Supplementary Materials to:

The association between lower educational attainment and depression due to shared genetic effects? Results in ~25,000 subjects


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Genotyping, quality control, and imputation

Genotyping, quality control, and imputation of the PGC-cohorts have been described in detail previously.¹

In short, the PGC-cohorts were all genotyped following their own protocol and on separate platforms (Supplementary Table 1). During quality control SNPs were removed with missingness ≥ 0.02, case-
control difference in SNP missingness ≥ 0.02, difference in allele frequency to HapMap3 ≥ 0.15, or Hardy-Weinberg equilibrium (HWE) p-value < 1e-6; subjects were removed with missingness ≥ 0.02 or diverging ancestry. The PGC-cohorts were then imputed against the CEU+TSI HapMap3 reference panel, and post-imputation QC selected SNPs with imputation r² > 0.6 and MAF > 0.01.

The NESDA/NTR-2 cohort was genotyped on the Affymetrix 6.0 Human Genome-Wide SNP Array in three separate batches. SNPs with a significant different allele frequency between any two of the three batches (Chi-square p-value < 0.01) were excluded to correct for batch effects. Subsequent quality control was performed four times and based on information from the separate batches and the combined NESDA/NTR-2 sample and removed SNPs with MAF < 0.1, missingness > 0.05, HWE p-value < 0.05, Mendelian error rate ≥ 0.01. Based on the combined sample only, additional SNPs were removed with a significant difference in missingness between cases and controls (p < 0.05), and with a difference in allele frequency to HapMap3 ≥ 0.15. Subjects were removed, based on information of the combined sample, with SNP missingness > 0.01 or Mendelian error rate ≥ 0.01. The NESDA/NTR-2 cohort was then imputed against the CEU+TSI HapMap3 reference panel, and with post-imputation QC SNPs were selected with imputation INFO > 0.8 and MAF > 0.01.

The EGCUT-cohort was genotyped partly on Illumina Human 370 CNV-duo chip (unrelated N=1514) and partly on Illumina Human Omni Express (unrelated N=5188). Both of these parts of the EGCUT-cohort were processed separately. With quality control SNPs were removed with MAF ≤ 0.01 or HWE p-value < 1e-6. The SNPs were then imputed against the 1000 Genomes reference panel, and with post-imputation QC SNPs were selected with imputation INFO > 0.8 and MAF > 0.01. The HapMap3 SNPs were selected and lifted from hg19 to hg18 in order to align with the other cohorts.

The genotype data of the PGC-cohorts, NESDA/NTR-2 cohort, and EGCUT cohort were merged and yielded information on 884,105 overlapping SNPs.

**Genetic Profile Risk Scores (GPRS)**

The GPRS were based on EA discovery results (EA-GPRS) and MDD discovery results (MDD-GPRS) following the procedure described by Purcell et al and implemented in Plink. In order to test GPRS in a target cohort, it is essential for the target cohort to be independent from the discovery cohort. The EA
discovery results were from the recent meta-analyses on US years of schooling from the Social Science Genetics Association Consortium (SSGAC),\textsuperscript{7} which contains overlapping individuals with BMH, EGCUT, GenRED, NESDA/NTR-1, NESDA/NTR-2, QIMR, and STAR-D. We had available the SSGAC results separately excluding (i) EGCUT, (ii) NESDA/NTR-1 and 2, and (iii) QIMR. These three sets of EA discovery results were based on around 120,000 subjects, and applied to estimate the EA-GPRS in the respective cohorts. The EA discovery results excluding NESDA/NTR-1 and 2 were in addition applied to estimate risk scores in GSK, MPIP, and RADIANT. EA-GPRS were not estimated for BMH, GenRED, and STAR*D, because no independent discovery results were available.

To obtain the MDD discovery results was slightly more elaborate, because no large MDD cohort exists that is independent from PGC. Therefore, a ten-fold leave-one-cohort-out approach was followed, in which every cohort was once left out as target cohort, while the nine other cohorts would serve as MDD discovery set. In these discovery sets genome wide association studies were performed correcting for sex, covariates labelling the cohorts and genotype batches, and ten principal components. In this manner, independent MDD discovery results were obtained for all of the ten cohorts, and the discovery results were thus bases on around 8,000 cases and 12,000 controls depending on the size of the cohort left out (see Table 1 of main manuscript).

\textbf{Nagelkerke’s and the liability R}^2

For MDD, Nagelkerke’s R^2 were derived and corrected for the covariates by substituting the null (or intercept) model in Nagelkerke’s equation for the model including the covariates. The corrected Nagelkerke’s R^2 were thus estimated as

\[
R^2_{NK} = \left\{ 1 - \left( \frac{\text{Likelihood model covariates only}}{\text{Likelihood full model}} \right)^{2/N} \right\} / \left\{ 1 - \left( \text{Likelihood model covariates only} \right)^{2/N} \right\}
\]

Lee at all indicated that Nagelkerke’s R^2 can be biased by ascertainment, when the proportion of cases in the study sample differs from the population disease frequency.\textsuperscript{8} Therefore, they proposed a R^2 measure that is robust against ascertainment bias and interpretable on the liability scale. This R^2 was obtained by
rescaling Nagelkerke’s $R^2$ for a MDD population prevalence of $K=0.2$ following equation (15) from Lee et al.\cite{8} Suppose that Nagelkerke’s $R^2_{NK}$ has been estimated on a sample with a proportion of cases $P$ for a disease with population frequency $K$. From Table 1 from Lee et al it follows that $R^2_{\text{Cox & Snell}} = \varepsilon \cdot R^2_{NK}$, with $\varepsilon = 1 - P^2P (1 - P)^2(1 - P)$. On page 216 Lee et al show that $R^2_{\text{Cox & Snell}}$ is approximately equal to the $R^2_{\text{Occ}}$ on the observed scale in a linear model. Subsequently, equation (15) from Lee et al can be applied

$$R^2_{\text{Liability}} = CR^2_{\text{Occ}} / \left(1 + C\theta R^2_{\text{Occ}}\right),$$

where

$$C = \frac{K(1-K)K(1-K)}{x^2} \frac{P(1-P)}{P(1-P)}$$

and

$$\theta = m \frac{P-K}{1-K} \left(m \frac{P-K}{1-K} - t\right),$$

with $t$: the threshold of the standard normal distribution above which a proportion of $P$ is found, and $m$: the selection intensity, which equals $z/K$ where $z$ equals the height of the standard normal distribution at $t$.

**Gene-by-environment interaction**

In post-hoc analyses we tested if the polygenic effects on MDD were moderated by EA. First, we tested if the effect of MDD-GPRS ($P_T=1$) on MDD was moderated by EA (continuous measure), but found no such evidence with an interaction effect of OR=1.02 ($p=0.26$). Second, we applied GREML analyses. Therefore, EA was partitioned in two equal parts per study: low EA and high EA. Subsequently, the MDD SNP-$h^2$ on the observed scale was estimated at 0.11 (SE=0.04; $p=0.008$) in low EA and 0.08 (SE=0.04; $p=0.047$) in high EA. The genetic correlation between MDD in low EA and MDD in high EA was estimated at 0.87 (SE=0.40; $p=0.755$ for $H_0: r_G=1$), showing no evidence for a difference of the genetic effects on MDD in low and in high EA.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cases</th>
<th>Controls</th>
<th>Genotyping platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric Genomics Consortium (PGC MDD1) - cohorts</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Bonn/Mannheim (BMH)</td>
<td>Inpatients</td>
<td>Population-based, non-screened</td>
<td>Illumina 610K</td>
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<tr>
<td>GenRED (GE)</td>
<td>Volunteers with early onset/ recurrent MDD</td>
<td>Population-based, screened</td>
<td>Affymetrix 6.0</td>
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<tr>
<td>GSK (GS)</td>
<td>Recurrent MDD from clinical centre</td>
<td>Population-based and clinical, screened</td>
<td>Illumina 550K</td>
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<tr>
<td>MPIP (M)</td>
<td>Inpatients</td>
<td>Population-based, screened</td>
<td>Illumina 317K</td>
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<tr>
<td>NESDA/NTR-1 (N1)</td>
<td>Outpatients &amp; population-based</td>
<td>Population-based, screened</td>
<td>Perligen 600K</td>
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<td>QIMR (Q)</td>
<td>Population-based from Australia</td>
<td>Population-based, screened</td>
<td>Illumina 317 &amp; Illumina 610</td>
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<tr>
<td>RADIANT (R)</td>
<td>Cases with MDD from clinical centres</td>
<td>Population-based and volunteer, screened</td>
<td>Illumina 610K</td>
</tr>
<tr>
<td>STAR*D (S)</td>
<td>Cases from clinical trial</td>
<td>Population-based, screened</td>
<td>Affymetrix 500K/5.0</td>
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<tr>
<td>Other cohorts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NESDA/NTR-2 (N2)</td>
<td>Outpatients &amp; population-based</td>
<td>Population-based, screened</td>
<td>Affymetrix 6.0</td>
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<tr>
<td>EGCUT (E)</td>
<td>Population-based volunteers</td>
<td>Population-based volunteers, screened</td>
<td>Illumina 370 &amp; Illumina HOE</td>
</tr>
</tbody>
</table>

Basic information of the eight PGC cohorts is displayed. This Table closely resembles Supplementary Table 2 from the Psychiatric Genomics Consortium; see the publication from the Psychiatric Genomics Consortium for more details.
**Supplementary Table 2. Number of SNPs included in Genetic Profile Risk Scores (GPRS)**

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>B</th>
<th>N2</th>
<th>E</th>
<th>N1</th>
<th>GE</th>
<th>GS</th>
<th>M</th>
<th>Q</th>
<th>R</th>
<th>S</th>
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</thead>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>p &lt; 0.001</td>
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<td>88</td>
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<td>104</td>
<td>104</td>
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<td>76516</td>
<td>76516</td>
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<td>76516</td>
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<tr>
<td><strong>Discovery EA years (EA-GPRS) with threshold (P&lt;sub&gt;T&lt;/sub&gt;)</strong></td>
<td></td>
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<td>203</td>
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<td>76516</td>
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<td>76516</td>
<td>76516</td>
<td>76516</td>
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<td>-</td>
</tr>
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</table>

The Genetic Profile Risk Scores (GPRS) were based on a set of 76,516 independent SNPs with results available from all discovery sets. The GPRS based on all SNPs (threshold of discovery p-value <1) are thus based on the exact same SNPs. The GPRS based on the lower thresholds (0.001, 0.01, and 0.1) are based on different set of SNPs based on significance in the respective discovery results. EA-GPRS could not be estimated for B, GE and S, because we had no independent discovery results available for these cohorts. B=Bonn/Mannheim; E=EGCUT; GE=GenRED; GS=GSK; M=MPIP; N1=NESDA/NTR-1; N2=NESDA/NTR-2; Q=QIMR; R=RADIANT; S=STAR*D
### Supplementary Table 3. Correlation between Genetic Profile Risk Scores (GPRS) and the first ten principal components

<table>
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<tr>
<th></th>
<th>PC1</th>
<th>PC2</th>
<th>PC3</th>
<th>PC4</th>
<th>PC5</th>
<th>PC6</th>
<th>PC7</th>
<th>PC8</th>
<th>PC9</th>
<th>PC10</th>
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<td><strong>Discovery MDD (MDD-GPRS) with threshold (P₁)</strong></td>
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<tr>
<td>p &lt; 0.001</td>
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<td>0.01</td>
<td>-0.01</td>
<td>-0.00</td>
<td>-0.01</td>
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<td>0.01*</td>
<td>-0.02**</td>
<td>0.02*</td>
<td>-0.02**</td>
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<td>0.01</td>
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<tr>
<td>p &lt; 0.1</td>
<td>-0.02**</td>
<td>0.01</td>
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<td>&lt;0.01</td>
<td>-0.01</td>
<td>-0.02***</td>
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<td>p &lt; 1</td>
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<td>0.01</td>
<td>-0.02***</td>
<td>-0.00</td>
<td>0.01</td>
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<td><strong>Discovery EA years (EA-GPRS) with threshold (P₁)</strong></td>
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<tr>
<td>p &lt; 0.001</td>
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<td>-0.02**</td>
<td>0.01*</td>
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<td>-0.00</td>
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<td>0.02*</td>
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<tr>
<td>p &lt; 0.01</td>
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<td>-0.00</td>
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<td>-0.03***</td>
<td>0.04***</td>
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<td>&lt;0.01</td>
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</table>

* p<0.01; ** p<0.01; *** p<0.001

Some of the GPRS were correlated to some of the first ten principal components. This underlines the necessity to correct the analyses for population stratification.
Supplementary Table 4. The effect of genomic risk profile scores based on College-completion discovery results (College-GRPS) on MDD and EA (in years of education) in the overall sample.

<table>
<thead>
<tr>
<th>Effect of College-GRPS</th>
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<th>Effect</th>
<th>R-squared (%)</th>
<th>Effect on EA</th>
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The main EA-GPRS analyses were based on discovery results from years of education. The SSGAC, however, also conducted a meta-analyses on the binary measure of College completion. This measure is also of interest, because it distinguishes in the extreme end of the EA-distribution. Therefore, additional analyses were performed with GPRS based on College completion discovery results (College-GPRS). The College-GPRS had a slightly smaller impact on EA than main EA-GPRS (main Table 2), and had no impact on MDD.
Supplementary Table 5. Comparing GREML estimates of the MDD SNP-\( h^2 \) on the observed scale to estimates on the liability scale

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>N</th>
<th>SNP-( h^2 ) observed scale</th>
<th>SNP-( h^2 ) liability scale</th>
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<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control</td>
<td>Estimate</td>
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<tr>
<td>All</td>
<td>9662</td>
<td>14949</td>
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</tr>
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<td>All excluding B</td>
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<td>8230</td>
<td>13263</td>
<td>0.144</td>
</tr>
<tr>
<td>All excluding R</td>
<td>8057</td>
<td>13376</td>
<td>0.116</td>
</tr>
<tr>
<td>All excluding S</td>
<td>8445</td>
<td>14821</td>
<td>0.133</td>
</tr>
</tbody>
</table>

The MDD SNP-\( h^2 \) on the observed scale was compared to the SNP-\( h^2 \)s on the liability scale for different disease population frequencies \( K \). In our sample the MDD SNP-\( h^2 \) was larger expressed on the liability than expressed on the observed scale. Furthermore, the MDD SNP-\( h^2 \) increased further when assuming a larger disease frequency \( K \). B=Bonn/Mannheim; E=EGCUT; GE=GenRED; GS=GSK; M=MPIP; N1=NESDA/NTR-1; N2=NESDA/NTR-2; Q=QIMR; R=RADIANT; S=STAR*D
Supplementary Figure 1. Distribution of Education Attainment

EGCUT

GSK

NESDA/NTR1

NESDA/NTR2

QIMR

STAR*D

GenRED

Density

EA zscore

Density

EA zscore

Density

EA zscore

Density

EA zscore

Density

EA zscore

Density

EA zscore

[Legend: MDD Case, MDD Control]
Supplementary Figure 2. Association between EA and MDD in male and female

All

<table>
<thead>
<tr>
<th>Cohort</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGCU</td>
<td>0.94 (0.85–1.03)</td>
</tr>
<tr>
<td>GSK</td>
<td>0.45 (0.40–0.50)</td>
</tr>
<tr>
<td>NESDA/NTR1</td>
<td>0.82 (0.75–0.89)</td>
</tr>
<tr>
<td>NESDA/NTR2</td>
<td>0.67 (0.57–0.79)</td>
</tr>
<tr>
<td>QIMR</td>
<td>0.97 (0.90–1.05)</td>
</tr>
<tr>
<td>STAR*D</td>
<td>0.72 (0.60–0.87)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78 (0.75–0.81)</td>
</tr>
</tbody>
</table>

OR for MDD per SD increase in EA

Male

<table>
<thead>
<tr>
<th>Cohort</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGCU</td>
<td>1.05 (0.89–1.24)</td>
</tr>
<tr>
<td>GSK</td>
<td>0.51 (0.42–0.61)</td>
</tr>
<tr>
<td>NESDA/NTR1</td>
<td>0.71 (0.61–0.81)</td>
</tr>
<tr>
<td>NESDA/NTR2</td>
<td>0.58 (0.44–0.77)</td>
</tr>
<tr>
<td>QIMR</td>
<td>0.93 (0.82–1.05)</td>
</tr>
<tr>
<td>STAR*D</td>
<td>0.72 (0.56–0.92)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.77 (0.72–0.83)</td>
</tr>
</tbody>
</table>

OR for MDD per SD increase in EA

Female

<table>
<thead>
<tr>
<th>Cohort</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGCU</td>
<td>0.88 (0.78–0.99)</td>
</tr>
<tr>
<td>GSK</td>
<td>0.42 (0.37–0.48)</td>
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<tr>
<td>NESDA/NTR1</td>
<td>0.90 (0.81–1.00)</td>
</tr>
<tr>
<td>NESDA/NTR2</td>
<td>0.72 (0.59–0.88)</td>
</tr>
<tr>
<td>QIMR</td>
<td>1.00 (0.91–1.10)</td>
</tr>
<tr>
<td>STAR*D</td>
<td>0.72 (0.55–0.94)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.78 (0.74–0.83)</td>
</tr>
</tbody>
</table>

OR for MDD per SD increase in EA
Supplementary Figure 3. Dudbridge power calculations for GPRS- analyses

Power to detect genetic correlation with GPRS- analyses

Dudbridge’s method (available at https://sites.google.com/site/fdudbridge/software/) was applied to estimate the power to detect genetic correlation with GPRS- analyses for $\alpha = 0.05$.\(^9\) This power can be derived from the SNP-h2 estimated with Dudbridge’s method, as well as with the SNP-h2 following from GREML analyses.\(^10\) Based on our results in main Table 2, Dudbridge’s method estimated the MDD SNP-h2 at 0.13 and the EA SNP-h2 at 0.09 (applying the R function “estimateVg2FromP”), which estimates used to calculate the power as displayed (applying the R function “polygenescore”). The power to detect genetic correlation was larger for the EA-GPRS predicting MDD than for the MDD-GPRS predicting EA, because of the difference in discovery sample size (~120,000 and ~20,000 respectively). Furthermore, our GPRS- analyses seemed well powered to detect a genetic correlation of -0.2, but could not exclude a smaller genetic correlation of around -0.1. Note that Dudbridge estimates of the SNP-h2’s were lower than the GREML-estimates from this study (main Table 3) and previous studies;\(^7,11\) these power analyses will therefore likely represent a lower bound of the power to detect genetic correlation with GPRS-analyses.
REFERENCES


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


