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

Supplemental Information

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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 .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).

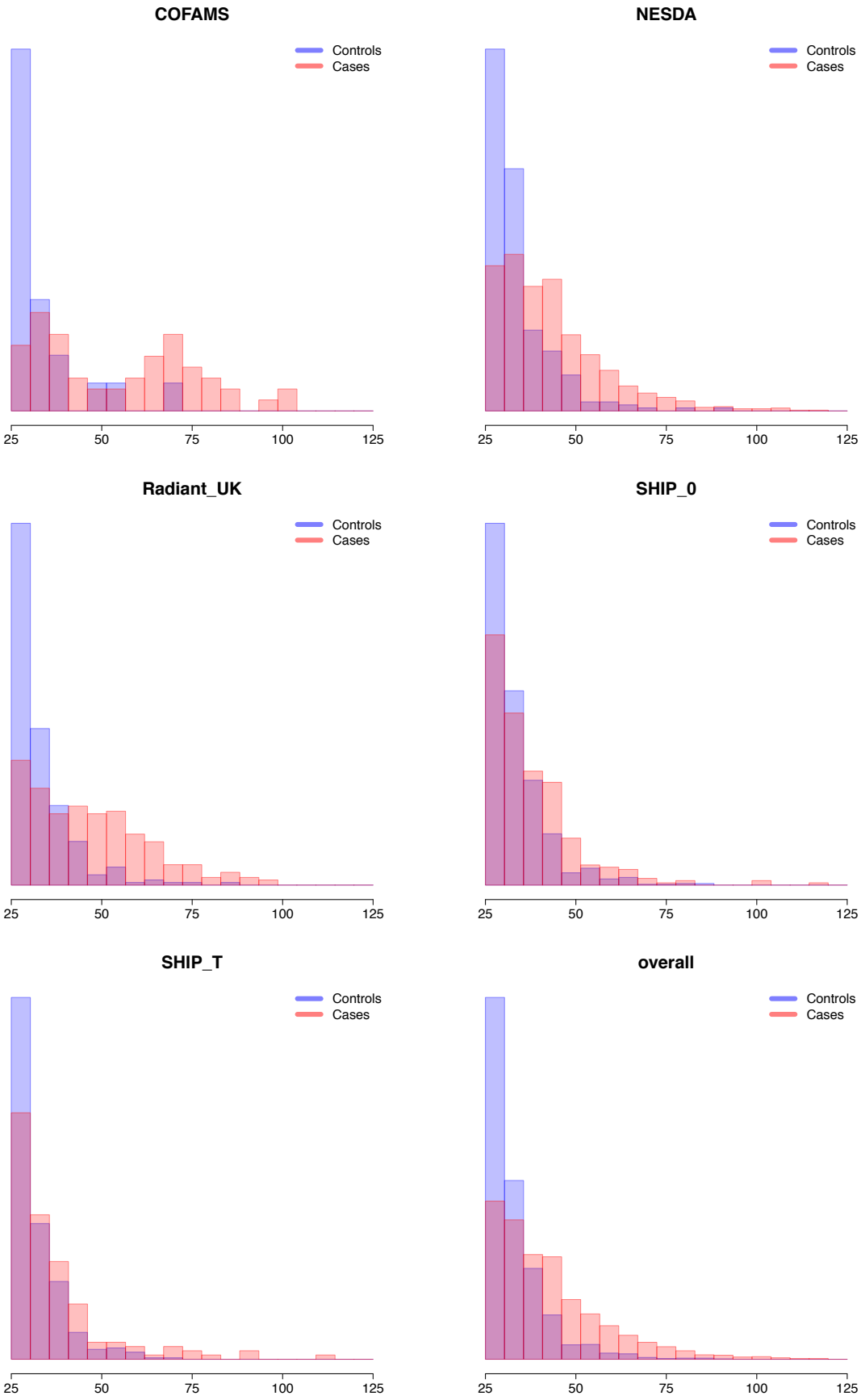

Figure S1. Distribution of the 5-domain continuous childhood trauma measure

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

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