RUNNING TITLE: EA polygenic score, SES, and depression.

Educational Attainment Polygenic Score is Associated with Depressive Symptoms via Socioeconomic Status: A Gene-Environment-Trait Correlation

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Abstract

Recently, I suggested that the environment can act as a mediator of genetic influences in a process termed Gene-Environment-Trait correlations (rGET). I further hypothesized that socioeconomic status (SES) may mediate the negative genetic correlation found between cognitive ability and depression. This hypothesis was based on previous research showing that SES is associated with both cognitive ability and depression. Thus, in the current study I aimed to test for an rGET in which genetic influences on cognitive ability were associated with depressive symptoms via SES. Educational attainment (EA) was used as a proxy for cognitive ability, due to the high genetic correlation between the phenotypes and the highly powerful genome-wide association study (GWAS) available for EA. Summary statistics from the EA GWAS were utilized to calculate EA polygenic scores, and mediation analyses were performed to examine if the EA polygenic scores predicted depressive symptoms via SES. Two independent samples were used for the analyses: 522 non-Hispanic Caucasian university students from the Duke Neurogenetics Study (DNS; 277 women, mean age 19.78±1.24 years) and 5,243 white British volunteers (2,669 women, mean age 62.30±7.41 years) from the UK biobank (UKB). Results indicated a significant mediation in both samples, wherein higher EA polygenic scores predicted higher SES, which in turn predicted lower depressive symptoms. Current findings suggest that some of the genetic correlates of depression represent environmental influences and consequently that public policy aiming to reduce socioeconomic inequalities may not only relieve the individual and societal burden of depression, but also decrease the genetic risk for depression.

Keywords: Depression; Socioeconomic status (SES); Educational attainment (EA); Gene-environment-trait correlation (rGET); Gene-environment-correlation (rGE); polygenic score.

Depression is a major cause of disability. It has a global prevalence of around 4.7% (Ferrari et al., 2013), and it is predicted to become one of the three leading causes of illness by 2030 (Mathers & Loncar, 2006). Interestingly, low cognitive ability in childhood has been shown to predict high levels of depression (e.g., Hung et al., 2016; Leech, Larkby, Day, & Day, 2006). Educational attainment (EA), which is often used as a proxy for cognitive ability, has been also linked to depression, so that the probability of experiencing depression decreases for additional years of education (Crespo, López-Noval, & Mira, 2014). Recent studies have found negative genetic associations between depression and both cognitive ability (Savage et al., 2018) and EA (Wray et al., 2018). Furthermore, by employing a genetically informed analysis (Mendelian randomization), both low cognitive ability and low EA were marked as risk factors for depression (Davies et al., 2019; Wray et al., 2018). Notably, how the genetic correlation between cognitive ability and depression is mediated has not been established.

Recently, I suggested that socioeconomic status may act as a mediator of the genetic link between cognitive ability and depression (Avinun, 2020). More generally, I hypothesized that the environment may mediate genetic correlations between two different phenotypes in a process termed gene-environment-trait correlations (Avinun, 2020). This hypothesis stemmed from accumulating research showing passive, active, and evocative processes that lead to correlations between genetic variations and environmental measures, such as parenting and stressful life events (Avinun & Knafo, 2014; Kendler & Baker, 2007). These passive, active, and evocative processes, known as gene-environment correlations (Plomin, DeFries, & Loehlin, 1977; Scarr & McCartney, 1983), occur due to genetically influenced characteristics that shape the individual's environment. As the environment can in turn substantially affect various

outcomes, it may act as a mediator of genetic effects and contribute to the widespread genetic correlations observed between numerous phenotypes (Bulik-Sullivan et al., 2015), including between depression and both cognitive ability and EA (Savage et al., 2018; Wray et al., 2018). Identifying gene-environment-depression correlations can provide modifiable targets for public policy and also demonstrate the importance of context in the discovery of the genetic variants that influence depression.

SES, which can be defined as an individual's or group's position within a social hierarchy that is determined by factors such as education, occupation, income, and wealth (Calixto & Anaya, 2014), has been shown to be genetically influenced (Hill et al., 2016; Marioni et al., 2014). In other words, genetically influenced traits affect an individual's SES. One of these traits, as has been found in a meta-analysis of longitudinal studies, is cognitive ability (Strenze, 2007), which is highly heritable (Plomin & Deary, 2015). SES has been associated with various physiological and mental disorders (e.g., Calixto & Anaya, 2014; Galobardes, Lynch, & Davey Smith, 2004; Werner, Malaspina, & Rabinowitz, 2007), including depression (Everson, Maty, Lynch, & Kaplan, 2002), and a genetic correlation between SES and depression has been also observed (Hill et al., 2016).

Based on the above I set out to test for a gene-environment-trait correlation in which SES mediates an association between a cognitive ability polygenic score and depression. As findings of a recent genome wide association study (GWAS) of cognitive ability were only able to explain 5.2% of the variance in this phenotype, I chose to use the GWAS of EA (Lee et al., 2018), which included 1.1 million European-descent participants, and produced a polygenic score that explained ~11% of the variance in EA. The use of EA as a proxy for cognitive ability due to their high phenotypic and genetic correlation (a single nucleotide polymorphism-based genetic

correlation of .95; Marioni et al., 2014), has been previously done to increase statistical power (e.g., Hill et al., 2019). Two independent samples were used: a sample of 522 non-Hispanic Caucasian university students from the Duke Neurogenetics Study and a sample of 5,243 adult white British volunteers from the UK Biobank (UKB). Because the GWAS included data from the UKB and this may bias the results, even though a different outcome is tested, in the analyses of the UKB data EA polygenic scores that were based on summary statistics from a GWAS that did not include the UKB as a discovery sample, were used (obtained from Dr. Aysu Okbay, who is one of the authors of the original GWAS).

Materials and Methods

Participants

The Duke Neurogenetics Study (DNS) sample consisted of 522 self-reported non-Hispanic Caucasian participants (277 women, mean age 19.78±1.24 years) who were not related and for whom there was complete data on genotypes, SES, depressive symptoms, and all covariates. Participants were recruited through posted flyers on the Duke University campus and through a Duke University listserv. All procedures were approved by the Institutional Review Board of the Duke University Medical Center, and participants provided informed consent before study initiation. All participants were free of the following study exclusions: 1) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension).

The UKB sample consisted of 5,243 white British volunteers (2,669 women, mean age 62.30±7.41 years), who participated in the UKB's first assessment and the imaging wave, completed an online mental health questionnaire (Davis et al., 2018), and had complete genotype, SES, depressive symptoms and covariate data. The UKB (www.ukbiobank.ac.uk; Sudlow et al., 2015) includes over 500,000 participants, between the ages of 40 and 69 years, who were recruited within the UK between 2006 and 2010. The UKB study was approved by the National Health Service Research Ethics Service (reference: 11/NW/0382), and current analyses were conducted under UKB application 28174 (because the application also included a request for neuroimaging data, the sample used in this study is limited to individuals who participated in the imaging wave).

Ancestry

Because self-reported race and ethnicity are not always an accurate reflection of genetic ancestry, an analysis of identity by state of whole-genome SNPs in the DNS was performed in PLINK v1.9 (Purcell et al., 2007). Before running the multidimensional scaling (MDS) components analysis, SNPs were pruned for high LD (r^2>0.1), and the following were removed: C/G and A/T SNPs, SNPs with a missing rate >.05 or a minor allele frequency <.01, SNPs that did not pass the Hardy-Weinberg equilibrium test (p<1e-6), sex chromosomes, and regions with long range LD (the MHC and 23 additional regions; Price et al., 2008). The first two MDS components computed for the non-Hispanic Caucasian subgroup, as determined by both self-reports and the MDS components of the entire mixed race/ethnicity DNS sample, were used as covariates in analyses of data from the DNS. The decision to use only the first two MDS components was based on an examination of a scree plot of

eigenvalues, which became very similar after the second MDS component (additional information and plots are available at https://www.haririlab.com/methods/genetics.html).

For analyses of data from the UKB, only those who were 'white British' based on both self-identification and a genetic principal components analysis were included. Additionally, the first 10 principal components received from the UKB's data repository (unique data identifiers: 22009-0.1-22009-0.10) were included as covariates as previously done (e.g., Avinun & Hariri, 2019; Whalley et al., 2016). Further details on the computation of the principal components can be found elsewhere (http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web.pdf).

Socioeconomic status

In the DNS, SES was assessed using the "social ladder" instrument (Adler, Epel, Castellazzo, & Ickovics, 2000), which asks participants to rank themselves relative to other people in the United States (or their origin country) on a scale from 0–10, with people who are best off in terms of money, education, and respected jobs, at the top (10) and people who are worst off at the bottom (0). The participants were also asked to rate their parents' SES during their childhood and adolescence. The correlation between the participants' SES and their mothers' SES was .50, and the correlation between the participants' SES and their fathers' SES was .49. Only the participants own SES was used.

In the UKB, SES was assessed based on the report of average household income before tax, coded as: 1 - Less than 18,000; 2 - 18,000 to 31,000; 3 - 31,000 to 52,000; 4 - 52,000 to 100,000; and 5 - Greater than 100,000. The reports made during the first

assessment (i.e., before the evaluation of depressive symptoms), between 2006 and 2010, were used.

Depressive symptoms

In the DNS, the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms in the past week (Radloff, 1977). All items were summed to create a total depressive symptoms score.

In the UKB, the Patient Health Questionnaire 9-question version (PHQ-9) was used to assess depressive symptoms in the past 2 weeks (Kroenke, Spitzer, & Williams, 2001). The participants answered these questions during a follow-up between 2016 and 2017. All items were summed to create a total depressive symptoms score.

Genotyping

In the DNS, DNA was isolated from saliva using Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed through 23andMe by the National Genetics Institute (NGI), a CLIA-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with custom content was used to provide genome-wide SNP data, the HumanOmniExpress (N=328) or HumanOmniExpress-24 (N=194; Do et al., 2011; Eriksson et al., 2010; Tung et al., 2011). In the UKB, samples were genotyped using either the UK BiLEVE (N=501) or the UKB axiom (N=4,742) array. Details regarding the UKB's quality control can be found elsewhere (Bycroft et al., 2017).

Quality control and polygenic scoring

For genetic data from both the DNS and UKB, PLINK v1.90 (Purcell et al., 2007) was used to apply quality control cutoffs and exclude SNPs or individuals based on the following criteria: missing genotype rate per individual >.10, missing rate per SNP >.10, minor allele frequency <.01, and Hardy-Weinberg equilibrium p<1e-6. Additionally, in the UKB, quality control variables that were provided with the dataset were used to exclude participants based on a sex mismatch (genetic sex different from reported sex), a genetic relationship to another participant, outliers for heterozygosity or missingness (unique Data Identifier 22010-0.0), and UKBiLEVE genotype quality control for samples (unique Data Identifiers 22050-0.0-22052-0.0).

Polygenic scores were calculated using PLINK's (Purcell et al., 2007) "--score" command based on published SNP-level summary statistics from the most recent EA GWAS (Lee et al., 2018). Published summary statistics do not include the data from 23andMe per the requirements of this company (i.e., N ≈ 766,345). For the UKB analyses, summary scores from a GWAS that did not include the UKB as a discovery sample were used (N ≈ 324,162). SNPs from the GWAS of EA were matched with SNPs from the DNS and the UKB. For each SNP the number of the alleles (0, 1, or 2) associated with EA was multiplied by the effect estimated in the GWAS. The polygenic score for each individual was an average of weighted EA-associated alleles. All SNPs matched with SNPs from the DNS and UKB were used regardless of effect size and significance in the original GWAS, as previously recommended and shown to be effective (Dudbridge, 2013; Ware et al., 2017).

Statistical analysis

The PROCESS SPSS macro, version 3.1 (Hayes, 2017), was used to conduct the mediation analyses in SPSS version 26. Participants' sex (coded as 0=males, 1=females), age, and ancestry (two genetic components for the DNS and 10 for the UK biobank) were entered as covariates in all analyses. In the mediation analyses, bias-corrected bootstrapping (set to 5,000) was used to allow for non-symmetric 95% confidence intervals (CIs). Specifically, indirect effects are likely to have a non-normal distribution, and consequently the use of non-symmetric CIs for the determination of significance is recommended (MacKinnon, Lockwood, & Williams, 2004). However, bias-corrected bootstrapping also has its faults (Hayes & Scharkow, 2013) and, consequently, as supportive evidence for the indirect effect, I also present the test of joint significance, which examines whether the *a path* (EA polygenic scores to SES) and the *b path* (SES to depressive symptoms, while controlling for the EA polygenic scores) are significant. The EA polygenic scores were standardized (i.e., M=0, SD=1) in SPSS to make interpretability easier.

As a post-hoc analysis, in the UKB it was possible to analyze the longitudinal data while excluding those who reported on ever seeing a general physician (N=1,843) or a psychiatrist (N=501) "for nerves, anxiety, tension or depression", at the first assessment.

Results

Descriptive statistics

In the DNS, the SES measure ranged between 2 and 10 (M=7.34, SD=1.43) and depressive symptoms ranged between 0 and 43 (M=8.94, SD=7.13). In the UKB, the SES measure ranged between 1 and 5 (M=2.92, SD=1.11), and depressive symptoms, estimated about 6 years later, ranged between 0 and 27 (M=2.50, SD=3.43).

EA polygenic scores and SES (a path) in the DNS

The EA polygenic scores were significantly associated with SES (b=.20, SE=.06, p=.0016; R^2=0.018), so that higher scores predicted higher SES. Of the covariates, age and sex were significantly associated with SES, so that older participants (b=.13, SE=.05, p=.008) and men (b=-.45, SE=.12, p=.0003) were characterized by higher SES.

SES and depressive symptoms (b path) in the DNS

With the EA polygenic scores in the model, SES significantly and negatively predicted depressive symptoms (b=-.61, SE=.22, p=.007; R^2=0.014), such that higher SES predicted lower depressive symptoms. Of the covariates, age was significantly associated with depressive symptoms, so that being younger was associated with higher depressive symptoms (b=-.53, SE=.25, p=.037).

EA polygenic scores and depressive symptoms in the DNS

The EA polygenic scores did not significantly predict depressive symptoms (b=-.11, SE=.32, p=.74). Notably, however, the significance of a direct path from X (EA polygenic scores) to Y (depressive symptoms) or the 'total effect' (the 'c' path), is not a prerequisite for the testing of a mediation/indirect effect (Hayes, 2009; MacKinnon, Krull, & Lockwood, 2000; Rucker, Preacher, Tormala, & Petty, 2011), which was the main interest of the current study.

Indirect Effects in the DNS

The indirect path (*a*b*), EA polygenic scores to depressive symptoms via SES was significant as indicated by the bias corrected bootstrapped 95% CI not including zero (Figure 1a; indirect effect=-.12, bootstrapped SE=.06, bootstrapped 95% CI: -.26 to -.02). The indirect effect remained significant when 10 MDS components of genetic ancestry and genotyping platform were included as covariates (indirect effect=-.12, bootstrapped SE=.06, bootstrapped 95% CI: -.27 to -.02).

Indirect Effects in the UBK

For the UKB, EA polygenic scores that were based on a GWAS that did not include the UKB as a discovery sample, were used. additionally, genotyping platform was included as a covariate in the analyses. The *a path*, from the EA polygenic scores to SES, and the *b path*, from SES to depressive symptoms while controlling for EA polygenic scores, were significant (*a path*: b=.10, SE=.01, p<.0001, R^2=0.008; *b path*: b=-.43, SE=.04, p<.0001, R^2=0.017). The indirect path was also significant (Figure 1b; indirect effect=-.04, bootstrapped SE=.008, bootstrapped 95% CI: -.06 to -.03).

To test the robustness of the finding, a post-hoc analysis that excluded participants who, at the first assessment, reported on ever seeing a professional for nerves or depression (leaving 3,447 participants), was conducted. This was done in an attempt to increase the likelihood of only including the individuals who became depressed between the first assessment, in which income was assessed, and the assessment a few years later, in which depressive symptoms were assessed. This analysis further supported a causal mediation, in which higher EA polygenic scores predicted higher SES, which in turn predicted lower depressive symptoms (*a path*: b=.08, SE=.02, p<.0001, R^2=0.005; *b path*: b=-.15, SE=.04, p=.0003, R^2=0.004; indirect effect=-.012, bootstrapped SE=.004, bootstrapped 95% CI: -.022 to -.005).

Discussion

The current results suggest that the negative genetic link previously found between cognitive ability and depressive symptoms may be partly mediated by SES. EA was used in the current study as a proxy for cognitive ability, due to the high phenotypic and genetic correlation between them (a single nucleotide polymorphism-based genetic correlation of .95; Marioni et al., 2014) and the highly powerful GWAS available for EA. The indirect effect was found in two independent samples with different characteristics and measures, demonstrating the robustness of the associations. Notably, in the UKB the indirect effect was tested longitudinally, with data on SES that was collected about 6 years before the assessment of depressive symptoms. A supplementary analysis that excluded participants who reported ever seeing a professional for nerves or depression at first assessment, was also significant, further supporting a causal temporal mediation.

The found mediation supports the gene-environment-trait correlations hypothesis (rGET; Avinun, 2020), which suggests that certain genetic correlations may be mediated, at least in part, by the environment, i.e., an environmentally mediated pleiotropy. The found EA polygenic scores→SES→depressive symptoms mediation stresses the importance of context in genetic studies of depression. More specifically, the current results suggest that a GWAS of depression that relies mostly on a sample that is homogeneous in terms of SES, will be less likely to capture the genetic influences that contribute to depression via SES. Consequently, polygenic scores that will be based on such a GWAS may be weaker predictors of depression. Put differently, because the environment can act as a mediator of some of the genetic influences on depression, if the environment differs between GWASs, the captured

genetic influences will differ. Importantly, the current results imply that social policies aimed at reducing socioeconomic inequalities may weaken the genetic effects on depression by decreasing the association between cognitive ability and depression. Lastly, this rGET means that statistically controlling for SES may help to remove environmentally mediated effects from the depression polygenic score and lead us a step closer to identifying the direct genetic influences on depression.

Low SES may be a risk factor for depression by leading to an increase in life stress that stems from having to make ends meet and from living in a disadvantaged neighborhood, which is associated with higher crime and fewer resources (Santiago, Wadsworth, & Stump, 2011). Low SES has also been associated with poorer access to green spaces (Dai, 2011), and with health damaging behaviors, such as physical inactivity, higher alcohol consumption, and poor nutrition (Nandi, Glymour, & Subramanian, 2014; Pampel, Krueger, & Denney, 2010), which are thought to affect mental health (e.g., Avinun & Hariri, 2019; Beyer et al., 2014; Boden & Fergusson, 2011). All of these mediators can be possible targets for policy makers.

The strengths of the current study include the use of two independent samples with markedly different measures and characteristics (e.g., young university students versus older community volunteers) and a GWAS-derived polygenic score, but it is also limited in ways that can be addressed in future studies. First, the findings are limited to populations of European descent and to the Western culture. Second, both samples consisted of volunteers and consequently do not fully represent the general population. However, it may be speculated that the observed associations would strengthen with the inclusion of more individuals from low SES backgrounds, which are usually characterized by higher levels of depression (Lorant et al., 2003). Third,

297 the mediation model should be replicated within longitudinal designs in which
298 measures of SES and depressive symptoms are available at multiple time points.

299 In conclusion, the current results shed light on the genetic associations that have
300 been observed between cognitive ability and depression (Savage et al., 2018), and
301 suggest that they are partly mediated by SES. The mediation by SES is important
302 because it suggests that the genetic influences on depression may be moderated by
303 public policy and that the genetic composition of depression is likely to depend on the
304 social context in which it is examined. Additionally, the current results suggest that
305 controlling for SES, or other environmental factors that can act as mediators of
306 genetic influences, can help to isolate the direct genetic influences on depression.

307

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316

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321

Conflict of Interest

The author declares no competing financial or other interests.

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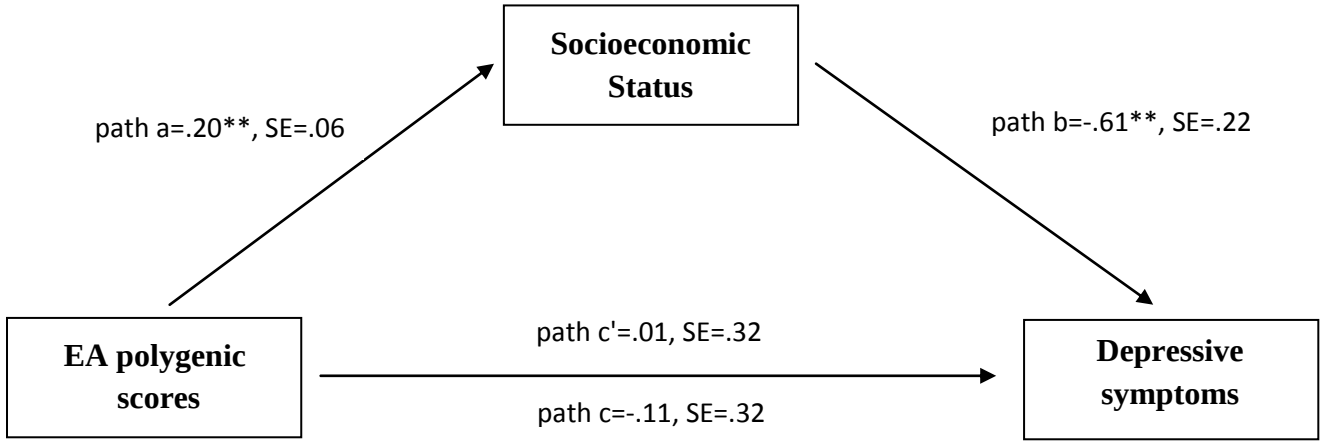
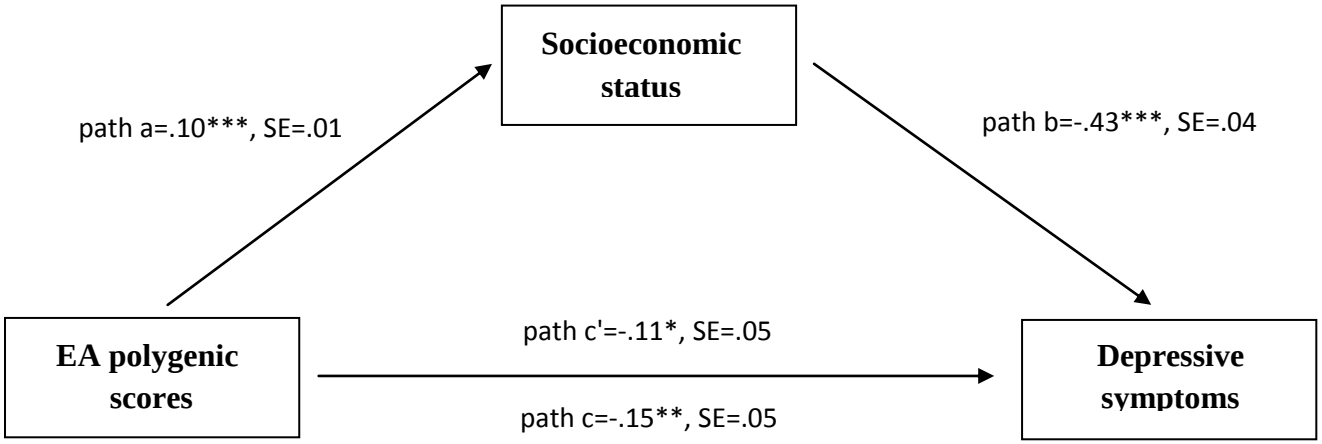
Figure 1. Mediation model linking genetic influences on educational attainment (EA), used as a proxy for cognitive ability, to depressive symptoms, via socioeconomic status

1a. Duke Neurogenetics Study



1b. UK Biobank



Note. *p<.05, **p<.01, ***p<.0001. EA - educational attainment. c- the total effect of the EA polygenic scores on depressive symptoms; c'-the effect of EA polygenic scores on depressive symptoms, while controlling for SES.