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

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Abstract

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CONFLICTS OF INTEREST

All other co-authors have no conflicts of interest.

An association between lower educational attainment (EA) and an increased risk for depression has been confirmed in various western countries. This study examines whether pleiotropic genetic effects contribute to this association. Therefore, data were analyzed from a total of 9,662 Major Depressive Disorder (MDD) cases and 14,949 controls (with no lifetime MDD diagnosis) from the Psychiatric Genomics Consortium with additional Dutch and Estonian data. The association of EA and MDD was assessed with logistic regression in 15,138 individuals indicating a significantly negative association in our sample with an odds ratio for MDD 0.78 [0.75–0.82] per standard deviation increase in EA. With data of 884,105 autosomal common SNPs, three methods were applied to test for pleiotropy between MDD and EA: (i) genetic profile risk scores (GPRS) derived from training data for EA (independent meta-analysis on 120,000 subjects) and MDD (using a ten-fold leave-one-out procedure in the current sample) (ii) bivariate Genomic-Relationship-Matrix Restricted Maximum Likelihood (GREML), and (iii) SNP effect concordance analysis (SECA). With these methods we found (i) that the EA-GPRS did not predict MDD status, and MDD-GPRS did not predict EA, (ii) a weak negative genetic correlation with bivariate GREML analyses, but this correlation was not consistently significant, (iii) no evidence for concordance of MDD and EA SNP effects with SECA analysis. To conclude, our study confirms an association of lower EA and MDD risk, but this association was not due to measurable pleiotropic genetic effects, which suggests that environmental factors could be involved such as, for example, socioeconomic status.

Keywords

Depression; Educational Attainment; Genetic Correlation; Pleiotropy

Introduction

An association between lower educational attainment (EA) and increased risk for Major Depressive Disorder (MDD) has been confirmed in various Western countries. A meta-analysis of 37 studies from mainly western countries found a 3 per cent decrease in log odds ratio for depression per additional year of education.¹ Research of the World Mental Health Survey Initiative also found that those with high educational levels are generally at lower risk for depression in high-income countries, although Japan showed an inverted association.² The international Consortium of Psychiatric Epidemiology found a negative correlation in the United States and the Netherlands,³ which was confirmed in a recent study in the Netherlands.⁴

The association of lower EA and increased MDD risk could result from multiple, not necessarily independent, effects; including causal, environmental or pleiotropic genetic effects. Lower EA could lead to an increased MDD risk (social causation), for example via stress associated with lower socioeconomic status, or via less effective coping strategies or unhealthier lifestyles among those with lower EA.^{5,6} However, lower EA could also be the result of MDD vulnerability, for example when the onset of MDD is at an early age before educational goals would have been achieved. Alternatively, a third factor could be in play impacting on both, such as personality characteristics or less developed cognitive abilities, causing lower EA and increased risk for MDD. Such a third factor could also consist of pleiotropic genetic effects (or linkage disequilibrium between effective variants) resulting in

genetic correlation (the part of the phenotypic correlation caused by shared additive genetic effects), because EA⁷ and MDD^{8–10} both have a confirmed genetic basis.

It is relevant to understand the mechanisms of the association between lower EA and MDD, because this can have important implications for prevention strategies of MDD and its consequences. When lower EA would increase MDD risk, the responsible mechanisms should be studied and subsequently addressed, for example by providing psycho-education about these mechanisms to those with lower EA. However, when shared genetic effects would link EA and MDD no responsible mechanisms can be addressed, and prevention would be restricted to general advice to prevent MDD.

The possible impact of pleiotropic genetic effects on lower EA and increased MDD risk has not received much study. We are aware of three such studies, of which two find a substantial negative genetic correlation between EA and cross-sectional measures of depressive symptoms obtained via self-report questionnaires.^{11,12} One study used DSM-IV based diagnosis of MDD with a twin design and generally supported the social causation model and found only a small genetic correlation.⁵ To the best of our knowledge, no study combined DSM-IV based diagnosis and genome-wide SNP data to test for pleiotropic genetic effects between lower EA and MDD risk.

The current study was conducted to test for pleiotropic genetic effects between lower EA and MDD diagnoses in a large sample of ~25,000 subjects from the Psychiatric Genomics Consortium¹³ with additional Estonian and Dutch data. We applied the following SNP-based methods: genetic profile risk score (GPRS) analyses, bivariate Genomic-Relationship-Matrix Restricted Maximum Likelihood (GREML) analysis, and SNP effect concordance analysis (SECA).

Methods

Subjects

Genotype and phenotype data of ten cohort studies were combined: eight cohorts^{14–21} included in the Psychiatric Genomics Consortium (PGC)¹³ plus two additional cohorts. The first additional cohort was from the Netherlands and combined additional independent data from the Netherlands Study of Depression and Anxiety²² and the Netherlands Twin Registry²³ (NESDA/NTR-2). The second additional cohort was a population-based sample from Estonia (EGCUT).²⁴ The numbers of cases and controls per cohort are displayed in Table 1.

MDD cases and controls

All cases (N=9,662) had a DSM-IV or ICD-10 based diagnosis of MDD in lifetime according to a structured diagnostic instrument. Most controls (N=14,949) were randomly selected from the population and screened for a lifetime history of MDD. A more detailed description of the PGC-cohorts was given previously¹³ and is summarized in Supplementary Table 1. For the NESDA/NTR-2 cohort, MDD-cases were diagnosed with the DSM-IV based CIDI interview (CIDI, version 2.1), and controls scored low on various mental health screening questionnaires (NTR)²⁵ or had no diagnosis of a psychiatric disorder in their

lifetime (NESDA). For the EGCUT cohort, MDD-cases were identified using International Classification of Diseases (ICD-10) codes F32 (*depressive disorder*) and/or F33 (*recurrent depressive disorder*), and MDD-controls excluded all subjects with a lifetime ICD10 psychiatric diagnosis (category F).²⁴

Educational attainment

Educational attainment (EA) was assessed in seven of the ten contributing cohorts (EGCUT, GenRED, GSK, NESDA/NTR-1, NESDA/NTR-2, QIMR, and STAR-D). For NESDA/NTR-1 and NESDA/NTR-2, EA was defined as the years of education required for the highest diploma attained following the Dutch educational system. For QIMR and EGCUT, EA was defined as the US years of education required for the highest diploma attained following the international ISCED classification.⁷ For GSK, EA was defined as the number of years that school was attended. For STAR*D, EA was expressed in years of education. For GenRED, EA was assessed in controls only as the highest diploma attained and ranged from 1 to 5 labeling the following educational levels: lower than high school (1), high school (2), some college (3), bachelor degree (4), higher than bachelor degree (5).

The EA measure was corrected per cohort for year of birth and sex, in line with the recent meta-analysis from the Social Science Genetic Association Consortium.⁷ Thereby, the standardized residuals were obtained after regression of EA on sex, year of birth (YOB), YOB², YOB³, and the interaction of sex with YOB, YOB², and YOB³. For STAR*D and GSK, YOB was not available and substituted with age. In all cohorts, EA was defined in individuals over 25 years of age only, so that they had time to achieve their educational potential. The distribution of EA z-scores is displayed in Supplementary Figure 1.

Genotyping, quality control, and imputation

Genotyping, quality control, and imputation were performed in line with previous publications and are described in detail in the Supplementary Materials. In short, quality controlled SNPs with a MAF > 0.01 from the HapMap3 reference panel²⁶ were imputed and yielded information on 884,105. With these SNPs the Genomic-Relationship-Matrix was estimated and unrelated subjects selected (with maximum pairwise genetic relationships 0.05, which is approximately equivalent to second cousins), using the GCTA software.²⁷ All of the subsequent genetic analyses were corrected for possible confounding cohort- and genotyping effects by including a categorical covariate labeling the ten cohorts, and within cohorts the different genotyping batches, where applicable (i.e. three batches within NESDA/NTR-2, two batches within EGCUT, and two batches within QIMR). Ancestry-informative principal components were based on the Genomic-Relationship-Matrix and estimated with the GCTA software.²⁷

Genetic Profile Risk Scores (GPRS)

Preparation of the genetic profile risk scores based on EA discovery results (EA-GPRS) and MDD discovery results (MDD-GPRS) is described in detail in the Supplementary Materials. In short, the procedure from Purcell et al²⁸ implemented in Plink²⁹ was applied. The independent EA discovery results were from the recent meta-analyses on US years of schooling from the Social Science Genetics Association Consortium (SSGAC)⁷ containing

around 120,000 subjects. EA-GPRS analyses were not conducted 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, and the discovery results were thus based on around 8,000 cases and 12,000 controls.

The GPRS were based on the same set of independent SNPs. First, the SNPs were selected with results available for all of the discovery sets. Second, this set of SNPs was pruned to a set of 76,516 independent SNPs with a maximum pairwise r^2 of 0.25 based on a sliding window of 200 SNPs with steps of 5 SNPs.²⁹ The EA-GPRS and MDD-GPRS were then estimated based on all SNPs up to p-value thresholds (P_T) in the respective discovery results of 0.001, 0.01, 0.1, and 1 respectively. Consequently, all GPRS with $P_T = 1$ were based on the exact same SNPs, but GPRS with different P_T were based on different sets of SNPs depending on the respective discovery results (see Supplementary Table 2). The GPRS were standardized per cohort to a mean of 0 and standard deviation of 1 to aid interpretability of results.

Statistical analyses

The association of EA to MDD risk (phenotypic correlation) was assessed with logistic regression within EGCUT, GSK, NESDA/NTR-1 and 2, QIMR, and STAR*D separately, and in the combined sample correcting for covariates labeling the cohorts.

Genetic Profile Risk Score analyses—In the first method to test for pleiotropic genetic effects we estimated the *across-trait* effects of EA-GPRS on MDD and, vice versa, the effects of MDD-GPRS on EA. For comparison, we also estimated the *within-trait* effects of EA-GPRS on EA and MDD-GPRS on MDD. The effects of GPRS on EA and MDD were assessed with linear and logistic regression respectively. For the full sample, the effects were assessed for the GPRS based on P_T of 0.001, 0.01, 0.1, and 1; for the individual cohorts, the effects were only assessed for the GPRS based on $P_T = 1$.

The proportions of variation explained in EA and MDD were estimated as additional measures of the impact of GPRS. For EA, this proportion was derived as the R^2 of the linear regression model including the covariates and the polygenic risk score, minus the R^2 of the model including the covariates only. For MDD, Nagelkerke's pseudo 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 (adjusted equation in Supplementary Materials). Lee et al indicated that Nagelkerke's pseudo R^2 can be biased by ascertainment, when the proportion of cases in the study sample differs from the population disease frequency.³⁰ Therefore, they proposed an R^2 measure that is robust against ascertainment bias and interpretable on the liability scale. This liability R^2 was obtained by rescaling Nagelkerke's R^2 for an MDD population prevalence of $K=0.2$ (see Supplementary Materials).³⁰

Bivariate Genomic-Relationship-Matrix Restricted Maximum Likelihood (GREML)—The GREML mixed linear model method was used (i) to assess the proportion of variation in EA and MDD explained by genome-wide common SNPs ($SNP-h^2$) and (ii) to

assess the pleiotropic genetic effects between MDD and EA (genetic correlation), as implemented in GCTA.^{27,31,32} The MDD SNP- h^2 was expressed on the liability scale for a population prevalence of $K=0.2$ by converting the SNP- h^2 on the observed scale (controls 0; cases 1) with equation (23) from Lee et al.³³ Bivariate GREML estimates of the genetic correlation are approximately the same on the liability scale as on the observed scale,³² which implies that (i) its value does not depend on population disease prevalence K and (ii) that the genetic correlation between the binary MDD status and continuous EA measure could be estimated. The genetic correlation was, first, estimated with EA information from both cases and controls. This estimate could, however, potentially be confounded by case ascertainment (which may not be education independent). Therefore, the genetic correlation was estimated a second time with EA information from controls only and MDD status from both cases and controls. The GPRS- and GREML-analyses were corrected for sex, the first 10 (GPRS) or 20 (GREML) principal components and covariates labeling the cohorts and genotype batches. The necessity to correct for the principal components is indicated by a significant correlation between some of the GPRS with some of the principal components (Supplementary Table 3).

SNP effect concordance analysis (SECA)—In SNP effect concordance analysis (SECA; <http://neurogenetics.qimrberghofer.edu.au/SECA>)³⁴ association results are analyzed, rather than individual genotyped data, to test for concordance between two traits with respect to the SNP effects significance as well as their directions. We applied SECA on the EA meta-analyses results from the Social Science Genetics Association Consortium (SSGAC)⁷ and MDD association results on our own sample.

Results

The overall sample consisted of 9,662 patients with MDD in lifetime and 14,949 controls with a mean age of 46.2 (SD 15.6) and 59.4% female; information on EA was available for 5,373 cases and 9,765 controls (Table 1). In all cohorts with EA information available for both cases and controls, the phenotypic associations between EA and MDD was negative, with an overall odds ratio of 0.78 (95% CI: 0.75–0.82, $p=2.2e-31$) per standard deviation increase in EA (Figure 1). This negative association was consistent for MDD cases with known age of onset > 30 . The strongest association was found in GSK with an OR of 0.45 (95% CI: 0.40–0.50). When GSK was left out of the analyses, the overall association remained significant with an OR of 0.88 (95% CI: 0.84–0.92). The association was comparable in male and female (Supplementary Figure 2).

GPRS analyses

The GPRS had *within-trait* predictive effects as expected. The MDD-GPRS predicted MDD with most predictive power for the polygenic risk score including all SNPs ($P_T=1$), with an odds ratio of 1.13 ($p=1.7e-16$) and an R^2 of 0.4% on the liability scale (Table 2A). The EA-GPRS predicted EA also in the expected direction, again with most predictive power for GPRS including all SNPs, with a beta of 0.11 ($p=2.7e-37$) and an R^2 of 1.2% (Table 2A). However, we found no significant *across-trait* prediction: the MDD-GPRS did not predict EA (beta=-0.01 $p=6.7e-2$) and the EA-GPRS did not predict MDD (OR=0.99 $p=5.9e-1$,

Table 2A). Secondary analyses, performed within all cohorts separately, indicated that the within-trait predictive effects were consistent in all cohorts, and that the lack of across-trait predictive power was also consistent for all cohorts (Table 2B). In addition, no correlation was found between the MDD-GPRS and the EA-GPRS themselves ($P_T=1$; correlation coefficient of 0.006, $p=0.413$). In additional analyses, across-trait predictive effects on MDD were tested for GPRS based on the SSGAC EA outcome tagging College completion (College-GPRS).⁷ College completion distinguishes more in the extreme end of the EA distribution, and has a confirmed genetic basis.⁷ However, no predictive effects of the College-GPRS on MDD were found ($OR=0.99$, $p=0.74$ for $P_T=1$; Supplementary Table 4).

GREML analyses

GREML analyses in the overall study sample generated an estimate of MDD SNP- h^2 of 0.173 ($SE=0.017$, $p<1e-16$) on the liability scale ($K=0.2$); this finding was not solely driven by one of the individual cohorts, because the MDD SNP- h^2 was estimated at consistent values when one cohort was left out at the time (Table 3). The MDD SNP- h^2 was larger when expressed on the liability scale (0.173) than on the observed scale (0.126), with a larger SNP- h^2 for larger values of disease frequency (as expected from equation (23) from Lee et al³³; Supplementary Table 5). The EA SNP- h^2 was estimated at 0.124 ($SE=0.019$, $p=2.8e-11$) when EA information in both cases and controls was taken into account (Table 3A), and at 0.144 ($SE=0.030$, $p=1.5e-6$) when EA information of controls only was utilized (Table 3B). Again, these estimates were not solely driven by one of the individual cohorts (Table 3). The genetic correlation between MDD and EA was estimated at -0.253 ($SE=0.087$, $p=0.004$) when EA information of both cases and controls was taken into account (Table 3A). Since a correlation between genetic and environmental factors is likely to be partitioned into the genetic variance and covariance components, we explored the robustness of this estimate by limiting EA to be measured only in controls. When taking into account EA of controls only and MDD status from cases and controls, the genetic correlation dropped considerably and was no longer significantly different from 0 with an estimate of -0.110 ($SE=0.105$, $p=0.298$; Table 3B). In post-hoc analyses we tested if EA moderated the polygenic effects on MDD, but found no such evidence with neither GPRS- nor GREML-analyses (Supplementary Materials).

SNP effect concordance analysis

SECA showed no evidence for genetic correlation. The primary SECA test divided the SNPs in 144 subsets based on significance of association with MDD and EA smaller than respectively 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0. Not a single of these subsets contained a larger number of SNPs than expected by chance, i.e. no concordance was found with respect to the MDD and EA SNP effect *significances*. When comparing the directions of SNP effects, only four of the 144 subsets showed nominally correlated directions of effect, which is not more than expected by chance (permuted empirical p-value 0.244), indicating no concordance with respect to the MDD and EA SNP effect *directions*.

Discussion

This study tested the existence of pleiotropic genetic effects (genetic correlation) between major depressive disorder (MDD) and lower educational attainment (EA) on individual genotype data from a large sample of approximately 25,000 subjects from Western countries. To start, a strong negative phenotypic association was found with an OR for MDD of 0.78 per SD increase in EA, which is in line with findings from a meta-analysis of 37 studies from mainly western countries by Lorant et al.¹ Our first test for genetic correlation was negative with no across-trait predictive power of the GPRS: EA-GPRS did not predict MDD, and MDD-GPRS did not predict EA. In the second test for genetic correlation, GREML analyses did not show consistent evidence for genetic correlation. The third test, SNP effect concordance analysis (SECA), also showed no evidence for concordance of EA and MDD SNP effects with respect to their significance or direction.

The GPRS in our study had within-trait predictive power in line with previous findings,^{7,13} and were based on an independent EA discovery sample from the SSGAC⁷ of approximately 120,000 subjects and independent MDD leave-one-cohort-out discovery samples of approximately 8,000 cases and 12,000 controls. These numbers seem adequate, but the discovery sets would ideally have been even larger, because most predictive power was still found for the GPRS including all SNPs ($P_T=1$) indicating that true effect SNPs were associated in the discovery sample with p-values close to 1.²⁸ Nevertheless, Dudbridge power calculations suggested that the EA-GPRS were well powered to predict MDD when the genetic correlation would have been around -0.2 (Supplementary Figure 3).³⁵ Our GPRS results, therefore, indicate that a large genetic correlation between EA and MDD is unlikely, but could not exclude a small genetic correlation of around -0.1 .

We performed GREML analyses to estimate the MDD SNP- h^2 , EA SNP- h^2 and genetic correlation. The MDD SNP- h^2 found (0.17) was considerably smaller than the one previously found by Lubke et al (0.32),¹⁰ which could well be due to the actual differences in SNP- h^2 across cohorts; the sample of Lubke was included in the current study as NESDA/NTR-1 and indeed had the largest contribution to the overall SNP- h^2 of all cohorts (Table 3). The EA SNP- h^2 (0.14 in controls only) was of the same magnitude (less than 2 SE difference) as the SNP- h^2 found by Rietveld et al (0.2).⁷ The GREML estimate of the genetic correlation was somewhat complicated to interpret. A significant negative genetic correlation was found (-0.25 , $p=0.004$) when EA information of both cases and controls was taken into account, but we fear this finding could be biased particularly in the context of genotype and environment correlation. In fact, when taking EA information of only controls into account, the estimate of genetic correlation dropped considerably and was no longer significant (-0.11 , $p=0.30$). However, we note that this estimate was conservative as it reduced variation in EA, and we note the negative point estimate and high standard error showing that this analyses was underpowered to draw definitive inference. Taken all together, the GREML analyses could be in line with a small genetic correlation of around -0.1 . In addition to the two methods based on individual level genotype data, we also performed analyses on GWAS summary statistics with the recently published SECA method³⁴ and found no evidence for genetic correlation.

To the best of our knowledge only three previous studies tested for a genetic correlation between MDD and EA. López-León et al used a family based approach in 2,383 subjects to find a negative genetic correlation of -0.65 and -0.50 between EA and self-reports of depressive symptoms based on respectively the Center for Epidemiologic Studies Depression Scale (CES-D) and the Hospital Anxiety and Depression Scale (HADS-D).¹¹ Boardman et al also used cross-sectional CES-D assessments and found a genetic correlation of -0.7 with GREML-analyses.¹² Mezuk et al used a twin design with depression assessed with the DSM-IV based Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID-I), and their study generally supported social causation as cause for the link between lower EA and increased MDD risk, and found only a small genetic correlation of -0.22 .⁵ The studies of López-León et al and Boardman et al contrast our finding of no, or at most a small, genetic correlation, but this could be because they tested symptom reports of depressive state at a specific point in time, whereas our study tested the presence of a more clinical construct: DSM-IV or ICD-10 based lifetime diagnosis of MDD. Indeed, our results appear in line with the findings from Mezuk et al who also used DSM-IV based diagnoses of MDD. Furthermore, we found that the association between lower EA and MDD remained when cases with an age of first MDD onset > 30 were taken into account exclusively. This indicates it is unlikely that MDD directly causes a lowering of EA, as it can be assumed that one reaches his or her education potential before the age of 30, which is in line with the suggested social causation by Mezuk et al.⁵

The finding that there is no, or at most a small, genetic correlation between lower EA and MDD is relevant, because this implies that non-genetic factors play an important role, and that underlying mechanisms may possibly be accessible to interventions. For example, when the social causation model would be studied in more detail, this could potentially lead to underlying clues on how lower socioeconomic status could contribute to vulnerability for MDD, or alternatively how higher socioeconomic status may buffer against vulnerability for MDD. For instance, lower socioeconomic status has shown to be associated to less healthy life styles (less physical exercise, more smoking, higher BMI, and more use of alcohol),^{36,37} less adequate medical treatment seeking behavior,³⁸ less knowledge about MDD,³⁹ and higher vulnerability to experience stressful life events.⁴⁰ These factors could all contribute to increased MDD risk. However, future research should be conducted to elucidate the most important underlying mechanism as these may hint to either public or personal actions to best prevent MDD amongst individuals with lower EA. Yet another mechanism underlying the link between lower EA and MDD could possibly be found in a third factor other than genetic effects, such as a certain personality characteristic or less developed cognitive abilities, that causes both lower EA and increased MDD risk.

Our study has several strengths, but also some limitations. First, our study is one of the first and largest studies to test for pleiotropy between lower EA and MDD, and we used individual level genotype data. In addition, we used clinically relevant DSM-IV and ICD-10 based diagnoses of MDD. Furthermore, we applied three distinct methods that essentially lead to the same conclusion. A limitation of our study is that the discovery samples of the polygenic risk score analyses were not optimally sized with maximum predictive power of the GPRS including all SNPs ($P_T=1$). However, this is a limitation of most current genetic studies, and we feel our discovery samples were adequately powered given the availability

of relevant genetic cohorts up to date. Furthermore, the genetic basis of MDD is strong enough to study pleiotropy, as has been indicated in previous work from the Psychiatric Genomics Consortium that indicate a genetic correlation between MDD-schizophrenia (0.43 ± 0.06), and MDD-bipolar disorder (0.47 ± 0.06) with both GREML⁴¹ and GPRS-analyses.⁴² Another limitation is that we could have missed pleiotropic effects amongst rare SNPs with a MAF < 0.01 . This limitation could be addressed with a family or twin study, but it would be surprising when SNPs with MAF < 0.01 would have large pleiotropic effects while SNPs with MAF > 0.01 show no such evidence.

To conclude, we did confirm a negative phenotypic association between MDD and EA, but found no evidence that this association is due to genetic factors, which indicates that a large genetic correlation between lower EA and MDD is unlikely, but does not exclude a small genetic correlation of around -0.1 . Understanding of the possible pathways between lower EA and MDD risk requires further research including twin analyses for an additional estimate of the upper bound of the genetic correlation. Nevertheless, we believe that the finding of the absence of large pleiotropic genetic effects underlying the established correlation of lower EA with increased MDD risk may be relevant, as it points to non-genetic mechanisms that may be accessible to interventions aimed at breaking this deleterious link.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX 1

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APPENDIX 2

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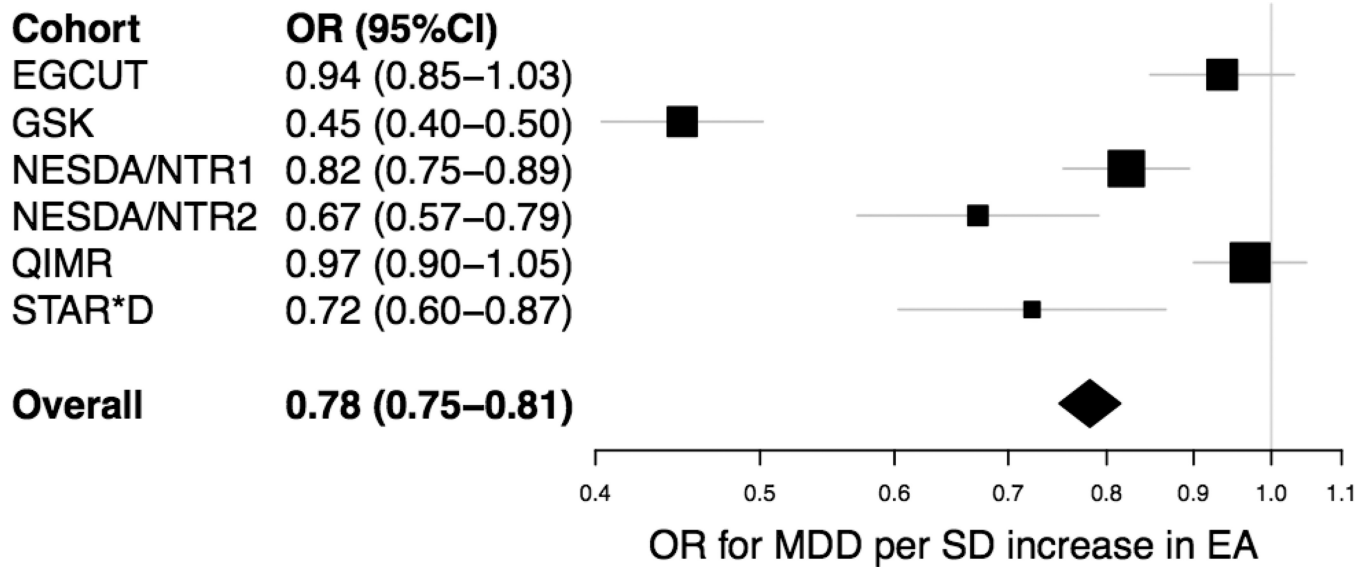


Figure 1. Forest plot of the phenotypic association between EA and MDD

The OR for MDD per SD increase in EA is displayed for the individual cohorts, as well as for the overall sample. The ORs were estimated with logistic regression of MDD on the corrected EA z-scores, which were defined as the standardized residuals of the regression of EA on sex, year of birth (YOB), YOB^2 , YOB^3 , and the interaction of sex with YOB , YOB^2 , and YOB^3 .

Table 1

Sample characteristics

Study (Abbreviation)	N with MDD		Age		N with EA		Mean EA z-score	
	Case	Control	Mean	SD	Case	Control	Case	Control
Bonn/Mannheim (B)	925	1282	46.9	13.3	0	0	-	-
EGCUT (E)	508	5345	48.8	20.1	446	4569	-0.06	0.01
GenRED (GE)	976	1215	47.0	16.2	0	1170	-	0.00
GSK (GS)	866	863	51.9	13.5	866	862	-0.36	0.36
MPIP (M)	337	533	48.1	13.9	0	0	-	-
NESDA/NTR-1 (N1)	1560	1123	44.5	13.2	1382	875	-0.08	0.12
NESDA/NTR-2 (N2)	236	1201	40.5	14.7	211	759	-0.28	0.09
QIMR (Q)	1432	1686	43.4	10.9	1258	1402	-0.02	0.01
RADIANT (R)	1605	1573	44.3	12.5	0	0	-	-
STAR*D (S)	1217	128	43.5	14.0	1210	128	-0.03	0.30
Overall	9662	14949	46.2	15.6	5373	9765	-0.10	0.06

The number of cases with a diagnosis of MDD in lifetime, controls without MDD, mean age and its standard deviation, and the percentage of female is displayed for the ten cohorts separately and for the overall sample. In addition, the number of cases and controls with information on EA available and their mean EA z-score are displayed. The EA z-scores were defined as the standardized residuals of the regression of EA on sex, year of birth (YOB), YOB², YOB³, and the interaction of sex with YOB, YOB², and YOB³.

Table 2

The effect of genomic risk profile scores (GRPS), based on depression (MDD-GRPS) and educational attainment (EA-GRPS) discovery results, on MDD and EA in the overall sample (upper rows) and the separate studies (lower rows).

Effect on MDD										
N		Effect		R-squared (%)		Effect on EA				
Case	Control	OR	P-value	NK	Liability	N	Beta	P-value	R2(%)	
A. Results in overall sample										
Effect of MDD-GRPS										
p < 0.001	9662	14949	1.03	0.021	0.03	0.03	15985	-0.01	0.188	0.01
p < 0.01	9662	14949	1.04	0.010	0.04	0.04	15985	-0.02	0.034	0.03
p < 0.1	9662	14949	1.11	1.0e-11	0.28	0.29	15985	-0.02	0.046	0.02
p < 1	9662	14949	1.13	1.7e-16	0.41	0.42	15985	-0.01	0.067	0.02
Effect of EA-GRPS										
p < 0.001	6544	12324	1.02	0.167	0.02	0.02	13477	0.05	1.2e-09	0.27
p < 0.01	6544	12324	1.00	0.842	0.00	0.00	13477	0.09	2.4e-23	0.73
p < 0.1	6544	12324	0.98	0.245	0.01	0.01	13477	0.10	2.1e-31	1.00
p < 1	6544	12324	0.99	0.594	0.00	0.00	13477	0.11	2.7e-37	1.20
B. Results in separate studies										
Effect of MDD-GRPS (all threshold p<1; letters represent separate studies)										
B	925	1282	1.14	0.003	0.54	0.54	-	-	-	-
E	508	5345	1.10	0.040	0.16	0.30	5015	-0.01	0.402	0.01
GE	976	1215	1.07	0.111	0.16	0.16	1170	-0.01	0.647	0.02
GS	866	863	1.09	0.097	0.22	0.21	1728	-0.04	0.111	0.14
M	337	533	1.05	0.461	0.08	0.09	-	-	-	-
N1	1560	1123	1.24	6.1e-08	1.50	1.50	2257	-0.02	0.373	0.04
N2	236	1201	1.19	0.019	0.70	0.98	1817	-0.02	0.330	0.05
Q	1432	1686	1.09	0.017	0.25	0.24	2660	-0.01	0.776	0.00

Effect on MDD									
N		Effect		R-squared (%)		Effect on EA			
Case	Control	OR	P-value	NK	Liability	N	Beta	P-value	R ² (%)
R	1605	1.15	9.7e-05	0.65	0.63	-	-	-	-
S	1217	1.17	0.098	0.45	0.79	1338	0.03	0.345	0.07
Effect of EA-GRPS (all threshold p<1; letters represent separate studies)									
E	508	5345	0.95	0.257	0.05	0.09	0.08	1.2e-08	0.64
GS	866	863	0.96	0.358	0.07	0.06	0.07	0.004	0.48
M	337	533	0.96	0.524	0.06	0.06	-	-	-
N1	1560	1123	0.94	0.151	0.10	0.10	0.17	1.1e-15	2.79
N2	236	1201	0.95	0.512	0.05	0.08	0.16	1.0e-11	2.52
Q	1432	1686	1.00	0.994	0.00	0.00	0.12	1.7e-09	1.36
R	1605	1573	1.04	0.241	0.06	0.06	-	-	-

The impact of the genetic profile risk scores (GPRS), based on EA discovery results (EA-GPRS) and MDD discovery results (MDD-GPRS), on target MDD and on target EA were estimated with respectively logistic and linear regression, while including sex, the first 10 principal components and covariates labeling the cohorts and genotype batches. The impact on MDD was, in addition, estimated as Nagelkerke's R² and the R² on the liability scale,³⁰ the impact on EA as the standard R² of linear regression. On the overall sample, the effects were estimated for GPRS on different sets of SNPs with different thresholds of significance in the discovery set (p<0.001; p<0.01; p<1) (Panel A). The impact on MDD and EA in the separate cohorts was, subsequently, estimated for the polygenic risk scores based on all SNPs (threshold p<1) (Panel B). The number of individuals included in the analyses is displayed: note that individuals from B, GE, and S are excluded from the analyses with polygenic risk scores based on EA discovery results, because these cohorts were (partly) included in the discovery phase. B=Bonn/Mannheim; E=EGCUT; GE=GenRED; GS=GSK; M=MPPI; N1=NESDA/NTR-1; N2=NESDA/NTR-2; Q=QIMR; R=RADIANT; S=STAR*D

Table 3

GREML estimates of the proportion of variation explained by common SNPs in major depressive disorder (MDD SNP-h²) and educational attainment (EA SNP-h²), and the genetic correlation between MDD and EA; estimated with EA information from both cases and controls (upper rows) and from controls only (lower rows).

Cohorts included	Case	Control	MDD SNP-h ²				EA SNP-h ²				Genetic correlation		
			Est	se	p-value	N	Est	se	p-value	Est	se	p-value	
A. EA in both cases and controls													
All	9662	14949	0.173	0.017	<1e-16	15985	0.124	0.019	2.8e-11	-0.253	0.087	0.004	
All excluding B	8737	13667	0.155	0.019	1.1e-16	15985	0.124	0.019	3.1e-11	-0.249	0.096	0.009	
All excluding E	9154	9604	0.207	0.022	<1e-16	10970	0.133	0.026	4.5e-07	-0.265	0.102	0.009	
All excluding GE	8686	13734	0.183	0.019	<1e-16	14815	0.130	0.020	9.0e-11	-0.345	0.091	1.4e-04	
All excluding GS	8796	14086	0.172	0.019	<1e-16	14257	0.120	0.021	7.6e-09	-0.231	0.099	0.020	
All excluding M	9325	14416	0.177	0.018	<1e-16	15985	0.124	0.019	3.9e-11	-0.208	0.088	0.018	
All excluding N1	8102	13826	0.150	0.020	2.1e-14	13728	0.120	0.022	3.0e-08	-0.239	0.109	0.028	
All excluding N2	9426	13748	0.174	0.018	<1e-16	14168	0.118	0.021	1.4e-08	-0.294	0.097	0.002	
All excluding Q	8230	13263	0.199	0.020	<1e-16	13325	0.133	0.022	1.6e-09	-0.237	0.091	0.009	
All excluding R	8057	13376	0.161	0.020	1.0e-15	15985	0.124	0.019	3.6e-11	-0.206	0.097	0.033	
All excluding S	8445	14821	0.187	0.019	<1e-16	14647	0.126	0.020	6.3e-10	-0.294	0.092	0.001	
B. EA in controls only													
All	9662	14949	0.173	0.017	<1e-16	9765	0.144	0.030	1.5e-06	-0.110	0.105	0.298	
All excluding B	8737	13667	0.156	0.019	1.1e-16	9765	0.144	0.030	1.6e-06	-0.113	0.115	0.327	
All excluding E	9154	9604	0.208	0.022	<1e-16	5196	0.177	0.054	0.001	0.004	0.130	0.972	
All excluding GE	8686	13734	0.183	0.019	<1e-16	8595	0.159	0.034	2.6e-06	-0.187	0.110	0.087	
All excluding GS	8796	14086	0.172	0.019	<1e-16	8903	0.133	0.033	4.4e-05	-0.120	0.119	0.310	
All excluding M	9325	14416	0.178	0.018	<1e-16	9765	0.144	0.030	1.4e-06	-0.065	0.105	0.537	
All excluding N1	8102	13826	0.151	0.020	1.7e-14	8890	0.144	0.033	9.4e-06	-0.112	0.124	0.369	
All excluding N2	9426	13748	0.174	0.018	<1e-16	9006	0.132	0.032	4.0e-05	-0.176	0.117	0.133	
All excluding Q	8230	13263	0.200	0.020	<1e-16	8363	0.143	0.035	3.6e-05	-0.148	0.114	0.196	
All excluding R	8057	13376	0.161	0.020	1.0e-15	9765	0.144	0.030	1.4e-06	-0.059	0.116	0.610	

Cohorts included	MDD SNP-h ²					EA SNP-h ²					Genetic correlation		
	Case	Control	Est	se	p-value	N	Est	se	p-value	Est	se	p-value	
All excluding S	8445	14821	0.188	0.019	<1e-16	9637	0.140	0.030	3.3e-06	-0.084	0.107	0.434	

Bivariate- GREML was performed to estimate the proportion of variation explained in MDD (MDD SNP-h²) and EA (EA SNP-h²) by genome-wide common SNPs, as well as the genetic correlation between MDD and EA. First, EA information of both cases and controls was analysed (first line upper Panel), but the correlation thus found should be interpreted with caution, because it could be biased (see Methods). Therefore, analyses were repeated taking EA information of controls only into account (first line lower Panel). In order to estimate the robustness of these findings, the analyses were repeated leaving one cohort at the time (additional lines in upper and lower Panel). The MDD SNP-h² was expressed on the liability scale assuming a population prevalence K of 20% (see Supplementary Table 5 for comparison of the MDD SNP-h² for different values of K with the SNP-h² on the observed scale). MDD was available for all ten cohorts; EA was only available for cohorts E, GE, GS, N1, N2, Q, and S. The analyses were corrected for sex, the first 20 principal components and a categorical covariate labelling the cohorts and genotype batches. 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