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VIKESH AMIN
Central Michigan University

JERE R. BEHRMAN
University of Pennsylvania

JASON M. FLETCHER
University of Wisconsin-Madison

CARLOS A. FLORES
California Polytechnic
State University

ALFONSO FLORES-LAGUNES
Syracuse University

HANS-PETER KOHLER
University of Pennsylvania

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Mental Health, Schooling Attainment and Polygenic Scores: Are There Significant Genetic-Environmental Associations?

Vikesh Amin[1]; Jere R. Behrman[2]; Jason M. Fletcher[3]; Carlos A. Flores[4]; Alfonso Flores-Lagunes[5]; Hans-Peter Kohler[6]

[1] Corresponding Author. Department of Economics, Central Michigan University, Mt Pleasant, MI 48859. Amin1v@cmich.edu
[2] William R. Kenan, Jr. Professor of Economics and Sociology, University of Pennsylvania
[3] Department of Sociology and La Follette School of Public Affairs, University of Wisconsin-Madison, and IZA
[4] Department of Economics, California Polytechnic State University
[5] Department of Economics, Syracuse University, IZA, and GLO
[6] Fredrick J. Warren Professor of Demography, University of Pennsylvania

Abstract:
We estimate associations between a polygenic score (PGS) for depressive symptoms, schooling attainment and genetic-environmental (GxE) associations with depressive symptoms and depression for 29 years old in the National Longitudinal Study of Adolescent Health (Add Health) and 53 years old in the Wisconsin Longitudinal Study (WLS). We find some suggestive evidence that the association of the PGS with mental health is lower for more-schooled older individuals in the WLS, but no evidence in Add Health. Quantile regression estimates also show that in the WLS the GxE associations are statistically significant only in the upper parts of the conditional depressive symptoms score distribution. We assess the robustness of the OLS results to possible omitted variable bias by estimating sibling fixed-effect regressions. The sibling fixed-effect results must be qualified, in part due to low statistical power. However, they show that college education is associated with fewer depressive symptoms in both datasets.

JEL Classification: I21, I10

Key words: Schooling; Mental Health; Genetics; Gene-Environment Interactions

1.   Introduction

Mental illness is an important public health issue in the US because of its high prevalence and economic and societal costs. Recently, 18.1% of adults aged 18 or older suffer from some mental illness (Center for Behavioral Health Statistics and Quality 2015). Serious mental illnesses cost $193.2 billion in lost earnings (Insel 2008) and reduce life expectancy by 10-20 years (Chesney et al. 2014). Suicide is the 10th leading cause of death in the US and one of the factors driving the recent fall in life expectancy (Murphy et al. 2018).

Mental illness is a complex health condition. There is increasing evidence suggesting that interactions between genetic and environmental factors (genetic-environmental interactions; GxE) may contribute to poor mental health. The first study to show this was Caspi et al. (2002). They found that associations between childhood maltreatment and antisocial behavior were modified by the MAOA gene, with those holding the low-activity variant being more responsive to maltreatment than the high-activity group. In a second paper, Caspi et al. (2003) found that a functional polymorphism in the 5-HTT gene moderated the influence of stressful life events on depression. Since the publication of these findings, several studies have looked at interactions between childhood maltreatment/stressful life events and candidate genes (MAOA, COMT, DRD4, BDNF, 5-HTTLPR) that predict poor mental health.

However, candidate genes are rarely used now to measure genetic predispositions. Candidate genes only are consistent with small proportions of the variation in mental health (Duncan and Keller 2011), whereas the genetic architecture of mental health is highly polygenic (involves multiple genes). Candidate gene studies are therefore underpowered, and previous significant candidate GxE associations are likely to be false positives (Border et al. 2019).[1] The current best practice is to use a polygenic score (PGS), which is a summary measure of an individual's genetic predisposition for a given trait. More specifically, a PGS is a weighted count of the number of trait-associated alleles possessed by an individual. The weights are based on effect sizes from genome-wide association studies (GWAS) conducted in large independent samples. PGSs can be limited to genome-wide significant single nucleotide polymorphisms (SNPs) ($p < 5 \times 10^{-8}$), or a series of more liberal thresholds can be applied (e.g., $p < .0.001, 0.01$). Studies using PGSs (for major depressive disorders; MDD) have reached mixed conclusions regarding GxE associations with respect to childhood trauma and stressful life events. Peyrot et al. (2014) found that individuals with a high PGS, and a history of childhood trauma were more likely to develop MDD than those with a low PGS and no exposure to trauma. Mullins et al. (2016) also found a significant GxE association between the PGS and childhood trauma. However, the GxE association was in the opposite direction—individuals who experienced moderate-to-severe childhood trauma had a lower PGS.[2] Both Mullins et al. (2016) and Musliner et al. (2016) found insignificant associations between the PGS and stressful life events in adulthood.

In this paper, we examine interactions between genes and another environmental factor, schooling attainment, which to our knowledge has not previously been examined in the GxE interaction literature for mental health. Several empirical studies have found that individuals with more schooling have better mental health and are less likely to be depressed (see Lorant et al.

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[1] Border et al. (2019) use the UK Biobank to look at candidate GxE associations across several measures of depression (lifetime diagnosis, current severity, episode recurrence) and environmental factors (sexual or physical abuse during childhood, socioeconomic adversity). Their study is well-powered with sample sizes ranging from 62,138 to 443,264. Despite the large sample sizes, they find no clear evidence for any candidate GxE associations.

[2] Mullins et al. (2016) explain this result by suggesting that childhood trauma is such a strong risk factor for MDD that it overrides some of the genetic risk of MDD.

2003 for a meta-analysis).[3] There are several theoretical reasons for this relationship. First, schooling can directly improve health by increasing productive efficiency (producing more health from a given set of inputs) and allocative efficiency (choosing better inputs) (Grossman 1972). Schooling also improves mental health because it is associated with fewer and less severe stressors. For example, higher schooling attainment is associated with higher wages (Card 1999), which reduce financial stress and provides the means to pursue better mental health. Moreover, higher schooling attainment is associated with lower risks of unemployment and work-related adverse life events, which are two factors that can lead to poor mental health (Audhoe et al. 2010). More schooling is further associated with leading healthier lifestyles (Cutler and Lleras-Muney 2010), and interacting with other healthy peers (Gaviria and Raphael 2001), which all positively affect mental health. More generally, schooling is called a fundamental cause of health disparities because of the perception that schooling embodies access to important resources and affects multiple health outcomes through several mechanisms (Link and Phlean 1995).

Given the apparent importance of schooling, we hypothesize that schooling may attenuate the genetic predisposition to poor mental health. There are theoretical models suggesting that schooling may interact with genes. The diathesis-stress model (Ellis et al. 2011) hypothesizes that unhealthy environments (low schooling attainment) trigger risk alleles, while healthy environments (high schooling attainment) protect against risk alleles. For example, a college graduate with a high genetic risk of depression may never be depressed because being a college graduate is associated with a higher income, leading a healthier lifestyle, and interacting more with other healthy peers. In contrast, a high school dropout with a high genetic risk is more likely to be depressed because he/she experiences financial stress due to having a low income or being unemployed, leads an unhealthy lifestyle and interacts with other depressed peers. The differential susceptibility (also commonly known as the orchids and dandelions) model (Belsky and Pluess 2009) hypothesizes that some individuals are dandelions, meaning they have a genetic make-up that is unaffected by both positive and negative environments. Others are orchids whose genetic make-up is highly sensitive to the environment. These individuals thrive in positive environments but wilt in negative environments. This model therefore predicts that schooling is more likely to lower the influence of genes for orchid individuals who have a high genetic predisposition of depression.

We examine the hypothesis that gene-education interactions are important for mental health by using OLS regressions to estimate associations between genes, schooling attainment (measured using college graduation) and GxE interactions with mental health for European-ancestry individuals in the National Longitudinal Study of Adolescent Health (Add Health) and the Wisconsin Longitudinal Study (WLS).[4] We analyze mental health when individuals are on average 29 years old in Add Health and 53 years old in the WLS. We measure mental health using the Center for Epidemiologic Studies Depression (CES-D) Scale in both datasets. The CES-D is widely used to measure symptoms of depression, and has been tested in multiple settings for validity and reliability (Cosco et al. 2017; Radloff 1977). We use a PGS for the number of depressive symptoms created by the Social Science Genetic Association Consortium (SSGAC) in both datasets. Both datasets also oversample siblings, which allows us to estimate sibling fixed-effect regression models. Sibling fixed-effect models control for (i) observed and unobserved

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[3] There is also some evidence that there is a causal relationship between schooling and mental health. See for example Crespo et al. (2014) and Mazzonna (2014). Both studies find evidence for a causal effect of schooling by exploiting variation in schooling arising from changes in compulsory education laws, which can be argued to be exogenous. However, other studies using the same methodology have found no protective effect of schooling on mental health (Avendano et al. 2017; Courtin et al. 2018; Dursuin and Cesur 2016)

[4] We limit the analyses to European-ancestry individuals to control for biases due to population stratification. This is explained in more detail in section 3.

shared family-level factors including shared childhood neighborhoods and schools and (ii) unobserved shared portions of the genome that affect schooling and mental health – both of which may bias OLS estimates. On the other hand, sibling fixed-effects do not eliminate sibling-specific differences that affect schooling and mental health, and thus may still yield biased estimates of causal effects. However, sibling fixed-effects estimates are probably still an improvement on OLS estimates that do not control for any unobserved confounding.

Other literature related to our paper includes the work by Amin et al. (2017), Liu et al. (2015), and Komulainen et al. (2018), who provide OLS associations between a PGS for BMI, schooling attainment and GxE associations with BMI and obesity. The general conclusion from these studies is that there are significant associations with the PGS and schooling attainment, but no strong evidence of significant GxE associations.[5]

To our knowledge, this is the first study to estimate associations between a PGS for depressive symptoms, schooling attainment and GxE interactions with mental health. Moreover, the comparison between Add Health and the WLS is interesting for at least two reasons. First, schooling-health gradients may differ over the life cycle. The cumulative advantage hypothesis (Ross and Wu 1996) predicts that schooling-health gaps emerge by early adulthood and widen over the life cycle as the benefits of schooling accumulate. The age-as-leveler hypothesis (Herd 2006) predicts that schooling-health gaps narrow over the life cycle, as the importance of biological determinants increase relative to the importance of schooling. The empirical evidence is consistent with the cumulative advantage hypothesis until middle age, and with biological determinants being more important in old age.[6] If schooling-mental health gaps are smaller at older ages, then one might expect smaller GxE associations in the WLS than in Add Health. Second, schooling is left-truncated at 12 grades in the WLS as it follows a sample of high school graduates. Therefore, there could be smaller schooling-mental health gradients in the WLS, and smaller GxE associations.

Our OLS results indicate that the associations of the PGS with mental health are similar in Add Health and the WLS, but mental health gradients by college graduation are much larger in Add Health than in the WLS. We find no evidence of any significant GxE associations in Add Health, but there is some suggestive evidence that the association of the PGS with mental health is lower for college graduates in the WLS. Quantile regression estimates also show that in the WLS the GxE associations are statistically significant only in the upper parts of the conditional depressive symptoms score distribution. It is difficult to draw firm conclusions from the sibling fixed-effect results, in part due to low statistical power. However, the sibling fixed-effects estimates do show that college education is associated with fewer depressive symptoms in both datasets.

The paper is organized as follows. We describe the datasets and the methodology in sections 2 and 3, respectively. We present and discuss the results in section 4. Finally, section 5 concludes.

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[5] The results from these studies cannot be given a causal interpretation because of possible omitted variable bias. A study that addresses omitted variable bias is Barcellos et al. (2018). They use the raising of the minimum school leaving age in the UK to form instruments for schooling attainment. Their instrumental variable results show robust and statistically significant negative GxE associations between schooling attainment and the PGS for BMI.

[6] For example, see Figure 1 in Galama and van Kippersluis (2013), which shows that socioeconomic health gradients exist by age 20. The gradient increases until about age 60, after which it narrows.

2. Data

2.1 The National Longitudinal Study of Adolescent Health (Add Health)

Add Health is a nationally-representative sample of 20,745 students in grades 7 through 12 (aged 12-21) in 1994-95 (wave 1). Adolescents were surveyed from 132 schools that were selected to ensure representativeness with respect to region, urbanicity, school size and type, and ethnicity. In wave 1, data were collected from adolescents, their parents, siblings, friends, relationship partners, fellow students, and school administrators. The adolescents have been followed after 1 year (wave 2, 1996), 6 years (wave 3, 2001-2002), 13 years (wave 4, 2008), and 21 years (wave 5, 2016-2018). Add Health includes oversamples of ethnic minorities, disabled students, and sibling pairs living in the same household.

We examine the relationships between genetics, schooling attainment, and mental health at wave 4.[7] Mental health is measured using the 10 item CES-D score. The CES-D score is created by summing responses (ranging from 0 to 3) to questions that asked respondents how often in the last week they (1) were bothered by things not normally bothersome; (2) could not shake the blues; (3) felt like they were not as good as others; (4) had trouble focusing; (5) were depressed; (6) were too tired to do things they enjoyed; (7) felt sad; (8) felt happy; (9) enjoyed life, and (10) felt disliked. The CES-D score ranges from 0 to 30, with higher values corresponding to poorer mental health. Depression is defined as having a score of 11 or higher (Suglia et al. 2015). Schooling attainment is based on responses to the question "what is the highest level of education that you have achieved to date?" Response options and their assigned grades of schooling (in parentheses) were: eighth grade or less (8), some high school (10), high school graduate (12), some vocational/technical training (13), completed vocational/technical training (14), some college (14), completed college (16), some graduate school (17), completed a master's degree (18), some graduate training beyond a master's degree (19), completed a doctoral degree (20), some post-baccalaureate professional education (18), and completed post-baccalaureate professional education (19).

At wave 4, 96% of participants consented to providing saliva samples. Approximately 12,200 (80% of those participants) consented to long-term archiving and were consequently eligible for genome-wide genotyping. Genotyping was done on two Illumina platforms, with approximately 80% of the sample genotyping performed with the Illumina Omni1-Quad BeadChip and 20% genotyped with the Illumina Omni2.5-Quad BeadChip. After quality-control procedures, genotyped data are available for 9,974 individuals (7,917 from the Omni1 chip and 2,057 from the Omni2 chip) on 609,130 SNPs common across both genotyping platforms.

The SSGAC created a PGS for depressive symptoms using the genetic data. Briefly, the PGS was constructed using LDpred, a Bayesian method that includes all measured SNPs and weights each SNP by an approximation to its conditional effect, given other SNPs.[8] The PGS was calculated with data from all SNPs; no statistical significance threshold was applied to restrict the SNPs that were included. The weights for the PGS are based on Multi-Trait Analysis of GWAS (MTAG; Turley et al. 2018) summary statistics. MTAG is a method that uses GWAS summary statistics for a primary phenotype (depressive symptoms in our case) and for one or more secondary phenotypes (neuroticism and subjective well-being in our case) to produce an updated set of summary statistics for the primary phenotype that, under certain assumptions, will be more precisely estimated than the input GWAS summary statistics.[9] A PGS constructed using MTAG

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[7] We do not use wave 5, as the data has not been released.

[8] Detailed information about the construction of the PGS is given by Add Health documentation at: https://www.cpc.unc.edu/projects/addhealth/documentation/guides/SSGACPGS_UsersGuide.pdf

[9] The key assumption is that all SNPs share the same variance-covariance matrix of effect sizes across traits. This assumption is violated, for example, if some SNPs influence only a subset of the traits. Turley

summary statistics has more predictive power than a PGS that employs standard GWAS summary statistics (Turley et al. 2018).

The SSGAC provides the standardized PGS for 5,690 European ancestry respondents.[10] Our final sample consists of 5,335 European ancestry individuals with non-missing information on the PGS, mental health, schooling attainment, and the control variables. The control variables are gender, age, birth order, mothers' schooling attainment, adolescent IQ, and a PGS for educational attainment constructed by the SSGAC using the MTAG method, which we use to control for unobserved ability. We measure mothers' schooling attainment using the schooling attainments of resident mothers from the wave 1 questionnaire. In order to increase the sample size, missing mothers' schooling is imputed with the sample mean, and controlled for by using a dummy variable for missing mothers' schooling.[11] Adolescent IQs are measured using the wave 1 Peabody Picture Vocabulary test.[12] Our sibling analyses are based on 457 full biological sibling pairs with non-missing information on the key variables.

2.2 The Wisconsin Longitudinal Study (WLS)

The WLS is a longitudinal study of a one-third random sample of the graduating high school class of 1957 in Wisconsin. Survey information from 10,317 of the graduates was collected at age 18 in 1957. Graduates were followed with a combination of in-person, telephone, and mail surveys at ages 36 (1975), 54 (1992-1993), 65 (2003-2004), and 72 years (2011). The WLS sample also includes information from a randomly-selected sibling (who may or may not be a high school graduate) that was collected in 1977, 1993-1994, 2004-2007, and 2011. The sample is broadly representative of white, non-Hispanic American men and women who have completed at least a high school education in Wisconsin (Herd et al. 2014). In total, 19,050 graduates and their siblings have contributed data.

We examine the relationships between genetics, schooling attainment, and mental health in 1992-1994, when mental health was first measured. Mental health is measured using the 20 item CES-D score. The scoring method in the WLS differs from the standard CES-D scoring procedure. Respondents were asked for the number of days they experienced a particular event, with options ranging from 0 to 7 days. This was converted to the standard CES-D scoring procedure by coding 0 days as 0, 1-2 days as 1, 3-4 days as 2, and 5-7 days as 3. The CES-D scale thus ranges from 0-60. Depression is defined as having a CES-D score of 22 or higher for men and 24 or higher for women (Roberts et al. 1991). Schooling attainment is measured from the 1975-1977 surveys. The WLS assigns 12 grades for graduating high school; 13 for one year of college; 14 for an associate degree; 15 for college-trained nurses; 16 for a bachelors degree;

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et al. (2018) analytically show that MTAG is still a consistent estimator, and that MTAG PGSs outperform PGSs based on standard GWAS summary statistics, even if this assumption is violated.

[10] Of the 9,974 individuals, 4,187 are of non-European ancestry and were dropped by the SSGAC. The SSGAC additionally excluded individuals who did not satisfy the following criteria: (i) genotype missingness rate is less than 0.05 in all chromosomes, (ii) there is no mismatch between surveyed sex and genetic sex, (iii) the individual is not an outlier in terms of heterozygosity/homozygosity, and (iv) the individual is not an ancestral outlier. SNPs were also dropped with a call rate less than 0.98, Hardy-Weinberg exact test P-value less than 10^{-4}, or minor allele frequency > 0.01.

[11] At wave 1, there are 20,745 individuals, and mothers' schooling is missing for 11% (2,332 individuals). For the European ancestry sample of 5690 individuals, mother's schooling is missing for 9% (503 individuals).

[12] Add Health implemented an abridged (87 items) version of the Peabody Picture Vocabulary Test (PPVT) - Revised. In the test, the interviewer reads a word aloud and the respondent selects the illustration that best fits its meaning. For example, the word "furry" has illustrations of a parrot, dolphin, frog, and cat from which to choose. The test proceeds through a series of rounds with increasing difficulty. Test scores are standardized by age with mean 100.

17 for a masters degree; 18 for a two-year masters degree; 19 for one or more years post the two-year masters degree, and 20 for a doctorate degree.

The WLS first collected saliva samples in 2007-2008 by mail. Additional samples were collected in the course of home interviews in 2010. A total of 9,472 study samples were successfully genotyped at the Center for Inherited Disease Research (CIDR) at Johns Hopkins University. Genotyping was performed at CIDR using the Illumina HumanOmniExpress array and using the calling algorithm GenomeStudio version 2011.1, Genotyping Module version 1.9.4, GenTrain Version 1.0. After quality control, genetic data are available for 9,012 respondents. Of these respondents, 64% are graduate members of the sample and 36% are siblings of graduates. The SSGAC created a PGS for depressive symptoms using the same procedure that was used with the Add Health genetic data.

The PGS is available for 8,509 respondents (5,414 graduates and 3,095 siblings). Our final sample consists of 5,521 European-ancestry individuals with non-missing information on the PGS, mental health, schooling attainment, and the control variables.[13] The control variables are gender, age, birth order, mothers' schooling attainment, adolescent IQs, and PGSs for educational attainment constructed by the SSGAC using the MTAG method. Mothers' schooling attainment comes from the graduate respondents' responses to the 1957 questionnaire. Mothers' schooling attainment is missing for siblings, who were not asked about their mothers' schooling. For siblings we impute mothers' schooling with the mothers' schooling reported by the graduates, and control for an indicator for missing mothers' schooling. Adolescent IQs are based on the Henmon-Nelson test of mental ability, which is a group-administered, 30-min, multiple-choice assessment that consists of 90 verbal or quantitative items and that all high school students in Wisconsin were required to take in their third year of high school. Our sibling analyses are based on 1,114 full biological sibling pairs with non-missing information on the key variables. We expect to have more statistical power with these data relative to the sample of siblings from Add Health given the larger sample size.

3. Methodology

We estimate associations between genetics, schooling, and GxE interactions with mental health through OLS regressions based on equation (1) in which the mental health outcome of individual i (MH_i) is related to PGSs for depressive symptoms (PGS_i), an indicator variable for being a college graduate ($CollegeGrad$), an interaction between the PGS and the college graduate indicator ($PGS_i * CollegeGrad$), a set of control variables noted above (X_i), and an error term (u_i).

(1) $MH_i = b_0 + b_1 PGS_i + b_2 CollegeGrad_i + b_3(PGS_i * CollegeGrad_i) + X_i\gamma + u_i$

Although genes are randomly inherited from parents at conception, b_1 and b_3 could be biased because of population stratification. Population stratification refers to a situation where the distribution of genes systematically differs by population subgroups (e.g. by ethnicity/race). If these subpopulations also systematically have different health outcomes that are not due to genetic make-up, then this could lead to a spurious correlation between the PGS and health. Population stratification can be controlled by limiting analyses to ethnically homogenous samples (Cardon and Palmer 2003) and by including principal components from genome-wide SNP data as control variables, which account for genetic differences across ethnic groups (Price et al. 2006). We include the first 10 principal components to control for population stratification and limit our analyses to individuals of European-ancestry. It is important to note though that the PGS may not necessarily reflect a pure genetic effect as it could be related to family environment. For example, parental genetics may influence the family environment provided to children, which in

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[13] Compared to Add Health, we lose considerably more observations in the WLS. This is because the CES-D score is only available for 6,876 respondents who also have data on the PGS.

turn may affect the outcomes employed in the creation of the PGS by MTAG. The PGS therefore may reflect the influence of both genes and family environment.

To reduce possible unobserved confounding, we estimate sibling fixed-effects regressions (equation 2) where the mental health outcome of sibling i in pair j (MH_{ij}) is related to the PGS (PGS_{ij}), the college graduate indicator ($CollegeGrad_{ij}$), an interaction between the PGS and the college graduate indicator ($PGS_{ij} * CollegeGrad_{ij}$), individual controls ($X_{ij}$), sibling fixed effects (dummy variables for each sibling pair, μ_j), and an error term (ε_{ij}).

(2) $MH_{ij} = \gamma_0 + \gamma_1 PGS_{ij} + \gamma_2 CollegeGrad_{ij} + \gamma_3(PGS_{ij} * CollegeGrad_{ij}) + X_{ij}\lambda + \mu_j + \varepsilon_{ij}$

Siblings share about 50% of their genes if mating is random (more if mating is positively assortative) and the family environment is very similar. This means that the inclusion of sibling fixed-effects controls for (i) population stratification, (ii) observed and unobserved family-level factors, and (iii) about 50% (or more) of unobserved genetic factors that may affect schooling and mental health. The variation is considered to be quasi-exogenous because differences in genotypes of full biological siblings are the outcomes of a genetic lottery (Fletcher and Lehrer 2011). Sibling fixed-effects estimates do not eliminate unobserved sibling-specific differences, and so may still be biased. Nevertheless, comparisons between OLS and sibling fixed-effects estimates may provide information about the extent to which OLS estimates are biased because of a failure to account for confounding due to the shared genes and family environment for which siblings fixed-effects estimates control.

4.   Results

4.1   Descriptive Statistics

Summary statistics for the Add Health and WLS estimation samples are in columns 1 and 4 in table 1. Add Health respondents are 29 years old on average, and WLS respondents are 53 years old. The proportion of women in both datasets is similar (53% in Add Health; 55% in the WLS). Add Health respondents have higher schooling attainment on average. They have a mean of 14.6 grades of schooling, compared to 13.8 grades for WLS respondents. The main difference is that a higher proportion of individuals have some post high-school education in Add Health. In Add Health, 44% have some (but not complete) college education and 33% are college graduates. In comparison, in the WLS only 15% have some (but not complete) college education and 30% are college graduates. Average mothers' schooling is also higher in Add Health (13.4 grades) than in the WLS (10.7 grades). The average CES-D score in Add Health is 5.88 and 10.55 in the WLS. Recall, that the CES-D scores are not directly comparable, because in Add Health the CES-D score is based on 10 items and ranges from 0-30, while the CES-D score in the WLS is based on 20 items and ranges from 0-60. A higher proportion of individuals are classified as being depressed in Add Health (15%) compared to the WLS (8%). Individuals who consented to provide genetic data may be different from those who did not give consent. In columns 2 and 5 we provide summary statistics for white individuals in Add Health and the WLS who have non-missing information on the key variables and do not have any genetic data. The summary statistics show that in Add Health white individuals who do not have any genetic data have on average slightly higher schooling attainment and better mental health compared to those who are in our estimation samples. In contrast, in the WLS individuals with no genetic data have slightly lower schooling attainment and worse mental health on average than those with genetic data.

Summary statistics for the Add Health and WLS sibling samples are given in columns 3 and 6, respectively. There are two key observations. First, the sibling samples are very similar to the full samples in terms of observed characteristics. For example, in Add Health (WLS, respectively) the average CES-D score for siblings is 5.97 (10.49), 15% (8%) are depressed, and 32% (33%) are college graduates. These summary statistics are similar to those for the estimation sample in column 1 (4). Figures 1 and 2 provide histograms of the CES-D score and depressive

symptoms PGSs for the sibling and main estimation samples. The distributions of the CES-D scores and PGSs in the sibling samples are very similar to those in the estimation samples in both datasets. The summary statistics and figures 1 and 2 suggest that the siblings samples may be random samples of the corresponding surveys' populations. Second, there is a fair amount of within-sibling variation in mental health and schooling attainment that is used to identify the sibling fixed-effects estimates. In Add Health (WLS) 22% (30%) of the sibling pairs are discordant on college graduation, and the absolute mean within-sibling difference in grades of schooling is 0.8 (1.9) grades. In terms of within-sibling differences in mental health 24% (15%) of sibling pairs are discordant on depression in Add Health (WLS), and the absolute mean within-sibling difference in the CES-D score is 2.49 (8.23) units. In terms of sample sizes, the Add Health siblings samples contains 914 siblings (457 sibling pairs) compared to 2,228 sibling (1,114 sibling pairs) in the WLS. We thus expect to have more statistical power using the WLS siblings sample.

4.2   OLS Results

The main results for the CES-D score are presented in table 2. Estimates for Add Health are in columns 1-4, and estimates for the WLS are in columns 5-8. Estimates in columns 1 and 5 show that the associations of the PGS with depressive symptoms in young adulthood and at older ages are similar. A 1 standard deviation increase in the PGS is associated with 0.119 and 0.090 standard deviation increases in the CES-D score in Add Health and the WLS, respectively. Columns 2 and 6 add the indicator variable for being a college graduate. The gradient in depressive symptoms between college and non-college graduates is much larger in young adulthood than at older ages. Conditional on the PGS, the average CES-D score for college graduates is 0.351 (0.135) of a standard deviation lower than for non-college graduates in Add Health (the WLS) The regression specification in columns 3 and 7 is the same as that in columns 2 and 6, but also controls for birth order, mothers' schooling attainment, adolescent IQ, and the education PGS. Adding these controls decreases the magnitude of the coefficient on college graduate slightly to 0.299 in Add Health. In contrast, in the WLS the average difference in the CES-D score between college and non-college graduates drops by over 50 percent to 0.056 of a standard deviation and is statistically significant only at the 10 percent level. Columns 4 and 8 add the interaction between the college graduate indicator and the PGS. The coefficient estimates of the interaction terms provide suggestive evidence that higher schooling attenuates the genetic predisposition of poor mental health at older ages but not in young adulthood. The estimates for the WLS in column 8 indicate that a 1 standard deviation increase in the PGS is associated with a 0.048 (=0.111-0.063) standard deviation increase in the CES-D score for college graduates, and a 0.111 standard deviation increase for non-college graduates, and this difference is statistically significant. In contrast, the GxE interaction coefficient for Add Health in column 4 is much smaller (-0.011) than in the WLS (-0.063) and statistically insignificant.

Results for depression are given in table 3. There are 3 important observations. First, a 1 standard deviation increase in the PGS is associated with a 2.9 (2.3) percentage point increase in the probability of being depressed in Add Health (the WLS) in column 1 (5). The percentage effect relative to the sample mean is much smaller in Add Health (8%) than in the WLS (28%), but the percentage effect relative to the sample standard deviation is similar in both datasets (8% in Add Health and 7% in the WLS). Second, the difference in the likelihood of depression by college graduation is 4 times larger in Add Health (-0.087, column 3) than in the WLS (-0.022, column 7). Third, there is some suggestive evidence of higher schooling attainment attenuating the genetic predisposition of depression at older ages but not in young adulthood. The coefficient estimate of the GxE interaction is negative and statistically significant at the 1% level in the WLS, whereas it is small in magnitude and statistically insignificant in Add Health. In particular, for the WLS in column 8, a 1 standard deviation increase in the PGS is associated with a 3.2 percentage point increase in the probability of being depressed for non-college graduates, but only a 0.005 (=0.032-0.027) percentage point increase for college graduates.

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The GxE associations could vary by gender. The resource substitution theory (Ross & Mirowsky 2006) hypothesizes schooling has a greater beneficial effect on the health of women than men, because women have fewer resources and opportunities. Accordingly, as women are more dependent upon schooling, GxE interactions are hypothesized to be stronger for women than men. In contrast, the resource multiplication theory (Ross & Mirowsky 2006) suggests that GxE interactions are stronger for men, because schooling multiplies with other resources that they have. Gender stratified results are shown in table 4, and the estimates do not reveal any statistically significant gender differences in the GxE associations.

Table 5 presents results using a nonlinear specification for the PGS. In particular, we use dummy variables indicating whether the individual is in the 1st, 2nd, 3rd (reference category), 4th, or 5th quintile of the PGS distribution. The results from the nonlinear PGS specifications show that individuals with a low (high) genetic predisposition have fewer (more) depressive symptoms relative to individuals in the middle of the PGS distribution in both datasets. For example, in Add Health the estimates in column 1 indicate that individuals in the 1st quintile of the PGS distribution have a CES-D score that is on average 0.164 standard deviations lower than individuals in the 3rd quintile. In contrast, individuals in the 5th quintile have a CES-D score that is on average 0.123 standard deviations higher than individuals in the 3rd quintile. The estimates in column 3 for the WLS show that the average difference in the CES-D score between individuals in the 1st and 3rd (5th and 3rd) quintiles is -0.067 (0.177) standard deviations. The nonlinear specification gives relatively similar results for depression. In Add Health (column 5) there is a statistically negative difference (-3.8 percentage points) in the probability of depression between individuals in the 1st and 3rd quintiles, and a positive (although insignificant) estimated difference between individuals in the 5th and 3rd quintiles. For the WLS (column 7), there is a statistically positive difference in the likelihood of depression (6.2 percentage points) between individuals in the 5th and 3rd quintile, and a negative (although insignificant) estimated difference between individuals in the 1st and 3rd quintiles. However, there is no strong evidence that the GxE associations for the CES-D score and depression significantly differs for individuals in the 1st and 5th quintile relative to individuals in the 3rd quintile.

Table 6 show results from quantile regressions to investigate whether there are any heterogeneous associations along the conditional CES-D score distribution. In both datasets, the association of the PGS is much larger in upper parts of the conditional CES-D score distribution. For example, conditional on college graduation, a 1 standard deviation increase in the PGS is associated with about a 0.11 standard deviation increase in the CES-D score at the 75th conditional percentile (column 5), and about a 0.21 standard deviation increase at the 90th conditional percentile (column 7) in both datasets. In Add Health, the gap in the CES-D score between college and non-college graduates is also larger in upper parts of the conditional CES-D score distribution. In comparison, in the WLS there is no consistent increase in the (absolute) difference in the CES-D score by college graduation. However, in the WLS there is some suggestive evidence of higher schooling attainment moderating genetic predisposition. Specifically, there are negative and statistically significant GxE associations at the 75th and 90th percentiles of the conditional CES-D score distribution, which are also fairly large in magnitude. For example, column 8 (6) in table 6 indicates that the marginal association of the PGS with the CES-D score is 0.222 (0.100) standard deviations smaller for college graduates at the 90th (75th) percentile than for non-college graduates.[14]

Overall, the OLS results show that there are large associations of the PGS with mental health, and large differences in mental health by college graduation in both datasets. There is

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[14] We tested whether the GxE coefficient estimates from the quantile regressions in table 6 are statistically different from each other across quantiles. In the WLS, we rejected the null hypothesis that the GxE coefficients are equal to each other. We could not reject the null hypothesis of the equality of GxE coefficients for Add Health.

some suggestive evidence of GxE associations in the WLS, but no consistent evidence in Add Health. The findings do not change if we measure schooling attainment using grades of schooling (results provided in appendix tables A1-A4) instead of the college graduate indicator. However, since there may be unobserved confounders left uncontrolled, the OLS estimates may be biased. We now turn to the sibling fixed-effects analyses, which control for unobserved family-level factors and about 50% of unobserved genetic factors that might bias the OLS estimates. On the other hand, focusing on siblings implies giving up statistical power, as the size of the siblings' samples is smaller.

4.3   Sibling Fixed-Effects Results

OLS and sibling fixed-effects results are shown in table 7. Panel A presents results for the CES-D score and panel B shows results for depression. The OLS and sibling fixed-effects estimates in columns 1 and 3 show that conditional on schooling attainment the PGS is not statistically significantly associated with depressive symptoms or depression in Add Health. In comparison, the OLS estimate for the WLS in column 5 shows that conditional on schooling attainment, a 1 standard deviation increase in the PGS is associated with a 0.096 standard deviation increase in the CES-D score and a 2.3 percentage point increase in the probability of being depressed. These OLS estimates are similar to the corresponding OLS estimates in tables 2 and 3 column 7 for the full estimation sample, which showed that 1 standard d a 0.093 standard deviation increase in the CES-D score and a 2.4 percentage point increase in the probability of being depressed conditional on schooling attainment. The sibling fixed-effects estimate in column 7 are slightly larger. A 1 standard deviation increase in the PGS is associated with a 0.121 standard deviation increase in the CES-D score and a 3.1 percentage point increase in the probability of being depressed, conditional on schooling attainment.

In terms of schooling attainment, the OLS results show that on average college graduates have a lower CES-D score and are less likely to be depressed than non-college graduates in both datasets. The sibling fixed-effects results in column 3 and 7 indicate that there is no significant difference in the likelihood of depression by college graduation in Add Health and the WLS. However, being a college graduate is still significantly associated with a lower CES-D score, even when controlling for unobserved family and shared genetic factors. Moreover, the magnitude of the sibling fixed-effects estimate (0.325) for the college graduate indicator is almost the same as the corresponding OLS estimate (0.334) in Add Health, and it is also similar to that for the corresponding estimate for the full sample in table 2 column 3 (-0.299). In the WLS, the sibling fixed-effects estimate (0.125) is twice the size of the OLS estimate (0.050). In both datasets, there is no strong evidence of any GxE associations, which are negative but statistically insignificant in OLS and sibling fixed-effect models.

Overall, for Add health, it is difficult to draw firm conclusions about GxE associations from the sibling fixed-effects estimates because the PGS is not associated with mental health in OLS models. One possible reason for this could be that the Add Health sibling pairs are a selected sample. However, the descriptive statistics in table 1 suggest that the sibling pairs are similar in terms of observed characteristics to individuals in the main estimation sample. We checked whether there are any statistically significant differences in schooling attainment, mental health, and background characteristics between the Add Health sibling pair sample and the Add Health estimation sample excluding siblings. Appendix table A5 shows that there are no statistically significant differences in schooling attainment or mental health.[15] There is however a statistically significant difference in adolescent IQ, with siblings having a slightly lower IQ score. Nevertheless, the OLS estimates for the siblings sample show statistically significant mental health gradients by

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[15] We also performed Kolmogornov-Smirnov tests for equality of distributions. We cannot reject the null hypotheses that the CES-D score, grades of schooling, and PGS distributions between the Add Health sibling sample and the Add Health main estimation sample (excluding siblings) are equal.

college graduation that are similar in magnitude to those for the main estimation sample. Another possible reason could be low statistical power given that the sample size is relatively small.

Regarding the WLS, the siblings fixed-effects results indicate that the PGS is associated with mental health but the GxE associations are statistically insignificant. This could also be due to low power. We note that the point estimates of the GxE associations in the sibling fixed-effects models are similar in magnitude to the GxE associations in the OLS analyses for the main estimation sample in section 4.2. For example, in the OLS analyses with the main estimation sample the estimate of the GxE interaction (standard error) for depressive symptoms was -0.063 (0.028) in table 2 column 8. The corresponding sibling fixed-effects estimate in table 7 column 8 is similar in magnitude (-0.073), but the standard error is more than double (0.062). Similarly, the sibling fixed-effects GxE estimate for depression (-0.023) is similar to the corresponding OLS estimate for the full sample (-0.027; table 3 column 8), but the higher standard error renders it insignificant. This may point to the lack of a statistical significance finding for the GxE associations in the sibling fixed-effects models being possibly driven more by the decrease in precision (low power) than by the OLS estimates being severely biased. This, however, cannot be determined with certainty.

Appendix table A6 shows OLS and sibling fixed-effect results using grades of schooling. While the findings are similar, it is interesting that the sibling fixed-effect estimates show that a college education is associated with fewer depressive symptoms even when controlling for shared family characteristics, but there is no association for grades of schooling.

5.   Conclusions

The diathesis-stress and the differential susceptibility theories for genetic influences on health suggest that higher schooling attainment may attenuate the genetic predisposition to poor health. A few studies have investigated this hypothesis for BMI and obesity (Amin et al. 2017; Liu et al; 2015; Komulainen et al. 2018). OLS results from these studies show statistically insignificant GxE associations. We contribute by examining this hypothesis for mental health in two distinct US datasets (Add Health and the WLS) at different adult ages. To our knowledge, this is the first study to provide estimates of the associations of genetics, schooling attainment, and GxE interactions with mental health.

Our OLS results indicate that the associations of the PGS with mental health are similar in Add Health and the WLS, but the mental health gradients by college graduation are much larger in Add Health than in the WLS. That the college-mental health gradient is smaller in the WLS is not surprising because the majority of respondents in the WLS are high school graduates. There is some suggestive evidence that the association of the PGS with mental health is lower for college graduates in the WLS, but there is no evidence of any significant GxE associations in Add Health. Our results from quantile regressions indicate that the GxE associations are larger and statistically significant in the upper part of the conditional CES-D score distribution. We assess the robustness of the OLS results to potential omitted variable bias by using the siblings samples in both datasets to estimate sibling fixed-effect regressions. It is difficult to draw firm conclusions from the sibling fixed-effects results, in part due to low statistical power. However, the sibling fixed-effects estimates show that college education is associated with fewer depressive symptoms in both datasets. Thus, the evidence differs between the two data sets, with fairly robust results concerning significant associations between PGS and schooling attainment and mental health, as well as suggestive evidence for protective effects of more schooling, for the WLS—but not robust significant results for PGS or for GxE associations for Add Health. Given the different ages of the two groups, this raises the question of whether the associations with PGS and schooling-PGS interactions are revealed only in mature adulthood. This suggests the value of future research to investigate the age-dependence of such associations over a broader age range.

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Table 1: Summary Statistics

	Add Health Estimation Sample	Add Health Whites Sample with no genetic data	Add Health Sibling Sample	WLS Estimation Sample with no genetic data	WLS Whites Sample	WLS Sibling Sample
	(1)	(2)	(3)	(4)	(5)	(6)
Basic Demographics						
Age	28.98 (1.73)	28.96 (1.72)	29.00 (1.69)	53.12 (3.24)	53.63 (4.37)	53.09 (4.69)
Female	0.53 (0.50)	0.53 (0.50)	0.53 (0.50)	0.55 (0.50)	0.55 (0.50)	0.55 (0.50)
Mental Health						
CES-D Score	5.88 (4.70)	5.75 (4.59)	5.97 (4.98)	10.55 (8.80)	11.33 (9.47)	10.49 (8.43)
Depressed	0.15 (0.36)	0.14 (0.35)	0.15 (0.36)	0.08 (0.28)	0.10 (0.31)	0.08 (0.27)
PGS for depressive symptoms	0.00 (1.00)	---	0.00 (1.00)	0.00 (1.00)	---	0.00 (1.00)
Schooling Attainment						
Grades of Schooling	14.56 (2.18)	14.89 (2.18)	14.46 (2.24)	13.76 (2.33)	13.44 (2.18)	13.91 (2.40)
High school dropout	0.07 (0.26)	0.06 (0.23)	0.09 (0.28)	0.01 (0.07)	0.01 (0.10)	0.01 (0.10)
High school graduate	0.16 (0.37)	0.14 (0.35)	0.17 (0.38)	0.55 (0.50)	0.60 (0.49)	0.51 (0.50)
Some college	0.44 (0.50)	0.41 (0.49)	0.42 (0.49)	0.15 (0.36)	0.16 (0.36)	0.16 (0.37)
College graduate	0.33 (0.47)	0.39 (0.49)	0.32 (0.47)	0.30 (0.46)	0.23 (0.42)	0.33 (0.47)
Education PGS	0.00 (1.00)	---	0.00 (1.00)	0.00 (1.00)	---	0.00 (1.00)
Individual and Family Background Characteristics						
IQ	104.39 (11.73)	105.50 (12.45)	103.97 (11.42)	103.93 (14.68)	101.56 (15.12)	104.96 (14.78)
Birth order	1.77 (1.04)	1.71 (0.99)	2.02 (1.11)	2.36 (1.65)	2.32 (1.63)	2.43 (1.61)
Mothers' grades of schooling	13.39 (1.97)	13.57 (2.01)	13.36 (1.85)	10.73 (2.96)	10.72 (2.97)	10.79 (3.02)
Mothers' schooling missing	0.09 (0.28)	0.08 (0.28)	0.07 (0.20)	0.23 (0.42)	0.36 (0.48)	0.50 (0.50)
Within-Sibling Differences						
% of sibling pairs discordant on						
Depression			24%			15%
College graduate			22%			30%
Absolute mean within-sibling difference						
In grades of schooling			0.82 (0.84)			1.85 (2.04)
In CES-D Score			2.49 (2.18)			8.23 (7.70)
N	5335	2779	914	5521	3344	2228

Notes: Standard deviations in parentheses.

Figure 1: Histogram of CES-D Score
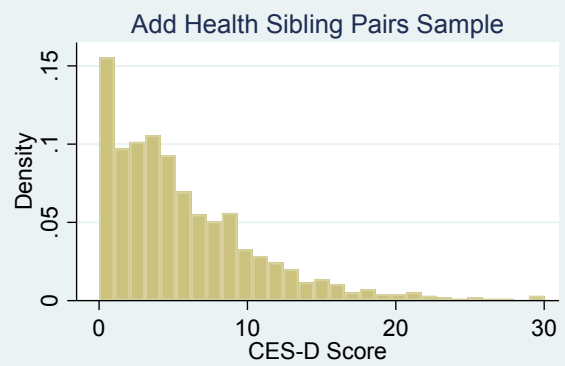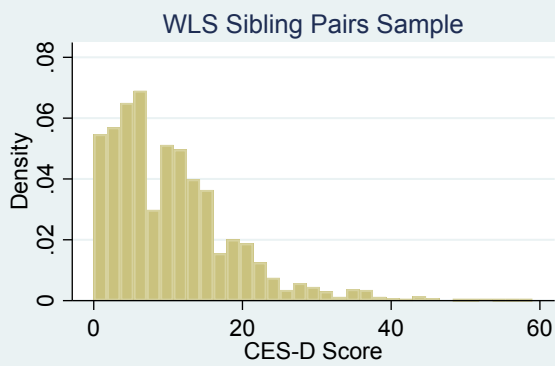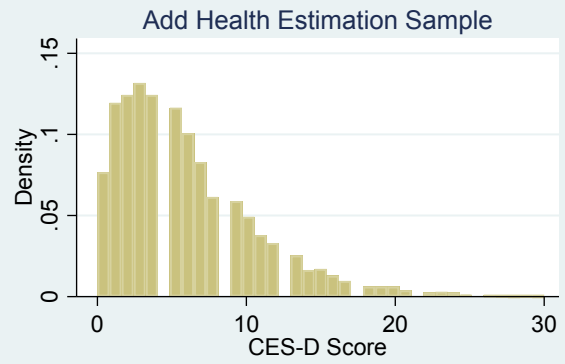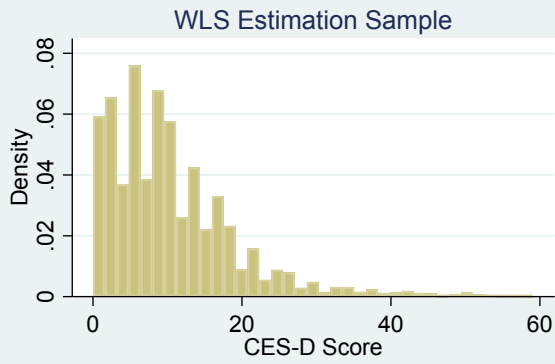
Figure 2: Histogram of PGS for Depressive Symptoms

Table 2: OLS Associations of the PGS, College Graduation, and GxE Interactions with the CES-D Score in Add Health and the WLS

	Add Health				WLS			
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Genetics								
PGS	0.119***	0.096***	0.099***	0.102***	0.090***	0.087***	0.093***	0.111***
	(.013)	(.014)	(.013)	(.017)	(.014)	(.014)	(.014)	(.017)
Schooling Attainment								
College Graduate		-0.351***	-0.299***	-0.301***		-0.135***	-0.056*	-0.059*
		(.028)	(.030)	(.030)		(.028)	(.031)	(.031)
GxE								
PGS*Grades of schooling				-0.011				-0.063**
				(.027)				(.028)
N	5335	5335	5335	5335	5521	5521	5521	5521

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. All regressions include year of birth indicators, a dummy variable for being female, and the first 10 principal components. Regressions in columns 3, 4, 7 and 8 additionally control for birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Table 3: OLS Associations of the PGS, College Graduation, and GxE Interactions with Depression in Add Health and the WLS

	Add Health				WLS			
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Outcome Mean	0.15	0.15	0.15	0.15	0.08	0.08	0.08	0.08
Genetics								
PGS	0.029***	0.023***	0.024***	0.025**	0.023***	0.022***	0.024***	0.032***
	(.005)	(.005)	(.005)	(.006)	(.004)	(.004)	(.004)	(.005)
Schooling Attainment								
College Graduate		-0.102***	-0.087***	-0.087***		-0.038***	-0.022***	-0.024***
		(.010)	(.011)	(.011)		(.008)	(.008)	(.002)
GxE								
PGS*Grades of schooling				-0.003				-0.027***
				(.009)				(.008)
N	5335	5335	5335	5335	5521	5521	5521	5521

Notes: All regressions include year of birth indicators, a dummy variable for being female, and the first 10 principal components. Regressions in columns 3, 4, 7 and 8 additionally control for birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Table 4: OLS Associations of the PGS, College Graduation, and GxE Interactions with Mental Health in Add Health and the WLS, by Gender

	Add Health				WLS			
	DEP Men (2)	DEP Women (2)	CES-D Men (3)	CES-D Women (4)	DEP Men (5)	DEP Women (6)	CES-D Men (7)	CES-D Women (8)
Outcome Mean	0.12	0.18	0.00	0.00	0.08	0.09	0.00	0.00
Genetics								
PGS	0.019**	0.030***	0.103***	0.104***	0.025***	0.037***	0.105***	0.118***
	(.008)	(.009)	(.025)	(.024)	(.007)	(.007)	(.026)	(.023)
Schooling Attainment								
College graduate	-0.054**	-0.112***	-0.259***	-0.324***	-0.023*	-0.027**	-0.046	-0.090**
	(.015)	(.015)	(.046)	(.041)	(.012)	(.012)	(.046)	(.044)
GxE								
Depression PGS*College	-0.008	0.003	-0.053	0.016	-0.024**	-0.027**	-0.062	-0.060
	(.012)	(.013)	(.041)	(.035)	(.011)	(.011)	(.041)	(.039)
N	2508	2508	2017	2827	2498	3023	2498	3023

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1.   All regressions include year of birth indicator, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, a PGS for educational attainment, and the first 10 principal components. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Table 5: OLS Associations of the PGS, College Graduation, and GxE Interactions with Mental Health in Add Health and the WLS, by PGS Quintile

	CES-D Score				Depression			
	Add Health (1)	Add Health (2)	WLS (3)	WLS (4)	Add Health (5)	Add Health (6)	WLS (7)	WLS (8)
Genetics								
PGS 1st quintile	-0.164***	-0.175***	-0.067*	-0.092*	-0.038**	-0.042**	-0.011	-0.018
	(.040)	(.055)	(.039)	(.050)	(.015)	(.020)	(.011)	(.013)
PGS 2nd quintile	-0.078*	-0.053	-0.012	-0.042	-0.019	-0.011	-0.010	0.003
	(.041)	(.055)	(.041)	(.050)	(.015)	(.020)	(.011)	(.014)
PGS 4th quintile	0.025	0.033	0.105**	0.120**	0.018	0.023	0.024**	0.029*
	(.044)	(.056)	(.042)	(.052)	(.016)	(.021)	(.012)	(.015)
PGS 5th quintile	0.123***	0.134***	0.177***	0.181***	0.026	0.030	0.062***	0.073***
	(.044)	(.056)	(.044)	(.054)	(.016)	(.021)	(.013)	(.016)
Schooling Attainment								
College graduate	-0.300***	-0.280***	-0.059*	-0.083	-0.087***	-0.079***	-0.023***	-0.020
	(.030)	(.078)	(.031)	(.058)	(.011)	(.017)	(.008)	(.016)
GxE								
PGS 1st quintile* College graduate		0.024		0.075		-0.010		0.020
		(.078)		(.079)		(.028)		(.021)
PGS 2nd quintile* College graduate		-0.070		0.100		-0.022		0.022
		(.078)		(.085)		(.029)		(.023)
PGS 4th quintile* College graduate		-0.023		-0.048		-0.015		-0.018
		(.088)		(.085)		(.032)		(.023)
PGS 5th quintile* College graduate		-0.036		-0.017		-0.014		-0.043*
		(.088)		(.090)		(.032)		(.025)
N	5335	5335	5521	5521	5335	5335	5521	5521

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. . The indicator for the 3rd quintile of the PGS distribution is the reference category. All regressions include year of birth indicators, a dummy variable for being female, the first 10 principal components, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Table 6: Quantile Regressions Associations of the PGS, College Graduation and GxE interactions with the CES-D score in Add Health and the WLS

	25th (1)	25th (2)	50th (3)	50th (4)	75th (5)	75th (6)	90th (7)	90th (8)
Panel A: Add Health								
Genetics								
PGS	0.056***	0.055***	0.088***	0.108***	0.113***	0.130***	0.212***	0.199***
	(.012)	(.016)	(.015)	(.019)	(.022)	(.027)	(.033)	(.041)
Schooling Attainment								
College Graduate	-0.139***	-0.139***	-0.253***	-0.262***	-0.462***	-0.402***	-0.528***	-0.512***
	(.028)	(.028)	(.034)	(.035)	(.050)	(.049)	(.080)	(.086)
GxE								
PGS*College Graduate		-0.001		-0.042		-0.034		0.035
		(.024)		(.030)		(.043)		(.064)
N	5335	5335	5335	5335	5335	5335	5335	5335
Panel B: WLS								
Genetics								
PGS	0.034***	0.041***	0.077***	0.081***	0.106***	0.147***	0.216***	0.260***
	(.010)	(.012)	(.012)	(.015)	(.016)	(.020)	(.028)	(.031)
Schooling Attainment								
College graduate	-0.009	-0.013	-0.001	-0.002	-0.056	-0.064*	-0.178***	-0.209***
	(.022)	(.021)	(.031)	(.033)	(.037)	(.026)	(.070)	(.073)
GxE								
PGS*College graduate		-0.020		-0.016		-0.100***		-0.222***
		(.019)		(.027)		(.032)		(.064)
N	5521	5521	5521	5521	5521	5521	5521	5521

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. All regressions include year of birth indicators, a dummy variable for being female, the first 10 principal components, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Table 7: OLS and Sibling Fixed-Effects Associations of the PGS, College Graduation, and GxE interactions with Mental Health in Add Health and the WLS

	Add Health				WLS			
	OLS (1)	OLS (2)	FE (3)	FE (4)	OLS (5)	OLS (6)	FE (7)	FE (8)
Panel A: CES-D Score								
Genetics								
PGS	0.035	0.049	0.008	0.035	0.096***	0.121***	0.104***	0.127***
	(.032)	(.041)	(.058)	(.072)	(.022)	(.027)	(.040)	(.045)
Schooling Attainment								
College graduate	-0.334***	-0.338***	-0.325***	-0.328***	-0.050	-0.054	-0.125*	-0.125*
	(.076)	(.076)	(.109)	(.110)	(.046)	(.045)	(.069)	(.068)
GxE								
PGS*College graduate	---	-0.044	---	-0.079	---	-0.077*	---	-0.073
		(.058)		(.090)		(.044)		(.062)
Panel B: Depressed								
Genetics								
PGS	0.010	0.014	0.009	0.027	0.023***	0.031***	0.036***	0.043***
	(.012)	(.015)	(.023)	(.029)	(.006)	(.008)	(.012)	(.014)
Schooling Attainment								
College Graduate	-0.086***	-0.087***	-0.070	-0.072	-0.022*	-0.023*	0.026	-0.026
	(.028)	(.028)	(.051)	(.051)	(.013)	(.013)	(.021)	(.021)
GxE								
PGS*College Graduate	---	-0.014	---	-0.053	---	-0.023		-0.023
		(.020)		(.038)		(.013)		(.018)
N	914	914	914	914	2228	2228	2228	2228

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. All regressions include year of birth indicators, a dummy variable for being female, the first 10 principal components, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors clustered by sibling pairs in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Appendix Table A1: OLS Associations of the PGS, Grades of Schooling, and GxE Interactions with Mental Health in Add Health and the WLS

	Add Health				WLS			
	CES-D (1)	CES-D (2)	DEP (3)	DEP (4)	CES-D (5)	CES-D (6)	DEP (7)	DEP (8)
Outcome Mean	0.00	0.00	0.15	0.15	0.00	0.00	0.08	0.08
Genetics								
PGS	0.098***	0.083***	0.023***	0.019***	0.093***	0.108***	0.024***	0.032***
	(.013)	(.021)	(.005)	(.009)	(.014)	(.018)	(.128)	(.005)
Schooling Attainment								
Grades of Schooling	-0.085***	-0.085***	-0.026***	-0.026***	-0.006	-0.006	-0.003*	-0.003*
	(.007)	(.007)	(.003)	(.003)	(.007)	(.007)	(.002)	(.002)
GxE								
PGS*Grades of Schooling		0.006		0.002		-0.008		-0.005**
		(.006)		(.002)		(.006)		(.002)
N	5335	5335	5335	5335	5521	5521	5521	5521

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. Grades of schooling is centered on 12 grades. All regressions include year of birth indicators, a dummy variable for being female, the first 10 principal components, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Appendix Table A2: OLS Associations of the PGS, Grades of Schooling, and GxE Interactions with Mental Health in Add Health and the WLS, by Gender

	Add Health				WLS			
	DEP Men (1)	DEP Women (2)	CES-D Men (3)	CES-D Women (4)	DEP Men (5)	DEP Women (6)	CES-D Men (7)	CES-D Women (8)
Outcome Mean	0.12	0.18	0.00	0.00	0.08	0.09	0.00	0.00
Genetics								
PGS	0.016	0.021	0.090***	0.076**	0.025***	0.038***	0.097***	0.116***
	(.011)	(.013)	(.030)	(.031)	(.007)	(.007)	(.027)	(.024)
Schooling Attainment								
Grades of Schooling	-0.018***	-0.034***	-0.078***	-0.093***	-0.004*	-0.004	-0.006	-0.013
	(.004)	(.004)	(.011)	(.010)	(.002)	(.003)	(.009)	(.010)
GxE								
PGS*Grades of Schooling	0.000	0.003	-0.001	0.012	-0.004**	-0.005**	-0.006	-0.009
	(.003)	(.004)	(.001)	(.008)	(.002)	(.003)	(.007)	(.009)
N	2508	2827	2508	2827	2498	3023	2498	3023

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. Grades of schooling is centered on 12 grades. All regressions include year of birth indicator, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, a PGS for educational attainment, and the first 10 principal components. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Appendix Table A3: OLS Associations of the PGS, Grades of Schooling, and GxE Interactions with Mental Health in Add Health and the WLS, by PGS Quintile

	CES-D Score				Depression			
	Add Health (1)	Add Health (2)	WLS (3)	WLS (4)	Add Health (5)	Add Health (6)	WLS (7)	WLS (8)
Genetics								
PGS 1st quintile	-0.162***	-0.131*	-0.069*	-0.090*	-0.037**	-0.021	-0.011	-0.017
	(.040)	(.073)	(.039)	(.053)	(.015)	(.028)	(.010)	(.014)
PGS 2nd quintile	-0.078*	0.042	-0.013	-0.037	-0.019	0.019	0.010	-0.001
	(.040)	(.071)	(.041)	(.052)	(.015)	(.028)	(.011)	(.014)
PGS 4th quintile	0.026	0.074	0.104**	0.110*	0.018	0.042	0.024**	0.029*
	(.044)	(.074)	(.042)	(.055)	(.017)	(.028)	(.012)	(.016)
PGS 5th quintile	0.122**	0.144**	0.177***	0.176***	0.025	0.034	0.062***	0.074***
	(.044)	(.070)	(.044)	(.056)	(.016)	(.027)	(.013)	(.016)
Schooling Attainment								
Grades of schooling	-0.085***	-0.068***	-0.007	-0.011	-0.026***	-0.019***	-0.003*	-0.003
	(.007)	(.015)	(.006)	(.012)	(.003)	(.005)	(.002)	(.003)
GxE								
PGS 1st quintile*		-0.012		0.011		-0.006		0.003
Grades of schooling		(.020)		(.016)		(.007)		(.004)
PGS 2nd quintile*		-0.045**		0.014		-0.014*		0.006
Grades of schooling		(.019)		(.017)		(.007)		(.005)
PGS 4th quintile*		-0.018		-0.003		-0.009		-0.003
Grades of schooling		(.022)		(.017)		(.008)		(.005)
PGS 5th quintile*		-0.007		0.000		-0.003		-0.008
Grades of schooling		(.020)		(.018)		(.007)		(.005)
N	5335	5335	5521	5521	5335	5335	5521	5521

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. The indicator for the 3rd quintile of the PGS distribution is the reference category. Grades of schooling is centered on 12 grades. All regressions include year of birth indicators, a dummy variable for being female, the first 10 principal components, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 10%

Appendix Table A4: Quantile Regressions Associations of the PGS, Grades of Schooling and GxE interactions with the CES-D score in Add Health and the WLS

	25th (1)	25th (2)	50th (3)	50th (4)	75th (5)	75th (6)	90th (7)	90th (8)
Panel A: Add Health								
Genetics								
PGS	0.060***	0.062***	0.092***	0.102***	0.106***	0.085***	0.211***	0.161***
	(.012)	(.018)	(.015)	(.027)	(.020)	(.028)	(.029)	(.052)
Schooling Attainment								
Grades of schooling	-0.048***	-0.048***	-0.079***	-0.081***	-0.122***	-0.121***	-0.158***	-0.151***
	(.006)	(.006)	(.008)	(.008)	(.011)	(.011)	(.018)	(.018)
GxE								
PGS*Grades of schooling		-0.001		-0.003		0.007		0.019
		(.005)		(.007)		(.007)		(.013)
N	5335	5335	5335	5335	5335	5335	5335	5335
Panel B: WLS								
Genetics								
PGS	0.005***	0.041***	0.075***	0.078***	0.106***	0.148***	0.222***	0.248***
	(.010)	(.013)	(.013)	(.017)	(.015)	(.019)	(.029)	(.036)
Schooling Attainment								
Grades of schooling	-0.001	-0.000	0.002	0.003	-0.000	-0.001***	-0.020***	-0.028*
	(.004)	(.005)	(.008)	(.006)	(.007)	(.007)	(.014)	(.014)
GxE								
PGS*Grades of schooling		-0.003		-0.002		-0.019***		-0.022*
		(.004)		(.005)		(.007)		(.013)
N	5521	5521	5521	5521	5521	5521	5521	5521

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. Grades of schooling is centered on 12 grades. All regressions include year of birth indicators, a dummy variable for being female, the first 10 principal components, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors in parentheses. ***significant at 1% **significant at 5% *significant at 1

Appendix Table A5: Comparison of Add Health Sibling Pair Sample and Add Health Main Estimation Sample Excluding Siblings

	Add Health Estimation Sample excluding siblings (1)	Add Health Sibling Pair Sample (2)	P-value (3)
Grades of Schooling	14.57 (0.033)	14.46 (0.074)	0.1448
College Graduate	0.33 (0.007)	0.32 (0.015)	0.6636
CES-D Score	5.87 (0.070)	5.97 (0.105)	0.5295
Depressed	0.15 (0.005)	0.15 (0.012)	0.7808
Adolescent IQ	105.13 (0.17)	103.97 (0.38)	0.006
Mothers' grades of schooling	13.40 (0.03)	13.36 (0.06)	0.5212
N	4421	914	

Notes: Standard errors in parentheses.

Appendix Table A6: OLS and Sibling Fixed-Effects Associations of the PGS, Grades of Schooling, and GxE interactions with Mental Health in Add Health and the WLS

	Add Health				WLS			
	OLS (1)	OLS (2)	FE (3)	FE (4)	OLS (5)	OLS (6)	FE (7)	FE (8)
Panel A: CES-D Score								
Genetics								
PGS	0.042	0.051	0.011	0.030	0.096***	0.113***	0.107***	0.116**
	(.033)	(.046)	(.058)	(.089)	(.022)	(.128)	(.040)	(.046)
Schooling Attainment								
Grades of schooling	-0.056***	-0.056***	-0.013	-0.012	-0.003	-0.003	-0.007	-0.007
	(.017)	(.017)	(.029)	(.029)	(.010)	(.010)	(.015)	(.010)
GxE								
PGS*Grades of schooling	---	-0.004	---	-0.008	---	-0.009	---	-0.005
		(.013)		(.025)		(.009)		(.012)
Panel B: Depressed								
Genetics								
PGS	0.011	0.017	0.010	0.040	0.023***	0.031***	0.037***	0.043***
	(.012)	(.019)	(.023)	(.035)	(.006)	(.008)	(.012)	(.014)
Schooling Attainment								
Grades of schooling	-0.020***	-0.020***	-0.001	0.000	-0.003	-0.003	0.000	0.000
	(.006)	(.006)	(.012)	(.012)	(.003)	(.003)	(.004)	(.004)
GxE								
PGS*Grades of schooling	---	-0.002	---	-0.012	---	-0.004		-0.004
		(.005)		(.009)		(.002)		(.002)
N	914	914	914	914	2228	2228	2228	2228

Notes: The CES-D score is normalized to have a mean of 0 and standard deviation of 1. Grades of schooling is centered on 12 grades. All regressions include year of birth indicators, a dummy variable for being female, the first 10 principal components, birth order, adolescent IQ, mothers' schooling, an indicator for missing mothers' schooling, and a PGS for educational attainment. Robust standard errors clustered by sibling pairs in parentheses. ***significant at 1% **significant at 5% *significant at 10%