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Chapter 4
Increased polygenic effects on depression in individuals exposed to childhood trauma in the Netherlands Study of Depression and Anxiety

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ABSTRACT

Background: Research on gene-by-environment interaction in major depressive disorder (MDD) has thus far primarily focused on candidate genes, while genetic effects are known to be polygenic.

Aims: To test whether the effect of polygenic risk scores on MDD is moderated by childhood trauma.

Methods: The study sample consisted of 1645 participants with a DSM-IV based diagnosis of MDD and 340 screened controls from the Netherlands. Chronic or remitted episodes (severe MDD) were present in 956 participants. The occurrence of childhood trauma was assessed with the Childhood Trauma Interview and the polygenic risk scores were based on genome-wide meta-analysis results from the Psychiatric Genomics Consortium.

Results: The polygenic risk scores and childhood trauma independently affected MDD risk, and evidence was found for interaction as departure from both multiplicativity and additivity, indicating that the effect of polygenic risk scores on depression is increased in the presence of childhood trauma. The interaction effects were similar in predicting all MDD risk and severe MDD risk and explained a comparable proportion of variation in MDD risk as the polygenic risk scores themselves.

Conclusions: The interaction effect found between polygenic risk scores and childhood trauma implies that (1) studies on direct genetic effect on MDD gain power by focusing on individuals exposed to childhood trauma, and that (2) individuals with both high polygenic risk scores and exposure to childhood trauma are particularly at risk for developing MDD.
INTRODUCTION
Research on gene-by-environment (GxE) interaction in major depressive disorder (MDD) aims to understand the heterogeneity of environmental and genetic risk factors, but has thus far primarily focused on candidate genes with inconclusive findings.\(^1,2\) On the one hand, research on GxE could select individuals with increased vulnerability for environmental factors based on their genetic make-up. Alternatively, research on GxE could select environmental conditions that lead to increased expression of genetic effects. Insights into GxE interaction is therefore of general importance for psychiatric research and contributes to the understanding of MDD's complex etiology.

Thus far, GxE interaction has primarily been tested for candidate genes such as the serotonin transporter gene (5-HTTLPR), for which opposing results were found in very similar single studies,\(^3,4\) as well as in meta-analyses.\(^5,6\) Several environmental factors have been analyzed in this respect, and among the most important factors is childhood trauma, which has a strong impact on MDD risk.\(^7\)–\(^10\) Nevertheless, although some consistent evidence for interaction between childhood trauma and 5-HTTLPR was found, these GxE findings remain controversial.\(^1\) The progress from a candidate-gene to a hypothesis-free genome-wide approach is hampered by lack of statistical power and inconsistent assessment of environmental stressors across GWAS cohorts.

Research on main genetic effects, on the other hand, has indicated that the risk of MDD is not merely increased by the effect of one or a few single nucleotide polymorphisms (SNPs), but by polygenic variation.\(^11,12\) One of the methods applied to point at these polygenic effects, first introduced for schizophrenia,\(^13\) uses polygenic risk scores and was later applied to MDD.\(^11\) The polygenic risk scores are obtained after carrying out a genome-wide association study in a discovery sample and then taking SNPs up to a certain threshold of significance, or even all SNPs, to predict MDD in an independent target sample. The contributions of these large numbers of SNPs are weighted by their effect size in a GWA or meta-analysis. The effect of polygenic risk scores on MDD was repeatedly confirmed and explains up to 1-2 percent of variation.\(^11,14,15\)

Even though this has not yet been studied for MDD, it is likely that causal genetic variants for MDD are located throughout all of the genome, as has been found for other complex traits such as height and body mass index.\(^16\) Also, SNPs contributing to pleiotropy between schizophrenia and bipolar disorder are found dispersed throughout the genome.\(^17\) The finding that the risk of MDD is increased by polygenic variation suggests that research of interaction effects should also focus on polygenic information. With an expected abundance of causal variants
for MDD, environmental conditions that increase genetic effects are more likely to be found when polygenic information is taken into account. When environmental conditions that increase genetic effects are found, individuals exposed to these conditions can be selected for future research to study the impact of single loci on MDD with increased power. Nevertheless, to the best of our knowledge, no research on GxE interaction in MDD has focused on polygenic information thus far.

The current study focused on polygenic information to test for gene-by-environment interaction in MDD, and examined whether polygenic risk scores interact with the presence of childhood trauma in a large and well-characterized sample from the Netherlands. This sample consists of participants with DSM-IV based diagnosis of MDD and screened controls, with the presence of childhood trauma assessed in face-to-face interviews. The meta-analysis from the Psychiatric Genomics Consortium (PGC)\textsuperscript{15} excluding our sample (leaving 7544 cases and 7754 controls) was used as discovery sample to construct the polygenic risk scores.

\textbf{METHODS}

\textbf{Subjects}

The sample consisted of participants from the Netherlands Study of Depression and Anxiety (NESDA), which is an ongoing longitudinal cohort study of depressive and anxiety disorders, with participants recruited from mental health care settings, general practices and the general population in the period from 2004 to 2007.\textsuperscript{18} Participants with MDD in their lifetime (N=1645) were diagnosed in a face-to-face interview with a trained clinical staff-member following the DSM-IV based Composite International Diagnostic Interview (CIDI, version 2.1). Over half of these participants (N=956) suffered from severe MDD with remitted (more than one) episodes and/or chronic (longer than two years of) complaints, as assessed with the life-chart, a calendar-approach to calculate the percentage of time symptoms were present during four years prior to baseline and two years following baseline.\textsuperscript{19} Controls (N=340) were screened in a similar face-to-face CIDI interview and had no diagnosis of a depressive, dysthymic, anxiety, or other psychiatric disorder in lifetime. Participants were from North-European ancestry and were excluded when they were not fluent in speaking Dutch or when they suffered from another primary diagnosis, such as a psychotic, obsessive compulsive, bipolar or severe substance use disorder. The NESDA study was approved by the institutional Review Board and all participants provided written informed consent.
**Childhood Trauma**

Childhood trauma was assessed in a face-to-face interview with a trained clinical staff-member following the Childhood Trauma Interview (CTI) from the Netherlands Mental Health Survey and Incidence Study. The CTI assesses the domains of emotional neglect, psychological abuse, physical abuse and sexual abuse before the age of sixteen, and yields a score ranging from 0 to 8 by adding the frequencies of occurrence (0- absent; 1- once or sometimes; 2- regularly, often or very often). In the CTI the four domains are assessed by a first question asking whether the traumatic event occurred (yes or no), and a subsequent second question asking how often the event occurred. In the first question the traumatic events were specified as follows: emotional neglect as the lack of parental attention or support and ignorance of one’s problems and experiences; psychological abuse as being verbally abused, undeserved punishment, subordinated to siblings and being blackmailed; physical abuse as being kicked or hit with hands or an object, beaten up or physical abuse in any other way; and sexual abuse as being sexually approached against one’s will, meaning being touched or having to touch someone in a sexual way. The CTI is a well-established instrument, which measurements of childhood trauma show a strong impact on depressive and anxiety disorders as well as on structural and functional brain abnormalities. The CTI also shows strong content validity when compared to the Childhood Trauma Questionnaire (CTQ) with Spearman’s rho correlation of 0.69 (p<0.001) in a subset of NESDA with both the CTI and CTQ assessed at different time points.

**Genotyping and Quality Control**

Methods for blood sampling and DNA extraction were described previously. The manufacturer’s protocol was followed to genotype the autosomal SNPs on the Affymetrix 6.0 Human Genome-Wide SNP Array. With quality control, SNPs were excluded that: had probes that mapped badly against NCBI Build 37/UCSC hg19; had a minor allele frequency smaller than 1%; had a missing rate greater than 5%; deviated from Hardy-Weinberg equilibrium with a p-value smaller than 0.001, thus leaving 498,592 SNPs to analyze. Participants were excluded when: they showed a Contrast QC < 0.4 (CQC, a quality metric from Affymetrix representing how well allele intensities separate into clusters); fell outside of the main cluster of a PCs reflecting a batch effect; had a missing rate greater than 5%; had excess genome-wide heterozygosity or inbreeding levels (F < -0.10 or > 0.10); had genotypes with inconsistencies regarding reported gender; or had non-European/non-Dutch ancestry as indicated with principal component analysis.
Polygenic Risk Scores

The polygenic risk scores were created based on the results from a large meta-analysis from the Psychiatric Genomics Consortium (PGC)\(^{15}\) excluding participants from the Dutch GWAS cohort\(^ {26}\) that included NESDA participants (thus yielding 7544 cases and 7754 controls in the discovery set). Risk scores were obtained following the method described by Purcell and colleagues\(^ {13}\) with the PLINK-software.\(^ {27}\) From the meta-analysis, SNPs were selected that had an imputation INFO score > 0.9 and MAF > 0.02, and low linkage disequilibrium (LD) to each other (\(r^2 < 0.25\) within 500kb window, filtering for significance; PLINK-command --clump--p1 1 --clump-p2 1 --clump-r2 0.25 --clump-kb 500). The meta-analysis results of SNPs up to eight p-value thresholds (0.001; 0.01; 0.05; 0.1; 0.2; 0.3; 0.4; and 0.5) were selected to compute the polygenic risk scores in our sample; the numbers of SNPs thus included were 150, 1209, 5028, 8905, 16081, 22355, 28018, and 32870 respectively. The polygenic risk scores were standardized to a mean of zero and standard deviation of one to aid interpretation of results.

Statistical analyses

Participants with MDD were compared to controls with respect to age, gender, and their childhood trauma score (range 0-8) with t-tests for continuous and chi-square-tests for binary variables. The effect of polygenic risk scores on the childhood trauma score, i.e. gene-environment correlation, was tested with linear regression, because such an effect could potentially bias tests for interaction.\(^ {28}\) Two binary MDD outcomes were analyzed as dependent variables: all participants with MDD versus controls (all MDD risk), and participants with severe MDD versus controls (severe MDD risk). The direct effects of polygenic risk scores (model 1) and the childhood trauma score (model 2) on MDD risks were assessed in separate logistic regression models. Subsequently, tests for interaction were performed with logistic regression to test for interaction as departure from multiplicativity (model 3) and, secondly, with analyses of relative excess risks due to interaction (RERI, model 4) to test for interaction as departure from additivity. The RERIs were computed with the method described by Knol and colleagues, as RERI=\(e^{BCT+\text{PRS}+\text{PRSxCT}}-e^{BCT}-e^{\text{PRS}}+1\).\(^ {29}\) The RERI's 95% confidence intervals were computed with bootstrapping with 10,000 iterations. The difference between interaction as departure from additivity and interaction as departure of multiplicativity is that the first represents a situation where the combined effect is larger than the sum of the individual effects of the polygenic risk score and childhood trauma, whereas the latter represents a situation where the combined effect is larger than the product of the individual effects. It has been argued that
interaction as departure from additivity is more in line with biological interaction.29

Nagelkerke’s R² were estimated to assess what proportion of variation in all MDD risk was explained by the polygenic risk scores (PRS) and childhood trauma (CT) independently, as well as their interaction CTxPRS. Therefore, several R² estimates were compared: between the model with only covariates and the model additionally including CT (R² of CT); between the model with covariates and CT and the model additionally including PRS (R² of PRS); and between the model with covariates, CT and PRS and the model additionally including PRSxCT (R² of CTxPRS). Nagelkerke's R² may, however, be biased by a sample's ascertainment when a disproportional number of cases is selected from the population.30 Therefore, we also computed an alternative R² measure for the PRSs, which was recently proposed by Lee and colleagues. This R² measure is based on the liability scale, directly comparable to the heritability, and robust against ascertainment bias.30 Lee's R² estimates in our sample were based on a Dutch lifetime prevalence of MDD of 18.7%.31

All analyses were corrected for age, gender, and three ancestry-informative principal components to take possible population stratification into account, and the tests for interaction (models 3 and 4) included polygenic risk scores and the childhood trauma score as additional covariates. Effects were considered significant when p-values were <0.05 or when RERIs 95% confidence intervals did not contain zero. All analyses were performed in R.32

| Table 1. Effect of polygenic risk scores (PRS) on childhood trauma |
|-----------------|--------|---------|
| PRS thresholds  | Beta   | P-value |
| p<0.001         | <0.01  | 0.991   |
| p<0.01          | -0.01  | 0.769   |
| p<0.05          | 0.02   | 0.733   |
| p<0.1           | 0.01   | 0.847   |
| p<0.2           | -0.01  | 0.883   |
| p<0.3           | -0.02  | 0.754   |
| p<0.4           | -0.01  | 0.904   |
| p<0.5           | 0.01   | 0.907   |

Effects of polygenic risk scores on childhood trauma (i.e. gene-environment correlation) were estimated with linear regression including three principal components, age and gender as covariates.
Figure 1. Interaction between childhood trauma (CT) and the polygenic risk score (PRS). The interaction-effects as departure of multiplicativity in predicting risk on all MDD and risk on severe MDD are visualized by displaying the direct effects of the polygenic risk scores (PRS) based on threshold p<0.1 and p<0.3 respectively for three childhood trauma levels, with childhood trauma (CT)-scores of 0-1; 2-3; and 4-8 respectively.

RESULTS

Participants with MDD (N=1645) had a mean age comparable to that of the 340 healthy controls (42.2 [SD 12.5] and 43.3 [SD 14.5] respectively, p=0.172), and were slightly more often female (68% and 57% respectively, p<0.001). The mean childhood trauma score was 1.75 (SD 2.17, range 0-8), and mean scores of the four childhood trauma domains (range 0-2) were 0.76 (0.95) for emotional neglect (EN), 0.50 (0.84) for psychological abuse (PsA), 0.22 (0.57) for physical abuse (PhA), and 0.24 (0.52) for sexual abuse (SA). The scores of the domains were all correlated with each other with Pearson correlation coefficients of 0.61 for EN-PsA, 0.40 for EN-PhA, 0.24 for EN-SA, 0.55 for PsA-PhA, 0.23 for PsA-SA, and 0.26 for PhA-SA (all p<0.001). Childhood trauma occurred more often in participants with MDD than in healthy controls with mean childhood trauma main scores of 1.99 (SD 2.24) and 0.56 (SD 1.29) respectively (p<0.001). None of the polygenic risk scores had an effect on childhood trauma with beta-estimates around zero and all p-values well over 0.05, thus excluding gene-environment correlation and its potential bias on interaction tests (Table 1). The polygenic risk scores significantly predicted MDD risk (model 1), with slightly larger but comparable effects in predicting severe MDD risk compared to predicting all MDD
The polygenic risk scores based on five of the eight studied thresholds were predictive in all MDD risk (thresholds 0.05; 0.1; 0.2; 0.3; 0.4) and the polygenic risk scores based on six thresholds were predictive in severe MDD risk (thresholds 0.05; 0.1; 0.2; 0.3; 0.4; 0.5). The polygenic risk scores based on threshold p<0.05 had the largest effect on all MDD risk, with an OR of 1.22 per standard deviation increase of the polygenic risk score (p=0.001). The presence of childhood trauma also predicted MDD risk (model 2), again with slightly larger but comparable effects in predicting severe MDD risk compared to all MDD risk (with ORs of 1.64 [p<0.001] and 1.69 [p<0.001] respectively, per childhood trauma score unit increase [range 0-8], Table 2). Evidence was then found for interaction as departure from both multiplicativity (model 3, odds ratios >1) and additivity (model 4, RERIs>0), indicating that the effect of polygenic risk scores on MDD is increased in the presence of childhood trauma (Table 2). The largest interaction effect in predicting all MDD was found for the polygenic risk score based on threshold p<0.1 with an OR of 1.15 (p=0.005); the largest interaction effect in predicting severe MDD was found for the polygenic risk score based on threshold p<0.3 with an OR of 1.16 (p=0.005). These two interaction-effects were visualized for their departure of multiplicativity by displaying the direct effects of the polygenic risk scores for three childhood trauma levels, with childhood trauma scores of 0-1; 2-3 and 4-8 respectively (Figure 1). Figure 1 shows that the polygenic risk scores have limited impact in predicting MDD risk in individuals with no/low exposure to childhood trauma, but large impact in individuals with high exposure to childhood trauma. The impact of the four separate childhood trauma domains on the interaction effects were compared by conducting analyses of each domain separately in predicting all MDD risk. The estimates of interaction thus found were in the same direction for all domains (OR>1), but appeared more significant for the domains of emotional neglect and psychological abuse, than for the domains of physical abuse and sexual abuse (Table 3). This difference in significance is possibly due to the lower frequency of occurrence of physical abuse and sexual abuse. Most variation in all MDD risk was explained by childhood trauma (~13%), but the proportions explained by the polygenic risk scores (in addition to the variation explained by childhood trauma) and their interaction-effects (in addition to the variation explained by childhood trauma and the polygenic risk score) were of comparable magnitude (~0.5%, Table 4). Note that Lee's $R^2$ estimates were comparable to Nagelkerke's $R^2$ estimates for the polygenic risk scores, which indicates that ascertainment bias did not largely impact our results (Table 4).
Table 2. Interaction between polygenic risk scores (PRS) and childhood trauma (CT) in predicting MDD risk and direct effects of PRSs and CT

<table>
<thead>
<tr>
<th>PRS thresholds</th>
<th>Direct effects</th>
<th>PRS-by-CT interaction</th>
<th>Multiplicative (model 3)</th>
<th>Additive (model 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRS (model 1)</td>
<td>CT (model 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>P-value</td>
<td>OR</td>
<td>P-value</td>
</tr>
<tr>
<td>All MDD (1645 cases and 340 controls)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>1.01</td>
<td>0.808</td>
<td>1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td>1.12</td>
<td>0.059</td>
<td>1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td>1.22</td>
<td>0.001</td>
<td>1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.1</td>
<td>1.18</td>
<td>0.005</td>
<td>1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.2</td>
<td>1.15</td>
<td>0.021</td>
<td>1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.3</td>
<td>1.13</td>
<td>0.037</td>
<td>1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.4</td>
<td>1.13</td>
<td>0.035</td>
<td>1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.5</td>
<td>1.11</td>
<td>0.081</td>
<td>1.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe MDD (956 cases and 340 controls)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>1.02</td>
<td>0.805</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td>1.11</td>
<td>0.116</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td>1.22</td>
<td>0.002</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.1</td>
<td>1.2</td>
<td>0.005</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.2</td>
<td>1.17</td>
<td>0.016</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.3</td>
<td>1.17</td>
<td>0.017</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.4</td>
<td>1.17</td>
<td>0.016</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p&lt;0.5</td>
<td>1.15</td>
<td>0.032</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Direct effects of the polygenic risk scores (PRS), childhood trauma (CT) and their interaction-effects were estimated in four separate logistic regression models. The effects of the PRS (model 1) and CT (model 2) were estimated in models with age, gender and three principal components as covariates. The interaction effects were estimated in a model additionally including PRS and CT as covariates (model 3 and model 4). The RERI’s represent tests for interaction as departure from additivity and were computed by $e^{\beta_{CT}+\beta_{PRS}+\beta_{PRSCXCT}} - e^{\beta_{CT}} - e^{\beta_{PRS}} - 1$. 
Table 3. Interaction between polygenic risk scores (PRS) and four childhood trauma (CT) domains in predicting all MDD risk and direct effects of the four CT domains (1645 cases and 340 controls).

<table>
<thead>
<tr>
<th>PRS thresholds</th>
<th>Emotional neglect (EN)</th>
<th>Psychological abuse (PsA)</th>
<th>Physical abuse (PhA)</th>
<th>Sexual abuse (SA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EN</td>
<td>PRS x EN</td>
<td>EN</td>
<td>PRS x PsA</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>2.57 &lt;0.001</td>
<td>1.10 0.307</td>
<td>2.40 &lt;0.001</td>
<td>1.03 0.809</td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td>2.57 &lt;0.001</td>
<td>1.15 0.130</td>
<td>2.40 &lt;0.001</td>
<td>1.16 0.216</td>
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<tr>
<td>p&lt;0.05</td>
<td>2.57 &lt;0.001</td>
<td>1.15 0.128</td>
<td>2.40 &lt;0.001</td>
<td>1.37 0.006</td>
</tr>
<tr>
<td>p&lt;0.1</td>
<td>2.57 &lt;0.001</td>
<td>1.18 0.069</td>
<td>2.40 &lt;0.001</td>
<td>1.36 0.007</td>
</tr>
<tr>
<td>p&lt;0.2</td>
<td>2.57 &lt;0.001</td>
<td>1.21 0.032</td>
<td>2.40 &lt;0.001</td>
<td>1.29 0.025</td>
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<td>p&lt;0.3</td>
<td>2.57 &lt;0.001</td>
<td>1.22 0.027</td>
<td>2.40 &lt;0.001</td>
<td>1.36 0.007</td>
</tr>
<tr>
<td>p&lt;0.4</td>
<td>2.57 &lt;0.001</td>
<td>1.21 0.035</td>
<td>2.40 &lt;0.001</td>
<td>1.32 0.016</td>
</tr>
<tr>
<td>p&lt;0.5</td>
<td>2.57 &lt;0.001</td>
<td>1.19 0.056</td>
<td>2.40 &lt;0.001</td>
<td>1.31 0.018</td>
</tr>
<tr>
<td></td>
<td>PhA</td>
<td>PRS x PhA</td>
<td>SA</td>
<td>PRS x SA</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>2.90 &lt;0.001</td>
<td>1.24 0.297</td>
<td>2.19 &lt;0.001</td>
<td>1.12 0.503</td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td>2.90 &lt;0.001</td>
<td>1.30 0.215</td>
<td>2.19 &lt;0.001</td>
<td>1.05 0.785</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td>2.90 &lt;0.001</td>
<td>1.42 0.081</td>
<td>2.19 &lt;0.001</td>
<td>1.08 0.653</td>
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<tr>
<td>p&lt;0.1</td>
<td>2.90 &lt;0.001</td>
<td>1.36 0.137</td>
<td>2.19 &lt;0.001</td>
<td>1.11 0.508</td>
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<tr>
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<td>2.90 &lt;0.001</td>
<td>1.23 0.288</td>
<td>2.19 &lt;0.001</td>
<td>1.10 0.561</td>
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<tr>
<td>p&lt;0.3</td>
<td>2.90 &lt;0.001</td>
<td>1.18 0.381</td>
<td>2.19 &lt;0.001</td>
<td>1.12 0.460</td>
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<tr>
<td>p&lt;0.4</td>
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<td>1.11 0.577</td>
<td>2.19 &lt;0.001</td>
<td>1.14 0.393</td>
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<tr>
<td>p&lt;0.5</td>
<td>2.90 &lt;0.001</td>
<td>1.10 0.609</td>
<td>2.19 &lt;0.001</td>
<td>1.16 0.356</td>
</tr>
</tbody>
</table>

Four childhood trauma domains (ranging from 0 to 2) were tested for their direct-effects and interaction-effects with polygenic risk scores on all MDD risk, using logistic regression analyses adjusted for age, gender and three principal components. The main effect of the polygenic risk scores is displayed in Table 2 (model 1).
This is the first study that focuses on polygenic risk scores to test for gene-by-
environment interaction in major depressive disorder (MDD). Within our sample
we found increased effects of polygenic risk scores on MDD in the presence of
childhood trauma, with evidence for interaction as departure from both
multiplicativity and additivity. These interaction-effects were comparable in
predicting all MDD risk and severe (chronic or recurrent) MDD risk, although
effects were slightly larger in the latter. The interaction-effects were driven by all
of the four domains included in the childhood trauma measure (emotional
neglect, psychological abuse, physical abuse and sexual abuse). We found that
the proportion of variation in all MDD risk explained by the interaction effects
was comparable to the proportion explained by the polygenic risk scores (both
~0.5%).

Thus far, polygenic information has not been taken into account in
research on gene-by-environment interaction in MDD, but there has been
ongoing research for interaction with candidate genes. The motivation for
research on gene-by-environment interaction in MDD is found in its contribution
to understanding the complex etiology of MDD, and its possibility to select
environmental conditions with increased genetic effects. Nevertheless, research

<table>
<thead>
<tr>
<th>PRS thresholds</th>
<th>Nagelkerke’s R² (in percentages)</th>
<th>Lee’s R²</th>
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<tr>
<td></td>
<td>CT</td>
<td>PRS</td>
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<td>p&lt;0.5</td>
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</table>

To estimate proportions of variation in risk on all MDD explained by childhood trauma (CT),
polygenic risk scores (PRS) and their interaction (CTxPRS), Nagelkerke’s R² were compared: between
the model with only covariates and the model additionally including CT (R² of CT); between
the model with covariates and CT and the model additionally including PRS (R² of PRS); and between
the model with covariates, CT and PRS and the model additionally including PRSxCT (R² of CTxPRS).
Age, gender and three principal components were included as covariates. Lee’s proposed estimate
of R² was computed using a Dutch lifetime prevalence of MDD of 18.7%.

DISCUSSION

This is the first study that focuses on polygenic risk scores to test for gene-by-
environment interaction in major depressive disorder (MDD). Within our sample
we found increased effects of polygenic risk scores on MDD in the presence of
childhood trauma, with evidence for interaction as departure from both
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Thus far, polygenic information has not been taken into account in
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ongoing research for interaction with candidate genes. The motivation for
research on gene-by-environment interaction in MDD is found in its contribution
to understanding the complex etiology of MDD, and its possibility to select
environmental conditions with increased genetic effects. Nevertheless, research
on candidate genes has led to rather contradictory results: in research on the well-known serotonin transporter gene (5-HTTLPR) even meta-analyses differ in their conclusions⁵,⁶,³⁴ with concerns about publications bias.¹ However, because genetic effects on MDD are polygenic in nature,¹¹,¹² we argued that gene-by-
environment interaction should be tested with polygenic information.

The interaction effect thus found within our sample between polygenic risk scores and childhood trauma in MDD has two implications. The first implication is that polygenic risk scores have increased effects in the presence of childhood trauma, as illustrated in Figure 1, which indicates that research on direct genetic effects potentially gains power by focusing on individuals exposed to childhood trauma. Therefore, if numbers would allow it would be very useful to perform a genome-wide association study within, for example, the collaborative Psychiatric Genomics Consortium¹⁵ in individuals who experienced childhood trauma. Because interaction-effects are symmetrical, we could, however, also have illustrated that childhood trauma has more impact in individuals with high polygenic risk scores. Thus, the second implication is that individuals with high polygenic risk scores are more vulnerable for the effects of childhood trauma, which has potential clinical relevance, for example in profiling of MDD, but also in possible future prevention programs. When replicated in independent samples, the interaction effect found might add a modest but important piece to the complex puzzle of MDD's etiology.

The direct effects of the polygenic risk scores and childhood trauma in predicting MDD risk in our sample are in line with previous findings. The proportion of variation in MDD explained by the polygenic risk scores (R² ~0.5%) was in line with previous findings of Demirkan and colleagues¹¹ and the Psychiatric GWAS Consortium.¹⁵ Although Nagelkerke’s R² could have suffered from ascertainment bias because of the large proportion of participants with MDD in our sample, its estimates were of the same magnitude as Lee’s estimates of R², indicating that ascertainment did not largely affect our results.³⁰ The choice of the SNP p-value cut-off in the discovery sample tends to be arbitrary, which is why we presented results for eight different cut-offs in this study, and results were comparable for cut-offs larger than 0.05. In general, we anticipate that lower cut-offs are preferable over higher cut-offs when the discovery sample size increases and SNP effects can be found with more certainty. The impact of childhood trauma in predicting MDD risk in our sample is also in line with previous findings, for example those of MacMillan⁹ and De Graaf.⁷ Furthermore, evidence for interaction was found as departure from both multiplicativity and
additivity, the latter of which has been argued to be more in line with biological interaction.\textsuperscript{29,35}

The impact of polygenic risk scores on MDD could have been studied in several environmental conditions, but we hypothesized that the presence of childhood trauma is a likely candidate. The presence of childhood trauma showed most consistent results in previous research on interaction with candidate genes,\textsuperscript{5} and it is a severe form of stress with a large and life-long impact, resulting in a large main effect on MDD prevalence.\textsuperscript{8,10} Furthermore, childhood trauma generally occurs before the onset of MDD (in our sample 84.7\% of the MDD subjects had their first episode after age 16), thereby largely excluding the potential source of bias from reciprocal causation, i.e. when MDD results in environmental stress.\textsuperscript{36} In our study, childhood trauma was assessed with the Childhood Trauma Interview (CTI), which is a well-established instrument that has shown to predict onset of depressive and anxiety disorders\textsuperscript{7,20} as well as an enduring impact on structural and functional brain abnormalities.\textsuperscript{21,22} Our finding that childhood trauma increases the effects of polygenic risk scores on MDD fits with a recent review of Teicher and Samson, which indicates that MDD patients with childhood trauma have more severe mood, neurovegetative and endogenous symptoms, and more comorbidities and psychotic features than MDD patients without childhood trauma.\textsuperscript{10}

The approach applied in this study, to test for gene-by-environment interaction with polygenic risk scores, has both advantages and disadvantages. This is the first study to apply this approach to MDD, but Meyers and colleagues have applied it to smoking behaviour before. They observed interaction effects on smoking behaviour between polygenic risk scores for smoking and the number of traumatic events experienced as well as for polygenic risk scores and neighborhood social cohesion (effective n=399).\textsuperscript{37} An advantage of the polygenic risk scores -approach is that polygenic risk scores are based on genome-wide SNP data, but result in a one-dimensional summary measure, with corresponding requirements of significance (p<0.05). Consequently, the sample size of the target sample can be much smaller than in GWAS studies testing SNPs independently. A disadvantage is, however, that particular aspects of the multi-dimensional polygenic information is lost, which could lead to biased results, for example when certain SNPs show increased effects on MDD in the presence of childhood trauma while other SNPs show decreased effects on MDD in the presence of childhood trauma. If this hypothetical situation would occur, both interaction-effects would be leveled out in tests with the one-dimensional polygenic risk scores summary measure. Nevertheless, at the present time sample sizes are
insufficient to examine the impact of many SNPs in GxE studies and, therefore, studying polygenic risk scores seems an elegant approach for testing the general hypothesis of the existence of gene-by-environment interaction.

Our study has several strengths. First, it was based on DSM-IV based diagnoses of MDD, which ensures we studied participants with clinically relevant MDD. Second, controls were carefully screened for any lifetime psychiatric diagnosis. Third, childhood trauma was assessed in a face-to-face interview by specially trained clinical staff. Fourth, polygenic risk scores were based on a large and independent discovery sample, which adds to the accuracy of the polygenic risk scores. However, there are also some limitations, including potential recall bias of childhood trauma by the mood of participants with MDD. The number of controls in our sample was rather limited, but we carefully checked for ascertainment bias and found none. Even though controls were carefully screened for MDD, they could potentially develop MDD later in life, especially because MDD has a high prevalence of approximately 20 percent.

To conclude, we show that the effect of polygenic risk scores on MDD is increased in the presence of childhood trauma in our sample. Our finding implicates that power in research on direct genetic effects is larger in the presence of childhood trauma, but it also implicates that subjects with high polygenic risk scores form a potential group for MDD prevention, because of their increased vulnerability for childhood trauma. Future research should be conducted to replicate our finding, especially in the light of the inconclusive findings in research on interaction in MDD thus far. In addition, future research could also be designed to test interaction with polygenic information applying different techniques. A possible technique to apply could be genome-wide complex trait analyses (GCTA) to test for interaction with the genetic relationship matrix. The present study was underpowered to conduct such analyses, but future efforts combining data from several independent GWAS cohorts could potentially reach power to test for interaction with GCTA. Further research is required, but our results suggest that gene-by-environment interaction plays a considerable role in the polygenic effects on MDD.

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