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Short communication

Genetic risk for psychiatric illness is associated with the number of hospitalizations of bipolar disorder patients

Janos L. Kalman [a,b,c,*], Sergi Papiol [a,b,d], Maria Grigoroiu-Serbanescu [e], Kristina Adorjan [a,b], Heike Anderson-Schmidt [f], Katharina Brosch [g,h], Monika Budde [a], Ashley L. Comes [a], Katrin Gade [f], Andreas Forstner [i,j,k], Dominik Grotegerd [l], Tim Hahn [l], Maria Heilbronner [a], Urs Heilbronner [a], Stefanie Heilmann-Heimbach [i], Farah Klöhn-Saghatolislam [a], Mojtaba Oraki Kohshour [a,m], Susanne Meinert [l], Tina Meller [g,h], Niamh Mullins [n,o], Igor Nenadić [g,h], Markus M Nöthen [i], Julia-Katharina Pfarr [g,h], Daniela Reich-Erkelenz [a], Marcella Rietschel [q], Kai G. Ringwald [g,h], Sabrina Schaupp [a], Eva C. Schulte [a,b], Fanny Senner [a,b], Frederike Stein [g,h], Fabian Streit [p], Thomas Vogl [a], Peter Falkai [b], Udo Dannlowski [l], Tilo Kircher [g,h], Thomas G. Schulze [a,q,r,#], Till F.M. Andlauer [s,t,#]

[a] *Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany*
[b] *Department of Psychiatry and Psychotherapy, University Hospital Munich, Munich, Germany*
[c] *International Max Planck Research School for Translational Psychiatry, Munich, Germany*
[d] *Centro de Investigación Biomedica en Red de Salud Mental (CIBERSAM), Barcelona, Spain*
[e] *Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania*
[f] *Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany*
[g] *Department of Psychiatry and Psychotherapy, Philipps-University Marburg, Marburg, Germany*
[h] *Center for Mind, Brain and Behavior (CMBB), Marburg, Germany*
[i] *Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany*
[j] *Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany*
[k] *Centre for Human Genetics, University of Marburg, Marburg, Germany*
[l] *Institute for Translational Psychiatry, University of Munster, Munster, Germany*
[m] *Department of Immunology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran*
[n] *Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA*
[o] *Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA*
[p] *Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany*
[q] *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[r] *Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, USA*
[s] *Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany*
[t] *Present address: Global Computational Biology and Data Sciences, Boehringer Ingelheim Pharma GmbH & Co. KG, 88397 Biberach an der Riß, Germany*

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ABSTRACT

Objectives: Bipolar disorder (BD) has a highly heterogeneous clinical course that is characterized by relapses and increased health care utilization in a significant fraction of patients. A thorough understanding of factors influencing illness course is essential for predicting disorder severity and developing targeted therapies.
Methods: We performed polygenic score analyses in four cohorts ($N = 954$) to test whether the genetic risk for BD, schizophrenia, or major depression is associated with a severe course of BD. We analyzed BD patients with a minimum illness duration of five years. The severity of the disease course was assessed by using the number of hospitalizations in a mental health facility and a composite measure of longitudinal illness severity (OPCRIT item 90).
Results: Our analyses showed that higher polygenic scores for BD ($\beta = 0.11$, SE = 0.03, $p = 1.17 \times 10^{-3}$) and schizophrenia ($\beta = 0.09$, SE = 0.03, $p = 4.24 \times 10^{-3}$), but not for major depression, were associated with more

* Corresponding author.
E-mail address: janos.kalman@med.uni-muenchen.de (J.L. Kalman).
Thomas G. Schulze and Till F. M. Andlauer should be considered joint senior author.

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hospitalizations. None of the investigated polygenic scores was associated with the composite measure of longitudinal illness severity (OPCRIT item 90).
Limitations: We could not account for non-genetic influences on disease course. Our clinical sample contained more severe cases.
Conclusions: This study demonstrates that the genetic risk burden for psychiatric illness is associated with increased health care utilization, a proxy for disease severity, in BD patients. The findings are in line with previous observations made for patients diagnosed with schizophrenia or major depression. Therefore, in the future psychiatric disorder polygenic scores might become helpful for stratifying patients with high risk of a chronic manifestation and predicting disease course.

1. Introduction

Bipolar disorder (BD) is characterized by a heterogeneous clinical presentation with alternating periods of mania and depression. At least 50% of patients experience recurrent illness episodes, and 20% to 35% have chronic, subclinical symptoms (Angst, 1986; Fagiolini et al., 2013). Almost 80% of patients with BD are hospitalized in a mental health facility within the first 15 years of their disease course and 17% to 40% are hospitalized within the first year after diagnosis (Licht et al., 2008; Nestsiarovich et al., 2018). Patients with severe symptoms, functional impairment, and treatment resistance are more likely to require inpatient treatment (Altshuler et al., 2007). Prevention of repeated admissions is of great public health relevance because frequent or prolonged inpatient stays in a mental health facility can alter the trajectory of patients' educational, professional, and interpersonal development. For example, absences from work and social activities can decrease patients' productivity, social status, quality of life, and ability to maintain employment (Altshuler et al., 2007).

BD is highly heritable, and 75% of its phenotypic variance is attributed to genetic factors, a significant proportion (18.6%) of which can be explained by common genetic variants (Mullins et al., 2021). Many of the 64 BD-associated genetic loci identified in the most recent BD GWAS play a role in neuronal communication and calcium channel signaling (Mullins et al., 2021). The associated variants are enriched in genes expressed in brain tissues and genes coding for targets of antipsychotics and mood stabilizers. Polygenic scores (PGS) summarize the additive risk conferred by common variants and have shown promise in understanding the genetic architecture of mental health disorders (Andlauer and Nöthen, 2020). PGS have been reported to be associated with different symptom profiles in BD patients, but not with the number of hospitalizations (Coleman et al., 2020; Guzman-Parra et al., 2021; Mullins et al., 2019; Ruderfer et al., 2018; Kalman et al., 2021).

The present study aimed to elucidate whether genetic factors play a role in the disease course of BD. To this end, we investigated whether PGS for major psychiatric disorders were associated with two parameters of chronicity: the lifetime number of hospitalizations and the Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT) item 90, a composite measure of longitudinal illness severity.

2. Methods

References to published methods are listed in Supplementary Note 1.

2.1. Sample description

Participants with a DSM-IV diagnosis of BD type I (BD-I) or II (BD-II) and available information on the past number of hospitalizations were selected from four independent datasets: 1) the FOR2107 cohort (N = 141), which includes patients recruited as part of an ongoing multicenter study at the universities of Marburg and Münster, Germany (German Research Foundation [DFG] research group FOR2107, www.for2107.de); 2) the PsyCourse cohort (N = 330) from a multi-site German/Austrian longitudinal study (www.psycourse.de); and 3) and 4) two Romanian cohorts of patients with BD-I (Romania1 (N = 388) and Romania2 (N = 95)) recruited at the Obregia Clinical Psychiatric Hospital, Bucharest, Romania (Table 1) (Budde et al., 2019; Kircher et al., 2019; Stahl et al., 2019). For a description of the sample ascertainment, see the *Supplementary Material*. The study protocols were approved by the local ethics committees; the study was performed in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

2.2. Phenotype description

The illness duration was defined as the difference between the age at the interview and the age at disorder onset. For the primary analyses, we selected cases with a minimum illness duration of five years; for the sensitivity analyses, we tested two additional duration of illness thresholds ($\geq$ 0 years and $\geq$ 10 years) to ensure that results were not driven by the choice of the illness duration threshold. The distribution of the number of hospitalizations was highly skewed, so we transformed it separately in each cohort by rank-based inverse normal transformation (Supplemental Fig. S1). The resulting normalized variable was used as the primary dependent variable in all analyses (Table 1).

For a subset of patients in the PsyCourse, FOR2107, and Romania1 cohorts, OPCRIT item 90 ("Course of disorder") was available as an additional measure of longitudinal disease course/severity (McGuffin et al., 1991). The OPCRIT system constitutes an established, validated, and reliable tool comprising a 90-item psychiatric signs and symptoms checklist. It was designed to enable the objective diagnosis of psychotic and affective disorders in research and clinical settings. OPCRIT item 90 assesses the course of the disorder and has five categories: a) "Single episode with good recovery"; b) "Multiple episodes with good recovery in between"; c) "Multiple episodes with partial recovery in between"; d) "Continuous chronic illness"; e) "Continuous chronic illness with deterioration". To improve interpretability and generate more balanced subgroups, we grouped the original five item levels into two broader categories: (1) *Good recovery* (items a and b) and (2) *Chronic illness with residual symptoms* (items c-e). In secondary analyses, we grouped the item levels into (1) *Episodic illness* (items a-c) and (2) *Chronic illness* (items d and e).

2.3. Genetic analyses

The cohorts were genotyped on different Illumina microarrays, following local protocols. Quality control, population substructure analyses, and imputation were performed with PLINK v1.9 and either *R* (for the PsyCourse and FOR2107 cohorts) or the RICOPILI pipeline (for the Romania1 and Romania2 cohorts), as described previously (Budde et al., 2019; Kalman et al., 2021; Pelin et al., 2021) *(Supplementary Notes S1 and S2, and Suplementary Table S1)*. Imputation was conducted with SHAPEIT and IMPUTE2 using the 1000 Genomes phase 3 (for the FOR2107 and PsyCourse cohorts) or the Haplotype Reference Consortium v1.0 (for the Romania1 and Romania2 cohorts) reference panels. For the present analyses, we selected variants from the PRS-CS 1000 genomes phase 3 EUR reference dataset.

PGS were calculated with PRS-CS, which uses Bayesian regression to infer PGS weights and models the local linkage disequilibrium patterns

of all single nucleotide variants. The global shrinkage parameter φ was determined automatically *(Supplementary Table S2)*. Summary statistics from the BD 2021, schizophrenia (SZ) 2020, and major depressive disorder (MDD) 2018 (without 23andMe) Psychiatric Genomics Consortium (PGC) genome-wide association studies (GWASs) were used as training datasets *(Supplementary Table S2, which includes references)*. To avoid bias caused by sample overlap, we used leave-one-out summary statistics of the BD GWAS, excluding the our respective study cohorts.

2.4. Statistical analyses

For the descriptive analyses, non-parametric pairwise Mann-Whitney U, Kruskal-Wallis, and χ^2 tests were used for the variable *untransformed number of hospitalizations* and for the illness severity categories.

We analyzed associations of PGS with the number of hospitalizations and illness severity by linear and logistic regression, respectively. Covariates were sex, duration of illness, BD subtype (for the PsyCourse and FOR2107 cohorts), genotyping batch (for Romania1), and the first eight multidimensional scaling (MDS) ancestry components. The residuals of the linear regression models analyzing the transformed number of hospitalizations were normally distributed (*Supplementary Table S3*). Next, we performed an inverse variance-weighted fixed-effects meta-analysis combining the cohort-specific regression results. The significance threshold was corrected for six tests by Bonferroni's method ($\alpha = 0.05$ / [3 PGS × 2 phenotypes] $= 8.33 \times 10^{-3}$).

3. Results

The median number of hospitalizations differed significantly between cohorts (Kruskal-Wallis test, $p = 5.69 \times 10^{-38}$) and illness severity categories ($p = 3.39 \times 10^{-21}$) (Table 1). We found that 41.8%, 49.3%, and 47.1% of the patients in the FOR2107, PsyCourse, and Romania1 cohorts, respectively, experienced a chronic disease course characterized by residual symptoms. There was no significant difference in illness course between the cohorts ($p = 0.45$).

After correcting for six tests, higher PGS for BD ($\beta = 0.11$, standard error [SE] $= 0.03$, $p = 1.17 \times 10^{-3}$; significance threshold corrected for multiple testing by Bonferroni's method, $\alpha = 8.33 \times 10^{-3}$) and SZ ($\beta = 0.09$, SE $= 0.03$, $p = 4.24 \times 10^{-3}$) were significantly associated with an increased number of hospitalizations (Fig. 1, Table 2); the PGS for MDD was not associated with hospitalizations ($\beta = 0.04$, SE $= 0.03$, $p = 0.19$). Sensitivity analyses showed that, for BD PGS, these associations were robust when different thresholds (zero, five, or 10 years) were used for the illness duration. The assocations also remained stable for SZ PGS when using different thresholds, but were not significant after correction for multiple testing in the 10-years illness duration subgroup (Table 2). Note that the sample size for analysis of the 10-year illness duration was smaller ($N = 618$) than for the five-year threshold ($N = 788$), reducing the statistical power of this secondary analysis. None of the tested PGS were significantly associated with OPCRIT item 90-defined illness severity (Table 2).

4. Discussion

We investigated whether the genetic risk burden of three major psychiatric disorders is associated with measures of severe BD illness course. To our knowledge, this is the first study to demonstrate that patients with BD who have increased genetic liability for BD and SZ are more frequently hospitalized during their disease course than patients with lower genetic liability. The effect direction was the same in different study cohorts and countries, suggesting that the association was not driven by health system- or cohort-specific characteristics. We found no significant association of PGS with the second investigated disease course-related phenotype, OPCRIT item 90.

Accumulating evidence demonstrates that genetic variants associated with the risk of mental health disorders also influence the clinical manifestation of the disease (Allardyce et al., 2018; Guzman-Parra et al., 2021; Meier et al., 2016; Ruderfer et al., 2018; Wray et al., 2018; Kalman et al., 2021). In BD, previous studies have described associations of SZ PGS with psychotic symptoms, MDD PGS with depressive symptoms, MDD and SZ PGS with the age at illness onset, and MDD and BD PGS with suicidality (Coleman et al., 2020; Guzman-Parra et al., 2021; Mullins et al., 2019; Ruderfer et al., 2018; Kalman et al., 2021). So far, only two studies have investigated the influence of genetic factors on the course of BD. Neither of these studies found a significant association of BD or SZ PGS with the number of hospitalizations (Guzman-Parra et al., 2021; Ruderfer et al., 2018), although Ruderfer *et al.* did find a

Table 1
Sample characteristics.

		Cohorts				χ^2	p
		FOR2107	PsyCourse	Romania 1	Romania 2		
N		120	264	323	81		
Diagnosis, % BD-I		56.7	82.9	100	100		
Sex, % male		43.3	50.0	43.0	29.6	10.79	1.30×10^{-2} *
Age, mean (SD)		43.7 (12.2)	47.7 (12.0)	44.2 (11.8)	43.0 (12.0)	13.69	3.00×10^{-3} *
Age at onset, median (MAD; range)		20 (7.4; 4-52)	27 (11.1; 2.5-57.5)	24 (8.9; 12-52)	24 (8.9; 9-54)	24.95	1.59×10^{-5} *
Duration of illness, median years (MAD; range)		16.5 (9.6; 5-47)	16.5 (10.0; 5-54)	16 (10.4; 5-52)	15 (8.9; 5-47)	7.41	6.00×10^{-2}
Number of hospitalizations, median (MAD, range)		3 (3.0; 0-22)	5 (4.4; 1-61)	9 (5.9; 2-51)	9 (5.9; 2-33)	176.25	5.69×10^{-38} *
OPCRIT item 90, N (%)	**Good recovery**	71 (58.2)	73 (50.7)	171 (53.1)	NA	1.57	4.50×10^{-1}
	Chronic illness with residual symptoms	51 (41.8)	71 (49.3)	151 (47.1)	NA		

Note: See the Supplementary Material for detailed sample descriptions. Differences between the four cohorts were analyzed using Kruskal-Wallis tests. Significant differences without correction for multiple testing ($p<0.05$) are indicated using an asterisk symbol. The PsyCourse and FOR2107 cohorts included patients diagnosed with BD type I (BD-I) and II; the other cohorts included only patients with BD-I. The median absolute deviation was calculated by using 1.4826 as a constant. OPCRIT was available only for a subset of the study participants.

The table shows the characteristics of patients included in the primary analyses, i.e., with an illness duration ≥5 years. Sample sizes of the individual cohorts for the secondary sensitivity analyses were $N_{FOR2107} = 141$, $N_{PsyCourse} = 330$, $N_{Romania1} = 388$, $N_{Romania2} = 95$ for the full sample (illness duration ≥0 years) and $N_{FOR2107} = 102$, $N_{PsyCourse} = 217$, $N_{Romania1} = 239$, $N_{Romania2} = 60$ for the patients with an illness duration ≥10.

Abbreviations: BD-I, bipolar disorder type I; MAD, median absolute deviation; SD, standard deviation; OPCRIT item 90, Operational Criteria Checklist for Psychotic Illness and Affective Illness, variable used to assess the "course of disorder".

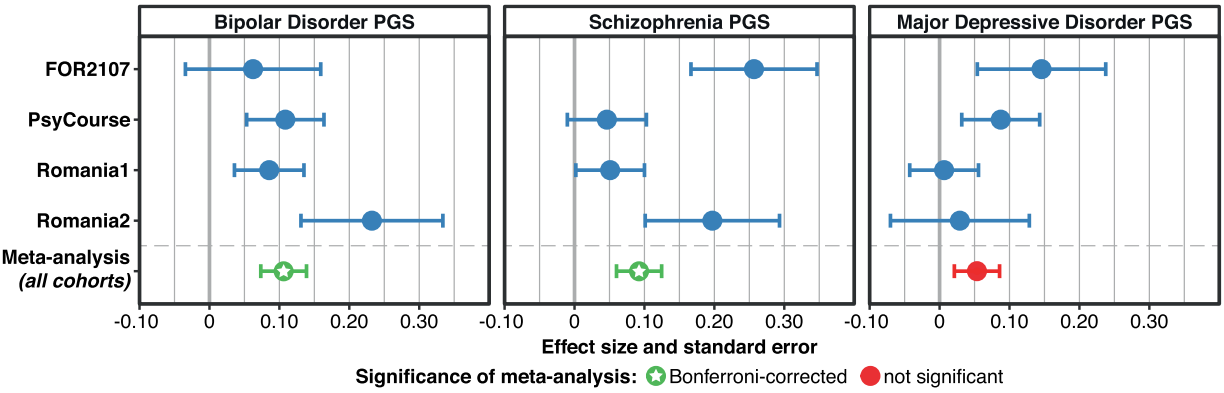

Fig. 1. Results of polygenic score (PGS) analyses. Associations of BD, SZ, and MDD PGS with the number of hospitalizations were investigated in patients with an illness duration ≥*5* years ($N_{FOR2107} = 120$; $N_{PsyCourse} = 264$; $N_{Romania1} = 323$; $N_{Romania2} = 81$). Significance threshold corrected for multiple testing using Bonferroni's method: $\alpha = 8.33 \times 10^{-3}$. Meta-analysis: Inverse variance-weighted fixed-effects meta-analysis.

Table 2
Results of polygenic score analyses.

			Number of hospitalizations				Disease course (OPCRIT 90)			
	Duration of illness	PGS	N	β	SE	*p*	N	OR	95% CI	*p*
Primary analyses	≥ 5 years	BD	788	0.11	0.03	1.17×10^{-3} *	589	1.09	0.91-1.31	0.33
		SZ		0.09	0.03	4.24×10^{-3} *		1.10	0.92-1.31	0.29
		MDD		0.05	0.03	9.84×10^{-2}		1.12	0.93-1.34	0.23
Secondary sensitivity analyses	≥ 0 years	BD	954	0.09	0.03	9.86×10^{-4} +	712	1.10	0.93-1.29	0.26
		SZ		0.09	0.03	1.05×10^{-3} +		1.41	0.97-1.34	0.11
		MDD		0.04	0.03	0.19		1.13	0.96-1.32	0.15
	≥ 10 years	BD	618	0.10	0.04	8.00×10^{-3} +	464	1.12	0.91-1.37	0.28
		SZ		0.10	0.04	9.07×10^{-3}		1.10	0.90-1.34	0.37
		MDD		0.07	0.04	7.17×10^{-2}		1.22	0.99-1.50	0.06

Note: The table shows the association analysis results of polygenic scores (PGS) for bipolar disorder (BD), schizophrenia (SZ), and major depression (MDD) with the number of hospitalizations and OPCRIT item 90. Primary analysis: investigation of patients with an illness duration ≥*5* years. Secondary sensitivity analyses with two additional illness duration thresholds were conducted to ensure that the results were not driven by the choice of this threshold.
The PsyCourse and FOR2107 cohorts included patients diagnosed with BD type I (BD-I) and II; the other cohorts contained only patients with BD-I. The phenotype "number of hospitalizations" was normalized by rank-based inverse normal transformation because the original distribution was highly skewed (*Supplemental Fig. S1 and Supplementary Table S3*).
Abbreviations: PGS, polygenic score; β, unstandardized beta ($\beta > 0$ indicates that a higher number of hospitalizations was associated with increased PGS); SE, standard error; *p*, unadjusted p-value (significance threshold corrected for multiple testing by Bonferroni's method: $\alpha = 8.33 \times 10^{-3}$; significant p-values are indicated with an asterisk symbol for the primary analyses and with a plus symbol for the secondary sensitivity analyses); OR, odds ratio (a higher OR indicates an association with "Chronic illness with residual symptoms"); 95% CI, 95% confidence intervals (the 95% CIs were constrained to a minimum of 0 and a maximum of 1); OPCRIT, Operational Criteria Checklist for Psychotic Illness and Affective Illness (available only for a subset of the study participants).

nominally significant association of a PGS based on a combined BD+SZ GWAS with hospitalizations (Ruderfer et al., 2018). This study also investigated the association of PGS with the number of manic or depressive episodes, but the results were not significant. Importantly, to calculate PGS both studies used older, statistically less powerful BD and SZ GWASs with smaller sample sizes (Ripke et al., 2014; Stahl et al., 2019) than we did in the present study.

Interestingly, previous analyses on patients with MDD and SZ, disorders that share marked symptomatic and genetic similarities with BD (Anttila et al., 2018), found that PGS increase proportionally with illness severity (Coleman et al., 2020; Meier et al., 2016; Wray et al., 2018). Meier *et al.* described a positive association between SZ PGS and the number of hospitalizations, rehospitalizations and living in supported housing facilities (Meier et al., 2016). Although no study has investigated the same relationship in patients with MDD, an association of BD PGS with recurrent depression and of MDD PGS with disease severity (measured in different ways) have been described (Coleman et al., 2020; Meier et al., 2016; Wray et al., 2018). Furthermore, a recent study generated transdiagnostic, symptom-based clusters from MDD, BD, SZ, and schizoaffective patients and healthy controls. Here, the authors observed that individuals in the most severely affected cluster had higher MDD and SZ PGS than those in the lowest severity cluster (Pelin et al., 2021).

Notably, in the present study SZ and BD PGS accounted for only a small proportion of the risk of frequent hospitalization ($R^2_{BD} = 0.015$, $R^2_{SZ} = 0.017$), indicating that other factors also affect the number of hospitalizations. Additional factors known to contribute to rehospitalizations include a higher rate of previous hospitalizations, lower levels of functioning, and being uninsured (Hamilton et al., 2016). The fact that we could not control for these potential confounders constitutes a relevant limitation of the present study. Moreover, our study might be biased towards more severe or treatment-resistant cases: most study participants were diagnosed with BD type I, recruited in academic hospitals, and previously treated as inpatients. However, FOR2107 contained a larger share of patients recruited in outpatient settings than the other cohorts. Accordingly, FOR2107 patients showed a lower number of hospitalizations. Thus, differences in the ascertainment strategies and proportions of BD subtypes between the analyzed cohorts may have impacted the analyses. Population-based samples, e.g., registers or electronic health record data originating from large health care systems, might be more balanced and also include cases with a good prognosis. Ideally, such data should form the basis of future analyses.

Given the small phenotypic variance explained, psychiatric PGS cannot yet be used in clinical settings. Nevertheless, our findings

indicate, in line with previous studies (Allardyce et al., 2018; Guzman-Parra et al., 2021; Meier et al., 2016; Ruderfer et al., 2018; Wray et al., 2018; Kalman et al., 2021), that common variants, as represented by PGS, influence the disease course of psychiatric disorders in combination and interaction with additional genetic and environmental factors. Therefore, prediction models that combine PGS with other genetic (e.g., low-frequency and copy number variants) and non-genetic risk factors may become helpful for stratifying patients and predicting disease courses. Thus, PGS might support informed decisions regarding the efficient allocation of health care resources (Murray et al., 2021).

The present study is the first to investigate whether BD, SZ, or MDD PGS are associated with the OPCRIT item 90 score, a direct measure of longitudinal illness severity. We found that patients who experienced a *chronic illness with residual symptoms* according to item 90 had more lifetime hospitalizations than those in the *good recovery* category. This observation supports the validity of item 90 as a measure of illness severity. However, none of the investigated PGS was significantly associated with this variable, suggesting that environmental and/or other genetic factors might play a more prominent role in determining this phenotype. Importantly, OPCRIT item 90 is a composite measure that is likely influenced by several factors, such as a patient's clinical characteristics, the time period considered for scoring, and the rater's experience, training, and motivation. We could not account for any of these factors in the present analysis. Furthermore, the dichotomization of the original five-level measure, which was necessary for improving the interpretability and generating more balanced subgroups, might have also influenced the results. However, using a different dichotomization strategy did not influence the results significantly (*Supplementary Table S4*).

In summary, the present study is the first to provide evidence that the genetic predisposition to major mental health disorders influences the health care utilization of BD patients. These findings are in line with evidence that PGS are associated with markers of a severe psychiatric illness course and support further investigation into the genetic and environmental determinants of disease trajectories in BD. We suggest that future studies should assess the clinical utility of PGS for stratifying patients at higher risk of experiencing an unfavorable disease course.

CRediT authorship contribution statement

Concept and design: Kalman, Papiol, Andlauer

Analysis and interpretation of data: Kalman, Andlauer

Drafting of the manuscript: Kalman, Andlauer

Supervision and critical revision of the manuscript: Schulze, Andlauer

All other authors provided data, contributed ideas and suggestions for analyses, interpreted results and revised the final manuscript.

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Declaration of Competing Interest

None of the authors have any conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.09.073.

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