# Association of Occupational Dysfunction and Hospital Admissions With Different Polygenic Profiles in Bipolar Disorder

# Not all bipolar disorder outcomes are created equal: occupational dysfunction and hospital admissions associate with different polygenic profiles

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**Word count:** 3,905 words

**Number of tables:** 3

**Number of figures:** 1

**Disclosures:** ML declares that he has received lecture honoraria from Lundbeck pharmaceuticals outside the present work. The other authors declare no conflict of interest.

## ABSTRACT

**Objective:** Hospital care due to severe mood episodes are consequences for many but not all persons with bipolar disorder. Likewise, some but not all patients suffer long-term occupational dysfunction that extend beyond acute mood episodes. It is not known whether these dissimilar outcomes of bipolar disorder are driven by different polygenic profiles. We assessed how polygenic scores (PGS) for major psychiatric disorders and educational attainment associate with occupational functioning and psychiatric hospital admissions in bipolar disorder.

**Method:** A total of 4,782 bipolar disorder patients and 2,907 control subjects were genotyped and linked to Swedish national registers. Longitudinal measures from at least 10 years of registry data were used to derive percent of years without employment, with long-term sick leave, and the mean number of psychiatric hospital admissions per year. Ordinal regression was used to test the associations between outcomes and PGS for bipolar disorder, schizophrenia, major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), and educational attainment. Replication analyses of hospital admissions were conducted in the Bipolar Disorder Research Network (N=4,219).

**Results**: Long-term sick leave and unemployment in bipolar disorder were significantly associated with PGS for schizophrenia, ADHD, MDD, and educational attainment, but not bipolar disorder. By contrast, the number of hospital admissions per year associated with higher PGS for bipolar disorder and schizophrenia, but not with the other PGS.

**Conclusions:** Bipolar disorder severity (indexed by hospital admissions) associates with a different polygenic profile than long-term occupational dysfunction. This has clinical implications, suggesting that mitigating occupational dysfunction requires other interventions than those deployed to prevent mood episodes.

## INTRODUCTION

Bipolar disorder is characterized by recurring periods of elevated or depressed mood. Acute mood episodes are managed in psychiatric outpatient or inpatient care depending on the severity. Manic episodes typically warrant hospital care. Hospitalisation is also considered when a depressive episode is too severe to be managed in psychiatric outpatient care. The need for inpatient care varies among persons with bipolar disorder and many bipolar disorder patients can be successfully managed in outpatient care only. The need for hospitalisation thus reflects the severity of acute mood episodes.

Aside from the impairments associated with acute mood episodes, persons with bipolar disorder might suffer from persistent psychosocial and occupational deficits. Indeed, as many as 30–60% of bipolar disorder patients fail to regain full functioning in occupational and social domains after illness onset[1]. Only half of persons with bipolar disorder are within the workforce[2,3]. This is not only much lower than the general population, but also lower than persons with unipolar depression[3]. Bipolar disorder is in fact one of the main causes of disability among young adults[4]. Occupational disability is also an important driver of the societal costs associated with bipolar disorder, where one estimate found that 75% of the total societal costs could be attributed to sick leave and early retirement[5].

To mitigate occupational dysfunction in bipolar disorder, it is key to identify the driving mechanisms. One would assume that persons with more severe mood episodes have worse long-term functional outcome. But classical measures of illness severity—such as the number of psychiatric hospital admissions—in fact correlates poorly with psychosocial functioning[6]. Instead, we and others showed an association between executive functioning and occupational functioning[7,8]. This suggests that abiding functional sequels of bipolar disorder is determined by other factors than those that cause mood symptoms manifested during acute mood episodes.

Polygenic scores (PGS) can be calculated for a range of different traits and is a tool to unearth genetic components that drive specific subphenotypes within a diagnostic category. In bipolar disorder, specific subphenotypes such as number of hospital admissions[9] and psychosis[10] have previously been associated with polygenic risk for schizophrenia. It is, however, not known whether long-term occupational functioning associates with particular polygenic liabilities.

The aim of this study is to assess the respective polygenic profiles of occupational functioning and severity of mood episodes in bipolar disorder. To this end, we calculated PGS for bipolar disorder, schizophrenia, Major Depressive Disorder (MDD), Attention Deficit Hyperactivity Disorder (ADHD), and educational attainment in a cohort of persons with bipolar disorder (N=4,782), control sample (N=2,907), and in the replication cohort Bipolar Disorder Research Network (BDRN, N=4,219). Long-term longitudinal data on occupational functioning (unemployment and long-term sick leave) and psychiatric hospital admissions in the main analyses were obtained by linkage to Swedish national registers.

## METHODS

### Population

Persons diagnosed with bipolar disorder type 1, bipolar disorder type 2, or bipolar disorder not otherwise specified (NOS) in the Swedish Bipolar Collection (SWEBIC) were included in the study. Most study participants in SWEBIC were enrolled through the Swedish National Quality Register for bipolar disorder (BipoläR) [11]. A smaller number were recruited from the St. Göran Bipolar Project[12-14], and some were identified in the Swedish National Patient Register using a validated algorithm[15].

Controls were obtained from the general population in Sweden. They were selected at random from Swedish population registers, where the inclusion criteria included never being hospitalized for schizophrenia or bipolar disorder, both parents born in Scandinavia and age

18 years or older[16]. To avoid a "supernormal" control sample, we chose not to exclude subjects hospitalized for other psychiatric reasons. [16]

We linked patients in SWEBIC and the control sample to longitudinal Swedish population-based registers using the unique personal identification number assigned to all persons living in Sweden[17]. Both SWEBIC and the control sample collection were approved by the Regional Ethical Review Board in Stockholm, Sweden, and all participants provided written informed consent.

**Phenotypic measures**

*Unemployment and long-term sick leave*

To capture occupational functioning in bipolar disorder, we included measures of employment and long-term sick leave gathered from the longitudinal integrated database for health insurance and labour market studies (LISA) [18]. We included registrations between the ages 25 and 65 (retirement age in Sweden) and only considered individuals with at least 10 years of registrations during 1993–2015.

For measures of employment, we included yearly reports in October and November capturing if a subject held an employment that year[18]. Long-term sick leave or early retirement for each year was defined as having more than 60 full sick leave days *or* receiving any reimbursement for early retirement. The number of years without employment or with long-term sick leave were divided by the total number of years with registrations to calculate the percentage of years without employment or on sick leave. Since the raw data had both ceiling and floor effects, with majority of patients towards the end of the extremes 0% and 100%, we grouped the percentage of years without employed or on long-term sick leave into four categories (<25%, 25–50%, 50–75% and >75% of the years) as outlined in Table 1. Given previous indications that occupational functioning decrease by age in bipolar disorder[2], we conducted

sensitivity analyses where we stratified occupational functioning by two age spans (25–39, and 40–65). A detailed description of the phenotype definitions is given in Supplementary methods.

*Number of psychiatric hospital admissions*

The patient register has full coverage of psychiatric hospital admissions since 1973. We retrieved information about psychiatric hospital admissions from the Swedish National Patient Register 1973-01-01 to 2016-12-31. To estimate how many years a subject had the possibility of being included in the patient register, we counted the number of years between 1973-01-01, or from the date subjects turned 15 years old, until subjects turned 70 years old, death, or 2016-12-31. Subjects with fewer than 10 years of possible inclusion in the register were excluded. We used the years of possible inclusion in the patient register to calculate the mean number of psychiatric hospital admissions per year. Since hospital admissions has a skewed distribution, we grouped subjects into four categories (0, 0–0.1, >0.1–0.3, and >0.3 psychiatric hospital admissions per year) where the categories correspond to no admissions (average of zero admissions), up to one admission per decade (average of >0 to 0.1 admissions per year), between >1 to 3 admissions per decade (average of >0.1 to 0.3 admissions per year), and patients with more than 3 admissions per decade (average >0.3 admissions per year). The intensity of hospital admissions might differ by age. We therefore conducted sensitivity analyses where we used age at hospital admissions to stratify the intensity during two age spans (15–39 and 40–70 years of age).

**Genotyping and polygenic scoring**

DNA extraction from whole blood samples and genotyping in SWEBIC patients[19] and the controls[16] has previously been described. In short, genotyping of patients and controls was done using three genotyping arrays: Affymetrix 6.0 chips (Affymetrix, Santa Clara, CA,

USA), Illumina OmniExpress chips (Illumina, San Diego, CA, USA), and Infinium PsychArray-24 v1.2 BeadChip (Illumina, San Diego, CA, USA). Quality control was done using the Ricopili pipeline[20] and genotypes were imputed to the HRC 1.1 reference panel using the Sanger imputation server[21].

We used publicly available summary statistics from genome-wide association studies to calculate PGS for psychiatric disorders and educational attainment in our study sample. These PGS were chosen to capture disorders on the psychotic/affective spectrum (bipolar disorder, schizophrenia, and MDD), a commonly comorbid disorder (ADHD), and cognitive abilities (educational attainment). Summary statistics for bipolar disorder (bip2021, excluding our SWEBIC sample)[22] and schizophrenia (scz2022, excluding all Swedish samples)[23] were received from Psychiatric Genomics Consortium (PGC). We also used publicly available summary statistics for MDD (mdd2018, excluding 23andMe)[24], ADHD (adhd2019)[25], educational attainment[26] and Alcohol Use Disorders Identification Test (AUDIT, excluding 23andMe)[27]. To minimize multiple testing, we only tested the *P*-value thresholds ($P_T$) that previously shown to best predict their respective phenotypes: $P_T<0.1$ for bipolar disorder, schizophrenia, ADHD and AUDIT; $P_T<0.5$ for MDD; and $P_T<0.05$ for educational attainment. We only included variants with INFO score >0.9 for all PGSs (INFO not available for educational attainment).

We calculated PGSs within each genotyping wave separately using hard call genotypes. We included autosomal single nucleotide polymorphisms (SNPs) with INFO score>0.9, MAF>0.01, strand unambiguous SNPs, >98% genotype success rate, and not in the extended MHC region (chr6:25-34 Mb, hg19). To exclude variants in linkage disequilibrium (LD), we clumped based on $r^2<0.2$ within a 500 kb window using the SWEBIC cohort as LD reference. PRSice (v. 2.3.3)[28] was used for LD clumping and polygenic scoring. PGSs standardized ([x

– mean] / SD) within each genotyping wave, including both bipolar disorder cases and controls, were used for statistical analyses.

**Statistical analyses**

We conducted ordinal regression for association analyses between the included phenotypes and PGSs using R (v. 4.0.2). We adjusted regression analyses for sex, the first six ancestry principal components, genotyping wave, and year of birth grouped into 6 categories (<1955, 1955–62, 1963–69, 1970–77, 1978–88, >1988). We used Bonferroni correction for multiple testing: correcting for six PGS and three phenotypes (18 tests) yielded a *P*-value threshold for significance $P_T$<0.0028. To correct for possible influence of age of onset, we included information about age at first symptom before and after age 24 (see description in supplementary methods). Results after correcting for age of first symptom are presented in Table S1 and Table S2.

**BDRN replication cohort**

The replication cohort included bipolar disorder patients from the UK Bipolar Disorder Research Network (BDRN) study[29,30]. Information about number of psychiatric hospital admissions and age at interview was available for 4,219 subjects with DSM-IV bipolar disorder type 1 (N=2,906), bipolar disorder type 2 (N=1,239), or bipolar disorder NOS (N=74). All the subjects used in the analysis have at least 10 years history of disease. Hospital admissions per year was calculated by dividing number of hospital admissions by the number of years between age 15 and age at interview. Number of admissions per year was grouped into four categories as in the main analysis.

Participants were genotyped on Affymetrix GeneChip 500K Mapping Array Set, Illumina Omni Express Array, and Illumina PsychChip. For each array strict quality control (QC) was performed separately. QC used PLINK 1.9[31] software excluding SNPs with MAF<0.01,

198 deviation from Hardy-Weinberg Equilibrium (HWE) at P≤ 10-6, call rate < 98%. Individuals
199 were excluded from the sample if they had increased or decreased heterozygosity of |F| > 0.1,
200 a discrepancy between their genotypic and reported sex, genotype call rate < 98%, high
201 pairwise relatedness (pi-hat > 0.2) or did not cluster with European population samples in
202 principal component analysis of 2000 participants from 19 populations of the 1000 Genomes
203 Project. After QC, data for each platform were phased using SHAPEIT version 3.4.0.1023[32]
204 and imputed using IMPUTE2[33] with the 1000 Genomes Project reference panel (phase 3).
205 Imputed genotype dosages were converted to the most probable genotypes (probability ≥ 0.9)
206 with additional SNPs excluded if the imputation INFO score was <0.8, MAF<0.01 or
207 HWEP<1e-6). Imputed data were then merged on common SNPs between platforms.

208 The polygenic scoring in BDRN were based on the same summary statistics as in the main
209 analyses. However, summary statistics for schizophrenia and bipolar disorder were based on
210 results excluding overlapping subjects from the BDRN cohort. PGS generation used PLINK
211 version 1.9[31] in PRSice[34]. Imputed genotypes were clumped for linkage disequilibrium
212 (window, 250 kb; r2 = 0.1) and single-nucleotide polymorphisms most significantly
213 associated with the different traits were retained. After clumping, PRSs were generated at
214 different P value thresholds ($P_T$) p < 1.00, p ≤ .50, p ≤ .20, p ≤ .10, p ≤ .05, p≤ .01, and p≤ .001
215 and converted to z scores. For each of the PGS, we included the same p-value thresholds in
216 the statistical analyses as described for the main analyses in the SWEBIC cohort. To test the
217 association between hospital admissions and the PGS, we conducted ordinal logistic
218 regression analyses adjusting for ten ancestry principal components, genotyping platform, and
219 sex using R.

220 **RESULTS**

221 *Sample characteristics*

A total of 4,782 bipolar disorder cases with phenotypic data from the SWEBIC population and 2,963 control subjects were included for association analyses between PGSs for selected traits and number of psychiatric hospital admissions per year and occupational functioning (unemployment and long-term sick leave) (Table 1). The number of years with information regarding employment and sick leave ranged between 10 and 23 years with a mean of 20 years for in total 4,139 patients and 2,963 controls. The mean percentage of years with registered long-term sick leave was 49% in cases and 13% in controls, while the mean percentage of years registered as unemployed were 40% in cases and 15% in controls. For sensitivity analyses, measures of employment and sick leave in bipolar disorder patients were also included during two age spans (age 25–39, N=1,649; age 40–65, N=2,999).

Information about psychiatric hospital admissions intensity between 1973 and 2016 were available for 4,782 bipolar disorder patients and 3,339 controls between ages 15 and 70. The mean years of possible inclusion in the national patient register in the patient group was 36 years (range 10–44 years) with a mean of 0.2 psychiatric hospital admissions per year, which corresponds to an average of two hospital admissions per decade. For sensitivity analyses, number of hospital admissions per year was analysed in two age spans (age 15–39, N=4,180; age 40–70, N=3,213), where 2,611 patients had at least 10 years hospital admission intensity measurements during both age spans. The control group had an average of 39 years' (range 12–44 years) worth of data on hospital admissions available; 134 control subjects had one or more psychiatric hospitalization for other indications than bipolar disorder or schizophrenia.

*Polygenic score analyses*

We tested the association between occupational functioning as well as psychiatric hospital admissions and PGS for four psychiatric disorders (bipolar disorder, schizophrenia, ADHD, and MDD), AUDIT, and educational attainment in bipolar disorder. This was followed up by

conducting association analyses between PGS and occupational functioning in a control sample, as well as psychiatric hospitalisations in the patient cohort BDRN.

In bipolar disorder cases, Figure 1 shows that the number of hospital admissions per year was significantly associated with higher PGS for bipolar disorder (OR=1.14, $P$=2.4x10$^{-6}$) and schizophrenia (OR=1.23, $P$=6.5x10$^{-12}$), but not significantly associated with PGS for ADHD, MDD, or educational attainment. By contrast, unemployment and long-term sick leave were significantly associated with higher PGS for MDD (unemployment: OR=1.17, $P$=1.9x10$^{-7}$; sick leave: OR=1.20, $P$=3.0x10$^{-10}$), schizophrenia (unemployment: OR=1.16, $P$=4.1x10$^{-6}$), and ADHD (unemployment: OR=1.13, $P$=3.9 x 10$^{-5}$; sick leave: OR=1.12, $P$=6.4x10$^{-5}$), as well as with lower PGS for educational attainment (unemployment: OR=0.83, $P$=7.6x10$^{-11}$; sick leave: OR=0.85, $P$=3.0 x 10$^{-9}$). PGS for bipolar disorder and AUDIT-PGS were not associated with unemployment or long-term sick leave. The results remained after correcting for age of first symptom (Table S1).

In controls, both measures of occupational functioning were associated with PGS for MDD, ADHD, and educational attainment in the same direction as in bipolar patients ($P$<0.05). PGS for bipolar disorder and schizophrenia were not associated with occupational functioning in control subjects (Figure 1).

In the BDRN cohort, we could replicate the association between psychiatric hospitalizations and PGS for bipolar disorder (OR=1.17, $P$=3.3 x10$^{-8}$) and schizophrenia (OR=1.19, $P$=2.5x10$^{-8}$; Table 3). In BDRN, a lower PGS for ADHD was also associated with increased psychiatric hospitalizations (OR=0.91, $P$=0.0013).

In Figure 1, we present the main association analyses separately for bipolar disorder type 1, type 2, and NOS. For bipolar disorder type 1, the occupational phenotypes were significantly associated with PGS in the same direction as the whole group, whereas hospitalizations only

associated with SCZ-PGS (OR=1.17, P=6.9x10$^{-4}$). With respect to bipolar disorder type 2, we observe consistent trends with the overall sample between PGS and phenotypes. However, only certain PGS showed significant associations ($P$<0.05) with employment (ADHD-PGS and EA-PGS), sick leave (MDD-PGS, ADHD-PGS, and EA-PGS), and hospitalizations (MDD-PGS and SCZ-PGS). Within the NOS category, we found similar results to the whole group analysis with regards to employment, where the same PGS associated at $P$<0.05 (SCZ-PGS, MDD-PGS, ADHD-PGS, and EA-PGS). However, only MDD-PGS associated with sick leave and there were no significant associations at $P$<0.05 with hospitalizations. In bipolar subtype specific analyses in BDRN, bipolar disorder-PGS, SCZ-PGS, and ADHD-PGS were associated ($P$<0.05) with hospitalizations in bipolar disorder type 1 (Table 3).

Occupational dysfunction and hospital admission intensity might differ depending on age[2]. We conducted sensitivity analyses stratified by intensities during the time before and after age 40 (Table S2). In the older age group, the effect sizes for the PGS associations with long-term sick leave and employment resembled the main analyses and were generally larger (Table S2). In the younger age group, however, not all PGS were significantly associated with occupational outcomes: Unemployment associated with SCZ-PGS (OR=1.11, $P$=0.043), ADHD-PGS (OR=1.13, $P$=0.012), and EA-PGS (OR=0.86, $P$=6.5x10$^{-4}$). Long-term sick leave associated with MDD-PGS (OR=1.04, $P$=0.015), ADHD-PGS (OR=1.11, $P$=0.034), and EA-PGS (OR=0.85, P=4.7x10$^{-4}$). Further, in the older age group hospital admission intensity was positively correlated with MDD-PGS (OR=1.12, $P$=6.3x10$^{-4}$) and schizophrenia-PGS (OR=1.16, $P$=4.1x10$^{-5}$), but negatively correlated with PGS for educational attainment (OR=0.89, $P$=4.3x10$^{-4}$). In the younger age group, hospital admission intensity was associated with PGS for bipolar disorder (OR=1.20, $P$=3.2x10$^{-9}$), schizophrenia (OR=1.23, $P$=2.9x10$^{-10}$), and educational attainment (OR=1.12, $P$=4.9x10$^{-5}$). To test if these results were driven by age of onset, we corrected the regression analyses for age at first

symptom (before/after age 24) and the main results remained associated after correction as seen in table S2.

## DISCUSSION

Hospitalization due to severe acute mood episodes and long-term occupational dysfunction are both serious consequences of bipolar disorder. Here we demonstrate that these key outcomes are differentially related to genetic factors: Psychiatric hospitalizations are associated with polygenic risk for bipolar disorder and schizophrenia, but not MDD, ADHD, or educational attainment. We replicate the association between hospitalizations and PGS for schizophrenia and bipolar disorder in the BDRN cohort. By contrast, occupational dysfunction correlated with polygenic scores for educational attainment, ADHD, MDD, and schizophrenia, but showed no association with polygenic risk for bipolar disorder. Interestingly, similar polygenic liabilities associated with occupational dysfunction in controls, suggesting that the polygenic links to occupational dysfunction demonstrated here are not specific for persons with bipolar disorder.

The observation that polygenic risk for bipolar disorder is associated with psychiatric hospitalizations accords previous findings[9,10]. This association could be expected as most patients in the PGC training set for the PGS have bipolar disorder type 1, who typically have a higher number of hospitalizations than type 2. The polygenic risks associated with unemployment and long-term sick leave are novel findings that have bearing on clinical strategies for improving outcomes in bipolar disorder. The management of bipolar disorder primarily revolves around prevention of mood episodes with the assumption that patients will functionally recover with subsiding symptoms. But many patients remain functionally impaired despite best available treatment, and deficits in psychosocial functioning in bipolar disorder may persist long after symptom recovery[35]. The high rates of occupational

dysfunction not only affect patients' quality of life and socioeconomic status[2], but is also a major driver of the societal costs caused by the disorder[5].

Polygenic risk for ADHD has previously been associated with rapid cycling[36] and age of onset[37] in bipolar disorder. Our finding that polygenic scores for ADHD and educational attainment are also associated with occupational dysfunction echoes the clinical observations that comorbid ADHD[14], years of education, and cognitive performance[2,7,38] are strong predictors of occupational functioning. Our result for educational attainment PGS in controls accords the positive correlation between education and occupational functioning[39]. Clinical studies have also found that comorbid ADHD is associated with worse clinical outcome in bipolar disorder, including earlier onset and higher frequency of depressive—but not manic—episodes[14]. Given that hospitalization is more common for manic than depressive episodes, this might partly explain why lower ADHD-PGS was associated with hospitalizations in the replication BDRN cohort. Taken together, our findings extend these clinical observations by demonstrating that not only a clinical ADHD diagnosis, but also higher polygenic risk for ADHD, increase the risk for long-term impairment. Together these results suggest that a developmental perspective is needed to improve long-term outcome also in bipolar disorder[40]. Occupational outcomes in bipolar disorder patients might be improved by addressing other domains than core mood symptoms including ADHD symptoms—potentially also subsyndromal manifestations—and cognitive dysfunction.

Polygenic risk for MDD has previously been associated with rapid cycling[36] and suicide attempts[41] in bipolar disorder. Here, we add occupational dysfunction to the list of negative consequences of high polygenic liability for MDD.

Polygenic risk for schizophrenia was the only trait in our study that significantly associated with both occupational functioning and hospital admissions in persons with bipolar disorder. Although a genetic overlap between schizophrenia and bipolar disorder has been

demonstrated[10], these findings show that polygenic liability for bipolar disorder and schizophrenia differ with respect to functional outcomes. Consistent with our findings on occupational functioning, schizophrenia risk alleles have previously been associated with poorer cognitive performance, whereas bipolar disorder risk alleles have been associated with better cognitive performance[42].

To account for the potentially increasing risk of occupational dysfunction with higher age[2], we stratified analyses by intensities before and after age 40. The effect sizes for PGSs associated with long-term sick leave in the main analyses (SCZ, MDD, ADHD, and educational attainment) were slightly larger in the older age group. Conversely, the association between hospital admissions and bipolar disorder-PGS was limited to the younger age group (age 15–39). In addition, educational attainment-PGS exhibited associations with hospital admissions in opposite directions within the two age groups. This suggest that our outcomes capture different traits depending on age. The intensity of hospital admissions appears to relate to more frequent severe mood episodes in the younger age group, but may be confounded by treatment response or cognitive ability to cope with the disorder in older age.

Strengths of this study include that we capture complete data on hospital care, employment, and sick leave during at least 10 years for each subject in a large sample of bipolar disorder patients. There are also some limitations to consider. First, register data do not include reasons for being without employment. In fact, one reason could be due to university studies, which is why we restricted the inclusion to subjects at least 25 years of age as most students have finished their education by the age of 25. Further, the frequency of long-term sick leave and early retirement are to some extent influenced by changes in social security policy during the study period. This might influence the age-specific analyses. Moreover, as we do not have information on the specific reason for sick-leave or early retirement, some of these recordings might reflect sick leave for reasons other than bipolar disorder. Second, although we observe

and replicate associations between PGSs and important bipolar disorder phenotypes, the variance explained is still insufficient to be considered for clinical use in personalized psychiatry. Finally, some of our findings in the sensitivity analyses could be chance findings that would need to be followed up in future studies.

In conclusion, our results suggest that the underlying polygenetic liability for the severity of bipolar illness in terms of psychiatric hospitalisations clearly differs from the occupational outcome. This is important information given that much of the lifetime burden of bipolar disorder is driven by prolonged periods of sick leave and/or unemployment rather than acute mood episodes. Even if clinical symptoms are improved, psychosocial impairments may persist[43], which suggests that interventions other than those used to prevent mood episodes might be required to mitigate functional impairment. This might include addressing co-morbid symptoms (e.g., ADHD) or cognitive dysfunction through cognitive remediation therapy. Clarifying the underlying mechanisms of poor outcome is an important step towards targeted treatment interventions, and might also be used for prognostic purposes.

**ACKNOWLEDGEMENT**

We are deeply grateful for the participation of all subjects contributing to this research, and to the collection team that worked to recruit them including project leaders Dennis Hellgren, data manager Bozenna Illiadou, study nurses Birgitta Ohlander, Radja Satgunanthan-Dawoud, Martina Wennberg, and Caroline Westerberg Hake. We also wish to thank the Swedish National Quality Register for Bipolar Disorders (BipoläR). Funding support for SWEBIC was provided by the Stanley Center for Psychiatric Research, Broad Institute from a grant from Stanley Medical Research Institute. Funding for this specific project was provided by the Swedish Research Council (2022-01643) and the Swedish Brain foundation (FO2022-0217). BDRN wishes to acknowledge funding from the Wellcome Trust and Stanley Medical Research Institute, and to thank all BDRN research participants for ongoing support. LJ is

394 supported by ALFGBG-966370 and Genomic Medicine Sweden (GMS K131050263). ES is
395 supported by ALFGBG-933732. ML was supported by Wenner-Gren foundation (SSv2019-
396 0008).

## REFERENCES


1. MacQueen GM, Young LT, Joffe RT. A review of psychosocial outcome in patients with bipolar disorder. Acta Psychiatr Scand. 2001;103(3):163-70.
2. Hakulinen C, Musliner KL, Agerbo E. Bipolar disorder and depression in early adulthood and long-term employment, income, and educational attainment: A nationwide cohort study of 2,390,127 individuals. Depress Anxiety. 2019;36(11):1080-8.
3. Marwaha S, Durrani A, Singh S. Employment outcomes in people with bipolar disorder: a systematic review. Acta Psychiatr Scand. 2013;128(3):179-93.
4. Alonso J, Petukhova M, Vilagut G, et al. Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. Mol Psychiatry. 2011;16(12):1234-46.
5. Ekman M, Granstrom O, Omerov S, et al. The societal cost of bipolar disorder in Sweden. Soc Psychiatry Psychiatr Epidemiol. 2013;48(10):1601-10.
6. Sole B, Bonnin CM, Jimenez E, et al. Heterogeneity of functional outcomes in patients with bipolar disorder: a cluster-analytic approach. Acta Psychiatr Scand. 2018;137(6):516-27.
7. Drakopoulos J, Sparding T, Clements C, et al. Executive functioning but not IQ or illness severity predicts occupational status in bipolar disorder. Int J Bipolar Disord. 2020;8(1):7.
8. Koene J, Zyto S, van der Stel J, et al. The relations between executive functions and occupational functioning in individuals with bipolar disorder: a scoping review. Int J Bipolar Disord. 2022;10(1):8.
9. Kalman JL, Papiol S, Grigoroiu-Serbanescu M, et al. Genetic risk for psychiatric illness is associated with the number of hospitalizations of bipolar disorder patients. J Affect Disord. 2021;296:532-40.

10. Ruderfer D, Bipolar D, Schizophrenia Working Group of the Psychiatric Genomics Consortium. Electronic address drve, et al. Genomic Dissection of Bipolar Disorder and Schizophrenia, Including 28 Subphenotypes. Cell. 2018;173(7):1705-15 e16.
11. Pålsson E, Melchior L, Lindwall Sundel K, et al. Cohort profile: the Swedish National Quality Register for bipolar disorder(BipoläR). BMJ Open. 2022;12.
12. Ekman CJ, Lind J, Ryden E, et al. Manic episodes are associated with grey matter volume reduction - a voxel-based morphometry brain analysis. Acta Psychiatr Scand. 2010;122(6):507-15.
13. Jakobsson J, Zetterberg H, Blennow K, et al. Altered concentrations of amyloid precursor protein metabolites in the cerebrospinal fluid of patients with bipolar disorder. Neuropsychopharmacology. 2013;38(4):664-72.
14. Ryden E, Thase ME, Straht D, et al. A history of childhood attention-deficit hyperactivity disorder (ADHD) impacts clinical outcome in adult bipolar patients regardless of current ADHD. Acta Psychiatr Scand. 2009;120(3):239-46.
15. Sellgren C, Landen M, Lichtenstein P, et al. Validity of bipolar disorder hospital discharge diagnoses: file review and multiple register linkage in Sweden. Acta Psychiatr Scand. 2011;124(6):447-53.
16. Ripke S, O'Dushlaine C, Chambert K, et al. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. Nat Genet. 2013;45(10):1150-9.
17. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.
18. Ludvigsson JF, Svedberg P, Olen O, et al. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423-37.

19. Charney AW, Stahl EA, Green EK, et al. Contribution of Rare Copy Number Variants to Bipolar Disorder Risk Is Limited to Schizoaffective Cases. Biol Psychiatry. 2019;86(2):110-9.
20. Lam M, Awasthi S, Watson HJ, et al. RICOPILI: Rapid Imputation for COnsortias PIpeLIne. Bioinformatics. 2020;36(3):930-3.
21. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. Nat Genet. 2016;48(10):1279-83.
22. Mullins N, Forstner AJ, O'Connell KS, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. Nat Genet. 2021;53(6):817-29.
23. Trubetskoy V, Pardinas AF, Qi T, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature. 2022;604(7906):502-8.
24. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50(5):668-81.
25. Demontis D, Walters RK, Martin J, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51(1):63-75.
26. Lee JJ, Wedow R, Okbay A, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. Nat Genet. 2018;50(8):1112-21.
27. Sanchez-Roige S, Palmer AA, Fontanillas P, et al. Genome-Wide Association Study Meta-Analysis of the Alcohol Use Disorders Identification Test (AUDIT) in Two Population-Based Cohorts. Am J Psychiatry. 2019;176(2):107-18.
28. Choi SW, O'Reilly PF. PRSice-2: Polygenic Risk Score software for biobank-scale data. Gigascience. 2019;8(7).

29. Gordon-Smith K, Forty L, Chan C, et al. Rapid cycling as a feature of bipolar disorder and comorbid migraine. Journal of affective disorders. 2015;175:320-4.
30. Di Florio A, Mei Kay Yang J, Crawford K, et al. Post-partum psychosis and its association with bipolar disorder in the UK: a case-control study using polygenic risk scores. Lancet Psychiatry. 2021;8(12):1045-52.
31. Chang CC, Chow CC, Tellier LC, et al. Second-generation PLINK: rising to the challenge of larger and richer datasets. Gigascience. 2015;4:7.
32. Delaneau O, Marchini J, Genomes Project C, et al. Integrating sequence and array data to create an improved 1000 Genomes Project haplotype reference panel. Nat Commun. 2014;5:3934.
33. Howie B, Fuchsberger C, Stephens M, et al. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat Genet. 2012;44(8):955-9.
34. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. Bioinformatics. 2015;31(9):1466-8.
35. Sanchez-Moreno J, Martinez-Aran A, Tabares-Seisdedos R, et al. Functioning and disability in bipolar disorder: an extensive review. Psychother Psychosom. 2009;78(5):285-97.
36. Coombes BJ, Markota M, Mann JJ, et al. Dissecting clinical heterogeneity of bipolar disorder using multiple polygenic risk scores. Transl Psychiatry. 2020;10(1):314.
37. Grigoroiu-Serbanescu M, Giaroli G, Thygesen JH, et al. Predictive power of the ADHD GWAS 2019 polygenic risk scores in independent samples of bipolar patients with childhood ADHD. J Affect Disord. 2020;265:651-9.
38. Tse S, Chan S, Ng KL, et al. Meta-analysis of predictors of favorable employment outcomes among individuals with bipolar disorder. Bipolar Disord. 2014;16(3):217-29.

39. Cutler DM, Lleras-Muney A. Education and Health: Evaluating Theories and Evidence. National Bureau of Economic Research Working Paper Series. 2006;No. 12352.
40. Thapar A, Riglin L. The importance of a developmental perspective in Psychiatry: what do recent genetic-epidemiological findings show? Mol Psychiatry. 2020;25(8):1631-9.
41. Mullins N, Bigdeli TB, Borglum AD, et al. GWAS of Suicide Attempt in Psychiatric Disorders and Association With Major Depression Polygenic Risk Scores. Am J Psychiatry. 2019;176(8):651-60.
42. Smeland OB, Bahrami S, Frei O, et al. Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. Mol Psychiatry. 2020;25(4):844-53.
43. Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: a longitudinal follow-up study. Am J Psychiatry. 1995;152(3):379-84.

## FIGURE LEGEND

**Figure 1. Results from polygenic score association analyses of occupational functioning and psychiatric hospital admissions in bipolar disorder and controls.** *Bonferroni corrected *P*-value threshold for significance $P < 0.0028$ (correcting for 18 tests). OR=odds ratio.

## TABLES

**Table 1.** Description of the SWEBIC bipolar disorder cohort and controls for the included phenotypes.

| | SWEBIC | | Controls |
|---|---|---|---|
| | **BD (all)** | **BD-I / BD-II / NOS** | |
| | (N=4,782) | (N=2,175 / N=1,638 / N=969) | (N=3,339) |
| **Phenotype** | | | |
| **Sex (% females)** | 2,986 (62%) | 1,253 (58%) / 910 (66%) / 630 (65%) | 1,667 (50%) |
| **Percent of years without employment (1993–2015, age 25-65)[a]** | | | |
| | N=4,139 | N=1,905 / N=1,389 / N=845 | N = 2,963 |
| <25 % | 1,686 (44%) | 769 (40%) / 644 (46%) / 353 (42%) | 2,319 (78%) |
| 25-50% | 739 (19%) | 373 (20%) / 320 (23%) / 189 (22%) | 383 (13%) |
| 50-75% | 585 (15%) | 298 (16%) / 225 (16%) / 148 (18%) | 130 (4%) |
| >75% | 813 (21%) | 465 (24%) / 200 (14%) / 155 (18%) | 131 (4%) |
| **Percent of years with long-term sick leave (1993–2015, age 25-65)[a]** | | | |
| | N = 4,139 | N=1,905 / N=1,389 / N=845 | N = 2,963 |
| <25% | 1,159 (30%) | 588 (31%) / 498 (36%) / 248 (29%) | 2,483 (84%) |
| 25-50% | 647 (17%) | 295 (15%) / 296 (21%) / 157 (19%) | 150 (5%) |
| 50-75% | 847 (23%) | 404 (21%) / 344 (25%) / 207 (24%) | 184 (6%) |
| >75% | 1,170 (31%) | 618 (32%) / 251 (18%) / 233 (28%) | 146 (5%) |
| **Number of hospital admissions per year (1973–2016, age 15-70)[b]** | | | |
| | N = 4,782 | N=2,175 / N=1,638 / N=969 | N = 3,339 |
| 0 | 949 (20%) | 164 (7%) / 566 (35%) / 219 (24%) | 3,205 (96%) |
| 0-0.1 | 1,497 (31%) | 633 (29%) / 526 (32%) / 338 (35%) | 114 (3%) |
| 0.1-0.3 | 1,434 (30%) | 803 (37%) / 370 (23%) / 261 (27%) | 16 (<1%) |
| >0.3 | 902 (19%) | 575 (26%) / 176 (11%) / 151 (16%) | 4 (<1%) |

[a]Mean years with phenotype information: 20 years (10-23 years). [b]Mean years with phenotype information: 36 years (10-44 years).

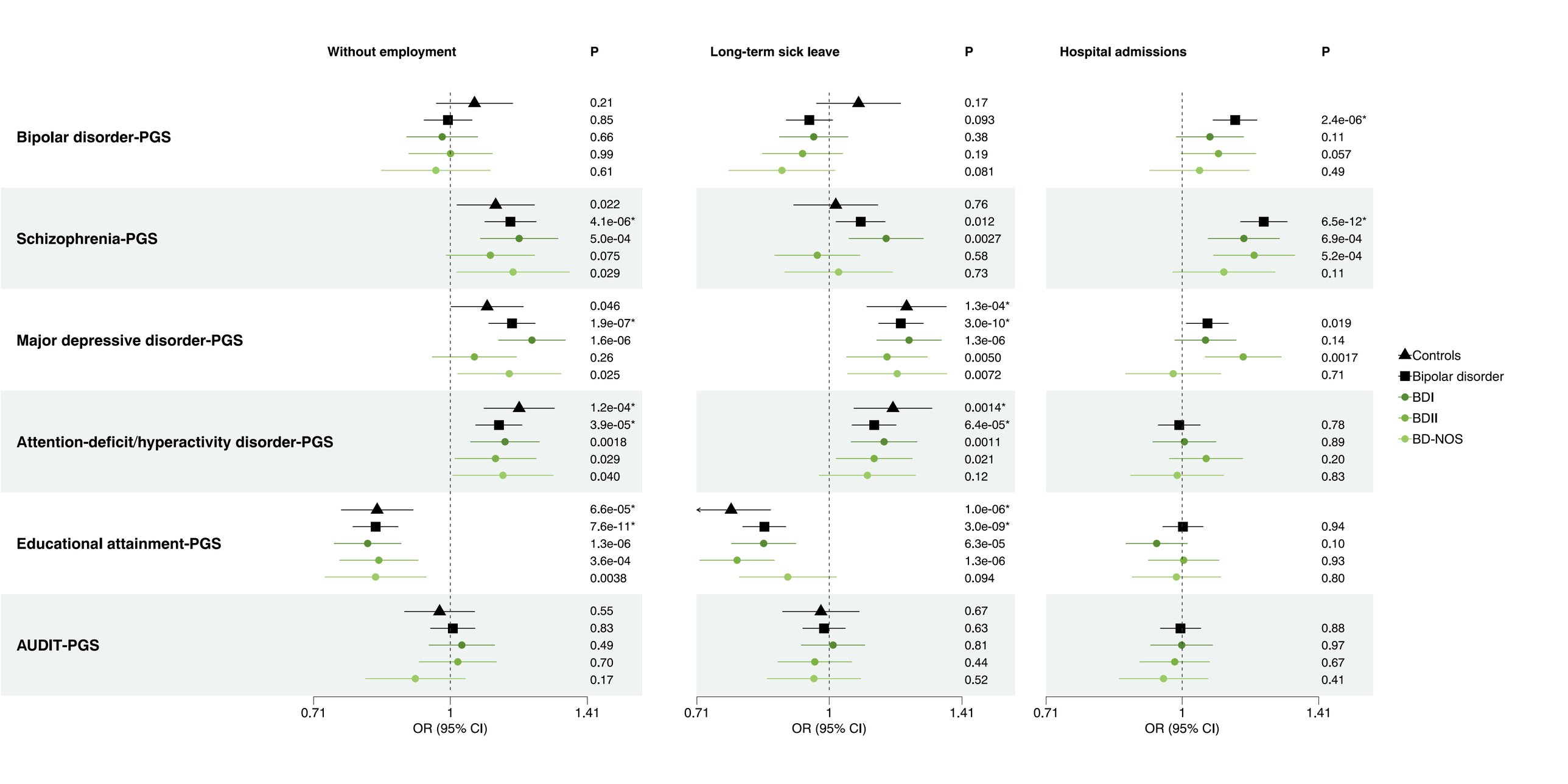
**Table 2.** Description of the bipolar disorder replication cohort Bipolar Disorder Research Network (BDRN).

| **Phenotype** | **BD (all)** | **BD-I / BD-II** |
|---|---|---|
| | N=4,219 | N=2,906 / N=1,239 |
| **Sex (% females)** | 2,859 (68%) | 1,971 (68%) / 841 (68%) |
| **Number of hospital admissions per year (age 15-70)** | | |
| 0 | 1091 (26%) | 340 (12%) / 713 (58%) |
| 0-0.1 | 1446 (34%) | 1101 (38%) / 324 (26%) |
| 0.1-0.3 | 1229 (29%) | 1077 (37%) / 142 (11%) |
| >0.3 | 320 (8%) | 286 (10%) / 33 (3%) |

**Table 3.** Replication association analyses between PGS and psychiatric hospital admissions in the BDRN cohort (N=4,219).

| | **ALL (N=4,219)** | | **BD-I (N=2,906)** | | **BD-II (N=1,239)** | |
|---|---|---|---|---|---|---|
| **PGS** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** | **OR (95% CI)** | **P** |
| BD-PGS | 1.17 (1.11-1.24) | $3.3 \times 10^{-8}$ | 1.15 (1.08-1.24) | $6.6 \times 10^{-5}$ | 0.92 (0.82-1.04) | 0.17 |
| SCZ-PGS | 1.19 (1.12-1.27) | $2.5 \times 10^{-8}$ | 1.19 (1.10-1.28) | $9.9 \times 10^{-6}$ | 0.90 (0.79-1.02) | 0.092 |
| MDD-PGS | 0.96 (0.91-1.02) | 0.16 | 0.99 (0.92-1.06) | 0.71 | 0.97 (0.87-1.09) | 0.59 |
| ADHD-PGS | 0.91 (0.86-0.96) | 0.0013 | 0.91 (0.85-0.98) | 0.011 | 1.02 (0.91-1.15) | 0.68 |
| EA-PGS | 0.97 (0.92-1.03) | 0.38 | 0.99 (0.93-1.07) | 0.85 | 0.95 (0.84-1.07) | 0.40 |
| AUDIT-PGS | 0.98 (0.92-1.03) | 0.41 | 1.01 (0.95-1.09) | 0.71 | 1.00 (0.89-1.13) | 0.99 |

BD=Bipolar disorder, SCZ=Schizophrenia, MDD=Major Depressive Disorder, ADHD=Attention Deficit Hyperactivity Disorder, EA=educational attainment, AUDIT=Alcohol Use Disorders Identification Test.


Without employment
P
Long-term sick leave
P
Hospital admissions
P
Bipolar disorder-PGS
0.21
0.85
0.66
0.99
0.61
0.17
0.093
0.38
0.19
0.081
2.4e-06*
0.11
0.057
0.49
Schizophrenia-PGS
0.022
4.1e-06*
5.0e-04
0.075
0.029
0.76
0.012
0.0027
0.58
0.73
6.5e-12*
6.9e-04
5.2e-04
0.11
Major depressive disorder-PGS
0.046
1.9e-07*
1.6e-06
0.26
0.025
1.3e-04*
3.0e-10*
1.3e-06
0.0050
0.0072
0.019
0.14
0.0017
0.71
Attention-deficit/hyperactivity disorder-PGS
1.2e-04*
3.9e-05*
0.0018
0.029
0.040
0.0014*
6.4e-05*
0.0011
0.021
0.12
0.78
0.89
0.20
0.83
Educational attainment-PGS
6.6e-05*
7.6e-11*
1.3e-06
3.6e-04
0.0038
1.0e-06*
3.0e-09*
6.3e-05
1.3e-06
0.094
0.94
0.10
0.93
0.80
AUDIT-PGS
0.55
0.83
0.49
0.70
0.17
0.67
0.63
0.81
0.44
0.52
0.88
0.97
0.67
0.41
0.71
1
1.41
OR (95% CI)
Controls
Bipolar disorder
BDI
BDII
BD-NOS