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▶ **To cite this version:**

K. Burdick, C. Millett, A. Yocum, C. Altimus, O. Andreassen, et al.. Predictors of Functional Impairment in Bipolar Disorder: Results from 13 Cohorts from Seven Countries by The Global Bipolar Cohort Collaborative. Bipolar Disorders, 2022, 24 (7), pp.709-719. 10.1111/bdi.13208 . hal-03625156

HAL Id: hal-03625156
https://hal.science/hal-03625156

Submitted on 30 May 2022

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DOI: 10.1111/bdi.13208

ORIGINAL ARTICLE

BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES
WILEY

Predictors of functional impairment in bipolar disorder: Results from 13 cohorts from seven countries by the global bipolar cohort collaborative

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Funding information
Supported in part by (1) National Alliance for Ment al Illness (NAMI) gift to KEB, AN, and MGM; (2) The Baszucki Brain Research Foundation. Individual investigator funding sources include: KEB is supported by R01MH124381; CEM is supported by the Stuart T. Hauser Research Training Program in Biological and Social Psychiatry Federal Postdoctoral Training Grant NIMH T32 016259–40. OAA received support from the Research Council of Norway (223273), the KG Jebsen Stiftelsen (SKGJ-MED-021), EU's H2020 RIA grant # 847776 CoMorMent, South-East Norway Health Authority (2019–108). HPB is supported by R01MH113230. MB is supported by a NHMRC Senior Principal Research Fellowship (1156072). The FACE-BD cohort was supported by the Foundation FondaMental, Institut National de la Santé et de la Recherche Médicale (INSERM), AP-HP, and by the Investissements d'Avenir program managed by the ANR under reference ANR-11-IDEX-0004-02 and ANR-10-COHO-10-01. LTE is supported by the International Society for Bipolar Disorder Bowden-Massey

Abstract

Objectives: Persistent functional impairment is common in bipolar disorder (BD) and is influenced by a number of demographic, clinical, and cognitive features. The goal of this project was to estimate and compare the influence of key factors on community function in multiple cohorts of well-characterized samples of individuals with BD.

Methods: Thirteen cohorts from 7 countries included $n = 5882$ individuals with BD across multiple sites. The statistical approach consisted of a systematic uniform application of analyses across sites. Each site performed a logistic regression analysis with empirically derived "higher versus lower function" as the dependent variable and selected clinical and demographic variables as predictors.

Results: We found high rates of functional impairment, ranging from 41 to 75%. Lower community functioning was associated with depressive symptoms in 10 of 12 of the cohorts that included this variable in the analysis. Lower levels of education, a greater number of prior mood episodes, the presence of a comorbid substance use disorder, and a greater total number of psychotropic medications were also associated with low functioning.

Conclusions: The bipolar clinical research community is poised to work together to characterize the multi-dimensional contributors to impairment and address the barriers that impede patients' complete recovery. We must also identify the core features which enable many to thrive and live successfully with BD. A large-scale, worldwide, prospective longitudinal study focused squarely on BD and its heterogeneous presentations will serve as a platform for discovery and promote major advances toward optimizing outcomes for every individual with this illness.

Strategic Research Initiative and the Desert-Pacific VA Mental Illness Research Education and Clinical Center. MAF, JMB, and SLM are supported by the Marriott Foundation and the Mayo Foundation. JMF acknowledges the Janette Mary O'Neil Research Fellowship. TVL received support from the Research Council of Norway (288542). FK is supported by the Early Postdoc Mobility Fellowship of the Swiss National Science Foundation (SNSF) and a Fellowship by the Novartis Foundation for medical-biological Research. BPF has recently received funding from NIH, Biogen, Lilly, Eisai, Rogers Family Foundation, Spier Family Foundation. MGM is supported by the HC Prechter Bipolar Research Program, the Richard Tam Foundation, NIMH (MH114835 & UL1TR002240). PBM is supported by an Australian NHMRC Investigator Grant (1177991). AAN was supported, in part, by the Dauten Family Center for Bipolar Treatment Innovation and the Thomas P. Hackett, MD Chair in Psychiatry at Massachusetts General Hospital. AP is supported by NIMH 1K23MH122676. MS has received research grants within the past 3 years: Nuromate, Otsuka, Alkermes, International Society for Bipolar Disorders (ISBD), National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), Patient-Centered Outcomes Research Institute (PCORI). EV thanks the support of the Spanish Ministry of Science and Innovation (PI15/00283, PI18/00805) integrated into the Plan Nacional de I + D + I and co-financed by the ISCIII-Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER); the Instituto de Salud Carlos III; the CIBER of Mental Health (CIBERSAM); the Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017 SGR 1365), the CERCA Programme, and the Departament de Salut de la Generalitat de Catalunya for the PERIS grant SLT006/17/00357. LJW is supported by a NHMRC Emerging Leadership Fellowship (1174060). AHY has received funding from NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). Janssen (UK). AS, LW, and MB (Deakin) are supported by a competitive project grant from the National Health and Medical Research Council (NHMRC; ID 1104438).

1 | INTRODUCTION

Bipolar disorder (BD) is one of the most impairing mental health conditions worldwide.[1] A meta-analysis by Léda-Rêgo (2020) focused on community function in BD, as measured by the Functional Assessment Short Test (FAST) indicated that 65.6% of people with euthymic BD experience work-related impairment (e.g., unable to maintain a job and reduced efficiency performing tasks). The same

study reported that 49.2% of patients had cognitive impairments on the FAST (e.g., difficulty in concentrating, performing mental calculations and solving problems), 42.6% had impairments on autonomy, and 42.1% reported impairment in maintaining interpersonal relationships.

The BD-related factors that contribute to functional impairment are not fully understood but include: primary affective symptoms, both syndromal and subsyndromal,[2] high rates of comorbid psychiatric[3] and medical disorders,[4–6] substance misuse,[7] sleep quality deficits,[8] and cognitive impairment (deficits in attention, memory and executive functioning),[9] among other factors. An enhanced understanding of the key predictors of functional impairment in individuals with BD would chart a clearer path to interventions that promote full recovery for every individual.

The field has embraced a mandate to improve the lives of individuals suffering from this disease; many challenges and hurdles impede progress, yet offer opportunities to deepen the knowledge base behind this complex disorder: (1) *BD is heterogeneous*. This contributes to a high rate of partial treatment response, and in many individuals, treatment resistance. This heterogeneity has also confounded our ability to identify pathophysiological mechanisms that drive disease and limited the development of novel, more effective treatments. Heterogeneity in BD exists at the level of diagnosis, stage, clinical profile and course, cognitive capacity,[10–12] and everyday functioning[13]; (2) *BD is a highly comorbid disease*. As noted above, common mental health conditions (e.g., substance use disorders, personality disorder, anxiety disorders) and environmental influences (e.g., lifestyle risks, early life exposure to trauma) add to the complexity of illness presentation and comorbid chronic cardiometabolic conditions[14] lead to a shortened life span.[15] While there may be risk factors that are shared among all individuals diagnosed with BD, each patient has a unique combination that complicates the illness trajectory and related outcomes; (3) *BD is a dynamic illness*. After diagnosis, the average BD patient is symptomatic 50% of the time with changes in symptom status approximately 6 times/year, and switches in polarity about 3 times/year.[16–19] Few longitudinal studies of representative first-episode cohorts have been conducted and thus that our knowledge about the course of BD is still limited. Alongside the episodic mood state changes that define the illness are impairments in sleep, cognitive capacity, substance use, motivation, and energy. There are intermittent stressors in social support systems and socioeconomic health. There is evidence of the cumulative burden of illness recurrence, with effects on the brain (e.g., grey matter abnormalities, cognitive decline)[20–22] that contribute to the high rates of functional impairment in individuals with BD. There are also indications of improvement in cognitive function after the first manic episode in those who do not relapse[23]; (4) Finally, beyond challenges inherent to the illness and its care, *resources for BD research remain insufficient*. The research focused on individuals with BD has consistently been, and remains, underfunded relative to other serious psychiatric disorders,[24] despite the exceptionally high rates of disability and societal costs. Splitting of existing funds across smaller and shorter cohort studies[25] that are generally underpowered to examine the clinical variability inhibits our ability to truly parse the dynamics of illness course. This has wide-ranging implications that include the support for ongoing research and the challenges of attracting early career researchers to the field, all of which contribute to the slow pace at which new discoveries are made.

The recent progress in the field has been largely due to the collaborative efforts of prescient researchers with a shared vision. A better, albeit very much incomplete, understanding of the underlying genetic architecture of BD has been mustered through massive data-sharing efforts. Genotype data from tens of thousands of individuals with BD have been merged in a common platform for genome-wide association studies through the Psychiatric Genomics Consortium, and replicable risk loci have successfully been identified.[26] The collective energy of the ENIGMA neuroimaging consortium further exemplifies a highly collaborative international network that has made major contributions to the knowledge of the neurobiology of the disorder. Cognitive impairment, previously considered more relevant to schizophrenia, is now known to be a core component of BD,[22] and a key contributor to the noted functional disability.[1,27] This has led to efforts in BD to target cognition with specific treatment.[28] Finally, more recent collaborative studies have begun to elucidate biological mechanisms that drive the disease, including evidence from neuroimaging paradigms, immune biomarkers, and epigenetics. Inducible pluripotent stem cells and other cutting-edge methodologies are now being applied in BD. It is an exciting time in the field, but more coordinated efforts are needed if we are to gain a full understanding of this highly complex and disabling condition.

The primary goal of the current study was to pool resources from multiple international groups in a capacity-building exercise to define the current state of collaborative research opportunities and identify the barriers that need to be lifted to realize a common vision that includes optimal outcomes for every single person living with BD. With a common mission, an international group of investigators leveraged the added value from combining existing BD data to investigate core predictors of functional outcome, independent of treatment organization or societal differences. The present work, as well as our continued collaboration, will allow for us to disentangle core bipolar disorder features from secondary phenomena which are not possible in small, one-site studies. Ultimately, we plan to launch a worldwide prospective longitudinal study of BD to more rapidly advance progress via large-scale collaborations.

2 | METHODS

2.1 | Participants

Initially, 11 groups were identified via ongoing collaborative relationships. These groups do not represent all ongoing BD research

worldwide, rather a starting point and an outline of an iterative process. There are many investigators worldwide conducting high-quality BD research in cohorts of variable sizes. As is illustrated in Table 1, 13 independent BD cohorts are included, with 2 sites contributing 2 cohorts (Mass General Hospital, MGH; and King's College London, KCL), and 2 cohorts representing consortium-based samples that were collected at multiple different sites (FondaMental Advanced Centers of Expertise for Bipolar Disorder, [FACE-BD, Fondation FondaMental, France[29]] and Global Aging and Geriatric Experiments in Bipolar Disorder, GAGE-BD[30]). Each of the other 7 sites contributed data from a single cohort.

TABLE 1 Defining "lower" functioning at each site

Cohort	Country	Lower function defined
FACE-BD (Fondation FondaMental)	France	FAST ≥21
University of Michigan	USA	Best Estimate Illness Impact ≥2
King's College London PROMPT	England	WSAS ≥20
King's College London CRIB	England	FAST ≥21
University of British Colombia	Canada	MSIF ≥4
University of Barcelona	Spain	FAST ≥21
Deakin University	Australia	GAF ≤60
Mass General Hospital LITMUS	USA	LIFTRIFT ≥14
Mass General Hospital CHOICE	USA	LIFTRIFT ≥14
Mayo Clinic	USA	Not working full time
Oslo University Hospital	Norway	GAF <60
GAGE-BD (consortium)	USA	GAF ≤60
Brigham and Women's Hospital/ Icahn School of Medicine at Mount Sinai	USA	WHODAS >5

Note: FAST is a 24 item assessment of 6 domains of function (autonomy, occupational functioning, cognitive functioning, financial, interpersonal, and leisure time); MSIF assesses occupational, education, and residential domains of function; WSAS is a brief, 5-item questionnaire that assesses one's ability to work, home management, social and private leisure activities, and close relationships; WHODAS assesses 6 domains of function (cognition, mobility, self-care, getting along, life activities, and participation); LIFE-RIFT assesses 4 domains of function (work, interpersonal, satisfaction, and recreation); GAF is a continuous scale of function based on the DSM-IV, rated from 0 to 100, with higher scores indicating higher functional capacity; Best Estimate of Illness Impact is derived from a diagnostic interview that classifies the impact of the patient's illness on their life.

Abbreviations: FAST, Functional Assessment Short Test[33]; WSAS, Work and Social Adjustment Scale[32]; MSIF, Multidimensional Scale of Independent Functioning[38]; GAF, Global Assessment of Function[39]; LIFE-RIFT, Longitudinal Interval Follow Up Evaluation-Range of Impaired Functioning Tool[40]; WHODAS, WHO Disability Adjustment Schedule[31]; DIGS, Best Estimate of Illness Impact from Diagnostic Interview for Genetic Studies.[41]

2.2 | Measures

The approach was planned as purposefully simplistic with a focus on one question via systematic uniform application of analyses across sites. Because the existing data at each site are highly variable, we allowed for substantial flexibility in the measures that were included from each site. First, each site was asked to empirically identify how they defined "high versus low functioning" in their BD cohort. This was kept purposefully coarse in its definition, as some sites use detailed questionnaires (e.g., WHO disability adjustment schedule (DAS),[31] work and social adjustment scale,[32] functional assessment short test (FAST),[33] etc.), while others may only have documented employment status or some other high-level indicator of everyday functionality. Sites were required to dichotomize whatever measure was chosen for defining function in their study, such that individuals with BD were described as having either higher or lower functional status. The way in which the variable was dichotomized was also up to the investigator, based upon the measure used at each site (e.g., some scales have recognized cutoffs, some used median splits, etc.), and are defined in Table 1.

Each site was then asked to provide detailed characteristics of their cohort(s), including demographics, diagnostic, clinical, cognitive, and functional features in the format of Table 2. Each site provided results from a Shapiro–Wilk statistical test for normality (for relevant variables), where a $p < 0.05$ indicated non-normal distribution.

Participating sites were not required to have all of the variables described in Table 2. Only "level one" measures were required. For those sites with cognitive data, we included a composite of general cognitive ability (g) (see below for derivation of g) and a premorbid estimate of IQ (typically a reading-based task).

The listing of the variables available at each site was reviewed by the first and second authors (KEB; CEM) and recommendations were made as to which variables should be included in the regression model at each site. This decision was based upon considerations of statistical power (e.g., the sample size at each site) and the validity of the data collected for each variable. After a consensus was achieved, sites were instructed to conduct a logistic regression with the functional outcome as the dependent variable (dichotomized as higher versus lower global functioning) using the entry method while model-level and predictor-level results were collated. Example analysis scripts and instructions were provided to each participating site for consistency and checked upon completion. These are provided in the supplemental materials.

2.3 | Analyses

In preparation for collating results, each site coded dichotomous variables as 0 or 1 (yes) to allow for uniform interpretation of results and to label variables in English. Any site that had cognitive data from at least three different cognitive domains was instructed to derive a general cognitive ability index "g" using an unrotated principal

TABLE 2 An informational table completed by each site

	Mean (SD)	Range	Distribution[a] Shapiro–Wilk (p)	Descriptor
Level one measures	–	–	–	–
Age	In years			e.g., first episode
Sex	%Female			
Race	%White			
Education level	In years			Primary/secondary
Level two measures	–	–	–	–
BD subtype	%BDI/BDII/NOS			
Psychosis Hx	%yes/no			Lifetime presence
Current depressive sx	HDRS/MDRS score			mild/mod/severe
Current manic sx	YMRS/other score			mild/mod/severe
Age at onset dep	In years			
Age at onset mania	In years			
# Prior manias				
#Prior depressions				
# total episodes				Full mania/depression
#Hospitalizations				
#Suicide attempts				
Comorbid substance dx	%yes/no			Lifetime presence
Comorbid anxiety dx	%yes/no			Lifetime presence
Level three measures		–	–	–
Global cognition				Calculated g using PCA
Premorbid IQ				e.g., proxy WRAT/NART
Medications				
Lithium	% Yes			
Anticonvulsants	% Yes			
Antipsychotics	% Yes			
Antidepressants	% Yes			
Benzodiazepines	% Yes			
Total number of psychotropic meds	Mean (SD)			
Outcome measures				
Global functioning				Provide name of scale
Global functioning impaired				Provide name of scale
Social functioning				Provide name of scale
Occupational fx				Provide name of scale
Independent living				Provide name of scale
Employed	Yes/no			

[a]Shapiro–Wilk test for normality should be reported for each measure.

components analysis (PCA) with up to two representative measures per cognitive domain. Estimates of *g* can be reliably derived with only 3 measures provided that they assay different domains and the measure is stable across different datasets regardless of the measures included in analyses.[34] Sites were instructed to select one or more tests within a purported "domain" as most representative of that domain, allowing for more than one test per domain (e.g. "attention") if available, provided they did not violate the 10:1 ratio rule (10 participants per one variable). Next, they were asked to select the "best" or most representative item-level variable from each test to be included in the analysis (only one per test). These variables were standardized on a z-score scale using the mean and standard deviation from their own BD sample (within-sample normalization). Finally, an unrotated PCA was conducted to include factors with eigenvalues >1.0, and component 1 was defined as *g*. Individual scores for each *g* factor for each patient were analyzed by logistic regression. The results of each site's logistic regression were then compared descriptively side-by-side, i.e., the results were not *directly* combined as each site had different predictors/definitions of the outcome. The goal herein was to find consistencies across samples and to identify

where differences exist by individual site. Thus, meta-analyses were not conducted, rather a multiple cohort replication and expansion approach was used.

3 | RESULTS

In total, analyses included 5882 individuals with a diagnosis of BD. Each site was different with regard to sample characteristics and measures included. These individual cohort descriptives are presented by the site in Table S1.

The prevalence of a priori defined "lower" functioning across sites ranged from 41 to 75% (Figure 1). Although different measures were used at nearly every site, each of which had had different ascertainment criteria and target populations ranging from population-based through to tertiary referral centers, these estimates are consistent with prior literature reporting high rates of lower functioning or impairment in BD.

Regression results by the site are presented in detail in Table S2. The differences in the regression results at each site likely reflect differences in the sample characteristics, sample size, and the measures used at each site.

Table 3 illustrates the frequency at which each of the measures contributed at a statistically significant or trend level to the regression models predicting outcome (e.g., how many sites reported any given factor as significant in their regression model). There are several findings that are consistent across sites, and some that are relatively site-specific. The most commonly reported finding was that depressive symptoms (even subthreshold symptoms) were the strongest predictor of lower community functioning (10/12 sites reported). Several additional factors that were noted as significant or trend level predictors of lower function across at least 25% of the sites reporting on that factor included: (1) Lower levels of education. (2) Greater number of prior manic episodes. (3) Greater number of prior depressive episodes. (4) Comorbid substance use. (5) Comorbid anxiety disorders. (6) Greater of the total number of psychotropic medications. We include a detailed discussion below on any factor that was found to be significant or trend-level significant ($p \leq 0.10$) in at least 25% of the sites reporting on that measure.

4 | DISCUSSION

The current study set out to measure the influence of key demographic, clinical, and cognitive factors on community function in multiple international cohorts of well-characterized populations with BD (n = 5882) and to collate and compare results. The study design was intentionally inclusive, allowing sites to contribute results regardless of the specific measures used to assess mood, disability, and other illness features. As such, and for other practical reasons, we did not combine *data* across cohorts but used a distributed data analyses framework. This approach has inherent limitations but served as an opportunity to pool resources from multiple international groups, *as a necessary first step in building the field-wide capacity for a scalable global initiative* and to define the current state of the field, recognizing that more cohorts are available that were not included in this project.

First, our results are consistent with prior reports of high rates of functional impairment in individuals diagnosed with BD. This is consistent with a multitude of single-site studies as well as a recent meta-analysis of 13 studies that reported prevalence rates of functional impairment in several domains using the FAST (global, 58.6%; occupational, 65.6%; cognitive, 49.2%; autonomy, 42.6%; interpersonal relationships, 42.1%; leisure, 29.2%; and financial issues, 28.8%).[27] The range of functional impairment that we report here is broad; being dependent upon site-specific sample characteristics as well as the granularity of the measure used to assess function. Still, these data capture the pressing need to assess everyday functioning

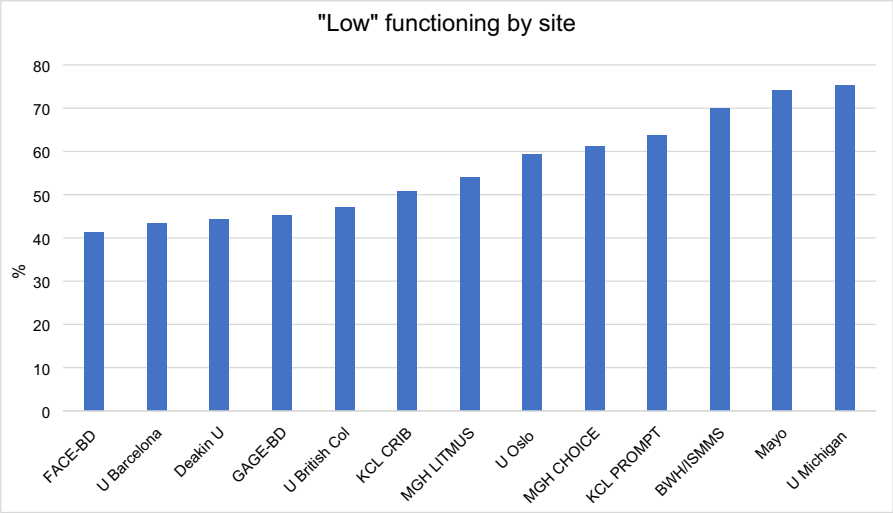


FIGURE 1 The rate of low functioning at each site

TABLE 3 Summary of results from logistic regression analyses

Characteristic	Proportion of sites reporting significance	Direction of results
Age	1/13 (8%)	Older age➔ more impairment
Sex	2/13 (16%)	Female➔ more impairment
Race	0/8 (0%)	–
Education level	3/12 (25%)	Lower education➔ more impairment
BD subtype	3/12 (25%)	BD I and SZA/BD ➔ more impairment
Psychosis history	3/11 (27%)	Mixed direction: 2 sites Psychosis hx ➔ more impairment; 1 site Psychosis hx ➔ less impairment
Current depressive symptoms	10/12 (83%)	More severe depression ➔ more impairment
Current manic symptoms	2/11 (18%)	More severe mania ➔ more impairment
Age at onset depression	0/6 (0%)	–
Age at onset mania	0/6 (0%)	–
# Prior manias	2/7 (29%)	More prior episodes ➔ more impairment
#Prior depressions	2/8 (25%)	More prior episodes ➔ more impairment
# Total episodes	0/2 (0%)	–
Comorbid substance diagnosis	2/8 (25%)	Comorbid substance use d/o ➔ more impairment
Comorbid anxiety diagnosis	3/6 (50%)	Comorbid anxiety d/o ➔ more impairment
Global cognition (*g*)	1/6 (17%)	Lower *g* ➔ more impairment
Premorbid intelligence quotient	0/5 (0%)	–
Lithium	1/6 (17%)	Lithium use➔ less impairment
Anticonvulsants	2/6 (33%)	Anticonvulsant use ➔ more impairment
Antipsychotics	3/7 (43%)	Antipsychotic use➔ more impairment
Antidepressants	0/7 (0%)	–
Benzodiazepines	0/6 (0%)	–
Total number of psychotropic meds	2/7 (29%)	More psychotropic meds➔ more impairment

in BD and to consider interventions that aggressively target those illness features that contribute to disability in hopes of promoting full recovery.

Second, across the majority of our cohorts, our results were consistent with prior reports showing the critical role that depressive symptoms play in functional status. Of the 12 cohorts where depression was examined (one site, Mayo Clinic, did not include current mood symptoms in the regression due to a loss of sample size), 10 report that the severity of depression symptoms present at the time of assessment significantly contributed to low functional status. Consistent with prior work[1,27] this points to the consistent and deleterious effects of depressive symptoms on how people with BD function in their daily lives, and further emphasizes the need for treatment beyond the acute phase of the illness to include the low-grade persistent affective symptoms that are common even in "remitted" individuals.

Third, additional factors that were significant predictors of lower function across at least 25% of the sites reporting on that feature included: (1) Lower levels of education. (2) Greater number of prior manic episodes. (3) Greater number of prior depressive episodes. (4) Comorbid substance use. (5) Comorbid anxiety disorders. (6) Greater of the total number of psychotropic medications. Each of these premorbid and illness-related factors has been previously reported as contributing to poor outcomes.[1,27]

With regard to medication, several sites were able to evaluate the effects of the use of a specific medication classes in their cohort (including lithium, anticonvulsants, antidepressants, antipsychotics, and benzodiazepines); however, we did not examine polypharmacy, which is highly prevalent in BD. Further, we did not explicitly ask for timing and length of treatment with each medication class. One site reported that lithium use was associated with better community functioning, consistent with a recent report of benefits to cognition[35]; while other medication classes showed negative effects (anticonvulsants and antipsychotics) on broad community functioning. These effects may be related to the medications themselves or the patient characteristics that are associated with the use of certain medications but are concordant with historical and emergent data on the primacy of lithium for bipolar disorder.[36] Of note, we cannot rule out the possibility that those taking anticonvulsants and antipsychotics were initial lithium non-responders (i.e., these individuals would have a poor outcome regardless)—more granular, time-course data are necessary to tease apart the subtleties in medication usage and outcomes.

Measures of cognitive function were of great interest to us, as many studies have reported a relationship between cognitive impairment and psychosocial impairment in BD[9,37]; however, only 6 of the sites had cognitive data available for inclusion in the prediction

models. Somewhat surprisingly, only 1 site found cognitive impairment was a significant predictor of lower function. This may be due to cohort characteristic differences by site, differences in the cognitive tasks included at each site, relatively small sample sizes of some cohorts, or different functional outcome measures. Indeed, since the cognitive batteries did not overlap completely, we opted to calculate a general cognitive ability (*g*) index using factor analyses to capture a single measure of global cognition that has been shown to be stable and valid regardless of the tasks included in the factor analysis.[34] As a result, we sacrificed potentially relevant granularity in our measurement, as we were unable to look at deficits in specific cognitive domains (e.g., attention, memory, executive function) as potential predictors of functioning. Often used as a proxy of intellectual capacity, educational attainment was found to be a significant predictor of lower functioning in 25% of the sites that collected that information, notwithstanding that education is also a proxy of other variables such as socioeconomic advantage or disadvantage.

There are several limitations to this study. While we were able to convene a large team of collaborators, we did not directly combine data; therefore, the limitations that apply to single-site data (e.g., limited sample sizes) still apply here. Moreover, there are a number of additional factors that contribute to community functioning in BD beyond what we were able to capture, including financial and social support, among others. We acknowledge that the planned analyses across cohorts using the identical analytic methods inherently reduced the granularity that could be achieved if any single site attempted to address the same question independently (e.g., by dichotomizing the functional measure). This indeed was part of the exercise and illustrates the need for a unified protocol to be adopted for future prospective studies.

Our findings are consistent with a convergent body of literature on functional impairment in BD. However, the primary purpose of this study was to demonstrate the value of large-scale collaborative networks in order to provide a snapshot of the BD global research landscape and to highlight the current barriers to move beyond typical within-cohort analytic frameworks in order to advance progress in BD research and care. While we provide data and results from parallel analyses across cohorts, this manuscript is, in many ways, a perspective piece that serves as a call to arms. Specifically, the information gathered emphasizes several necessary next steps: (1) We need large samples, that reach beyond single sites and encompass the full spectrum of diversity within this heterogeneous condition, taking geographic, cultural, and societal aspects into account. It is critical to include participants from non-European ancestries, to address the global impact of BD, which was not included in these analyses. Existing consortia have been fruitful and highly successful (e.g., Psychiatric Genomics Consortium, ENIGMA) but are inherently limited for fine-grained analysis, typically only including relatively superficial clinical phenotype data, allowing for limited to no follow-up over time. (2) We need comprehensive and integrated phenotyping with standardized measures which allow for data sharing and harmonization across studies. Many individual investigators are successful at collecting well-characterized cohorts but the sample size is inherently limited at any single site and merging of data across sites is difficult because measures are not uniform, preventing more optimal meta- or mega-analyses. (3) Long-term, repeated assessment of clinical, cognitive, and functional measures alongside key biomarkers (e.g., genetic, immune, imaging, digital) is necessary if we are to unravel the complexity of this illness. There are several longitudinal studies that are ongoing around the world, but the duration and frequency of follow-up are both limited and variable, usually due to funding constraints, and protocols are not uniform across sites. (4) A centralized coordinating center to direct the complex infrastructure of a global research effort (e.g., compliance/human subjects oversight, data use and sharing agreements, and database management). We propose the imminent and urgent need for a carefully designed, well-resourced, prospective global longitudinal study of BD that will allow the necessary methods to be applied in order to make game-changing discoveries and substantive improvements to the lives of individuals living with BD.

ACKNOWLEDGMENTS

The authors are grateful to all people with BD who participated and research staff at each site.

AUTHOR CONTRIBUTIONS

KEB conceived of the project idea, organized data analyses of sites, and wrote the manuscript. AN and MM organized and managed the central research body (GBC). All other members of the GBC Collaborative took part in their respective site's data analysis and reviewed the manuscript.

CONFLICT OF INTEREST

KEB has served as a consultant or advisor to Sunovion and Dainippon Sumitomo Pharma; OAA has received speaker's honorarium from Lundbeck and Sunovion and is a consultant to HealthLytix. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health, and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer, and Servier—all unrelated to this work. AJC has received honoraria for lectures or consulting from Lundbeck, Livanova, Janssen & Allergan, and a research grant from Protexin Probiotics International Ltd. MAF has had grant seed support from Assurex Health, Mayo Foundation, Medibio. Mayo Clinic has a financial interest in AssureRX and OneOme. BPF has served on advisory boards for Biogen and Acadia Pharmaceuticals, as an Advisor to Patina Health, and has served on the Pharmacy and Therapeutics Committee for CVS Health. SLM has been a consultant to or member of the scientific advisory boards of Avanir, F. Hoffmann-La Roche

Ltd., Idorsia, Intra-Cellular Therapies, Janssen, Mitsubishi Tanabe Pharma America, Myriad, Novo Nordisk, Otsuka, Signant Health (formerly Brackett), Sunovion, and Takeda (formerly Shire), has been a principal or co-investigator on studies sponsored by Allergan, Brainsway, Janssen, Jazz, Marriott Foundation, Myriad, National Institute of Mental Health, Novo Nordisk, Otsuka, Sunovion, and Takeda (formerly Shire), is also an inventor on United States Patent No. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and along with the patent's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson, which has exclusive rights under the patent. MGM has received consulting fees and research support from Janssen Pharmaceuticals. In the past 12 months, AAN received consulting fees, grants, or honoraria from Alkermes, Belvior Publishing, Ginger Inc., Merck, Myriad, Neuronetics, Patient-Centered Outcomes Research Institute, Physician's Postgraduate Press, Protagenics, Slack Publishing, Sunovion, UpToDate Wolters Kluwer, and Wiley Publishing. PBM has received honoraria from Sanofi (Hangzhou) and Janssen Australia. MS has served as a consultant for Alkermes, Otsuka, Janssen, Myriad, Health Analytics, Frontline Medical Communications, has received royalties from Springer Press, Johns Hopkins University Press, Oxford Press, UpToDate, and received compensation for the preparation of CME activities: American Physician's Institute, MCM Education, CMEology, Potomac Center for Medical Education, Global Medical Education, Creative Educational Concepts, Psychopharmacology Institute. IJT has served as a consultant for Community Living British Columbia. RS has received honoraria from Lundbeck. EV has received grants and served as consultant, advisor, or CME speaker for the following entities: AB-Biotics, Abbott, AbbVie, Angelini, Boehringer-Ingelheim, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Janssen, Lundbeck, Novartis, Otsuka, Sage, Sanofi-Aventis, Sunovion, and Takeda, outside the submitted work. LJW has received Grant/Research support from Eli Lilly, Pfizer, The University of Melbourne, Deakin University, and the NHMRC. LNY has been on the speaker/advisory boards for or has received research grants from Abbvie, Alkermes, Allergan, Canadian Network for Mood and Anxiety Treatments (CANMAT), Canadian Institutes of Health Research (CIHR), DSP, Gideon Richter, Intracellular Therapies, Merck, Sanofi, and Sunovion. AHY has received honoraria for lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders including: Astrazenaca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, COMPASS, as well as investigator-initiated studies from AZ, Eli Lilly, and Lundbeck. CMA, JMB, HPB, CDB, FK, AMA, CEM, PO, DLP, AP, JP, MS, BS, AY have nothing to disclose.

DATA AVAILABILITY STATEMENT

Deidentified data that underlie the results reported in this Article will be made available upon reasonable request to the PI at the relevant organizing institution.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Burdick KE, Millett CE, Yocum AK, et al. Predictors of functional impairment in bipolar disorder: Results from 13 cohorts from seven countries by the global bipolar cohort collaborative. *Bipolar Disord*. 2022;00:1-11. doi: 10.1111/bdi.13208