Polygenic Risk of Mental Disorders and Subject-Specific School Grades


ABSTRACT

BACKGROUND: Education is essential for socioeconomic security and long-term mental health; however, mental disorders are often detrimental to the educational trajectory. Genetic correlations between mental disorders and educational attainment do not always align with corresponding phenotypic associations, implying heterogeneity in the genetic overlap.

METHODS: We unraveled this heterogeneity by investigating associations between polygenic risk scores for 6 mental disorders and fine-grained school outcomes: school grades in language and mathematics in ninth grade and high school, as well as educational attainment by age 25, using nationwide-representative data from established cohorts (N = 79,489).

RESULTS: High polygenic liability of attention-deficit/hyperactivity disorder was associated with lower grades in language and mathematics, whereas high polygenic risk of anorexia nervosa or bipolar disorder was associated with higher grades in language and mathematics. Associations between polygenic risk and school grades were mixed for schizophrenia and major depressive disorder and neutral for autism spectrum disorder.

CONCLUSIONS: Polygenic risk scores for mental disorders are differentially associated with language and mathematics school grades.

https://doi.org/10.1016/j.biopsych.2023.11.020

Mental disorders are common and are associated with poor long-term health outcomes, decreased participation in the workforce, and increased mortality (1–3). Educational attainment represents a key factor in this context, being both strongly linked to mental disorders and predictive of long-term health (4). The educational trajectory begins during childhood when school performance is associated with future educational attainment (5) and socioeconomic position (6). Mental disorders also often have their onsets early in life (2) and may affect the educational trajectory either directly (e.g., if illness affects school attendance) or indirectly (e.g., through pre-morbid neurocognitive impairment) (7,8). Mental health problems at school entry (age ~6 years) have been shown to be predictive of poorer school performance in fourth grade (age ~10 years) (9), and individuals with mental disorders have been found to have a lower likelihood of passing an exit examination of compulsory schooling and get lower grades than their peers without mental disorders (10). An exception to this is anorexia nervosa (AN). Individuals diagnosed with AN have a lower likelihood of taking ninth grade examinations, but those who do tend to obtain higher grades than individuals without AN (10). Moreover, high or low school performance may be associated with subsequent illness. For example, individuals with poor school performance have a higher risk of developing schizophrenia (SCZ) (11). Intriguingly, individuals with very good school performance have a higher risk of developing bipolar disorder (BD) (12,13) later in life—a paradoxical finding given that individuals diagnosed with BD display poorer school performance on average. These findings suggest a complex relationship between mental disorders and school performance that requires closer inspection.

Genetic studies are providing new insight into the relationship between mental disorders and educational attainment. Large-scale genome-wide association studies (GWASs) have been conducted for most of the major mental disorders (14–19), revealing complex genetic architectures and widespread genetic correlations with a broad range of phenotypes, including educational attainment and intelligence (20,21). Although educational attainment and intelligence are highly correlated, the relationship between educational attainment and intelligence is complex (22), and mental disorders may be associated with one but not the other. For example, SCZ shows a negative genetic correlation with intelligence but a neutral or slightly positive genetic correlation with educational attainment (23) despite individuals with SCZ showing lower educational attainment on average (10,24). In addition, SCZ shows a positive genetic correlation with noncognitive skills underlying educational attainment, as was investigated in a
Polygenic Risk of Mental Disorders and School Grades

recent GWAS-by-subtraction study (22). Consequently, there is a need to examine the association between genetic liability to mental disorders and more fine-grained components underlying educational attainment to address this gap.

School grades offer a more nuanced phenotype than educational attainment. We recently leveraged genetic data from the iPSYCH2012 (25) and ANGI (Anorexia Nervosa Genetics Initiative) (26) cohorts \((N = 30,982)\) and performed a GWAS of school grades in Danish ninth grade, which represents the exit examination of compulsory schooling in Denmark (27). When decomposing school grades using principal component analysis, the second factor, E2, which represented being better at language relative to mathematics, was associated with increased risk of several mental disorders, indicating a genetic overlap between language abilities and mental disorders. Here, we extended our previous analyses by using the expanded iPSYCH2015 sample along with additional phenotypic information (high school grades and educational attainment by age 25 years) from the nested ANGI and EDGI (Eating Disorders Genetics Initiative) samples \((N = 78,438)\). We investigated associations between polygenic risk scores (PRSs) of mental disorders and ninth grade school grades, high school grades, and educational attainment by age 25 years using nationwide register data. We hypothesized that individuals with mental disorders would have a lower likelihood of passing ninth grade examinations and obtain lower grades in language and mathematics, except for individuals with AN, for whom we hypothesized higher grades based on previous findings (10). We hypothesized that associations between PRSs and school performance (ninth grade and high school outcomes) and educational attainment by age 25 years would be consistent with previously reported genetic correlations between the disorders and educational attainment. Specifically, we hypothesized negative associations between polygenic risk of attention-deficit/hyperactivity disorder (ADHD) (14) or major depressive disorder (MDD) (18) and school performance and positive associations between polygenic risk of AN (15), autism spectrum disorder (ASD) (16), BD (17), or SCZ (19) and school performance based on previous findings.

METHODS AND MATERIALS

Ethical Approval

All analyses conducted using the current dataset are within the permissions received from the Danish Scientific Ethics Committee, the Danish Health Data Authority, the Danish Data Protection Agency, and the Danish Neonatal Screening Biobank Steering Committee (28).

Data Sources

We used relevant data from multiple Danish population-wide registers that are linked using a unique personal identification number (29). We obtained biological material for genotyping from the Neonatal Screening Biobank, which stores dried blood spots taken 5 to 7 days after birth from almost all infants born in Denmark after 1981. The genotyping is described in detail by Bybjerg-Grauholm et al. (28). We obtained information on mental disorders from the Danish Psychiatric Central Research Register (30) and the Danish National Patient Register (for AN) (31) and information on school performance from the Primary Education Register (32).

Study Population

We used data from the established population-based case-cohort sample (iPSYCH2015), as well as the ANGI and EDGI Denmark cohorts (the combination of which is henceforth referred to as iPSYCH2015). Detailed descriptions of these cohorts are available elsewhere (26,28,33). In brief, the iPSYCH2015 case-cohort sample is an expansion of the iPSYCH2012 cohort (29) and includes individuals with ADHD, ASD, BD, MDD, or SCZ identified from diagnostic codes in the Danish Psychiatric Central Research Register based on ICD-10 (Table S1). Additionally, the iPSYCH2015 cohort includes a population-based cohort of 51,000 randomly selected individuals representative of the entire Danish population. For the current study, we only included individuals born as singletons in Denmark between January 1, 1987, and July 1, 2000, who were alive and living in Denmark at age 15 years. Thus, the total study population was a combination of individuals selected based on a register-based diagnosis of a mental disorder and the population-based subcohort. Finally, we excluded individuals without a record of a ninth grade examination if they were 1) not alive at age 18 years, or 2) did not live in Denmark at age 18.

Polygenic Risk Scores

We derived PRSs for ADHD, ASD, AN, BD, MDD, and SCZ using a meta-PRS, which combines externally and internally generated PRSs (34). We derived the externally generated PRSs using single nucleotide polymorphism (SNP) weights from external GWAS summary statistics from European discovery samples excluding iPSYCH4 samples using the LDpred2 software (35). We generated internal PRSs using SNP weights obtained from a best linear unbiased prediction of SNPs in the iPSYCH2015 sample using BOLT-LMM (36). Finally, we constructed a linear combination of the externally and internally generated SNPs weighted by the square root of the respective PRS training data sample sizes. A detailed description of meta-PRS derivation and how the PRSs were constructed for the 6 different psychiatric disorders in the iPSYCH sample can be found elsewhere (34).

School Outcomes

We investigated school outcomes at 3 time points: 1) ninth grade examinations, 2) high school examinations, and 3) educational attainment at age 25 years. In Denmark, compulsory schooling covers school from age ~6 to ~16 years. After this, some children go on to take 2 to 3 years of high school (optional), typically from age 16 to 19. Ninth grade examinations represent the exit examination of compulsory schooling in Denmark and typically take place around age 16, and high school exit examinations typically take place around age 19. In both ninth grade and high school, we focused on 2 school subjects: 1) Danish, the only official language in Denmark and the native one for most of the population, from here on referred to simply as language, and 2) mathematics. We chose these 2 subjects because they represent fundamental educational skills and putatively rely on different neurocognitive abilities (37,38). Since 2007, performances on the school examinations
in Denmark have been graded on a 7-point scale: −3 (unacceptable), 00 (inadequate), 02 (adequate), 4 (fair), 7 (good), 10 (very good), and 12 (excellent). A minimum grade of 02 is required to pass an examination. Prior to 2007, a 10-point grading system was used. We converted grades from the older 10-point scale to the newer 7-point scale using the official conversion table (https://ufm.dk/en/education/the-danish-education-system/grading-system/old-grading-scale, which was accessed on December 12, 2022, and is also supplied in Table S2). We first analyzed a binary outcome indicating whether individuals had passed ninth grade examinations. Passing requires taking all necessary examinations in both language and mathematics and getting a mean grade of at least 02 (passed) in these subjects. We categorized individuals who did not receive a ninth grade examination before age 18 (median age at completion plus 2 years) as having not passed the ninth grade examination. Next, we calculated ninth grade and high school mean grades in language and mathematics from all examinations under each subject from individuals who passed the examinations as separate outcomes. Although the grades themselves are ordinal, the mean of multiple examination grades is assumed to be continuously distributed. Some individuals may have taken the ninth grade or high school examinations more than once, in which case we only included the first examination.

Statistical Analysis
To investigate the association between diagnosed mental disorders and school outcomes, we identified individuals from the case samples who were diagnosed before their ninth grade examinations (with diagnosis) as well as individuals from the population-based subcohort who were not diagnosed with the respective disorder before their ninth grade examinations (without diagnosis). To investigate the association between polygenic risk and school outcomes, we used the total study population and weighted individuals without a diagnosis of ADHD, AN, ASD, BD, MDD, or SCZ using a weight of X, which corresponds to the total number of individuals in the background population divided by the number of individuals in the study population without 1 of the 6 diagnoses. This weighting served to make the total study population representative of the entire Danish population. Accordingly, the PRS-based analyses are not enriched for mental disorders beyond what is observed naturally in the Danish population. We then used linear regression to examine the estimated marginal means of grades in language and mathematics. We compared the proportion of students who passed ninth grade between individuals with and without diagnoses of mental disorders (using logistic regression of the binary outcome variable) and tested for a linear trend between mental disorder–specific PRSs (per SD increase) and the outcomes, proportion passed and subject-specific mean grades. We derived partial \( R^2 \) values to determine the proportion of variance explained by the PRSs for all outcomes. In all of the above analyses, we adjusted for 4 principal components: sex, birth year, age at ninth grade examination, parental birth country (Denmark vs. abroad), and genotyping batch. To investigate the association between polygenic risk of mental disorders and long-term educational attainment, we used the total weighted study population. We used logistic regression analysis to examine the association between PRSs (SDs) and 1) the proportion of individuals who completed only ninth grade or lower secondary school (low educational attainment) versus the rest, and 2) the proportion of individuals who completed a medium/long cycle of education (high educational attainment) versus the rest. In these analyses, we adjusted for 4 principal components: sex, birth year, parental birth country, and genotyping batch. By examining proportions of low and high educational attainment separately, potential non-monotonic associations would be detectable (e.g., a PRS for a specific trait being associated with more extreme educational attainment). Because the iPSYCH case cohort is enriched with individuals with the target mental disorders (ADHD, AN, ASD, BD, MDD, and SCZ), as a planned sensitivity analysis, we also repeated the analyses on PRSs and language and mathematics in the population-based subcohort (n = 25,026). Although we did not filter for European genetic ancestry in the main analyses, we did so in a supplementary analysis to investigate whether any findings could be driven by ancestral effects. We defined European genetic ancestry using the 20 first genetic principal components. We first defined individual genetic distance as the Mahalanobis distance between the individuals’ 20 principal components. Using the method dist ogk from the R package bigutilsr, we then considered individuals with genetic distance less than the logarithm of 4.5 from the sample average to be of European genetic ancestry. As exploratory post hoc analyses, we tested for interactions between PRSSs and 1) biological sex, and 2) highest level of maternal education (nonacademic vs. bachelor or above) as a proxy for effects of parental educational level on ninth grade passing, ninth grade grades, and high school grades.

RESULTS
Sample Characteristics
We identified 79,489 individuals born as singletons in Denmark between January 1, 1987, and July 1, 2000, who were alive and living in Denmark at age 15 years (Table 1 and Figure S1).

Ninth Grade Examination Passing in Individuals With and Without Mental Disorders
First, we examined associations between mental disorders diagnosed before ninth grade examinations and school outcomes in ninth grade. Individuals diagnosed with each of the 6 studied mental disorders had a lower likelihood of passing ninth grade examinations compared with individuals without the respective disorder (Figure 1A and Table S3).

Subject-Specific School Grades in Individuals With and Without Mental Disorders
When examining subject-specific grades, individuals with ADHD and ASD obtained lower grades in both language and mathematics on average than individuals without each of these disorders (Figure 1B and Table S4). Individuals with BD obtained lower grades in mathematics on average than individuals without BD (Figure 1B and Table S4). Individuals diagnosed with AN obtained higher grades in both language and
Polygenic Risk of Mental Disorders and School Grades

Table 1. Number of Included Participants in the Study Cohorts and Sample Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADHD Sample</th>
<th>AN Sample</th>
<th>ASD Sample</th>
<th>BD Sample</th>
<th>MDD Sample</th>
<th>SCZ Sample</th>
<th>Population-Based Subcohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19,897</td>
<td>5065</td>
<td>13,784</td>
<td>2522</td>
<td>23,026</td>
<td>5586</td>
<td>25,026</td>
</tr>
<tr>
<td>Sex, Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed Before Ninth Grade Examination</td>
<td>11,920 (61%)</td>
<td>2243 (44%)</td>
<td>10,444 (76%)</td>
<td>192 (7.6%)</td>
<td>5286 (23%)</td>
<td>663 (12%)</td>
<td>NA</td>
</tr>
<tr>
<td>Age at Diagnosis, Years</td>
<td>15 (10, 19)</td>
<td>16 (14, 19)</td>
<td>13 (9, 16)</td>
<td>21 (19, 24)</td>
<td>19 (16, 21)</td>
<td>20 (18, 22)</td>
<td>NA</td>
</tr>
<tr>
<td>Age at Ninth Grade Examination, Years</td>
<td>16 (16, 17)</td>
<td>16 (15, 16)</td>
<td>16 (16, 17)</td>
<td>16 (15, 16)</td>
<td>16 (16, 17)</td>
<td>16 (15, 16)</td>
<td></td>
</tr>
<tr>
<td>Took the High-School Examination</td>
<td>3233</td>
<td>3347</td>
<td>3349</td>
<td>1032</td>
<td>9084</td>
<td>1120</td>
<td>15,172</td>
</tr>
</tbody>
</table>

Values are presented as median (25th, 75th centile), n, or n (%). Study population was derived from the iPSYCH and ANGI (Anorexia Nervosa Genetics Initiative) samples but was additionally filtered to individuals born in Denmark between January 1, 1987, and July 1, 2000, who were alive and living in Denmark at age 15. For individuals without a record of a ninth grade exam, we excluded those who were not both alive and living in Denmark at age 18.

AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; MDD, major depressive disorder; NA, not applicable; SCZ, schizophrenia.

Polygenic Risk of Mental Disorders and Ninth Grade School Performance

Next, we investigated the association between polygenic scores of mental disorders and ninth grade school outcomes in the entire weighted case-cohort sample, which is representative of the entire Danish population (Figure 2A and Table S5). Higher polygenic risk of ADHD or MDD was associated with a lower likelihood of passing ninth grade examinations (Figure 2A), and higher polygenic risk of AN was associated with a higher likelihood of passing ninth grade. We then examined subject-specific school grades (Figure 2B and Table S6). Higher polygenic risk of ADHD was associated with lower grades in language and mathematics. High polygenic risk of AN was associated with higher grades in language and mathematics. High polygenic risk of ASD was associated with higher grades in language. High polygenic risk of BD was associated with higher grades in both language and mathematics, whereas high polygenic risk of MDD was associated with lower grades in both subjects. High polygenic risk of SCZ was associated with higher grades in language and lower grades in mathematics. Similar results were found when restricting the analyses to the population-based subcohort and individuals with European ancestry (Figures S2 and S3). Post hoc analyses revealed a marginally significant ($p = .02$) interaction between the PRS for ASD and sex for ninth grade mathematics (Table S7) and several statistically significant interactions between parental education and PRSs for the investigated disorders (Table S8).

Polygenic Risk of Mental Disorders and High School Grades

We then investigated the association between high school grades and polygenic risk scores for mental disorders (Figure 2C and Table S9). High polygenic risk of ADHD was associated with lower high school grades in both language and mathematics. High polygenic risk of AN was associated with lower high school grades in mathematics, whereas high polygenic risk of MDD was associated with higher grades in both language and mathematics. Similar results were found when restricting the analyses to the population-based subcohort and individuals with European ancestry (Figures S2 and S3). Post hoc analyses revealed a marginally significant ($p = .02$) interaction between the PRS for ASD and sex for ninth grade mathematics (Table S7) and several statistically significant interactions between parental education and PRSs for the investigated disorders (Table S8).

![Figure 1](https://example.com/figure1.png)

Figure 1. Ninth grade school performances among individuals with and without the 6 mental disorders. Ninth grade examinations represent the exit examinations of compulsory schooling in Denmark and typically take place around age 16. Each subject is rated on a 7-point grading scale (1–3, 4, 5, 6, 7, 8, 9). Passing ninth grade examinations requires taking all required examinations and achieving a minimum mean grade of 02 in both language and mathematics. (A) The proportion of students who passed ninth grade examinations. (B) Estimated marginal means of mean grades in mathematics and language for individuals who passed ninth grade examinations, with and without the respective mental disorders diagnosed by the time of ninth grade examinations. ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorder; BD, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia.
higher grades in both language and mathematics. No statistically significant associations were found between polygenic risk of ASD and high school grades. High polygenic risk of BD was associated with higher grades in both language and mathematics. High polygenic risk of MDD was associated with lower grades in mathematics, but not high school language grades. High polygenic risk of schizophrenia was associated with higher grades in language but lower grades in mathematics. Similar results were found when restricting the analyses to the population-based subcohort and individuals with European ancestry (Figures S2 and S3).

DISCUSSION

In this nationwide representative study of 78,438 individuals, PRSs for different mental disorders were differentially associated with passing ninth grade, subject-specific school grades in language and mathematics in ninth grade and high school, and educational attainment by age 25 after adjusting for potential confounders. Despite the overall negative impact of being diagnosed with ADHD, ASD, BD, MDD, and SCZ on school performance [as previously demonstrated (10)], we found positive associations between polygenic risk of AN, ASD, BD, MDD, and SCZ and different measures of school performance, which for AN, BD, and SCZ is consistent with the positive genetic correlations with educational attainment that had been reported previously (15–17,19).

A recent GWAS on subject-specific school grades by Donati et al. (39) investigated genetic correlations with mental disorders. Only one of these was statistically significant: a positive genetic correlation between ASD and mathematics grades. We found the ASD PRS to be associated with higher grades in language, but not mathematics. The remaining trend-level associations reported by Donati et al. were generally consistent with our results. The current study builds upon our previous GWAS of ninth grade school grades (27). Here, we replicated previously discovered associations between PRSs and school grades [see Figure 4B in (27)] and detected novel associations for the BD PRS (and mathematics), MDD PRS (and language), ASD PRS (and language), and AN PRS (and mathematics). Moreover, we replicated these findings with high school grades and investigated associations with...
for ninth grade school performance, which may warrant further between mental disorder PRSs and parental educational level AN). We detected several statistically signi associated with a lower likelihood of passing ninth grade ex--

subtraction between educational attainment and cognitive noncognitive skills [as previously investigated in a GWAS-by--

Conclusions

In summary, we showed that polygenic risk of 6 mental dis-

ACKNOWLEDGMENTS AND DISCLOSURES

The collection of samples was funded by the Lundbeck Foundation Initiative for Integrative Psychiatric Research, IPSYCH (Grant Nos. R102-A9118, R155-2014-1724, and R248-2017-2003) and by the ANG (Anorexia Nervosa Genetics Initiative), an initiative of the Klarman Family Foundation. OHJ was supported by the Health Research Foundation of the Central Denmark Re--

Strengths and Limitations

Our study has several strengths, including its large sample size, the representativeness of the cohorts, and the access to longitudinal register data with fine-grained, objectively assessed phenotypes (assessed by teachers). By measuring subject-specific school grades, we measured actual educa--

ARTICLE INFORMATION

From the Psychosis Research Unit, Aarhus University Hospital, Psychiatry, Aarhus, Denmark (OHJ, OM); Center of Functionally Integrative Neurosci--

Biological Psychiatry August 1, 2024; 96:222–229 www.sobp.org/journal 227
REFERENCES


