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Archival Report

Polygenic Risk of Mental Disorders and Subject-Specific School Grades

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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.

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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 premorbid 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

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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 (25) 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 iPSYCH 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 PRSs 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

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

Characteristic	ADHD Sample	AN Sample	ASD Sample	BD Sample	MDD Sample	SCZ Sample	Population-Based Subcohort
n	19,697	5065	13,784	2522	23,026	5585	25,026
Sex, Females	6827 (35%)	4717 (93%)	3719 (27%)	1652 (66%)	15,711 (68%)	2669 (48%)	12,233 (49%)
Diagnosed Before Ninth Grade Examination	11,920 (61%)	2243 (44%)	10,444 (76%)	192 (7.6%)	5286 (23%)	663 (12%)	NA
Age at Diagnosis, Years	15 (10, 19)	16 (14, 19)	13 (9, 16)	21 (19, 24)	19 (16, 21)	20 (18, 22)	NA
Age at Ninth Grade Examination, Years	16 (16, 17)	16 (15, 16)	16 (16, 17)	16 (15, 16)	16 (15, 16)	16 (16, 17)	16 (15, 16)
Took the High-School Examination	3233	3347	3349	1032	9084	1120	15,172

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.

mathematics on average than individuals without AN (Figure 1B and Table S4). Individuals with MDD and SCZ obtained lower grades in mathematics on average than individuals without each respective disorder (Figure 1B and Table S4).

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

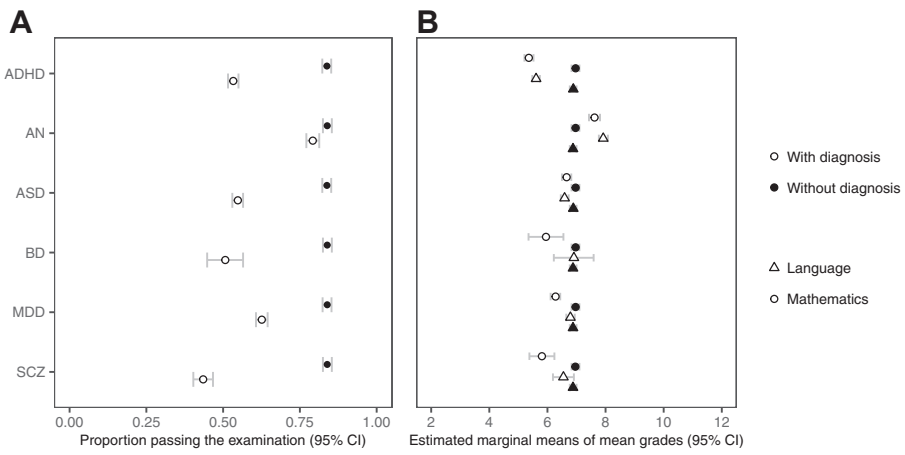

Figure 1. Ninth grade school performances among individuals with and without the 6 mental disorders. Ninth grade examinations represent the exit examinations of compulsory schooling in Denmark and typically take place around age 16. Each subject is rated on a 7-point grading scale (−3, 00, 02, 4, 7, 10, 12). 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.

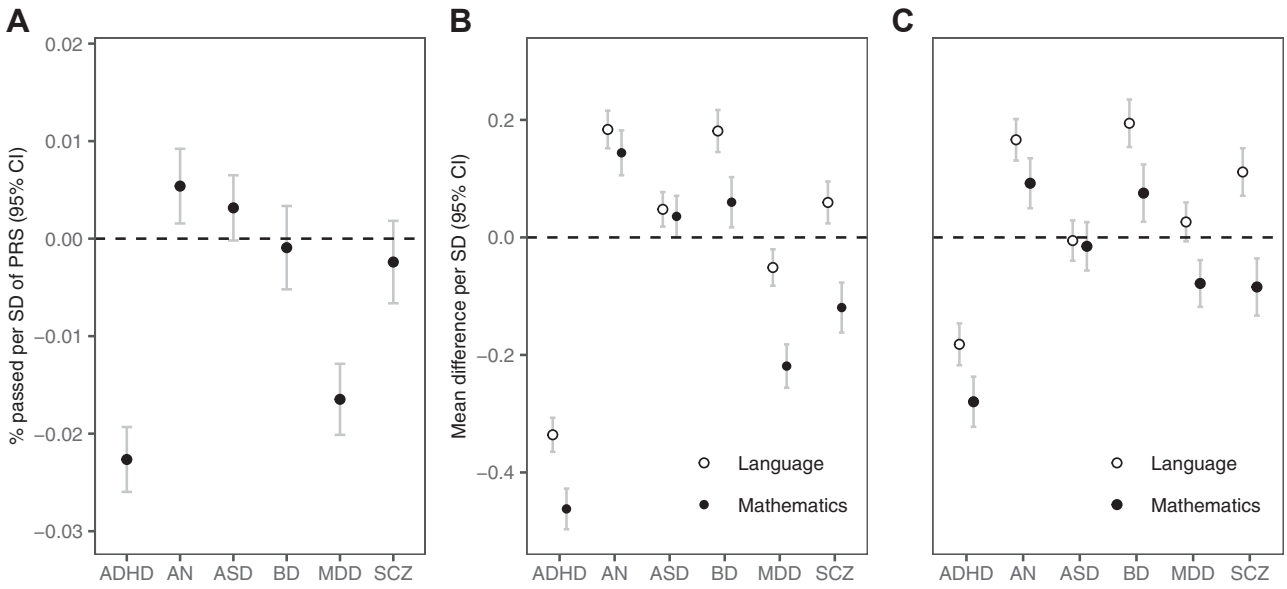

Figure 2. School outcomes by polygenic risk score (PRS) standard deviations for 6 mental disorders. Ninth grade examinations represent the exit examinations of compulsory schooling in Denmark and typically take place around age 16, whereas high school is optional, and high school examinations take place around age 19. Each subject is rated on a 7-point grading scale (−3, 00, 02, 4, 7, 10, 12). Passing ninth grade examinations requires taking all required examinations and achieving a minimum mean grade of 02 in both language and mathematics. **(A)** Proportion who passed ninth grade examinations per SD of PRS. **(B)** Estimated marginal mean of mean grades in language and mathematics (from 02 to 12) in ninth grade examinations per SD of PRS, only for individuals who passed ninth grade exams. **(C)** Estimated marginal mean of mean grades in language and mathematics (from 02 to 12) in high school examinations, only for individuals who passed high school 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).

Polygenic Risk of Mental Disorders and Educational Attainment at Age 25

We investigated the association between polygenic risk of mental disorders and educational attainment at age 25. We tested for linear trends between PRSs and the proportion of participants who obtained only a low level of education (vs. the rest) or the proportion who obtained a high level of education (vs. the rest) (Table S10). We found that high polygenic risk of ADHD, ASD, BD, or SCZ was associated with larger proportions of participants with low educational attainment, whereas high polygenic risk of AN was associated with smaller proportions of participants with low educational attainment (Table S10). High polygenic risk of ADHD or MDD was associated with smaller proportions of individuals with high educational attainment, and high polygenic risk of AN or BD was associated with higher proportions of individuals with high educational attainment (Table S10).

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

educational attainment at age 25. Our previous study included a GWAS of principal components underlying ninth-grade grades (27). While the first component represented general school performance, the second principal component represented better performance in language subjects relative to mathematics and was positively associated with MDD and SCZ and, to some degree, BD and ADHD (27). We did not replicate these analyses here, but we did detect a similar pattern for SCZ, with higher polygenic risk of SCZ being associated with poorer mathematics performance but better language performance in both ninth grade and high school.

Studying subject-specific school grades provides new insight into the links between genetic liability to mental disorder and later educational outcomes. Performance in the subjects of language and mathematics likely depends on both shared and unique cognitive skills (37,38) and neural functions (40,41), which may have distinct associations with (polygenic liability for) different mental disorders, as suggested by our findings. However, more research is needed to unravel these shared and distinct effects, and the current findings must be interpreted with caution. An important feature of PRSs is the shared variance between multiple phenotypes (42). The PRS-based associations reported here are likely not driven by the effects of having a mental disorder, but rather by traits (e.g., cognitive or behavioral) found in the general population that are associated with the disorders. This could be impulsivity (43) or attentional problems (44) associated with ADHD (14), noncognitive skills [as previously investigated in a GWAS-by-subtraction between educational attainment and cognitive performance (22)], and personality traits, such as perfectionism (45) associated with AN, intelligence (46), and cognitive abilities (22) associated with ASD, and noncognitive (22) and creative (47,48) skills associated with BD, MDD, and SCZ. Another aspect that requires careful interpretation is that the presence of a positive association between polygenic risk for a mental disorder and school performance does not mean that it is beneficial, in terms of school performance, to have the disorder. As shown, being diagnosed with a mental disorder was associated with a lower likelihood of passing ninth grade examinations and getting lower mean grades (although not for AN). We detected several statistically significant interactions between mental disorder PRSs and parental educational level for ninth grade school performance, which may warrant further investigation.

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 educational achievement compared with the more general educational attainment (years of schooling) that is often assessed. Putatively, this partially protects our analyses from confounding by factors affecting school performance more generally (not subject-specifically). However, there are also important limitations. First, although the samples do not have voluntary participation bias in the ascertainment of the exposure (i.e., genotyping), not all individuals took ninth grade examinations and high school examinations. Second, we did not have outcome information on children attending private schools, and we were thus unable to distinguish between whether a child had attended private school or had not taken ninth grade examinations. Both these limitations could bias the associations between PRSs and subject-specific school grades. Third, we were unable to control for dynastic effects (49) (also termed indirect genetic effects), i.e., an association between the polygenic risk score and school performance that arises due to an association with parental genotypes and downstream parental phenotypes that impact the child's school performance. Dynastic effects could inflate the reported effect sizes, and future studies applying within-family designs could help address this limitation. Fourth, the effect sizes detected here were relatively small, much smaller than the effect sizes associated with being diagnosed with any of the disorders, and the variance explained by the PRS was limited. Fifth, our results may have limited generalizability to other populations, especially countries with very different educational and health care systems.

Conclusions

In summary, we showed that polygenic risk of 6 mental disorders was associated with subject-specific school grades in ninth grade and high school and with educational attainment in the general population. Future studies applying within-family designs and studies with even more detailed cognitive phenotyping may help disentangle direct from dynastic effects and dissect the different skills, traits, and behaviors underlying educational attainment.

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REFERENCES

1. Plana-Ripoll O, Pedersen CB, Agerbo E, Holtz Y, Erlangsen A, Canudas-Romo V, *et al.* (2019): A comprehensive analysis of mortality-related health metrics associated with mental disorders: A nationwide, register-based cohort study. Lancet 394:1827–1835.
2. Pedersen CB, Mors O, Bertelsen A, Waltoft BL, Agerbo E, McGrath JJ, *et al.* (2014): A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. JAMA Psychiatry 71:573–581.
3. Plana-Ripoll O, Weye N, Knudsen AK, Hakulinen C, Madsen KB, Christensen MK, *et al.* (2023): The association between mental disorders and subsequent years of working life: A Danish population-based cohort study. Lancet Psychiatry 10:30–39.
4. Marioni RE, Ritchie SJ, Joshi PK, Hagenaars SP, Okbay A, Fischer K, *et al.* (2016): Genetic variants linked to education predict longevity. Proc Natl Acad Sci USA 113:13366–13371.
5. Entwisle DR, Alexander KL, Olson LS (2005): First grade and educational attainment by age 22: A new story. Am J Sociol 110:1458–1502.
6. French MT, Homer JF, Popovici I, Robins PK (2015): What you do in high school matters: High school GPA, educational attainment, and labor market earnings as a young adult. East Econ J 41:370–386.
7. Cannon M, Jones P, Huttunen MO, Tanskanen A, Huttunen T, Rabe-Hesketh S, Murray RM (1999): School performance in Finnish children and later development of schizophrenia: A population-based longitudinal study. Arch Gen Psychiatry 56:457–463.
8. Zammit S, Allebeck P, David AS, Dalman C, Hemmingsson T, Lundberg I, Lewis G (2004): A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. Arch Gen Psychiatry 61:354–360.
9. Guzman MP, Jellinek M, George M, Hartley M, Squicciarini AM, Canenguez KM, *et al.* (2011): Mental health matters in elementary school: First-grade screening predicts fourth grade achievement test scores. Eur Child Adolesc Psychiatry 20:401–411.
10. Dalsgaard S, McGrath J, Østergaard SD, Wray NR, Pedersen CB, Mortensen PB, Petersen L (2020): Association of mental disorder in childhood and adolescence with subsequent educational achievement. JAMA Psychiatry 77:797–805.
11. MacCabe JH, Lambe MP, Cnattingius S, Torrång A, Björk C, Sham PC, *et al.* (2008): Scholastic achievement at age 16 and risk of schizophrenia and other psychoses: A national cohort study. Psychol Med 38:1133–1140.
12. MacCabe JH, Lambe MP, Cnattingius S, Sham PC, David AS, Reichenberg A, *et al.* (2010): Excellent school performance at age 16 and risk of adult bipolar disorder: National cohort study. Br J Psychiatry 196:109–115.
13. Pedersen SD, Østergaard SD, Petersen L (2018): The association between school exam grades and subsequent development of bipolar disorder. Acta Neuropsychiatr 30:209–217.
14. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, *et al.* (2019): Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 51:63–75.
15. Watson HJ, Yilmaz Z, Thornton LM, Hübel C, Coleman JRI, Gaspar HA, *et al.* (2019): Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet 51:1207–1214.
16. Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, *et al.* (2019): Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 51:431–444.
17. Mullins N, Forstner AJ, O'Connell KS, Coombes B, Coleman JRI, Qiao Z, *et al.* (2021): Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet 53:817–829.
18. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, *et al.* (2018): Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet 50:668–681.
19. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, *et al.* (2022): Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604:502–508.
20. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, De Leeuw CA, *et al.* (2018): Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat Genet 50:912–919.
21. Okbay A, Wu Y, Wang N, Jayashankar H, Bennett M, Nehzati SM, *et al.* (2022): Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. Nat Genet 54:437–449.
22. Demange PA, Malanchini M, Mallard TT, Biroli P, Cox SR, Grotzinger AD, *et al.* (2021): Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction. Nat Genet 53:35–44.
23. Bansal V, Mitjans M, Burik CAP, Linnér RK, Okbay A, Rietveld CA, *et al.* (2018): Genome-wide association study results for educational attainment aid in identifying genetic heterogeneity of schizophrenia. Nat Commun 9:3078.
24. Tempelaar WM, Termorshuizen F, MacCabe JH, Boks MP, Kahn RS (2017): Educational achievement in psychiatric patients and their siblings: A register-based study in 30 000 individuals in the Netherlands. Psychol Med 47:776–784.
25. Pedersen CB, Bybjerg-Grauholm J, Pedersen MG, Grove J, Agerbo E, Bækvad-Hansen M, *et al.* (2018): The iPSYCH2012 case–cohort sample: New directions for unravelling genetic and environmental architectures of severe mental disorders. Mol Psychiatry 23:6–14.
26. Thornton LM, Munn-Chernoff MA, Baker JH, Juréus A, Parker R, Henders AK, *et al.* (2018): The anorexia nervosa genetics initiative (ANGI): Overview and methods. Contemp Clin Trials 74:61–69.
27. Rajagopal VM, Ganna A, Coleman JRI, Allegrini A, Voloudakis G, Grove J, *et al.* (2023): Genome-wide association study of school grades identifies genetic overlap between language ability, psychopathology and creativity. Sci Rep 13:429.
28. Bybjerg-Grauholm J, Pedersen CB, Bækvad-Hansen M, Pedersen MG, Adamsen D, Hansen CS, *et al.* (2020): The iPSYCH2015 Case-Cohort sample: Updated directions for unravelling genetic and environmental architectures of severe mental disorders. medRxiv. https://doi.org/10.1101/2020.11.30.20237768.
29. Pedersen CB (2011): The Danish civil registration system. Scand J Public Health 39(7)(suppl):22–25.
30. Mors O, Perto GP, Mortensen PB (2011): The Danish psychiatric central research register. Scand J Public Health 39(7)(suppl):54–57.
31. Lynge E, Sandegaard JL, Rebolj M (2011): The Danish national patient register. Scand J Public Health 39(7)(suppl):30–33.

32. Jensen VM, Rasmussen AW (2011): Danish education registers. Scand J Public Health 39(7_suppl):91–94.
33. Bulik CM, Thornton LM, Parker R, Kennedy H, Baker JH, MacDermod C, *et al.* (2021): The eating disorders genetics initiative (EDGI): Study protocol. BMC Psychiatry 21:234.
34. Albiñana C, Grove J, McGrath JJ, Agerbo E, Wray NR, Bulik CM, *et al.* (2021): Leveraging both individual-level genetic data and GWAS summary statistics increases polygenic prediction. Am J Hum Genet 108:1001–1011.
35. Vilhjálmsson BJ, Yang J, Finucane HK, Gusev A, Lindström S, Ripke S, *et al.* (2015): Modeling linkage disequilibrium increases accuracy of polygenic risk scores. Am J Hum Genet 97:576–592.
36. Loh PR, Tucker G, Bulik-Sullivan BK, Vilhjálmsson BJ, Finucane HK, Salem RM, *et al.* (2015): Efficient Bayesian mixed-model analysis increases association power in large cohorts. Nat Genet 47: 284–290.
37. Raghubar KP, Barnes MA, Hecht SA (2010): Working memory and mathematics: A review of developmental, individual difference, and cognitive approaches. Learn Individ Differ 20:110–122.
38. Gathercole SE, Alloway TP, Willis C, Adams AM (2006): Working memory in children with reading disabilities. J Exp Child Psychol 93:265–281.
39. Donati G, Dumontheil I, Pain O, Asbury K, Meaburn EL (2021): Evidence for specificity of polygenic contributions to attainment in English, maths and science during adolescence. Sci Rep 11:3851.
40. Siok WT, Perfetti CA, Jin Z, Tan LH (2004): Biological abnormality of impaired reading is constrained by culture. Nature 431:71–76.
41. Price GR, Mazzocco MM, Ansari D (2013): Why mental arithmetic counts: Brain activation during single digit arithmetic predicts high school math scores. J Neurosci 33:156–163.
42. Leppert B, Millard LAC, Riglin L, Davey Smith G, Thapar A, Tilling K, *et al.* (2020): A cross-disorder PRS-pheWAS of 5 major psychiatric disorders in UK Biobank. PLoS Genet 16:e1008185.
43. Groen-Blokhuis MM, Middeldorp CM, Kan KJ, Abdellaoui A, Van Beijsterveldt CE, Ehli EA, *et al.* (2014): Attention-deficit/hyperactivity disorder polygenic risk scores predict attention problems in a population-based sample of children. J Am Acad Child Adolesc Psychiatry 53:1123–1129.e6.
44. Lahey BB, Tong L, Pierce B, Hedeker D, Berman MG, Cardenas-Iniguez C, *et al.* (2022): Associations of polygenic risk for attention-deficit/hyperactivity disorder with general and specific dimensions of childhood psychological problems and facets of impulsivity. J Psychiatr Res 152:187–193.
45. Bulik CM, Tozzi F, Anderson C, Mazzeo SE, Aggen S, Sullivan PF (2003): The relation between eating disorders and components of perfectionism. Am J Psychiatry 160:366–368.
46. Hill WD, Marioni RE, Maghzian O, Ritchie SJ, Hagenaars SP, McIntosh AM, *et al.* (2019): A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence. Mol Psychiatry 24:169–181.
47. Power RA, Steinberg S, Bjornsdottir G, Rietveld CA, Abdellaoui A, Nivard MM, *et al.* (2015): Polygenic risk scores for schizophrenia and bipolar disorder predict creativity. Nat Neurosci 18:953–955.
48. Li H, Zhang C, Cai X, Wang L, Luo F, Ma Y, *et al.* (2020): Genome-wide association study of creativity reveals genetic overlap with psychiatric disorders, risk tolerance, and risky behaviors. Schizophr Bull 46:1317–1326.
49. Kong A, Thorleifsson G, Frigge ML, Vilhjalmsson BJ, Young AI, Thorgeirsson TE, *et al.* (2018): The nature of nurture: Effects of parental genotypes. Science 359:424–428.