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

4

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28 **ABSTRACT**

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

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

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

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

52

53 INTRODUCTION

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

61 Aside from the impairments associated with acute mood episodes, persons with bipolar
62 disorder might suffer from persistent psychosocial and occupational deficits. Indeed, as many
63 as 30–60% of bipolar disorder patients fail to regain full functioning in occupational and
64 social domains after illness onset¹. Only half of persons with bipolar disorder are within the
65 workforce^{2,3}. This is not only much lower than the general population, but also lower than
66 persons with unipolar depression³. Bipolar disorder is in fact one of the main causes of
67 disability among young adults⁴. Occupational disability is also an important driver of the
68 societal costs associated with bipolar disorder, where one estimate found that 75% of the total
69 societal costs could be attributed to sick leave and early retirement⁵.

70 To mitigate occupational dysfunction in bipolar disorder, it is key to identify the driving
71 mechanisms. One would assume that persons with more severe mood episodes have worse
72 long-term functional outcome. But classical measures of illness severity—such as the number
73 of psychiatric hospital admissions—in fact correlates poorly with psychosocial functioning⁶.
74 Instead, we and others showed an association between executive functioning and occupational
75 functioning^{7,8}. This suggests that abiding functional sequels of bipolar disorder is determined
76 by other factors than those that cause mood symptoms manifested during acute mood
77 episodes.

78 Polygenic scores (PGS) can be calculated for a range of different traits and is a tool to unearth
79 genetic components that drive specific subphenotypes within a diagnostic category. In bipolar
80 disorder, specific subphenotypes such as number of hospital admissions⁹ and psychosis¹⁰ have
81 previously been associated with polygenic risk for schizophrenia. It is, however, not known
82 whether long-term occupational functioning associates with particular polygenic liabilities.

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

91 **METHODS**

92 **Population**

93 Persons diagnosed with bipolar disorder type 1, bipolar disorder type 2, or bipolar disorder
94 not otherwise specified (NOS) in the Swedish Bipolar Collection (SWEBIC) were included in
95 the study. Most study participants in SWEBIC were enrolled through the Swedish National
96 Quality Register for bipolar disorder (Bipolär)¹¹. A smaller number were recruited from the
97 St. Göran Bipolar Project¹²⁻¹⁴, and some were identified in the Swedish National Patient
98 Register using a validated algorithm¹⁵.

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

102 18 years or older¹⁶. To avoid a “supernormal” control sample, we chose not to exclude
103 subjects hospitalized for other psychiatric reasons.¹⁶

104 We linked patients in SWEBIC and the control sample to longitudinal Swedish population-
105 based registers using the unique personal identification number assigned to all persons living
106 in Sweden¹⁷. Both SWEBIC and the control sample collection were approved by the Regional
107 Ethical Review Board in Stockholm, Sweden, and all participants provided written informed
108 consent.

109 **Phenotypic measures**

110 *Unemployment and long-term sick leave*

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

116 For measures of employment, we included yearly reports in October and November capturing
117 if a subject held an employment that year¹⁸. Long-term sick leave or early retirement for each
118 year was defined as having more than 60 full sick leave days *or* receiving any reimbursement
119 for early retirement. The number of years without employment or with long-term sick leave
120 were divided by the total number of years with registrations to calculate the percentage of
121 years without employment or on sick leave. Since the raw data had both ceiling and floor
122 effects, with majority of patients towards the end of the extremes 0% and 100%, we grouped
123 the percentage of years without employed or on long-term sick leave into four categories
124 (<25%, 25–50%, 50–75% and >75% of the years) as outlined in Table 1. Given previous
125 indications that occupational functioning decrease by age in bipolar disorder², we conducted

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

129 *Number of psychiatric hospital admissions*

130 The patient register has full coverage of psychiatric hospital admissions since 1973. We
131 retrieved information about psychiatric hospital admissions from the Swedish National Patient
132 Register 1973-01-01 to 2016-12-31. To estimate how many years a subject had the possibility
133 of being included in the patient register, we counted the number of years between 1973-01-01,
134 or from the date subjects turned 15 years old, until subjects turned 70 years old, death, or
135 2016-12-31. Subjects with fewer than 10 years of possible inclusion in the register were
136 excluded. We used the years of possible inclusion in the patient register to calculate the mean
137 number of psychiatric hospital admissions per year. Since hospital admissions has a skewed
138 distribution, we grouped subjects into four categories (0, 0–0.1, >0.1–0.3, and >0.3
139 psychiatric hospital admissions per year) where the categories correspond to no admissions
140 (average of zero admissions), up to one admission per decade (average of >0 to 0.1
141 admissions per year), between >1 to 3 admissions per decade (average of >0.1 to 0.3
142 admissions per year), and patients with more than 3 admissions per decade (average >0.3
143 admissions per year). The intensity of hospital admissions might differ by age. We therefore
144 conducted sensitivity analyses where we used age at hospital admissions to stratify the
145 intensity during two age spans (15–39 and 40–70 years of age).

146 **Genotyping and polygenic scoring**

147 DNA extraction from whole blood samples and genotyping in SWEBIC patients¹⁹ and the
148 controls¹⁶ has previously been described. In short, genotyping of patients and controls was
149 done using three genotyping arrays: Affymetrix 6.0 chips (Affymetrix, Santa Clara, CA,

150 USA), Illumina OmniExpress chips (Illumina, San Diego, CA, USA), and Infinium
151 PsychArray-24 v1.2 BeadChip (Illumina, San Diego, CA, USA). Quality control was done
152 using the Ricopili pipeline²⁰ and genotypes were imputed to the HRC 1.1 reference panel
153 using the Sanger imputation server²¹.

154 We used publicly available summary statistics from genome-wide association studies to
155 calculate PGS for psychiatric disorders and educational attainment in our study sample. These
156 PGS were chosen to capture disorders on the psychotic/affective spectrum (bipolar disorder,
157 schizophrenia, and MDD), a commonly comorbid disorder (ADHD), and cognitive abilities
158 (educational attainment). Summary statistics for bipolar disorder (bip2021, excluding our
159 SWEBIC sample)²² and schizophrenia (scz2022, excluding all Swedish samples)²³ were
160 received from Psychiatric Genomics Consortium (PGC). We also used publicly available
161 summary statistics for MDD (mdd2018, excluding 23andMe)²⁴, ADHD (adhd2019)²⁵,
162 educational attainment²⁶ and Alcohol Use Disorders Identification Test (AUDIT, excluding
163 23andMe)²⁷. To minimize multiple testing, we only tested the P -value thresholds (P_T) that
164 previously shown to best predict their respective phenotypes: $P_T < 0.1$ for bipolar disorder,
165 schizophrenia, ADHD and AUDIT; $P_T < 0.5$ for MDD; and $P_T < 0.05$ for educational attainment.
166 We only included variants with INFO score > 0.9 for all PGSs (INFO not available for
167 educational attainment).

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

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

176 **Statistical analyses**

177 We conducted ordinal regression for association analyses between the included phenotypes
178 and PGSs using R (v. 4.0.2). We adjusted regression analyses for sex, the first six ancestry
179 principal components, genotyping wave, and year of birth grouped into 6 categories (<1955,
180 1955–62, 1963–69, 1970–77, 1978–88, >1988). We used Bonferroni correction for multiple
181 testing: correcting for six PGS and three phenotypes (18 tests) yielded a *P*-value threshold for
182 significance $P_T < 0.0028$. To correct for possible influence of age of onset, we included
183 information about age at first symptom before and after age 24 (see description in
184 supplementary methods). Results after correcting for age of first symptom are presented in
185 Table S1 and Table S2.

186 **BDRN replication cohort**

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

195 Participants were genotyped on Affymetrix GeneChip 500K Mapping Array Set, Illumina
196 Omni Express Array, and Illumina PsychChip. For each array strict quality control (QC) was
197 performed separately. QC used PLINK 1.9³¹ software excluding SNPs with $MAF < 0.01$,

198 deviation from Hardy-Weinberg Equilibrium (HWE) at $P \leq 10^{-6}$, 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 ($\pi\text{-hat} > 0.2$) 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 3.4.0.1023³²
204 and imputed using IMPUTE2³³ 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 , $\text{MAF} < 0.01$ or
207 $\text{HWE} < 1e^{-6}$). 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 1.9³¹ in PRSice³⁴. Imputed genotypes were clumped for linkage disequilibrium
212 (window, 250 kb; $r^2 = 0.1$) 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) $p < 1.00$, $p \leq .50$, $p \leq .20$, $p \leq .10$, $p \leq .05$, $p \leq .01$, and $p \leq .001$
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*

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

232 Information about psychiatric hospital admissions intensity between 1973 and 2016 were
233 available for 4,782 bipolar disorder patients and 3,339 controls between ages 15 and 70. The
234 mean years of possible inclusion in the national patient register in the patient group was 36
235 years (range 10–44 years) with a mean of 0.2 psychiatric hospital admissions per year, which
236 corresponds to an average of two hospital admissions per decade. For sensitivity analyses,
237 number of hospital admissions per year was analysed in two age spans (age 15–39, N=4,180;
238 age 40–70, N=3,213), where 2,611 patients had at least 10 years hospital admission intensity
239 measurements during both age spans. The control group had an average of 39 years' (range
240 12–44 years) worth of data on hospital admissions available; 134 control subjects had one or
241 more psychiatric hospitalization for other indications than bipolar disorder or schizophrenia.

242 *Polygenic score analyses*

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

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

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

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

263 In the BDRN cohort, we could replicate the association between psychiatric hospitalizations
264 and PGS for bipolar disorder ($OR=1.17$, $P=3.3 \times 10^{-8}$) and schizophrenia ($OR=1.19$,
265 $P=2.5 \times 10^{-8}$; Table 3). In BDRN, a lower PGS for ADHD was also associated with increased
266 psychiatric hospitalizations ($OR=0.91$, $P=0.0013$).

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

270 associated with SCZ-PGS (OR=1.17, $P=6.9 \times 10^{-4}$). With respect to bipolar disorder type 2, we
271 observe consistent trends with the overall sample between PGS and phenotypes. However,
272 only certain PGS showed significant associations ($P<0.05$) with employment (ADHD-PGS
273 and EA-PGS), sick leave (MDD-PGS, ADHD-PGS, and EA-PGS), and hospitalizations
274 (MDD-PGS and SCZ-PGS). Within the NOS category, we found similar results to the whole
275 group analysis with regards to employment, where the same PGS associated at $P<0.05$ (SCZ-
276 PGS, MDD-PGS, ADHD-PGS, and EA-PGS). However, only MDD-PGS associated with
277 sick leave and there were no significant associations at $P<0.05$ with hospitalizations. In
278 bipolar subtype specific analyses in BDRN, bipolar disorder-PGS, SCZ-PGS, and ADHD-
279 PGS were associated ($P<0.05$) with hospitalizations in bipolar disorder type 1 (Table 3).

280 Occupational dysfunction and hospital admission intensity might differ depending on age².
281 We conducted sensitivity analyses stratified by intensities during the time before and after age
282 40 (Table S2). In the older age group, the effect sizes for the PGS associations with long-term
283 sick leave and employment resembled the main analyses and were generally larger (Table
284 S2). In the younger age group, however, not all PGS were significantly associated with
285 occupational outcomes: Unemployment associated with SCZ-PGS (OR=1.11, $P=0.043$),
286 ADHD-PGS (OR=1.13, $P=0.012$), and EA-PGS (OR=0.86, $P=6.5 \times 10^{-4}$). Long-term sick
287 leave associated with MDD-PGS (OR=1.04, $P=0.015$), ADHD-PGS (OR=1.11, $P=0.034$),
288 and EA-PGS (OR=0.85, $P=4.7 \times 10^{-4}$). Further, in the older age group hospital admission
289 intensity was positively correlated with MDD-PGS (OR=1.12, $P=6.3 \times 10^{-4}$) and
290 schizophrenia-PGS (OR=1.16, $P=4.1 \times 10^{-5}$), but negatively correlated with PGS for
291 educational attainment (OR=0.89, $P=4.3 \times 10^{-4}$). In the younger age group, hospital admission
292 intensity was associated with PGS for bipolar disorder (OR=1.20, $P=3.2 \times 10^{-9}$), schizophrenia
293 (OR=1.23, $P=2.9 \times 10^{-10}$), and educational attainment (OR=1.12, $P=4.9 \times 10^{-5}$). To test if these
294 results were driven by age of onset, we corrected the regression analyses for age at first

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

297 **DISCUSSION**

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

309 The observation that polygenic risk for bipolar disorder is associated with psychiatric
310 hospitalizations accords previous findings^{9,10}. This association could be expected as most
311 patients in the PGC training set for the PGS have bipolar disorder type 1, who typically have a
312 higher number of hospitalizations than type 2. The polygenic risks associated with
313 unemployment and long-term sick leave are novel findings that have bearing on clinical
314 strategies for improving outcomes in bipolar disorder. The management of bipolar disorder
315 primarily revolves around prevention of mood episodes with the assumption that patients will
316 functionally recover with subsiding symptoms. But many patients remain functionally
317 impaired despite best available treatment, and deficits in psychosocial functioning in bipolar
318 disorder may persist long after symptom recovery³⁵. The high rates of occupational

319 dysfunction not only affect patients' quality of life and socioeconomic status², but is also a
320 major driver of the societal costs caused by the disorder⁵.

321 Polygenic risk for ADHD has previously been associated with rapid cycling³⁶ and age of
322 onset³⁷ in bipolar disorder. Our finding that polygenic scores for ADHD and educational
323 attainment are also associated with occupational dysfunction echoes the clinical observations
324 that comorbid ADHD¹⁴, years of education, and cognitive performance^{2,7,38} are strong
325 predictors of occupational functioning. Our result for educational attainment PGS in controls
326 accords the positive correlation between education and occupational functioning³⁹. Clinical
327 studies have also found that comorbid ADHD is associated with worse clinical outcome in
328 bipolar disorder, including earlier onset and higher frequency of depressive—but not manic—
329 episodes¹⁴. Given that hospitalization is more common for manic than depressive episodes,
330 this might partly explain why lower ADHD-PGS was associated with hospitalizations in the
331 replication BDRN cohort. Taken together, our findings extend these clinical observations by
332 demonstrating that not only a clinical ADHD diagnosis, but also higher polygenic risk for
333 ADHD, increase the risk for long-term impairment. Together these results suggest that a
334 developmental perspective is needed to improve long-term outcome also in bipolar disorder⁴⁰.
335 Occupational outcomes in bipolar disorder patients might be improved by addressing other
336 domains than core mood symptoms including ADHD symptoms—potentially also
337 subsyndromal manifestations—and cognitive dysfunction.

338 Polygenic risk for MDD has previously been associated with rapid cycling³⁶ and suicide
339 attempts⁴¹ in bipolar disorder. Here, we add occupational dysfunction to the list of negative
340 consequences of high polygenic liability for MDD.

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

344 demonstrated¹⁰, these findings show that polygenic liability for bipolar disorder and
345 schizophrenia differ with respect to functional outcomes. Consistent with our findings on
346 occupational functioning, schizophrenia risk alleles have previously been associated with
347 poorer cognitive performance, whereas bipolar disorder risk alleles have been associated with
348 better cognitive performance⁴².

349 To account for the potentially increasing risk of occupational dysfunction with higher age²,
350 we stratified analyses by intensities before and after age 40. The effect sizes for PGSs
351 associated with long-term sick leave in the main analyses (SCZ, MDD, ADHD, and
352 educational attainment) were slightly larger in the older age group. Conversely, the
353 association between hospital admissions and bipolar disorder-PGS was limited to the younger
354 age group (age 15–39). In addition, educational attainment-PGS exhibited associations with
355 hospital admissions in opposite directions within the two age groups. This suggest that our
356 outcomes capture different traits depending on age. The intensity of hospital admissions
357 appears to relate to more frequent severe mood episodes in the younger age group, but may be
358 confounded by treatment response or cognitive ability to cope with the disorder in older age.

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

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

373 In conclusion, our results suggest that the underlying polygenetic liability for the severity of
374 bipolar illness in terms of psychiatric hospitalisations clearly differs from the occupational
375 outcome. This is important information given that much of the lifetime burden of bipolar
376 disorder is driven by prolonged periods of sick leave and/or unemployment rather than acute
377 mood episodes. Even if clinical symptoms are improved, psychosocial impairments may
378 persist⁴³, which suggests that interventions other than those used to prevent mood episodes
379 might be required to mitigate functional impairment. This might include addressing co-
380 morbid symptoms (e.g., ADHD) or cognitive dysfunction through cognitive remediation
381 therapy. Clarifying the underlying mechanisms of poor outcome is an important step towards
382 targeted treatment interventions, and might also be used for prognostic purposes.

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- 507

508 **FIGURE LEGEND**

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

513 TABLES

514 **Table 1.** Description of the SWEBIC bipolar disorder cohort and controls for the included
 515 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%)

516 ^aMean years with phenotype information: 20 years (10-23 years). ^bMean years with phenotype

517 information: 36 years (10-44 years).

518 **Table 2.** Description of the bipolar disorder replication cohort Bipolar Disorder Research
 519 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%)

520

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

PGS	ALL (N=4,219)		BD-I (N=2,906)		BD-II (N=1,239)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
BD-PGS	1.17 (1.11-1.24)	3.3 x 10 ⁻⁸	1.15 (1.08-1.24)	6.6x10 ⁻⁵	0.92 (0.82-1.04)	0.17
SCZ-PGS	1.19 (1.12-1.27)	2.5 x 10 ⁻⁸	1.19 (1.10-1.28)	9.9x10 ⁻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

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

525