL
89, Solid Biosciences, Boston, MA, US
90, Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, US
91, Department of Biochemistry and Molecular Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, ES
92, Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, NL
93, Department of Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich, DE
94, Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Campus Innenstadt, Munich, DE
95, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, US
96, Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, US
97, Faculty of Medicine, Department of Psychiatry, University of Iceland, Reykjavik, IS
98, School of Medicine and Dentistry, James Cook University, Townsville, QLD, AU
99, Institute of Health and Wellbeing, University of Glasgow, Glasgow, GB
100, deCODE Genetics / Amgen, Reykjavik, IS
101, College of Biomedical and Life Sciences, Cardiff University, Cardiff, GB
102, Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, DE
103, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
104, Department of Psychiatry, University of California, San Diego, San Diego, CA, US
105, KG Jebsen Centre for Psychosis Research, Norway Division of Mental Health and Addiction, Oslo University Hospital, Oslo, NO
106, Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, GB
107, Clinical Neurosciences, University of Cambridge, Cambridge, GB
108, Internal Medicine, Erasmus MC, Rotterdam, Zuid-Holland, NL
109, Roche Pharmaceutical Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH
110, Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE
111, Department of Psychiatry, Leiden University Medical Center, Leiden, NL
112, Virginia Institute of Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US
113, Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, US
114, Institute for Molecular Bioscience; Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU
115, Department of Psychiatry, University of Münster, Münster, Nordrhein-Westfalen, DE

116, Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, CH
117, Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, DE
118, Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, NL
119, Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, IT
120, Department of Psychiatry and Psychotherapy, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, DE
121, Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, US
122, Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, GB
123, Department of Psychiatry, University of Toronto, Toronto, ON, CA
124, Centre for Addiction and Mental Health, Toronto, ON, CA
125, Division of Psychiatry, University College London, London, GB
126, Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, US
127, Institute of Molecular and Cell Biology, University of Tartu, Tartu, EE
128, Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, DK
129, University of Liverpool, Liverpool, GB
130, Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, DK
131, Human Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, US
132, Psychiatry, Harvard Medical School, Boston, MA, US
133, Psychiatry, University of Iowa, Iowa City, IA, US
134, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US
135, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Goettingen, Niedersachsen, DE
136, Human Genetics Branch, NIMH Division of Intramural Research Programs, Bethesda, MD, US
137, Faculty of Medicine, University of Iceland, Reykjavik, IS
138, Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL
139, Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL
140, Psychiatry, Dalhousie University, Halifax, NS, CA
141, Division of Epidemiology, New York State Psychiatric Institute, New York, NY, US
142, Department of Clinical Medicine, University of Copenhagen, Copenhagen, DK
143, Department of Medical & Molecular Genetics, King's College London, London, GB
144, Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, US
145, NIHR BRC for Mental Health, King's College London, London, GB
146, Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US
147, Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

Dichotomous Childhood Trauma Questionnaire (CTQ) score

The CTQ covers the five domains of sexual abuse (SA), physical abuse (PA), emotional abuse (EA), emotional neglect (EN), and physical neglect (PN). Each domain is assessed by five questions (scored 1 to 5) resulting in a domain score ranging from 5 to 25. Per domain, cutoffs were applied to define a narrow definition of childhood trauma separating no or mild trauma from moderate or severe trauma, based on cut-offs for moderate/severe of > 7 (SA), > 9 (PA), > 12 (EA), > 14 (EN), > 9 (PN) respectively. These cut-offs are based on the CTQ manual. From this, an overall dichotomous CTQ indicator was constructed to separate trauma in any of the five domains (1) from trauma in none of the domains (0).

Childhood trauma in DGN and QIMR

In the Depression Gene Network (DGN) cohort, sexual abuse was assessed with two questions: "Someone touched parts of your body in a sexual way, or had you touch parts of the person in a sexual way"; and "Someone had or attempted to have oral sex, anal sex, or sexual intercourse with you". Physical abuse in DGN was also assessed with two questions: "Someone outside your household physically attacked or assaulted you, threatened you with a weapon or held you captive"; and "Your mother, father or another adult household member hurt you on purpose (for example, beat, choked, kicked, cut or burned you)". The narrow definition was defined as at least one of four questions occurring frequently versus sometimes, rarely or never, and the broad definition as at least one of four questions occurring frequently or sometimes versus rarely or never. For data from the Queensland Institute of Medical Research (QIMR), two instruments were used to assess childhood trauma before the age of 18. Most QIMR individuals were assessed with an instrument covering sexual abuse: touching your sexual parts, you touching their sexual parts, or sexual intercourse (SA assessed with one question for family members and one question for non-family); and physical abuse: being punished by hitting (one question), hurting from punishment next day (one question), being physically injured on purpose (one question). The other QIMR individuals (on the QIMR_3 genotype-batch labeled as M7) were assessed with a questionnaire covering sexual abuse as the occurrence of: exposure to sexual organs, exposure to masturbation, being touched, attempt to have sex, and have sex (SA specified in 16 separate questions); and for physical abuse the occurrence of: being hit, kicked, choked, throttled or locked in by either father, father-figure, mother, or mother-figure (PA specified in 13 separate questions). For QIMR the narrow and broad definitions were defined as above, except for physical abuse from the second questionnaire (QIMR_3_M7) that didn't distinguish between occurring "frequently" and "sometimes" resulting in converging of the narrow and broad definitions. For the analyses, we applied the broad definition.

Simulation study 1: impact of gene-environment correlation in tests for GxE-interaction

Tests of genotype by environment interaction are known to be scale dependent. In a linear regression model, where a continuous phenotype is regressed on a measured genetic variant (e.g. a candidate gene) and a measured exposure, non-normality of the phenotypic distribution can give rise to spurious interaction effects. We considered this issue given logistic regression of a binary phenotype by means of a small simulation study. We generated phenotypic data based on 12 binary symptoms, which were related to an underlying normally distributed depression liability by a Rasch model (1). The parameters of the Rasch model were chosen so that the distribution of the sum scores based on the 12 symptoms was highly skewed. We dichotomized the sum score of these 12 symptoms to arrive at the binary phenotype with a prevalence of .20. The underlying normally distributed depression liability was subject to main effects of genes (A; explaining 38.8% of the liability variance) and the main effects of a given exposure (explaining 11.1%). There was no interaction effect (AxE). We considered the type I error rate α of the interaction effect, where we regressed the binary phenotype on A, the dichotomized exposure variable (E; prevalence .10) and on the interaction AxE. We set the nominal α at .05. We varied the correlation between the exposure and the genetic variable. Based on 10,000 replications, we observed an inflated type I error rate of the interaction effect as a function of the correlation between the genetic variable and the exposure. However, this inflation was relatively small. The observed type I error rate was .046 (zero correlation), .056 (correlation .15) and .0752 (correlation .30). Note that .056 and .0752 both deviate significantly from the nominal value of .5 ($p=.003$ and $p<.0001$, respectively). So in this scenario, which is based on the NESDA and Radiant-UK data, we note that we expect some type I error rate inflation. However, we conclude that the type I error rate inflation in test of GxE in the present set-up is small and does not render the test useless. Specifically, in the NESDA and Radiant-UK data the correlation between the genetic variable (polygenic risk score) and the exposure (childhood trauma) is likely to be very low (Table S5).

Simulation study 2

The aim of this simulation study is to aid interpretation of interaction analyses with polygenic risk score (PRS) by simulating different underlying genetic architectures.

Liability threshold model and the impact of childhood trauma (CT) on major depressive disorder (MDD)

Simulation is based on the liability-threshold model, which can be modeled as MDD underpinned by an unobserved liability, l_{MDD}, where individuals are affected when liability exceeds disease threshold, T_{MDD}. The liability is assumed to be normally distributed and scaled to a population mean of 0 and variance of 1 (which defines T_{MDD} given the prevalence of MDD K_{MDD}), and to result from independent normally distributed environmental (e_{MDD}) and genetic effects (g_{MDD}) with $l_{MDD} = g_{MDD} + e_{MDD}$, where $var(g_{MDD})/var(l_{MDD}) = var(g_{MDD}) = h^2_{l,MDD}$, the heritability of MDD on the liability scale. Here, we subdivide the environmental effects as $e_{MDD} = CT_{liability\ scale} + e_{residual,MDD}$. We assume that $CT_{observed\ scale}$ is represented by a dichotomous measure that labels individuals as exposed (1) or unexposed (0) with an odd ratio for MDD of exposed of OR_{CT}. For a prevalence of MDD of $K_{MDD} = 0.15$, prevalence of CT of $K_{CT} = 0.25$ and $OR_{CT} = 3.2$, the $CT_{observed\ scale}$ can be transformed to $CT_{liability\ scale}$ as –0.16 (unexposed) and 0.47 (exposed), and explains 7.4% of variation on the liability scale (Appendix A). Assuming a heritability of MDD of $h^2_{l,MDD} = 0.35$, the variance explained by the residual environmental effects $e_{residual,MDD}$ follows as 57.6% (assuming that $CT_{liability\ scale}$, $e_{residual,MDD}$, and g_{MDD} are all independent). For Model 1, we consider CT as part of the environmental effects on MDD, but we note that CT has been found to be heritable itself (2); the consequences of which will be discussed later. In Model 1, we will, further, assume that the genetic and residual environmental effects are equal in those exposed and those unexposed to CT, which can thus be thought of as a "pure additive" model on the liability scale of $CT_{liability\ scale}$, $e_{residual,MDD}$, and g_{MDD} (i.e. no GxE-interaction). After describing simulation of SNP data, we will discuss decreasing the correlation of SNP-effects between those exposed and those unexposed to CT (Model 2), increasing a genetic contribution to CT through introducing a heritability for CT (Model 3), increasing magnitude of SNP-effects on MDD in those exposed compared to those unexposed to CT (Model 4), and decreasing magnitude of residual environmental effects on MDD in those exposed compared to those unexposed to CT (Model 5).

Simulation of SNP data and genetic effects

We simulated individuals in a population one-by-one until a total of 9,000 cases and 9,000 controls were obtained, from which 10,000 were used as discovery and 8,000 as target set. Therefore, we

first simulated the SNPs following the method of Golan et al (3), and subsequently modeled CT and MDD. Briefly, the properties of 10,000 SNPs in full linkage equilibrium were first defined by drawing their minor allele frequencies (MAF) from the uniform distribution from 0.05 to 0.5, and a proportion of 30% of these SNPs were set to have an effect on MDD with effects drawn from a normal distribution with variance $h^2_{l,MDD}/3{,}000$ while the effects of the other SNPs were set at 0. With these SNP effects, an individual i was simulated by first drawing its allele count (x_{ij}; 0,1 or 2) with probabilities of $(1-MAF_j)^2$, $2(1-MAF_j)MAF_j$, and MAF_j^2 respectively for all SNP j, and, second, defining its genetic effects as $g(i)_{MDD} = \sum_j effect_j(x_{ij} - 2MAF_j)/(2(1-MAF_j)MAF_j)$. Childhood trauma status of individual i was assigned with probability K_{CT}, and transformed to the liability scale $CT(i)_{liability\ scale}$ as described in Appendix A. The residual environmental effect $e(i)_{residual,MDD}$ was drawn from a normal distribution with variance $1 - h^2_{l,MDD} - var(CT_{liability\ scale})$, so that the liability of individual i followed as $l(i) = g(i)_{MDD} + CT(i)_{liability\ scale} + e(i)_{residual,MDD}$. Individual i was deemed affected with MDD when $l(i) > T_{MDD}$ and non affected otherwise, where disease threshold T_{MDD} was defined such that $K_{MDD} = P(z > T_{MDD} \mid z \sim N(0,1))$. This procedure was repeated until a total of 9,000 cases and 9,000 controls were obtained. Subsequently, a genome-wide association study (GWAS) was conducted with PLINK on 5,000 cases and 5,000 controls (4), the results of which were used to prepare polygenic risk scores in the target set of the other 4,000 cases and 4,000 controls. For every parameterization, the simulation was repeated 10 times.

Simulation - Model 1

For the base assumption of the genetic architecture we assumed a prevalence of MDD of $K_{MDD} = 0.15$, a heritability of MDD of $h^2_{l,MDD} = 0.35$, a prevalence of CT of $K_{CT} = 0.25$, no impact of SNPs in CT ($h^2_{l,CT} = 0$), and odds ratio for MDD in those exposed to childhood trauma of $OR = 3.2$, and pure additivity on the liability scale (identical genetic and residual environmental effects in those exposed and those unexposed to childhood trauma).

Simulation - Model 2

A clear case of GxE interaction would be when the individual SNP-effects on MDD in those exposed would differ from the effects in those unexposed, i.e. when $r_g = cor\left(effect_{SNP\ j \mid CT=1}, effect_{SNP\ j \mid CT=0}\right) = 0$ for the 3,000 effective SNPs. To model this scenario, we further assumed that the effects are on the same 3,000 SNPs and the variance explained is constant, that is $var\left(effect_{SNP\ j \mid CT=1}\right) = var\left(effect_{SNP\ j \mid CT=0}\right) = 0.35$.

Simulation - Model 3

For the Models 1, 2, 4 and 5 we have assumed that CT is purely environmental, but heritability of childhood trauma has been estimated at around 0.5 (2). Therefore, an impact of SNPs effects on CT is considered here. For this, we assume that CT is a "disease trait" itself with underlying liability as described above for MDD (not suggesting that children are to blame for the trauma they experience, rather we hypothesize that heritability arises from transmitted alleles that affect personality characteristics in parents). Nevertheless, we drew SNP-effects for CT from a random normal distribution with variance $h^2_{l,CT} = 0.5$ and environmental effects from a normal distribution with variance $1 - h^2_{l,CT}$ to construct a liability of CT l_{CT}, and individuals were deemed exposed to CT when $l_{CT}(i) > T_{CT}$ with the threshold defined such that $K_{CT} = P(z > T_{CT} \mid z \sim N(0,1))$. The effects were assigned to the same 3,000 SNPs impacting MDD, but drawn from an independent normal distribution. Given the CT status thus simulated, MDD was derived as described above.

Simulation - Model 4

Another way to think about GxE interaction is that environmental stress might potentiate genetic effects. This was modeled by setting a proportion of genetic effects on MDD in those exposed to those unexposed to CT as $var\left(effect_{SNP\ j \mid CT=1}\right)/var\left(effect_{SNP\ j \mid CT=0}\right) = 3$ while keeping $cor\left(effect_{SNP\ j \mid CT=1}, effect_{SNP\ j \mid CT=0}\right) = 1$. The variances of SNP-effects where chosen in such way that the variance of genetic effects in the full population were fixed at 0.35, while the residual environmental effects had the same variance in those exposed and those unexposed to CT (Appendix B).

Simulation - Model 5

A hypothetical scenario could be that environmental risk factors for MDD (such as socioeconomic status and life-stress in adulthood) cluster in those exposed to CT; the link between these environmental risk factors would be captured in estimates of the OR of CT, but could in addition result in less residual environmental variation in those exposed compared to those unexposed to childhood trauma. We modeled this as $var\left(e_{residual,MDD|CT=1}\right)/var\left(e_{residual,MDD|CT=0}\right) = 1/3$ while assuming constant genetic effects in those exposed and those unexposed to CT, $effect_{SNP\ j \mid CT=1}$=$effect_{SNP\ j \mid CT=0}$ (Appendix C).

Appendix A. Transformation of OR to liability scale

To transform the OR from CT on MDD to the liability scale the approach of Witte et al was applied (5). Therefore, the OR (set at 3.2) was first transformed to the RR (2.6) and consequently to the risk

on MDD in exposed ($CT = 1$ with MDD proportion 0.28) and unexposed ($CT = 0$ with MDD in proportion 0.11) assuming a population prevalence of $K_{MDD} = 0.15$ and $K_{CT} = 0.25$. The liability disease threshold for MDD in the full population was found as $T_{MDD,full\ population} = \Phi^{-1}(1 - K_{MDD}) = \Phi^{-1}(1 - 0.15) = 1.0364$. First assuming a liability variance of 1 in both exposed and unexposed, the threshold in exposed was found as $T_{MDD|CT=1} = \Phi^{-1}(1 - 0.28) = 0.589$ and in unexposed as $T_{MDD|CT=1} = \Phi^{-1}(1 - 0.11) = 1.241$. In line with Witte et al, the mean liability in exposed was found at $\mu_{l|CT=1} = T_{MDD,full\ population} - T_{MDD|CT=1}$ and in unexposed at $\mu_{l|CT=0} = T_{MDD,full\ population} - T_{MDD|CT=0}$, allowing to merge exposed and unexposed while ensuring the disease risks of 0.28 and 0.11 respectively. However, because the variance in both exposed and unexposed was assumed to equal 1, the merged sample had a variance larger than 1 introduced by the variance of CT and a mean slightly different from zero. To ease modeling of genetic effects, we rescaled to mean of zero and variance one, also correcting the disease threshold in this manner. With this, a model was derived transposing CT status of exposed and unexposed to the liability scale, while the overall variance of liability was set at 1, and mean at 0, as usual.

Appendix B. Modeling increased magnitude of SNP-effects in CT=1 compared to CT=0

When aiming to model increased variance of SNP effects in those exposed compared to those unexposed to CT, arbitrary choices have to be made about the residual environmental effects in exposed and unexposed, and the variance of liability, genetic effects and environmental effects in the overall population. We choose to fix the full population variance of liability at 1, variance of genetic effects at $h^2_{l,MDD} = 0.35$, and variance of environmental effects at $1 - h^2_{l,MDD} = 0.65$ (the latter including both the variance of $CT_{liability}$ as well as residual environmental effects). To obtain e.g. a variance of genetic effects in exposed three times the variance of genetic effects in unexposed $\left(var\left(effect_{SNP\ j\ |\ CT=1}\right)/var\left(effect_{SNP\ j\ |\ CT=0}\right) = 3\right)$, the variance of genetic effects followed as $var\left(effect_{SNP\ j\ |\ CT=1}\right) = 0.56$ and $var\left(effect_{SNP\ j\ |\ CT=0}\right) = 0.28$ thereby ensuring that the variance of genetic effect in the full population equals $var\left(effect_{SNP\ j}\right) =$
$0.25\mu^2_{effect_{SNP\ j\ |\ CT=1}} + 0.75\mu^2_{effect_{SNP\ j\ |\ CT=0}} - (0.2\mu_{effect_{SNP\ j\ |\ CT=1}} + 0.8\mu_{effect_{SNP\ j\ |\ CT=0}})^2 =$
$0.25(0.56 + 0^2) + 0.75(0.28 + 0^2) - 0 = 035$. We choose to fix the residual variance in both exposed and unexposed first at $var(e_{residual|CT=1}) = var(e_{residual|CT=1}) = 0.65$, and the overall variance of liability was thus larger in exposed than in unexposed. As a result, the sums in Appendix A were slightly adjusted as the variance and mean of the merged sample differed slightly to the above, and therefore correction to obtain variance of 1 and mean of zero in the full population also differed.

Appendix C. Decreased environmental variation in individuals exposed to CT

When aiming to model a smaller variance of residual environmental effects in those exposed compared to those unexposed to CT, several model choices have again to be made. We chose to fix the full population variance of liability at 1, variance of genetic effects at $h^2_{l,MDD} = 0.35$ equal in exposed and unexposed, and variance of environmental effects at $1 - h^2_{l,MDD} = 0.35$ (the latter including both the variance of $CT_{liability}$ as well as residual environmental effects).

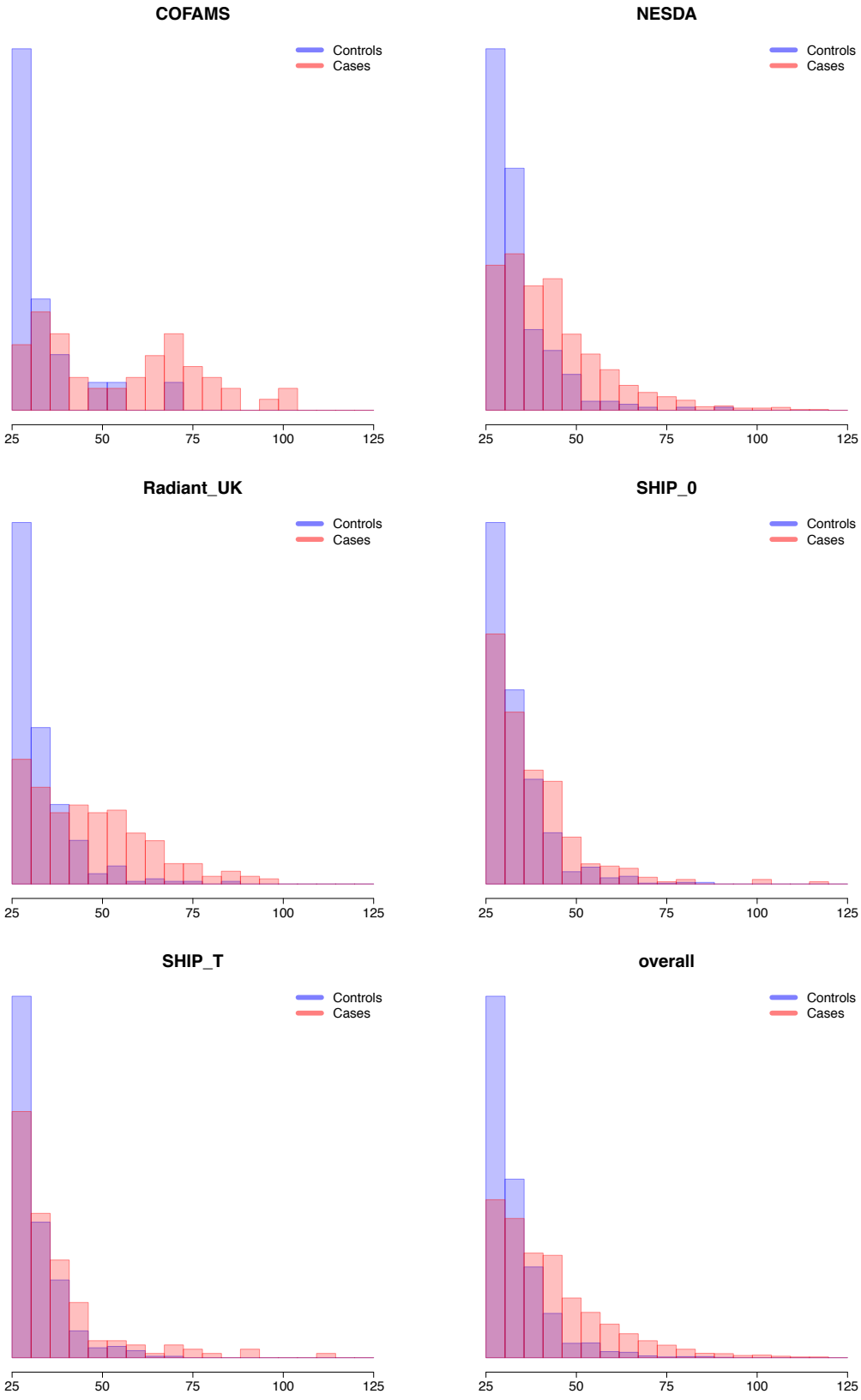

Figure S1. Distribution of the 5-domain continuous childhood trauma measure

Table S1. Demographic information for contributing cohorts of major depressive disorder cases and unaffected controls

		N		N with CT information		Demographics	
Cohort	Country	Cases	Controls	Cases	Controls	Mean age	% female
COFAMS	Australia	120	126	56	22	38.2	0.59
DGN	USA	463	459	461	458	-	0.70
NESDA	Netherlands	1493	1603	1133	271	42.9	0.67
QIMR (3 sub cohorts)	Australia	1902	1660	613	237	36.3	0.64
RADIANT UK	UK	1859	1519	262	264	46.0	0.66
SHIP (2 sub cohorts)	Germany	515	1529	499	1490	53.6	0.50

CT=childhood trauma

Table S2. Correlation of childhood trauma domains (N=3850)

	EA	PA	SA	EN	PN	SUM
Childhood Trauma Questionnaire subscales (continuous measures)						
Emotional Abuse (EA)	1	0.596	0.387	0.609	0.481	0.803
Physical Abuse (PA)	0.596	1	0.387	0.413	0.410	0.681
Sexual Abuse (SA)	0.387	0.387	1	0.246	0.285	0.539
Emotional Neglect (EN)	0.609	0.413	0.246	1	0.632	0.805
Physical Neglect (PN)	0.481	0.410	0.285	0.632	1	0.728
Sum score (SUM)	0.803	0.681	0.539	0.805	0.728	1
Dichotomous indicator of sexual or physical abuse						
SA/PA (dichotomous)	0.367	0.542	0.754	0.203	0.201	0.497

The Pearson correlation coefficients (all p-value<2e-16) are displayed between the five domains of the Childhood Trauma Questionnaire (CTQ) by applying the residuals of linear regression of the domains on sex and cohort (COFAMS, NESDA, Radiant-UK, SHIP). It can be seen that sexual abuse is slightly less correlated than the other domains, and that there seems no clear distinction between the abuse and neglect domains. In addition, the Spearman's rho correlation coefficient is displayed of the CTQ domains with the dichotomous indicator of sexual abuse and/or physical abuse (SA/PA) that was available for two additional cohorts.

Table S3. Number of overlapping SNPs between cohorts for GRM-based analyses

	COFAMS	DGN	NESDA	QIMR_3	QIMR_6	QIMR_C	RAD. UK	SHIP-0	SHIP-T
COFAMS	771,120	-	-	-	-	-	-	-	-
DGN	741,245	1,051,603	-	-	-	-	-	-	-
NESDA	675,669	851,244	924,741	-	-	-	-	-	-
QIMR_3	626,026	775,291	702,250	821,960	-	-	-	-	-
QIMR_6	716,604	930,576	822,954	803,446	1,000,453	-	-	-	-
QIMR_C	711,902	746,328	683,496	635,209	724,195	772,404	-	-	-
RAD. UK	729,795	954,007	840,621	811,506	983,793	736,767	1,028,612	-	-
SHIP-0	706,975	905,732	907,329	737,015	871,372	713,690	890,930	992,050	-
SHIP-T	762,091	1,037,269	903,725	809,699	981,370	765,093	1,008,254	967,781	1,131,800

Table S4. Impact of CTQ subdomain continuous measures on MDD

	Mean (SD)		
Subset	Cases	Controls	OR (p-value)
Emotional Abuse			
Male & Female	9.3 (4.8)	6.2 (2.3)	2.40 (1.1e-06)
Male	8.5 (4.2)	6.0 (2.0)	2.01 (7.1e-05)
Female	9.6 (5.0)	6.3 (2.5)	2.46 (2.1e-07)
Physical Abuse			
Male & Female	6.3 (2.8)	5.6 (1.6)	1.51 (4.6e-05)
Male	6.3 (2.6)	5.7 (1.6)	1.41 (1.1e-04)
Female	6.2 (2.9)	5.5 (1.5)	1.51 (8.8e-05)
Sexual Abuse			
Male & Female	6.3 (3.4)	5.2 (1.3)	1.64 (1.6e-03)
Male	5.8 (2.3)	5.1 (0.9)	1.25 (3.4e-03)
Female	6.5 (3.8)	5.3 (1.7)	1.95 (2.9e-03)
Emotional Neglect			
Male & Female	12.6 (5.4)	8.9 (4.0)	2.08 (8.4e-06)
Male	12.6 (5.2)	9.2 (4.1)	1.87 (2.8e-04)
Female	12.5 (5.4)	8.6 (3.9)	2.14 (4.7e-06)
Physical Neglect			
Male & Female	7.8 (3.0)	6.8 (2.4)	1.75 (8.4e-05)
Male	7.9 (2.9)	7.0 (2.5)	1.54 (2.9e-04)
Female	7.8 (3.1)	6.6 (2.3)	1.79 (9.3e-04)
Overall CTQ score			
Male & Female	42.4 (15.1)	32.7 (8.4)	2.62 (1.4e-05)
Male	41.3 (13.4)	33.0 (8.2)	2.18 (1.1e-04)
Female	42.8 (15.8)	32.3 (8.6)	2.74 (3.6e-05)

CTQ = Childhood Trauma Questionnaire; MDD = major depressive disorder; OR = odds ratio; SD = standard deviation

Table S5. Impact of polygenic risk score (based on MDD discovery p<1) on childhood trauma (i.e. gene-environment correlation)

			Impact of PRS on CT in						Approximation of full population by 100 times sampling case/control=0.15/0.85			
	N		All		Case only		Control only		Beta of regression		Correlation	
Cohort	Case	Control	Beta	P	Beta	P	Beta	P	Mean	SE	Mean	SE
Continuous CTQ measure covering five domains (linear regression)												
COFAMS	56	22	1.68	0.507	-0.52	0.871	2.03	0.426	-	-	-	-
NESDA	1143	272	1.10	0.004	1.03	0.020	-0.19	0.742	0.21	0.040	0.02	0.003
RADIANT UK	269	267	1.34	0.041	-0.51	0.640	0.01	0.988	0.68	0.033	0.06	0.003
SHIP-0	340	993	0.15	0.580	-0.08	0.905	-0.08	0.761	0.07	0.009	0.01	0.001
SHIP-TREND	149	448	1.17	0.004	3.21	0.007	0.15	0.682	0.79	0.018	0.09	0.002
Total	1957	2002	0.84	0.004	0.76	0.186	-0.01	0.975	0.37	0.010	0.04	0.001
Dichotomous measure covering sexual and physical abuse (logistic regression)												
COFAMS	56	22	-0.04	0.859	-0.37	0.233	0.71	0.269	-	-	-	-
DGN	461	458	0.11	0.143	0.11	0.256	-0.02	0.866	0.04	0.005	0.03	0.002
NESDA	1133	271	0.16	0.010	0.13	0.048	0.03	0.876	0.13	0.009	0.02	0.003
QIMR_3	186	55	0.10	0.462	0.02	0.876	0.36	0.266	-	-	-	-
QIMR_3_M7	126	29	0.14	0.423	0.13	0.505	0.20	0.672	-	-	-	-
QIMR_6	121	107	-0.10	0.547	-0.21	0.358	0.11	0.670	0.03	0.007	-0.04	0.004
QIMR_C	180	46	-0.06	0.675	-0.07	0.656	0.01	0.972	-	-	-	-
RADIANT UK	262	263	0.16	0.119	0.02	0.912	0.01	0.963	0.11	0.007	0.03	0.003
SHIP-0	352	1042	0.09	0.240	-0.04	0.781	0.10	0.290	0.10	0.003	0.03	0.001
SHIP-TREND	147	448	0.22	0.105	0.26	0.235	0.12	0.500	0.19	0.005	0.02	0.001
Total	3024	2741	0.11	5.4e-04	0.07	0.108	0.07	0.197	0.10	0.002	0.02	0.001

The impact of the polygenic risk scores (PRS) (based on major depressive disorder [MDD] discovery results p<1) on childhood trauma (CT) is displayed in all individuals, MDD cases only and controls only for the continuous Childhood Trauma Questionnaire (CTQ) measure covering five domains (applied in main Table 2) and the dichotomous measure covering sexual and/or physical abuse (applied in main Table 3). However, the potential bias of gene-environment correlation in gene-environment interaction analyses depends on the correlation in the full population. Therefore, cases were randomly sampled such that cases/controls=0.15/0.85 to mimic results in the full population. Sampling was repeated 100 times, and conducted for those cohorts with more than 100 controls only. The Pearson correlation was estimated for the continuous CTQ measure, and the Spearman correlation for the dichotomous CT measure, and analyses were corrected for sex and three principal components.

Table S6. Interaction-analyses for male and female separetely with the PRS based on MDD-PRS including all SNPs (discovery p<1 in the sample of N=112,268)

			Impact on MDD				
	N		PRS			PRSxCT	
Cohort	Case	Control	OR	P	R2 (SE, %)	OR	P
Male & female (i.e. results displayed in main Table 2)							
COFAMS	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.38 (0.08:1.74)	0.201
NESDA	1143	272	1.24 (1.08:1.42)	0.002	1.33 (0.84)	1.08 (0.83:1.39)	0.556
Radiant-UK	269	267	1.64 (1.35:2.00)	6.8e-07	5.90 (2.19)	0.93 (0.66:1.31)	0.670
SHIP-0	340	993	1.30 (1.14:1.48)	1.0e-04	1.81 (0.91)	1.02 (0.89:1.18)	0.737
SHIP-T	149	448	1.33 (1.09:1.63)	0.005	2.10 (1.47)	1.28 (0.96:1.72)	0.103
ALL	1957	2002	1.34 (1.23:1.47)	5.1e-11	1.71 (0.45)	1.05 (0.91:1.20)	0.519
Male only							
COFAMS	20	12	1.66 (0.73:4.21)	0.243	5.05 (7.95)	0.55 (0.06:4.21)	0.553
NESDA	357	111	1.23 (0.99:1.54)	0.061	1.24 (1.31)	1.13 (0.75:1.70)	0.565
Radiant-UK	73	109	1.47 (1.06:2.09)	0.025	3.58 (3.01)	0.84 (0.47:1.52)	0.561
SHIP-0	112	562	1.36 (1.10:1.68)	0.005	2.59 (1.79)	1.08 (0.90:1.32)	0.424
SHIP-T	44	246	1.37 (0.98:1.93)	0.072	2.57 (2.82)	1.22 (0.83:1.84)	0.316
ALL	606	1040	1.34 (1.18:1.52)	8.6e-06	1.71 (0.72)	1.09 (0.91:1.30)	0.367
Female only							
COFAMS	36	10	1.35 (0.65:2.96)	0.419	3.02 (6.29)	0.66 (0.05:6.75)	0.689
NESDA	786	161	1.24 (1.04:1.48)	0.015	1.33 (1.08)	1.09 (0.78:1.48)	0.609
Radiant-UK	196	158	1.72 (1.36:2.20)	1.0e-05	7.20 (2.96)	1.01 (0.66:1.56)	0.970
SHIP-0	228	431	1.26 (1.07:1.50)	0.006	1.54 (1.10)	1.01 (0.82:1.26)	0.912
SHIP-T	105	202	1.35 (1.05:1.74)	0.020	2.42 (2.00)	1.36 (0.93:2.21)	0.161
ALL	1351	962	1.35 (1.21:1.50)	5.2e-08	1.93 (0.63)	1.07 (0.90:1.27)	0.459

Table S7. Interaction-analyses for the separate CT domains with the MDD-PRS including all SNPs (discovery p<1)

			Impact on MDD				
	N		PRS			PRSxCT	
CT domain	Case	Control	OR	P	R2 (SE, %)	OR	P
COFAMS							
Sum	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.38 (0.08:1.74)	0.201
EA	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.36 (0.07:1.73)	0.187
PA	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.01 (0.00:1.05)	0.102
SA	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.36 (0.01:2.07)	0.369
EN	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.88 (0.30:2.98)	0.820
PN	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.27 (0.04:1.35)	0.132
NESDA							
Sum	1143	272	1.24 (1.08:1.42)	0.002	1.33 (0.84)	1.08 (0.83:1.39)	0.556
EA	1125	268	1.22 (1.07:1.41)	0.004	1.17 (0.80)	0.92 (0.72:1.19)	0.547
PA	1134	271	1.24 (1.08:1.42)	0.002	1.33 (0.84)	0.89 (0.68:1.15)	0.388
SA	1139	272	1.24 (1.08:1.42)	0.002	1.33 (0.84)	0.89 (0.60:1.33)	0.573
EN	1118	270	1.24 (1.08:1.42)	0.002	1.32 (0.84)	1.25 (1.04:1.51)	0.019
PN	1125	272	1.25 (1.09:1.43)	0.002	1.38 (0.86)	1.01 (0.83:1.23)	0.909
RADIANT UK							
Sum	269	267	1.64 (1.35:2.00)	6.8e-07	5.90 (2.19)	0.93 (0.66:1.31)	0.670
EA	266	267	1.64 (1.35:2.01)	7.4e-07	5.89 (2.19)	0.87 (0.65:1.18)	0.350
PA	263	265	1.63 (1.34:1.99)	1.2e-06	5.72 (2.17)	1.05 (0.75:1.50)	0.771
SA	264	265	1.64 (1.35:2.00)	9.0e-07	5.84 (2.19)	1.02 (0.73:1.49)	0.923
EN	260	266	1.64 (1.35:2.01)	8.8e-07	5.89 (2.21)	0.95 (0.72:1.26)	0.720
PN	261	267	1.65 (1.36:2.02)	5.4e-07	6.10 (2.24)	0.99 (0.76:1.29)	0.935
SHIP-0							
Sum	340	993	1.30 (1.14:1.48)	1.0e-04	1.81 (0.91)	1.02 (0.89:1.18)	0.737
EA	353	1039	1.31 (1.15:1.49)	5.0e-05	1.91 (0.92)	1.02 (0.89:1.17)	0.795
PA	353	1048	1.31 (1.16:1.50)	3.4e-05	2.00 (0.94)	1.00 (0.87:1.15)	0.976
SA	354	1045	1.31 (1.15:1.49)	5.1e-05	1.90 (0.92)	1.07 (0.95:1.24)	0.286
EN	350	1025	1.31 (1.16:1.50)	3.7e-05	2.00 (0.94)	1.05 (0.92:1.20)	0.497
PN	351	1030	1.30 (1.15:1.48)	6.0e-05	1.89 (0.92)	1.03 (0.90:1.18)	0.686
SHIP-TREND							
Sum	149	448	1.33 (1.09:1.63)	0.005	2.10 (1.47)	1.28 (0.96:1.72)	0.103
EA	148	446	1.33 (1.09:1.63)	0.005	2.06 (1.47)	1.12 (0.87:1.49)	0.426
PA	146	448	1.34 (1.09:1.64)	0.005	2.12 (1.49)	1.09 (0.89:1.42)	0.463
SA	149	448	1.33 (1.09:1.63)	0.005	2.10 (1.47)	1.70 (0.77:3.79)	0.166
EN	149	441	1.34 (1.10:1.64)	0.005	2.14 (1.49)	1.18 (0.94:1.49)	0.166
PN	147	443	1.33 (1.09:1.63)	0.006	2.06 (1.47)	1.30 (1.02:1.70)	0.044
ALL							
Sum	1957	2002	1.34 (1.23:1.47)	5.1e-11	1.71 (0.45)	1.05 (0.91:1.20)	0.519
EA	1948	2042	1.34 (1.22:1.47)	2.5e-10	1.69 (0.44)	0.96 (0.85:1.09)	0.545
PA	1952	2054	1.34 (1.24:1.46)	1.4e-12	1.74 (0.45)	1.00 (0.89:1.12)	0.947
SA	1962	2052	1.34 (1.23:1.46)	9.2e-12	1.72 (0.45)	1.05 (0.90:1.21)	0.551
EN	1933	2024	1.35 (1.24:1.47)	5.2e-12	1.76 (0.46)	1.11 (1.00:1.22)	0.043
PN	1940	2034	1.35 (1.23:1.47)	3.3e-11	1.76 (0.45)	1.05 (0.93:1.19)	0.441

Sum = sumscore of all five CT domains; EA = Emotional abuse; PA = Physical Abuse ; SA = Sexual Abuse ; EN = Emotional Neglect ; PN = Physical Neglect

Table S8. Comparing different discovery samples for MDD

	Effective N	N target		Effect of PRS			Effect of CT		Effect of PRSxCT	
Cohort	discovery	Case	Control	OR	P	R2	OR	P	OR	P
MDD discovery results from PGC, Decode, Genscot, Gera, iPsych and UKB										
COFAMS	112,268	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	6.25	8.0e-04	0.38 (0.08:1.74)	0.201
NESDA	112,268	1143	272	1.24 (1.08:1.42)	0.002	1.33 (0.84)	3.29	3.7e-21	1.08 (0.83:1.39)	0.556
RADIANT UK	112,268	269	267	1.64 (1.35:2.00)	6.8e-07	5.90 (2.19)	4.03	3.0e-20	0.93 (0.66:1.31)	0.670
SHIP-0	112,268	340	993	1.30 (1.14:1.48)	1.0e-04	1.81 (0.91)	1.52	7.0e-11	1.02 (0.89:1.18)	0.737
SHIP-TREND	112,268	149	448	1.33 (1.09:1.63)	0.005	2.10 (1.47)	1.71	3.7e-07	1.28 (0.96:1.72)	0.103
Total	112,268	1957	2002	1.34 (1.23:1.47)	5.1e-11	1.71 (0.45)	2.53	1.3e-09	1.05 (0.91:1.20)	0.519
MDD discovery results from PGC MDD wave 2 leaving the target cohort out										
COFAMS	40,373	56	22	1.02 (0.60:1.76)	0.928	0.02 (0.36)	6.25	8.0e-04	0.76 (0.17:3.80)	0.732
NESDA	37,435	1143	272	1.23 (1.08:1.41)	0.002	1.26 (0.82)	3.29	3.7e-21	1.38 (1.07:1.76)	0.011
RADIANT UK	36,909	269	267	1.32 (1.10:1.58)	0.003	2.07 (1.33)	4.03	3.0e-20	0.67 (0.51:0.90)	0.006
SHIP-0	39,406	340	993	1.08 (0.95:1.22)	0.246	0.16 (0.28)	1.52	7.0e-11	1.03 (0.91:1.17)	0.628
SHIP-TREND	40,084	149	448	1.32 (1.08:1.62)	0.006	1.98 (1.43)	1.71	3.7e-07	1.00 (0.79:1.27)	0.987
Total	-	1957	2002	1.20 (1.10:1.31)	2.8e-05	0.66 (0.28)	2.53	1.3e-09	1.00 (0.79:1.26)	0.972

Table S9. Polygenic risk scores analyses with simulated data

	Mean polygenic risk scores (SE)				Case-control PRS difference		PRSxCT Interaction-effect	
	Cases		Controls					
Cohort	CT=0	CT=1	CT=0	CT=1	CT=0	CT=1	OR	P
Model 1 ("additive")	0.32 (0.007)	0.17 (0.008)	-0.24 (0.003)	-0.30 (0.008)	0.57	0.47	0.91	0.157
Model 2 ("interaction")	0.24 (0.006)	0.03 (0.004)	-0.14 (0.003)	-0.16 (0.011)	0.38	0.19	0.83	0.013
Model 3 (h2l_CT=0.5)	0.26 (0.004)	0.27 (0.005)	-0.29 (0.003)	-0.18 (0.014)	0.55	0.45	0.90	0.185
Model 4 (increased G in CT=1)	0.24 (0.007)	0.24 (0.007)	-0.22 (0.004)	-0.32 (0.010)	0.46	0.56	1.15	0.099
Model 5 (decreased E in CT=1)	0.30 (0.005)	0.27 (0.006)	-0.26 (0.004)	-0.38 (0.010)	0.55	0.65	1.16	0.047

Simulated data of 10,000 SNPs were based on five models, all assuming heritability of MDD of 0.35, prevalence of MDD of 0.15, prevalence of CT of 0.25 and an odds ratio (OR) of CT on MDD of 3.2 (see Supplemental Methods). Model 1: SNP-effects are the same in exposed and unexposed; Model 2: correlation of 0 between SNP-effects in exposed and unexposed; Model 3: SNP-effects on MDD are the same in exposed and unexposed, heritability of CT of 0.5 (for Models 1,2,4, and 5, heritability of CT was set at 0); Models 4: same direction of SNP-effects in exposed and unexposed (correlation of 1), but 3 times larger variance of effects in exposed than unexposed; Model 5: SNP-effects the same in exposed and unexposed, but three times smaller environmental variance in exposed. Simulation was repeated ten times, the means of which are displayed with the standard error (SE) between brackets.

Supplemental References

1. Rasch G (1960): *Studies in mathematical psychology: I. Probabilistic models for some intelligence and attainment tests.* .

2. Sartor CE, Grant JD, Lynskey MT, McCutcheon V V, Waldron M, Statham DJ, *et al.* (2012): Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. *Arch Gen Psychiatry*. 69: 293–9.

3. Golan D, Lander ES, Rosset S (2014): Measuring missing heritability: Inferring the contribution of common variants. *Proc Natl Acad Sci U S A*. 111: E5272-81.

4. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, *et al.* (2007): PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet*. 81: 559–75.

5. Witte JS, Visscher PM, Wray NR (2014): The contribution of genetic variants to disease depends on the ruler. *Nat Rev Genet*. 15: 765–76.