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1 **Does childhood trauma moderate polygenic risk for depression? A meta-analysis of 5,765 subjects**
2 **from the Psychiatric Genomics Consortium**

3 Running title: Childhood trauma and polygenic risk for depression

4

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44 **ABSTRACT**

45 **Background:** The heterogeneity of genetic effects on Major Depressive Disorder (MDD) may be
46 partly attributable to moderation of genetic effects by environment, such as exposure to childhood
47 trauma (CT). Indeed, previous findings in two independent cohorts showed evidence for interaction
48 between polygenic risk scores (PRS) and CT, albeit in opposing directions. This study aims to meta-
49 analyze MDD-PRSxCT interaction results across these two and other cohorts, while applying more
50 accurate PRS based on a larger discovery sample.

51 **Methods and Materials:** Data were combined from 3,024 MDD cases and 2,741 controls from nine
52 cohorts contributing to the MDD Working Group of the Psychiatric Genomics Consortium. MDD-PRS
53 were based on a discovery sample of approximately 110,000 independent individuals. CT was
54 assessed as exposure to sexual or physical abuse during childhood. In a subset of 1957 cases and
55 2002 controls, a more detailed 5-domain measure additionally included emotional abuse, physical
56 neglect and emotional neglect.

57 **Results:** MDD was associated with the MDD-PRS (OR=1.24, $p=3.6e-5$, $R^2=1.18\%$) and with CT
58 (OR=2.63, $p=3.5e-18$ and OR=2.62, $p=1.4e-5$ for the 2- and 5-domain measures respectively). No
59 interaction was found between MDD-PRS and the 2-domain and 5-domain CT measure (OR=1.00,
60 $p=0.89$ and OR=1.05, $p=0.66$).

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

66

67

68 **INTRODUCTION**

69 Recent studies have found the first associated genetic variants for Major Depressive Disorder (MDD)
70 and depressive complaints (1–3), but research on MDD still hasn't met the success of research on
71 schizophrenia, for which 108 genetic variants were found in 2014 (4). This discrepancy is attributable
72 to several factors, including the higher population prevalence of MDD (so that the difference in
73 liability between cases and controls is smaller than in schizophrenia) (5, 6), the lower heritability of
74 MDD (assuming the same degree of polygenicity in terms of number of risk loci) (5), and the greater
75 genetic and phenotypic heterogeneity of MDD (7). To illustrate the possible consequence of
76 heterogeneity, Wray and Maier showed that the power to detect a causal SNP decreases
77 dramatically when a disorder is caused by two distinct pathways (8), while Milaneschi et al found
78 that genetic effects in those with typical MDD might partially differ from genetic effects in those
79 with atypical MDD (9, 10).

80 Another source of genetic heterogeneity may arise from gene-by-environment (GxE)
81 interaction: the moderation of genetic effects on MDD by specific environmental factors. Much
82 research concerning GxE-interaction has been conducted with candidate genes, in particular the
83 interaction between the serotonin transporter gene (5-HTTLPR) and childhood trauma (11), but this
84 research has produced contradictory findings (12–15) that have been attributed, at least in part, to
85 publication bias (16). Recently, Culverhouse et al published results from a collaborative meta-
86 analysis showing no evidence for interaction between 5-HTTLPR and childhood trauma (17) based on
87 a previously published protocol for analyses (18). Nevertheless, in the last couple of years, methods
88 have been developed to assess the combined impact of all genotyped SNPs, such as polygenic risk
89 score (PRS) analyses (19). Kendler proposed that a confirmed main effect is a desirable condition for
90 GxE-interaction testing (20). This suggests that PRS may be preferable over candidate genes to test
91 for GxE-interaction, because PRS have a confirmed significant effect on MDD (21, 22) contrasting the
92 non-replicated and non-consistent effects of candidate genes (23, 24).

93 In GxE interaction research numerous environmental factors can be tested, which may have
94 catalyzed publication bias in the candidate gene literature (16) and may also present as a challenge
95 for GxE interaction tests with PRS. Nevertheless, a plausible environmental factor to test in the
96 context of GxE-interaction is childhood trauma, which is one of the strongest risk factors with a
97 lifelong impact on MDD risk (25), and may perhaps be more uniformly defined than stress later in
98 life. Moreover, exposure to childhood trauma has been hypothesized to distinguish a clinically and
99 neurobiologically distinct subtype of MDD, because MDD patients exposed to childhood trauma
100 have an earlier onset, more chronic course, higher severity with more neurovegetative and psychotic

101 symptoms, more comorbidities, more suicide attempts and poorer treatment outcome than MDD
102 patients that did not experience childhood trauma (26).

103 Following this reasoning, Peyrot et al. tested for GxE interaction between PRS and CT in the
104 Netherlands Study of Depression and Anxiety (NESDA) and found a significantly stronger impact of
105 PRS on MDD risk in individuals exposed to childhood trauma compared to individuals not exposed to
106 childhood trauma (27). In a replication study, Mullins et al found a significant but opposing
107 interaction effect in the RADIANT UK sample with a stronger impact of PRS on MDD risk in those
108 unexposed to childhood trauma (28). These opposing findings, that were both significant, are not
109 well understood, and it remains unclear whether these reflect actual differences between cultures,
110 between recruitment of participants into cohorts, or chance-findings. The aim of the current study is
111 (i) to re-analyze NESDA and RADIANT UK with more accurate PRS based on discovery results from
112 approximately 110,000 individuals (compared to ~15,000 applied previously), and (ii) to place the
113 NESDA and RADIANT UK findings in a broader perspective by meta-analyzing their results with seven
114 additional cohorts from the Psychiatric Genomics Consortium (PGC) MDD wave 2 (29). Secondary
115 analyses used PRS calculated from discovery GWAS results for schizophrenia and bipolar disorder, as
116 these are genetically related to MDD (7, 30).

117

118 **METHODS**

119 **Subjects**

120 Subjects were recruited from the Psychiatric Genomics Consortium (PGC) wave 2, which combines
121 genotype and phenotype data of individuals of European ancestry in 29 different cohorts (29). The
122 combined samples include data of 16,823 MDD cases and 25,632 controls. Of these 29 cohorts, nine
123 cohorts included a measure of childhood trauma: Cognition and Function in Mood Disorders Study
124 (COFAMS) from Australia (31), Depression Gene Network (DGN) from the USA (32), the Netherlands
125 Study of Depression and Anxiety (NESDA) (33), the Queensland Institute of Medical Research (QIMR
126 in three different cohorts defined by genotyping platform) from Australia (23), RADIANT UK (34), and
127 Study of Health in Pomerania (SHIP-0, and SHIP-TREND) from Germany (see Table S1 for more
128 detailed information) (35). Briefly, SHIP-O, SHIP-T and QIMR are community studies with MDD cases
129 and screened controls defined from responses to self-report questionnaires, whilst the other studies
130 recruit MDD cases from in- or out-patient clinics and recruit screened controls with both cases and
131 controls completing the same childhood trauma questionnaires. The definition of MDD in all studies
132 was based on structured psychiatric interviews following DSM-criteria.

133

134 **Childhood Trauma Questionnaire**

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

148

149 **Other childhood trauma instruments**

150 In addition to the five cohorts that assessed childhood trauma with the CTQ instrument, four
151 additional PGC cohorts (DGN and the three sub-cohorts of QIMR) assessed childhood trauma with
152 other instruments (before the age of 18 in QIMR). To obtain the largest possible dataset, childhood
153 trauma information was matched across all nine cohorts for sexual abuse and physical abuse
154 (Supplemental Methods). A broad definition (no abuse versus mild, moderate or severe abuse) was
155 applied to create a childhood trauma indicator separating those with trauma (exposed to sexual
156 and/or physical abuse) from those not exposed to childhood trauma (neither exposed to sexual nor
157 physical abuse). The correlation (Spearman's rho) between the 2-domain dichotomous CT indicator
158 and the 5-domain continuous CT score equaled 0.50 ($p < 2 \cdot 10^{-16}$).

159

160 **Genotyping, quality control and imputation**

161 The cohorts were genotyped following their local protocols, after which quality control and
162 imputation against the 1000 genomes reference panel (38) were performed centrally in the PGC per
163 cohort (29). The SNP probabilities were converted to best guess data with a genotype call probability
164 cut-off of 0.8, after which individuals were removed with missing-rate $> 2\%$. A total of 1,171,526
165 HapMap 3 SNPs passed post-imputation QC in at least 2 of 9 batches (missing-rate $< 2\%$, minor allele
166 frequency > 0.01 , and imputation INFO-score > 0.6). These 1,171,526 SNPs were used to calculate the
167 genetic relatedness matrix (GRM) with PLINK2 (39), which was thus based on a different set of SNPs
168 for individuals from each cohort and between each pair of cohorts (Table S3), in this way providing

169 genome-wide coverage of well described HapMap 3 SNPs. From the GRM, unrelated individuals
170 were selected with relatedness <0.05 , and ancestry informative principal components were
171 calculated with GCTA (40).

172

173 **Polygenic risk scores**

174 Polygenic risk scores for MDD (MDD-PRS) were based on meta-analysis of the GWAS results from the
175 twenty PGC MDD wave 2 cohorts with no childhood trauma information available (10,409 cases,
176 18,640 controls) (29), deCODE (1,980 cases, 9,536 controls) (29), GenScotland (997 cases, 6,358
177 controls) (41, 42), GERA (7,162 cases, 38,307 controls) (43), iPsych (16,242 cases, 15,847 controls)
178 (29) and UK Biobank (8,248 cases, 16,089 controls) (44, 45). This discovery sample comprised 45,038
179 cases and 104,777 controls yielding a power similar to a sample of 56,134 cases and 56,134 controls
180 ($N_{\text{effective}} = 56,134 + 56,134 = 112,268$). Additional PRS were based on GWAS results from
181 schizophrenia (SCZ-PRS) (4) and bipolar disorder (BIP-PRS) (46), because these disorders are
182 genetically related to MDD (7, 30). PRS were calculated using 463,215 SNPs shared between the
183 discovery sample results and passing QC in all cohorts (missing-rate $<2\%$, minor allele frequency
184 >0.01 , and imputation INFO-score >0.6). Thus, PRS were based on the same set of SNPs in all
185 analyses to increase comparability of results across cohorts. These SNPs were clumped with PLINK (--
186 clump-p1 1 --clump-p2 1 --clump-r2 0.25 --clump-kb 500), and provided 73,576 lowly correlated
187 SNPs for MDD, 73,559 for SCZ, and 73,656 for BIP. The MDD-PRS were based on five different
188 thresholds of GWAS significance for SNP inclusion (p-value smaller than 0.01, 0.05, 0.1, 0.5 and 1
189 respectively). The SCZ-PRS was based on a threshold of $p < 0.05$, which provided optimal predictive
190 power on SCZ (4). The BIP-PRS was based on a threshold of $p < 0.5$ with best predictive performance
191 on BIP (46). The PRS were calculated by summing the number of risk alleles weighted by their effect
192 size (--score command in PLINK) (39).

193

194 **Statistical analyses**

195 The prevalences at the population level of the 5-domain and 2-domain dichotomous CT indicators
196 were approximated from this study assuming a population lifetime risk of MDD of 15%, with a
197 lifetime risk of 20% in women and 10% in men (5, 47). The impact of the PRS, CT and PRSxCT was
198 first estimated in the individual cohorts, and the effects in the total sample were subsequently
199 assessed with random-effect meta-analysis. Within each cohort, the impact of CT on MDD was
200 assessed with logistic regression including sex as covariate. The tests for the main effects of the PRS
201 on MDD included sex and the first three ancestry informative principal components as covariates.
202 Interaction analyses were conducted with the 5-domain continuous CT measure and with the 2-

203 domain dichotomous CT indicator. Interaction analyses of PRSxCT were corrected for sex, three
204 principal components, PRS, CT, and the interaction-terms of PRS and CT with sex and the principal
205 components in line with Keller's recommendation (48). With logistic regression, interaction is tested
206 as departure from multiplicativity (combined impact different from the *product* of the individual
207 effects), but it has been argued that interaction as departure from additivity (combined impact
208 different from the *sum* of the individual effects) is more meaningful biologically (49). For testing
209 interaction as departure from additivity, the relative excess risks due to interaction (RERI) were
210 estimated with the coefficients from logistic regression as $e^{\widehat{\beta}_{PRS} + \widehat{\beta}_{CT} + \widehat{\beta}_{PRSxCT}} - e^{\widehat{\beta}_{PRS}} - e^{\widehat{\beta}_{CT}} + 1$,
211 and their 95% confidence intervals by means of bootstrapping with 10,000 iterations. The impact of
212 the PRS on MDD was further expressed as variation explained on the liability scale, R^2 (50). The PRS
213 and continuous 5-domain CT measure were standardized (i.e. mean of 0 and variance of 1), and the
214 presented ORs can thus be interpreted as increased MDD risk per standard deviation increase in PRS
215 or CT. The analyses were conducted in R (51).

216

217 **Genetic Relationship Matrix (GRM)-based analyses**

218 The variance in MDD liability and CT explained by genotyped SNPs (SNP heritability) was assessed
219 with cross product Haseman-Elston regression (52). These analyses were corrected for covariates by
220 calculating the residuals of linear regression of MDD and CT on sex, genotyping batch and 20
221 ancestry informative principal components (PCs). We included 20 PCs, because GRM-based analyses
222 are more sensitive to population stratification than PRS analyses (7). To test for interaction between
223 CT and genome-wide genetic effects in MDD, the genetic correlation between MDD in unexposed
224 individuals and MDD in exposed individuals can give information about differences in genetic effects
225 (53). Unfortunately, the current data did not allow for the latter analyses because of limited sample
226 size (e.g. only 389 exposed controls) while analyses had to be corrected for 9 cohorts.

227

228 **RESULTS**

229 **Phenotypic association between MDD and CT**

230 The 5-domain continuous and dichotomous CT measures were available for 1957 cases and 2002
231 controls, and the 2-domain dichotomous indicator was available for 3024 cases and 2741 controls.
232 The prevalence of CT was estimated at 0.25 based on the 5-domain indicator (Table 1), and at 0.17
233 for the 2-domain indicator (Table 3). As expected, the prevalence was considerably larger in cases
234 than controls (0.50 vs 0.21 for the 5-domain measure and 0.35 vs 0.14 for the 2-domain measure).
235 This was reflected in an OR for MDD of 3.80 ($p=3.0e-6$) for the 5-domain dichotomous measure, and
236 an OR of 2.63 ($p=3.5e-18$) for the 2-domain measure. For the 5-domain continuous CT measure, an

237 OR for MDD of 2.62 ($p=1.4e-5$) per standard deviation increase in CT was found (Table 1 & Figure 1).
238 The impact of CT on MDD was comparable in men and women, with ORs of 2.18 (males, $p=1.1e-4$)
239 and 2.74 (females, $p=3.6e-5$) per standard deviation increase in the continuous 5-domain CT
240 measures (Table 1). CT had an impact on MDD risk in all cohorts (Table 1), and the five CTQ domains
241 all had an impact on MDD risk (Table S4).

242

243 **Polygenic risk score analyses**

244 The MDD-PRS based on all SNPs (inclusion threshold of $p<1$) had the greatest predictive power, with
245 an OR of 1.34 ($p=5.1e-11$, $R^2=1.71\%$) in the 1957 cases and 2002 controls with availability of the 5-
246 domain CT measures (Table 2). The SCZ-PRS and BIP-PRS also predicted MDD but to a lesser extent
247 than the MDD-PRS (Table 2), reflecting the well-described genetic correlation between MDD, BIP
248 and SCZ (7). Because GE-correlation can lead to spurious GxE-results (54), we tested for an
249 association between the MDD-PRS and CT. The MDD-PRS did predict the 5-domain continuous CT
250 measure ($\beta=0.76$, $p=0.004$ in linear regression), but this was approximated to only reflect a small
251 correlation in terms of the full population of ~ 0.04 (Table S5). No interaction between the PRS and
252 the 5-domain continuous CTQ measure was found, with an impact of MDD-PRSxCT on MDD of
253 $OR=1.05$ ($p=0.52$; Table 2). In addition, no evidence was found for interaction as departure from
254 additivity ($RERI=0.83$, $95\%CI= -0.62$ to 18.03). The BIP-PRS and SCZ-PRS showed no evidence for
255 interaction with the 5-domain CT measure.

256 Applying the 2-domain dichotomous CT indicator of sexual or physical abuse allowed
257 inclusion of four additional cohorts in the analyses (Table 3): DGN and 3 QIMR cohorts (one of the
258 QIMR cohorts was split in two to acknowledge different instruments applied to assess childhood
259 trauma). The total sample size thus increased to 3024 cases and 2741 controls, in which the MDD-
260 PRS had an impact on MDD with an OR of 1.24 ($p=3.6e-5$, $R^2=1.18\%$). The polygenic risk scores did
261 predict MDD in DGN, but not in all QIMR cohorts, which is attributable to the relatively small
262 number of QIMR subjects with CT information available compared to the full QIMR sample (in which
263 PRS predict MDD as expected). No interaction was found between the PRS and 2-domain
264 dichotomous CT indicator (Table 3).

265 An alternative method sometimes applied to test for interaction as departure from additivity
266 is linear regression with the disease trait as outcome (28). We suggest for caution in interpreting
267 findings from this approach, because this method has, to the best of our knowledge, not been
268 formally described. Nevertheless, for reasons of completeness, this approach was applied and also
269 showed no evidence for interaction with the 5-domain CT measure ($\beta=-0.004$, $p=0.67$) and the 2-
270 domain CT measure ($\beta=-0.005$, $p=0.45$).

271

272 **GRM based analyses**

273 The SNP heritability of MDD was estimated at 0.14 (SE=0.03; $p=3.7e-8$) based on the 6,348 cases and
274 6,751 controls across the nine cohorts (Table S1; these analyses included additional individuals with
275 no CT information available). The SNP heritability of CT was estimated at 0.00 (SE=0.07; $p=1$;
276 $N=3,959$) for the 5-domain continuous measure, and at 0.09 (SE=0.08; $p=0.27$; $N=5,765$) for the 2-
277 domain dichotomous indicator.

278

279 **DISCUSSION**

280 This study was conducted to test for interaction between polygenic risk for MDD and childhood
281 trauma (CT) in 5,765 individuals from nine cohorts contributing to the Psychiatric Genomics
282 Consortium that had a childhood trauma assessment available. CT occurred in 25% of individuals
283 based on an indicator of 5-domains (sexual abuse, physical abuse, emotional abuse, emotional
284 neglect, and physical neglect), and in 17% based on broad definition of 2-domains (sexual and/or
285 physical abuse). As expected, the prevalence was considerably higher in cases than controls (0.50 vs
286 0.21 for the 5-domain measure and 0.35 vs 0.14 for the 2-domain measure). The 5-domain measure
287 was more detailed and uniformly assessed in 1957 cases and 2002 controls; the 2-domain indicator
288 was assessed heterogeneous across cohorts, but available for a larger sample comprising of 3024
289 cases and 2741 controls. The polygenic risk scores (PRS) explained 1.18% to 1.71% of variation in
290 MDD risk. No evidence for interaction between PRS and childhood trauma was found with 5-domain
291 CT measure (Table 2) and the 2-domain CT indicator (Table 3). Secondary analyses also showed no
292 evidence for interaction in analyses with PRS based on discovery results from schizophrenia and
293 bipolar disorders, in tests for interaction as departure from additivity, in analyses in males and
294 females separately (Table S6), and in analysis in the five separate domains of CT (Table S7;
295 significance threshold $0.01=0.05/5$). Analyses excluding NESDA and RADIANT UK showed no
296 evidence for interaction between the MDD-PRS (p -value threshold 1) and 5-domain CT measure
297 (OR=1.06, $p=0.67$) and 2-domain CT measure (OR=0.98, $p=0.61$) in the remainder of the cohorts.

298 Remarkably, no interaction-effects were found in NESDA (OR=1.08, 95%CI=0.83-1.39,
299 $p=0.56$) and RADIANT UK (OR=0.93, 95%CI=0.66-1.31, $p=0.67$) with the 5-domain CT measure (Table
300 2), which contrasts previous findings in these respective cohorts by Peyrot et al (OR=1.12, $p=0.018$,
301 discovery sample $N_{\text{effective}}=15,295$) (27) and Mullins et al (OR=0.96 based on differently scaled PRS
302 and CT, $p=0.002$, discovery sample $N_{\text{effective}}=15,540$) (28). Aiming to clarify these discrepancies, we
303 analyzed PRS based on discovery results from PGC MDD wave 2 with an effective sample size of
304 approximately 37,000 (Table S8) and confirmed the previously reported interaction-effects in NESDA

305 (OR=1.38, 95%CI=1.07-1.76, p=0.011) and RADIANT UK (OR=0.67, 95%CI=0.51-0.90, p=0.006).
306 Therefore, it appears that the OR of the interaction-effects are reduced by adding deCODE (29),
307 GenScotland (41, 42), GERA (43), iPsych (29) and UK Biobank (44, 45) to the PRS discovery sample.
308 These discrepancies in interaction results may reflect different study designs in the discovery
309 datasets with application of self-reported depression status in UKB and clinical records in iPsych and
310 GERA, contrasting the semi-structured interviews (such as the SCID, CIDI and MINI) applied in most
311 PGC cohorts (29). However, these discrepancies may also reflect random variation in effects with
312 discovery sample size increasing from ~37,000 to ~110,000. The latter possibility seems more likely
313 since: (1) we observe an increase in the variance explained by the PRS from 0.66% ($p=2.8e-5$) to
314 1.71% ($p=5.1e-11$) (Table S8), which corresponds with the increase predicted from theory given the
315 increased sample size (55); (2) a genetic correlation of 0.91-0.96 between the PGC wave 2 discovery
316 results and the extended discovery results as estimated with LD-score regression (30); and (3) an
317 overlap of the 95% CI of the interaction-effects based on the PGC discovery sample and the larger
318 discovery sample applied in this paper (Table S8). In other words, our results suggest that the
319 additional discovery cohorts (deCODE, GenScotland, GERA, iPsych, and UK Biobank) capture the
320 same genetic information as the PGC cohorts. Therefore, we hypothesize that the previously
321 reported interaction results in NESDA (27) and RADIANT UK (28) were both chance findings. The fact
322 that these findings were both significant in an opposite direction may reflect the statistical
323 vulnerability of interaction testing (48, 54, 56).

324 A source of spurious interaction effects can be found in gene-environment (GE) correlation
325 as explained for twin analyses by Purcell (54). Notably, the PRS based on the PGC wave 2 discovery
326 results were slightly more correlated with childhood trauma in the full population (with
327 approximately -0.09 in NESDA and 0.13 in RADIANT UK) than the PRS based on the extended sample
328 (~0.02 and ~0.06 respectively). A simulation study suggested that the type I error rate can indeed be
329 inflated in the context of GE-correlation, but to a modest extent of 0.075 (with alpha set at 0.05) for
330 a strong correlation of 0.3 between G and E (Supplemental Methods). It is, therefore, unlikely that
331 the GxE-interactions previously found would be attributable to GE-correlation.

332 The current study has both strengths and limitations. First, this study is the largest to date to
333 test for interaction between polygenic risk scores and CT in MDD risk. Second, polygenic risk scores
334 were based on a powerful discovery GWAS with approximately 110,000 individuals. Third, diagnoses
335 were DSM-based aiming to select clinically relevant cases of MDD. A limitation of our study is that CT
336 was not assessed uniformly across cohorts for the 2-domain measure, but analyses restricted to
337 cohorts assessed uniformly with the 5-domain CTQ-instrument showed similar results. Although this
338 study is the largest to date, power to detect an interaction-effect between PRS and CT was still

339 limited (power \geq 0.8 for interaction effects with OR \leq 0.83 or OR \geq 1.21 for analyses with the 2-domain
340 CT measure in 5,765 individuals based on power analyses with the QUANTO software) (57). Of note,
341 tests of interaction with PRS do not rule out interaction with individual SNPs; the PRS were based on
342 many SNPs, some, but not all of which may be involved in interaction. The current study tested for
343 interaction with childhood trauma, because childhood trauma has been hypothesized to define a
344 distinct type of MDD,(26) but other environmental factors could have also been tested.
345 Nevertheless, testing too many environmental conditions assessed with a variety of instruments
346 may increase risk of publication bias when significant findings would be published selectively (16,
347 58).

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

363 To conclude, no overall evidence was found for interaction between PRS and CT. Previously
364 found interaction effects (27, 28) were no longer significant when applying more powerful discovery
365 results. This study provides a cautionary tale for interaction analyses with PRS: it emphasizes the
366 need to meta-analyze results across different cohorts to obtain external validity. The quest
367 continues to clarify the nature of the heterogeneity of MDD, but the present study has shown that
368 the heterogeneity is unlikely to be attributable to moderation of genome-wide genetic effects by CT.
369 Future research may focus on interaction effects between CT and individual SNPs. We hereby call for
370 large GWAS cohorts to assess CT in a uniform manner to facilitate such research in the years the
371 come.

372

373 **CONFLICTS OF INTEREST**

374 The authors declare no conflicts of interest.

375

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611 **Legend to Table 1**

612 Information is displayed for the cohorts that assessed childhood trauma with the Childhood Trauma
613 Questionnaire (CTQ) covering the 5 domains of sexual abuse, physical abuse, emotional abuse, physical neglect
614 and emotional neglect in a dichotomous 5-domain indicator (exposed versus unexposed) and continuous
615 measure (ranging from 25-125). For the dichotomous CT measure, the proportion of exposed individuals is
616 presented in cases, controls, and in terms of the full population (Pop) assuming a population prevalence of
617 MDD of 15% with twice the prevalence in females (20%) as in males (10%), as well as the odds ratio (OR) of
618 exposed versus unexposed to develop MDD. For the continuous CT measure, the means are displayed in the
619 original scale, and the odds ratio for MDD was assessed for the CTQ measure scaled to variance 1, and can
620 thus be interpreted as increased odds per standard deviation (SD) increase in childhood trauma. The ORs were
621 estimated with logistic regression including sex as covariate. The ORs in the Total sample were estimated with
622 random effect meta-analysis.

623

624 **Legend to Figure 1.**

625 Forest plot of impact on major depressive disorder of the continuous childhood trauma (CT) score
626 covering the 5 domains of sexual abuse, physical abuse, emotional abuse, emotional neglect, and
627 physical neglect. The odds ratio (OR) represents one standard deviation increased in CT. SHIP-O,
628 SHIP-T and QIMR are community studies with MDD cases and screened controls defined from
629 responses to self-report questionnaires, whilst the other studies recruit MDD cases from in- or out-
630 patient clinics and recruit screened controls with both cases and controls completing the same
631 childhood trauma questionnaires.

632

633 **Legend to Table 2**

634 The impact on major depressive disorder (MDD) is displayed for polygenic risk scores (PRS) and their
635 interaction with the 5-domain continuous childhood trauma (CT) measure including sexual abuse, physical
636 abuse, emotional abuse, physical neglect and emotional neglect. The impact of the PRS is presented as the
637 odds ratio (OR) from logistic regression corrected for sex and three principal components, as well as with the
638 variance explained by the PRS on the liability scale. Interaction of PRS with CT (PRSxCT) was assessed as
639 departure from multiplicativity with logistic regression while additionally correcting for the main effects of PRS
640 and CT. Interaction as departure from additivity was expressed as the relative excess risks due to interaction
641 (RERI) estimated as described in the main text, and their 95% confidence intervals (CI) were estimated with
642 bootstrapping with 10,000 iterations. The PRS were based on discovery GWAS results from MDD,
643 schizophrenia (SCZ) and bipolar disorder (BIP). Results in the Total sample were based on random-effect meta-
644 analysis of the effects in the individual cohorts.

645

646 **Legend to Table 3**

647 The impact on major depressive disorder (MDD) is displayed for polygenic risk scores (PRS) and their
648 interaction with the childhood trauma (CT) dichotomous indicator covering sexual abuse and physical abuse
649 (broad definition). The prevalence of CT is presented in MDD cases, controls, and in terms of the full
650 population (Pop) assuming a population prevalence of MDD of 15% with twice the prevalence in females (20%)
651 as in males (10%). The impact of the PRS and CT is presented as the odds ratio (OR) from logistic regression
652 corrected for sex and three principal components, as well as with the variance explained by the PRS on the
653 liability scale. Interaction of PRS with CT (PRSxCT) was assessed as departure from multiplicativity with logistic
654 regression while additionally correcting for the main effects of PRS and CT. The PRS were based on discovery
655 GWAS results from MDD including all SNPs, i.e. with significance threshold $p < 1$.
656

Table 1. Number of depression cases and controls and the 5-domain childhood trauma (CT) measure.

Cohort	N		Dichotomous CT indicator				Continuous CT measure		
	Case	Control	Proportion of CT			OR (p-value)	Mean (SD)		OR (p-value)
			Case	Control	Pop		Case	Control	
Male and female									
COFAMS	56	22	0.70	0.23	0.30	7.22 (8.6e-04)	54.7 (21.4)	33.2 (11.6)	5.60 (1.2e-03)
NESDA	1143	272	0.53	0.21	0.26	4.18 (6.9e-19)	43.0 (14.6)	33.6 (9.1)	3.29 (3.4e-21)
RADIANT UK	269	267	0.62	0.18	0.24	7.60 (1.1e-22)	46.4 (16.2)	32.7 (8.8)	4.08 (7.4e-21)
SHIP-0	340	993	0.36	0.23	0.25	1.94 (1.1e-06)	37.4 (12.3)	33.0 (8.4)	1.52 (7.4e-11)
SHIP-TREND	149	448	0.28	0.15	0.17	2.43 (1.5e-04)	36.9 (14.2)	31.6 (7.3)	1.72 (2.4e-07)
Total	1957	2002	0.50	0.21	0.25	3.80 (3.0e-06)	42.4 (15.1)	32.7 (8.4)	2.62 (1.4e-05)
Male only									
COFAMS	20	12	0.55	0.25	0.28	3.67 (1.1e-01)	50.2 (19.9)	34.8 (14.5)	2.94 (4.4e-02)
NESDA	357	111	0.53	0.19	0.22	4.70 (5.4e-09)	42.0 (13.5)	33.4 (9.1)	3.17 (3.4e-09)
RADIANT UK	73	109	0.62	0.18	0.23	7.42 (7.8e-09)	45.5 (14.5)	33.2 (9.1)	3.43 (4.4e-08)
SHIP-0	112	562	0.39	0.25	0.26	1.95 (1.8e-03)	37.0 (9.1)	33.2 (7.8)	1.48 (1.8e-05)
SHIP-TREND	44	246	0.27	0.18	0.19	1.71 (1.5e-01)	35.7 (10.9)	32.3 (7.5)	1.42 (1.3e-02)
Total	606	1040	0.49	0.22	0.25	3.30 (8.7e-05)	41.3 (13.4)	33.0 (8.2)	2.18 (1.1e-04)
Female only									
COFAMS	36	10	0.78	0.20	0.32	14.0 (2.9e-03)	57.2 (22.0)	31.4 (7.0)	18.44 (2.2e-02)
NESDA	786	161	0.53	0.23	0.29	3.90 (2.1e-11)	43.5 (15.1)	33.7 (9.0)	3.30 (1.5e-13)
RADIANT UK	196	158	0.61	0.17	0.26	7.70 (2.4e-15)	46.8 (16.8)	32.3 (8.6)	4.41 (3.0e-14)
SHIP-0	228	431	0.35	0.22	0.24	1.94 (1.7e-04)	37.5 (13.6)	32.6 (9.0)	1.57 (5.5e-07)
SHIP-TREND	105	202	0.29	0.11	0.15	3.10 (2.6e-04)	37.4 (15.4)	30.7 (6.9)	2.04 (1.2e-05)
Total	1351	962	0.50	0.19	0.25	4.03 (2.5e-06)	42.8 (15.8)	32.3 (8.6)	2.74 (3.6e-05)

657

658

Table 2. Impact on major depressive disorder of polygenic risk scores and their interaction with the 5-domain childhood trauma (CT) continuous measure of sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect

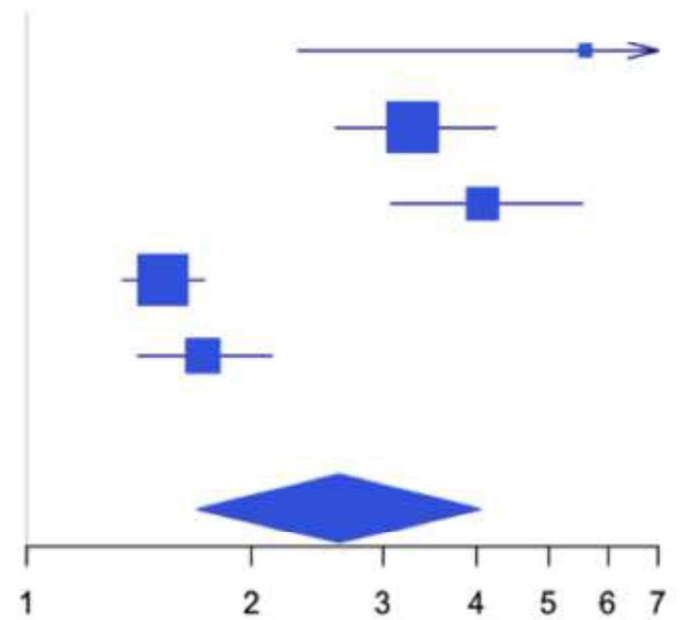
Discovery	N		Impact on MDD					
	Case	Control	PRS			PRSxCT		
			OR	P	R2 (SE, %)	OR	P	RERI (95% CI)
COFAMS								
MDD p<1	56	22	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.38 (0.08:1.74)	0.201	-2.07 (NA-NA)
SCZ p<0.05	56	22	1.18 (0.59:2.33)	0.623	0.54 (1.95)	0.01 (0.00:0.37)	0.030	-62.80 (NA-NA)
BIP p<0.5	56	22	0.85 (0.44:1.58)	0.612	0.44 (1.77)	0.13 (0.01:0.96)	0.076	-2.46 (NA-NA)
NESDA								
MDD p<1	1143	272	1.24 (1.08:1.42)	0.002	1.33 (0.84)	1.08 (0.83:1.39)	0.556	1.06 (-1.07:10.48)
SCZ p<0.05	1143	272	1.25 (1.07:1.46)	0.006	1.02 (0.74)	0.91 (0.68:1.22)	0.510	0.39 (-1.18:8.78)
BIP p<0.5	1143	272	1.14 (1.00:1.31)	0.049	0.53 (0.53)	1.19 (0.92:1.52)	0.182	1.97 (-0.28:17.61)
RADIANT UK								
MDD p<1	269	267	1.64 (1.35:2.00)	6.8e-07	5.90 (2.19)	0.93 (0.66:1.31)	0.670	4.42 (-1.78:178.22)
SCZ p<0.05	269	267	1.61 (1.31:2.01)	1.3e-05	4.44 (1.92)	0.90 (0.62:1.30)	0.581	9.87 (-0.43:275.79)
BIP p<0.5	269	267	1.19 (1.00:1.43)	0.053	0.85 (0.86)	1.02 (0.75:1.38)	0.920	4.25 (-0.95:137.22)
SHIP-0								
MDD p<1	340	993	1.30 (1.14:1.48)	1.0e-04	1.81 (0.91)	1.02 (0.89:1.18)	0.737	0.52 (-0.18:2.86)
SCZ p<0.05	340	993	1.05 (0.91:1.22)	0.470	0.06 (0.17)	0.95 (0.83:1.10)	0.497	-0.22 (-0.97:0.60)
BIP p<0.5	340	993	0.95 (0.84:1.09)	0.477	0.06 (0.16)	0.92 (0.81:1.05)	0.230	-0.12 (-0.89:0.96)
SHIP-TREND								
MDD p<1	149	448	1.33 (1.09:1.63)	0.005	2.10 (1.47)	1.28 (0.96:1.72)	0.103	0.22 (-0.50:1.43)
SCZ p<0.05	149	448	1.10 (0.89:1.37)	0.379	0.20 (0.46)	0.90 (0.71:1.15)	0.404	-0.09 (-1.09:1.62)
BIP p<0.5	149	448	1.20 (0.99:1.46)	0.071	0.86 (0.95)	1.05 (0.85:1.32)	0.659	0.07 (-0.75:1.51)
Total								
MDD p<0.01	1957	2002	1.22 (1.08:1.37)	0.001	0.58 (0.26)	1.02 (0.89:1.17)	0.790	-0.17 (-2.86:10.25)
MDD p<0.05	1957	2002	1.29 (1.14:1.45)	4.0e-05	1.08 (0.36)	0.98 (0.79:1.22)	0.846	0.27 (-2.46:15.37)
MDD p<0.1	1957	2002	1.34 (1.18:1.53)	1.0e-05	1.49 (0.42)	1.01 (0.84:1.22)	0.910	0.51 (-2.02:15.72)
MDD p<0.5	1957	2002	1.35 (1.22:1.48)	2.2e-09	1.70 (0.45)	1.03 (0.86:1.23)	0.755	0.84 (-0.52:22.18)
MDD p<1	1957	2002	1.34 (1.23:1.47)	5.1e-11	1.71 (0.45)	1.05 (0.91:1.20)	0.519	0.83 (-0.62:18.03)
SCZ p<0.05	1957	2002	1.22 (1.04:1.43)	0.013	0.57 (0.26)	0.91 (0.79:1.04)	0.172	-0.15 (-2.87:11.06)
BIP p<0.5	1957	2002	1.10 (0.98:1.23)	0.114	0.16 (0.14)	1.00 (0.85:1.18)	0.997	0.39 (-1.13:20.78)

Table 3. Proportion exposed to childhood trauma (CT) measured as either sexual or physical abuse, and its interaction with polygenic risk scores (PRS with SNP threshold $p < 1$) in predicting major depressive disorder (MDD)

Cohorts	N		Proportion exposed to			Impact on MDD						
	Case	Control	CT		Pop	CT		PRS			PRSxCT	
			Case	Control		OR	P	OR	P	R2 (SE, %)	OR	P
COFAMS	56	22	0.43	0.27	0.30	1.85	0.268	1.41 (0.82:2.49)	0.212	3.13 (4.61)	0.51 (0.21:1.05)	0.088
DGN	461	458	0.40	0.20	0.22	2.49	1.9e-09	1.30 (1.13:1.50)	2.5e-04	1.77 (0.94)	1.06 (0.91:1.22)	0.465
NESDA	1133	271	0.32	0.11	0.14	3.83	8.3e-11	1.24 (1.09:1.43)	0.002	1.36 (0.85)	1.06 (0.87:1.28)	0.587
QIMR_3	186	55	0.44	0.18	0.22	3.66	7.0e-04	1.07 (0.79:1.46)	0.670	0.13 (0.60)	0.82 (0.52:1.25)	0.355
QIMR_3_M7	126	29	0.48	0.31	0.34	2.10	0.092	1.16 (0.75:1.80)	0.494	0.66 (1.80)	0.83 (0.49:1.40)	0.496
QIMR_6	121	107	0.38	0.23	0.29	2.05	0.016	0.90 (0.67:1.19)	0.452	0.30 (0.78)	0.87 (0.61:1.22)	0.418
QIMR_C	180	46	0.40	0.33	0.33	1.36	0.387	0.83 (0.58:1.17)	0.297	0.92 (1.70)	0.89 (0.60:1.30)	0.564
RADIANT UK	262	263	0.42	0.15	0.19	4.33	1.5e-11	1.61 (1.33:1.97)	2.1e-06	5.46 (2.14)	1.04 (0.83:1.30)	0.761
SHIP_0	352	1042	0.22	0.12	0.14	2.10	6.0e-06	1.31 (1.15:1.49)	4.2e-05	1.95 (0.93)	0.97 (0.86:1.10)	0.606
SHIP-TREND	147	448	0.20	0.08	0.10	2.77	2.0e-04	1.34 (1.09:1.64)	0.005	2.14 (1.50)	1.08 (0.88:1.35)	0.460
Total	3024	2741	0.35	0.14	0.17	2.63	3.5e-18	1.24 (1.12:1.37)	3.6e-05	1.18 (0.31)	1.00 (0.93:1.07)	0.894

Figure
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Cohort	Cases	Controls	OR
COFAMS	56	22	5.60
NESDA	1143	272	3.29
RADIANT UK	269	267	4.08
SHIP-0	340	993	1.52
SHIP-TREND	149	448	1.72
Total	1957	2002	2.62



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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 .05 ($p=.003$ 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 $var(g_{MDD})/var(l_{MDD}) = var(g_{MDD}) = h_{l,MDD}^2$, 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 $h_{l,MDD}^2 = 0.35$, 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 $h_{i,MDD}^2/3,000$ 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 $1 - h_{i,MDD}^2 - var(CT_{liability\ scale})$, 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 $K_{MDD} = P(z > T_{MDD} | z \sim N(0,1))$. 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 $h_{i,MDD}^2 = 0.35$, a prevalence of CT of $K_{CT} = 0.25$, no impact of SNPs in CT ($h_{i,CT}^2 = 0$), 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

$r_g = cor(effect_{SNP\ j | CT=1}, effect_{SNP\ j | CT=0}) = 0$ 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 $var(effect_{SNP\ j | CT=1}) = var(effect_{SNP\ j | CT=0}) = 0.35$.

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 $h_{l,CT}^2 = 0.5$ and environmental effects from a normal distribution with variance $1 - h_{l,CT}^2$ 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 $K_{CT} = P(z > T_{CT} | z \sim N(0,1))$. 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 $var(effect_{SNP j | CT=1})/var(effect_{SNP j | CT=0}) = 3$ while keeping $cor(effect_{SNP j | CT=1}, effect_{SNP j | CT=0}) = 1$. The variances of SNP-effects were 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 $var(e_{residual,MDD|CT=1})/var(e_{residual,MDD|CT=0}) = 1/3$ while assuming constant genetic effects in those exposed and those unexposed to CT, $effect_{SNP j | CT=1} = effect_{SNP j | CT=0}$ (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 $T_{MDD|CT=0} = \Phi^{-1}(1 - 0.11) = 1.241$. 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 $h_{l,MDD}^2 = 0.35$, and variance of environmental effects at $1 - h_{l,MDD}^2 = 0.65$ (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 ($var(effect_{SNP\ j|CT=1})/var(effect_{SNP\ j|CT=0}) = 3$), the variance of genetic effects followed as $var(effect_{SNP\ j|CT=1}) = 0.56$ and $var(effect_{SNP\ j|CT=0}) = 0.28$ thereby ensuring that the variance of genetic effect in the full population equals $var(effect_{SNP\ j}) = 0.25\mu_{effect_{SNP\ j|CT=1}}^2 + 0.75\mu_{effect_{SNP\ j|CT=0}}^2 - (0.2\mu_{effect_{SNP\ j|CT=1}} + 0.8\mu_{effect_{SNP\ j|CT=0}})^2 = 0.25(0.56 + 0^2) + 0.75(0.28 + 0^2) - 0 = 0.35$. We choose to fix the residual variance in both exposed and unexposed first at $var(e_{residual|CT=1}) = var(e_{residual|CT=0}) = 0.65$, 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.

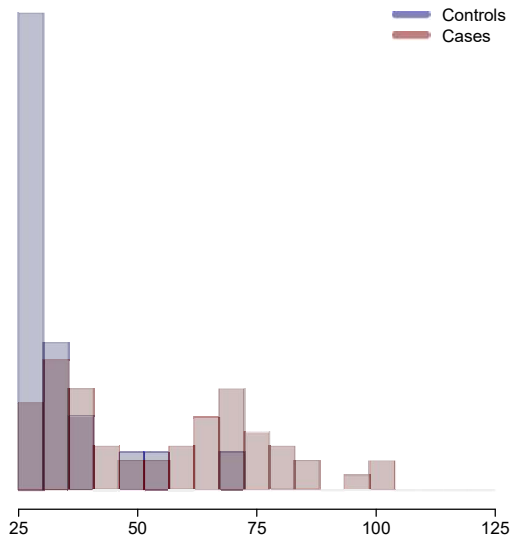
Appendix C. Decreased environmental variation in individuals exposed to CT

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 $h_{i,MDD}^2 = 0.35$ equal in exposed and unexposed, and variance of environmental effects at $1 - h_{i,MDD}^2 = 0.35$ (the latter including both the variance of $CT_{liability}$ as well as residual environmental effects).

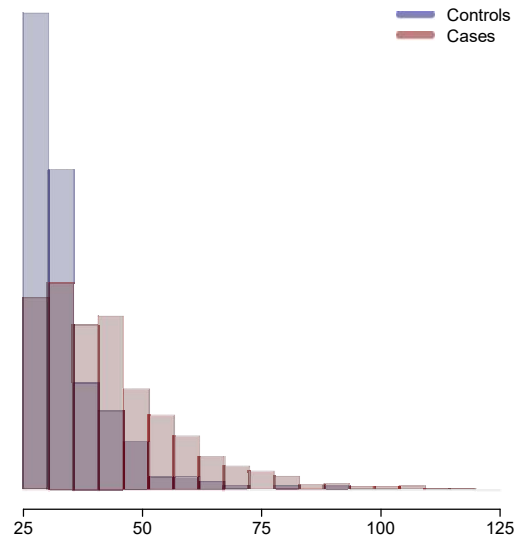
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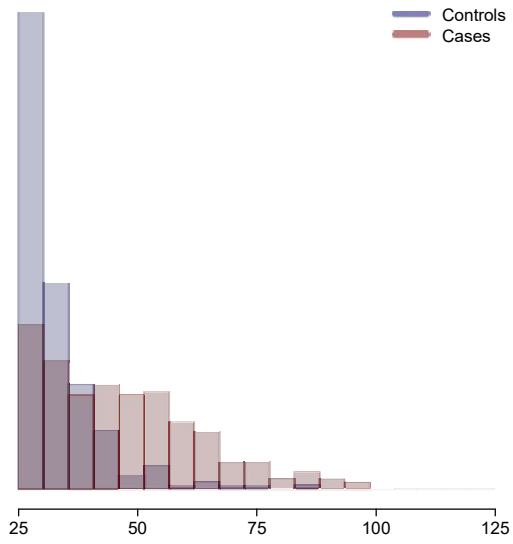
COFAMS



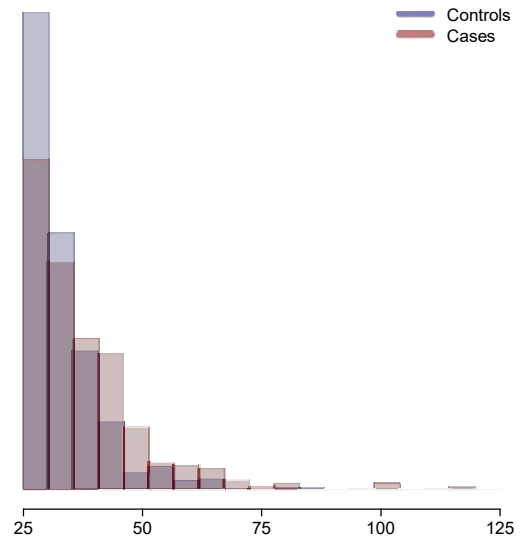
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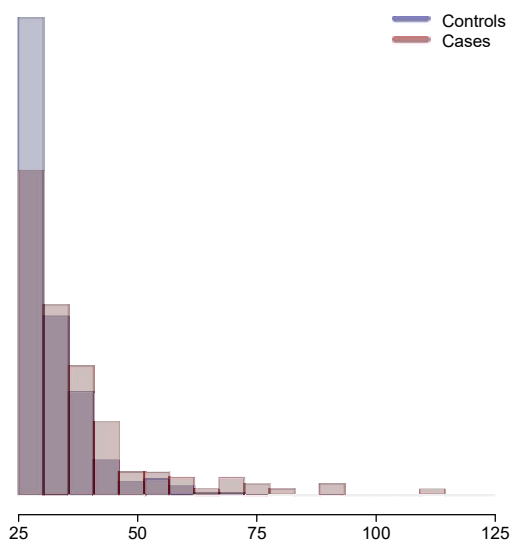
Radiant_UK



SHIP_0



SHIP_T



overall

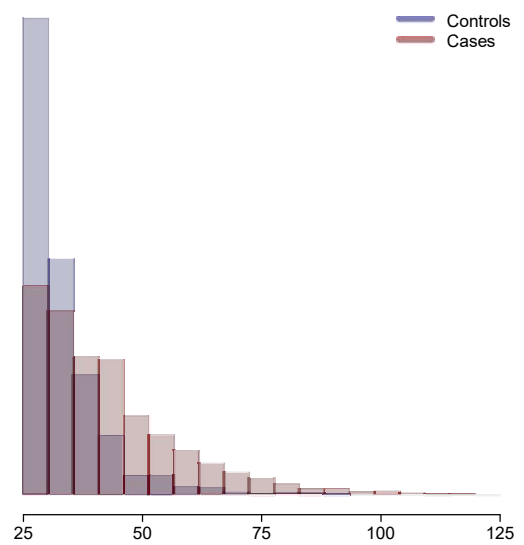


Table S1. Demographic information for contributing cohorts of major depressive disorder cases and unaffected controls

Cohort	Country	N		N with CT information		Demographics	
		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
<i>Childhood Trauma Questionnaire subscales (continuous measures)</i>						
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
<i>Dichotomous indicator of sexual or physical abuse</i>						
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, which is in line with previous findings from Spinhoven et al.⁸ 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

Subset	Mean (SD)		OR (p-value)
	Cases	Controls	
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)

Cohort	N		Impact of PRS on CT in						Approximation of full population by 100 times sampling case/control=0.15/0.85			
			All		Case only		Control only		Beta of regression		Correlation	
	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 separately with the PRS based on MDD-PRS including all SNPs (discovery $p < 1$ in the sample of $N=112,268$)

Cohort	N		Impact on MDD				
	Case	Control	PRS			PRsxCT	
			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 $p < 1$)

CT domain	N		Impact on MDD				
			PRS			PRSxCT	
			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

Cohort	Effective N discovery	N target		Effect of PRS			Effect of CT		Effect of PRSxCT	
		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

Cohort	Mean polygenic risk scores (emperic: SD; N) (simulated: SE)				Case-control PRS difference		PRSxCT Interaction-effect	
	Cases		Controls		CT=0	CT=1	OR	P
	CT=0	CT=1	CT=0	CT=1				
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 (h2 _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.