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Schizophrenia polygenic risk score and long-term success in the labour market: A cohort study

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ABSTRACT

Employment is rare among people with a schizophrenia diagnosis. Meanwhile, a genetic liability for schizophrenia may hinder labour market performance. We studied how the polygenic risk score (PGS) for schizophrenia related to education and labour market outcomes. We found that a higher PGS was linked to lower educational levels and weaker labour market outcomes as well as a higher likelihood of receiving social income transfers, particularly among men. Assuming that the link is causal, our results indicate that individuals with schizophrenia or schizophrenia-related traits have a weakened ability to fully participate in the labour market, potentially reinforcing social exclusion.

1. Introduction

Schizophrenia is a serious mental disorder characterized by psychotic symptoms, absence or lessening of normal behaviours, and cognitive impairment (Owen et al., 2016). Schizophrenia has a profound effect on the affected individual, and most people who receive a diagnosis are not employed (Hakulinen et al., 2020; Holm et al., 2021; Marwaha and Johnson, 2004). The heritability of schizophrenia and schizophrenia spectrum is very high at up to 80% (Hilker et al., 2018), and studies have confirmed its polygenic nature, with thousands of common risk alleles likely contributing to the disorder's liability (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). However, subclinical symptoms or traits associated with increased genetic risk may influence the individual's behaviour; for example, genetic risk for schizophrenia was linked to lower educational attainment for participants in a UK Biobank study (Escott-Price et al., 2020).

In the present study, we examined how the genetic liability for developing schizophrenia is associated with educational attainment and long-term labour market outcomes (LMO) in a population-based sample of Finnish adults. As an indicator of genetic liability, we used a polygenic score (PGS) that summarized the estimated effect of several genetic variants on an individual's risk of developing schizophrenia.

2. Method

2.1. Data

The Cardiovascular Risk in Young Finns Study (YFS, https://youngfinnsstudy.utu.fi) is a longitudinal prospective cohort study, with randomly chosen participants (N = 3596) representing inherently healthy individuals in six age cohorts (born between 1962 and 1977)

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from five Finnish university regions. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Participants gave a written informed consent after the nature of the procedures had been fully explained, and the study was approved by the local ethics committees. The PGSs and information on parental mental health disorders in 1980 and 1983 were drawn from the YFS. The YFS also contains information on schizophrenia diagnoses that originate from the Finnish Hospital Discharge Register (FHDR). The FHDR is a nationwide data on patients discharged from hospitals. Based on validation studies, the accuracy and completeness of the data are good (Sund, 2012). According to the FHDR, only 0.8% of the YFS participants in our estimation sample had been diagnosed with a schizophrenia over the period 1980–2018, which corresponds to the prevalence of schizophrenia in Finland (Perälä et al., 2007).

Register-based information on educational attainment and LMO was based on the Finnish Longitudinal Employer-Employee Data (FLEED) of Statistics Finland that was linked to the YFS using unique personal identifiers.

2.2. Data analysis

We estimated reduced-form models where educational attainment and LMO were regressed on a PGS for schizophrenia and control variables using linear ordinary least squares (OLS) regression (VanderWeele et al., 2014). Under three key assumptions, this approach identifies the causal effect between the genetic risk of developing schizophrenia and the outcome variable. *Independence:* The PGS is as good as randomly assigned. *Relevance:* The PGS is associated with schizophrenia. *Exclusion:* The PGS affects the outcome variable only through its association with schizophrenia.

Compared to Mendelian randomization (MR) studies identifying the effect of schizophrenia on outcome variables among those who have been diagnosed, the reduced-form model has the advantage of not requiring information on a schizophrenia diagnosis; thus, we can identify the link between the genetic risk for developing schizophrenia and outcomes without restricting the identification for those whose symptoms are severe enough for a clinical diagnosis. The limitation of reduced-form models is that they do not identify the quantitative size of the link between schizophrenia and outcomes (VanderWeele et al., 2014). The statistical analyses were performed using Stata 17.0 (Stata Corp, College Station, TX).

3. Measures

3.1. Outcome variables

We focused on five outcomes drawn from the FLEED: 1) years of education in 2001; 2) the logarithm of the average annual wage and salary earnings in 2001–2012; 3) the share of years employed in 2001–2012; 4) an indicator for whether an individual received any social income transfer payments in 2001–2012; and 5) the logarithm of the average annual social income transfers conditional on receiving any in 2001–2012.

3.2. Schizophrenia PGS

As an indicator of the genetic propensity for schizophrenia, we used a PGS calculated as a weighted sum of single nucleotide polymorphisms (SNPs) that were associated with schizophrenia ($p < 0.01$) in a genome-wide association study (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The weights indicated the effect sizes of each SNP to the propensity of developing schizophrenia. The threshold value $p < 0.01$ was chosen to maximize the PGS strength (*relevance*). For further technical information on genotyping and the calculation of the PGS, see Supplementary Appendix 1.

3.3. Control variables

To account for the possibility that the SNPs included in schizophrenia PGSs are not randomly assigned at the population level (*independence*), we controlled for birth cohort, sex, and four regional indicators indicating the region of residence in 1980. In addition, we used control variables, which equalled one if the mother or father had been, at some point, diagnosed with a mental health disorder. Information was based on parental self-reports in 1980 and 1983. Because of genetic overlap between schizophrenia and mood disorders (Witt et al., 2017), we also controlled for PGSs for bipolar disorders (Ruderfer et al., 2014) and major depression (Hyde et al., 2016).

4. Results

Descriptive statistics are reported in Supplementary Table A1. The OLS estimates (Table 1) showed that a one standard deviation (SD) increase in the schizophrenia PGS was related to 6% lower earnings ($p < 0.05$), 1% fewer years spent employed ($p < 0.05$), and a two-percentage point higher probability of receiving social income transfers ($p < 0.05$). A one SD increase in the schizophrenia PGS was also related to 0.1 fewer years of education, suggesting that education may partly mediate the link between the schizophrenia PGS and LMO. The links related to LMO were more pronounced among males. As there was no significant difference in the average schizophrenia PGS scores between males and females ($p = 0.987$), the results suggest that male sex is a risk factor for more severe schizophrenia-related symptoms, which is consistent with previous findings (Aleman et al., 2003).

Table 1 reported only the coefficients for schizophrenia PGS. Coefficients for PGSs for bipolar disorders and major depression are shown in Supplementary Table A2. These results showed that the coefficients for bipolar disorders and major depression PGSs were statistically insignificant, suggesting that genetic liability for these conditions did not lead to major negative effects in education and average labour market outcomes.

We tested the sensitivity of the results in Table 1 controlling for mother's and father's mental health diagnoses. We found that excluding both mother's and father's mental health diagnosis indicators from the set of controls had only a minor effect on the point estimates and our conclusions remain intact (Supplementary Table A3). As another sensitivity analysis, we excluded individuals who had received a schizophrenia diagnosis between 1980 and 2018 based on FHDR data

Table 1
Schizophrenia PGS and average labour market outcomes, 2001–2012.

	All β-coefficient (95% CI)	Sex	
		Male β-coefficient (95% CI)	Female β-coefficient (95% CI)
Panel A	n = 2424	n = 1116	n = 1308
Years of education, 2001	**−0.10 (-0.20, -0.00)**	−0.06 (−0.21, 0.08)	**−0.15 (-0.29, -0.01)**
Log of average earnings, 2001–2012	**−0.06 (-0.12, -0.00)**	−0.07 (−0.16, 0.01)	−0.05 (−0.13, 0.03)
Share of years employed, 2001–2012	**−0.01 (-0.02, -0.00)**	**−0.02 (-0.03, -0.00)**	−0.01 (−0.02, 0.00)
Indicator for social income transfers, 2001–2012	**0.02 (0.00, 0.03)**	**0.03 (0.01, 0.06)**	0.01 (−0.01, 0.03)
Panel B	n = 1997	n = 864	n = 1133
Log of average social income transfers	0.06 (−0.00, 0.12)	**0.12 (0.01, 0.23)**	0.03 (−0.05, 0.10)

Note: The models were estimated using OLS. The table reports the standardized OLS coefficients with 95% confidence intervals in parenthesis. All models control for birth cohort, region of residence in 1980, PGSs for bipolar disorders and major depression, parental mental health disorders (and sex). Bold text signifies $p < 0.05$.

(Supplementary Table A4). The results were similar to those in Table 1 indicating that our main results were not driven by individuals who had been diagnosed with schizophrenia.

5. Discussion

The results of this study showed that a higher genetic risk for developing schizophrenia, but not bipolar disorders and major depression, was related to lower educational attainment and weaker labour market performance. The present findings are consistent with studies indicating a link between schizophrenia PGS and lower educational attainment (Escott-Price et al., 2020). However, the association between schizophrenia PGS and long-term LMO has not been previously examined. Our findings suggested that a one SD increase in the schizophrenia PGS was related to 6% lower earnings in the long term.

The main strengths of this study are based on data combining longitudinal register-based information on LMO with information on schizophrenia PGS. By focusing on genetic risk instead of phenotype, the attrition problems stemming from severe diseases were reduced. Instead of identifying the effect of a serious mental health disorder (i.e., schizophrenia), our results conceivably capture the link between traits and symptoms associated with genetic liability for schizophrenia and its outcomes. In addition, the data avoid biases from self-reported labour market measures, and the use of long-term LMO information mitigates the effects of short-term business cycle fluctuations that might otherwise bias the estimates. The most important limitation stems from potential violations of the identifying assumptions. The independence assumption (i.e., that the SNPs are randomly assigned at the population level) is violated if allele frequencies differ between population subgroups, if phenotype affects the partner selection, or if the parental phenotype directly affects the offspring phenotype. The exclusion restriction, in turn, is violated if the schizophrenia PGS SNPs affect the outcome variables via routes other than schizophrenia-related symptoms. We used control variables to mitigate the possibility of the violation of independence or exclusion restriction affecting our results. However, this possibility cannot completely be ruled out.

In conclusion, genetic liability for schizophrenia may hinder individuals' ability to fully participate in the labour market, thus potentially reinforcing social exclusion. Assuming that the observed relationship is causal, our results conceivably capture the link between schizophrenia or schizophrenia-related traits, such as impaired motivation or cognition, which affect LMOs. In Finland, access to health care is universal, but in countries without such a health care system, the negative labour market effects may be even more pronounced.

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Data availability

The dataset supporting the conclusions of this article were obtained from the Cardiovascular Risk in Young Finns Study (YFS) and Statistics Finland register data after submission and approval of our study plan by the YFS coordinators. The YFS dataset comprises health related participant data and their use is therefore restricted under the regulations on professional secrecy (Act on the Openness of Government Activities, 612/1999) and on sensitive personal data (Personal Data Act, 523/1999, implementing the EU data protection directive 95/46/EC). Due to these legal restrictions, the data from this study cannot be stored in public repositories or otherwise made publicly available. However, data access may be permitted on a case-by-case basis upon request only. Data sharing outside the group is done in collaboration with YFS group and requires a data-sharing agreement with YFS representatives and appropriate contracts with Statistics Finland. The linked YFS-FLEED-LPC data can only be used in Statistics Finland remote access system (FIONA). Investigators can submit an expression of interest to the chairman of the publication committee (Prof. Mika Kähönen, Tampere University, Finland).

Author contributions

JV Conceptualization, Methodology, Formal Analysis, Writing – original draft, Writing – Review & Editing; PB Conceptualization, Methodology, Writing – Review & Editing; CH Conceptualization, Writing – Review & Editing; JTK Conceptualization, Writing – Review & Editing; TL Conceptualization, Writing – Review & Editing; OR Conceptualization, Methodology, Writing – Review & Editing, Funding acquisition, Project Administration (YFS); JP Conceptualization, Writing – Review & Editing, Funding acquisition, Project Administration (YFS-FLEED-LPC). All authors approved the final version of the paper.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.05.041.

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