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Demographic and clinical associations to employment status in older-age bipolar disorder: Analysis from the GAGE-BD database project

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Abstract

Objective: The current literature on employment in older adults with bipolar disorder (OABD) is limited. Using the Global Aging and Geriatric Experiments in Bipolar Disorder Database (GAGE-BD), we examined the relationship of occupational status in OABD to other demographic and clinical characteristics.

Methods: Seven hundred and thirty-eight participants from 11 international samples with data on educational level and occupational status were included. Employment status was dichotomized as employed versus unemployed. Generalized linear mixed models with random intercepts for the study cohort were used to examine the relationship between baseline characteristics and employment. Predictors in the models included baseline demographics, education, psychiatric symptom severity, psychiatric comorbidity, somatic comorbidity, and prior psychiatric hospitalizations.

Results: In the sample, 23.6% ($n = 174$) were employed, while 76.4% were unemployed ($n = 564$). In multivariable logistic regression models, less education, older age, a history of both anxiety and substance/alcohol use disorders, more prior psychiatric hospitalizations, and higher levels of BD depression severity were associated with greater odds of unemployment. In the subsample of individuals less than 65 years of age, findings were similar. No significant association between manic symptoms, gender, age of onset, or employment status was observed.

Conclusion: Results suggest an association between educational level, age, psychiatric severity and comorbidity in relation to employment in OABD. Implications include the need for management of psychiatric symptoms and comorbidity across the lifespan, as well as improving educational access for people with BD and skills training or other support for those with work-life breaks to re-enter employment and optimize the overall outcome.

KEYWORDS
aging, bipolar disorder, employment, functioning, somatic burden

1 | INTRODUCTION

The number of older adults with bipolar disorder (OABD) is projected to increase.[1] Despite this, the process of aging in bipolar disorder (BD) and optimal treatment for OABD patients have been incompletely studied.[2] Further, there is limited work exploring which factors relate to employment in BD.[3] Employment status is recognized as an important disability outcome measure for many illnesses, including BD.[4,5] Thus, factors that make patients susceptible to disability particularly need to be addressed.

Current evidence is mixed on the association between level of education and employment in BD; some have not observed an association[6,7] while others note an inverse relationship between higher education and unemployment.[8] Depressive symptoms, compared to manic symptoms, may be particularly associated with workforce disturbances.[9,10] Some findings indicate that early age of onset is associated with lower levels of educational attainment.[11] Others note that age of onset is not the key factor, but rather the age of first treatment and symptom severity.[6,12,13] Other reports note that high educational attainment is prevalent in BD[13] but despite similar or higher education, individuals with BD may have lower incomes and worse employment outcomes.[6]

The relationship between older age and unemployment has had a more consistent pattern of findings in the literature, and some have argued that functional losses accumulate with age.[4,6,14,15] Potentially independent of the impact of BD, many individuals in their 60s retire from the workforce, with the average Organization for Economic Co-operation and Development (OECD) retirement age being 64.2, though there are country-level and gender differences.[16] Additionally, several findings indicate that the number of hospitalizations, length of hospitalizations,[8,9] and symptom severity may contribute to reduced productivity and lost time at work, potentially leading to loss of employment.[17] Studies on employment in OABD are limited by small sample sizes, homogenous participation, or limited clinical information due to obtaining data from registers. There is a need for greater understanding of the demographic and clinical factors associated with occupational status among OABD.

Using data derived from the Global Aging and Geriatric Experiments in Bipolar Disorder Database (GAGE-BD), the aims of this study are to (1) investigate the relationship between employment status and educational level in OABD and (2) determine whether employment status may be associated with age, gender, age of onset, mania and BD depression severity, psychiatric hospitalizations, psychiatric and somatic comorbidity burden, and functioning. Based on the literature as noted above, we hypothesized that currently unemployed individuals would have lower levels of education, be older, have more severe BD symptoms, have an earlier onset of BD, be more likely to be men, have a greater number of psychiatric hospitalizations, and have more comorbidities compared to those who are employed.

2 | METHODS

2.1 | Study design

Data for these analyses were derived from the GAGE-BD collaboration, a harmonized dataset containing cross-sectional information for outpatients with OABD from multiple international study sites compiled by members of the International Society for Bipolar Disorders OABD taskforce. Briefly, the goal of the GAGE-BD project is to study the trajectory of BD with age.[18] The integrated database contains de-identified data adapted from archival research and clinical studies of OABD samples. Approval to contribute data was obtained by each site's institutional review boards or ethics committees. Investigators from each study participated in a centralized "intake"

process wherein de-identified data was uploaded to a shared and secure online drive. Site investigators provided meta-data information such as where the study was conducted, study inclusion and exclusion criteria, sample size, study design, and a data dictionary with variable listing and description. Investigators also reviewed meta-data and descriptive data from their own sites to help ensure that findings were consistent with individual, previously reported results.

Demographic characteristics (age, gender, education, and employment status) and clinical data (diagnosis, BD subtype, age of onset, depression severity, and mania severity) were harmonized across studies. Selected data domains were collected across studies in identical format, such as age in years, age of onset in years, and manic symptom severity using the Young Mania Rating Scale (YMRS) total score.[19] These variables were used in the master dataset "as is." It should be noted that while the method of recording age of onset was generally documented as chronological age in years, studies may have used different methods of defining onset (for example, first manic episode vs. first mood episode, regardless of polarity).

Some variables required recoding or harmonization based on meta-data or other variables, such as diagnostic group and subtype (e.g., BD Type I vs. BD Type II), or whether individuals were currently employed. Generally, when data were recoded or harmonized, some degree of granularity was lost. For example, depressive symptom severity from measures that used a continuous scale was regrouped into ordinal categories by converting scores from standardized depression rating scales into severity bands following procedures established in preliminary work on dataset integration.[20,21] Additionally, as might be expected in an archival dataset, not all measures were collected in each study. Additional details on harmonization, sample characteristics, and meta-data about the contributing studies to the first wave have also been described elsewhere.[20,21]

This analysis used baseline, cross-sectional data from Wave 1 of the GAGE-BD integrated dataset and included participants with BD for which both educational level and occupational status were collected ($n=738$). As noted in Table S1, a total of 11 studies from seven sites contributed data to this analysis: Case Western Reserve University's "Open-label, prospective trial of lamotrigine for Symptoms of Geriatric Bipolar Depression," "Asenapine in the Treatment of Older Adults with Bipolar Disorder," "Ziprasidone switching in response to adherence in psychotropic-related weight gain concerns among patients with bipolar disorder," and multisite study "Treatment Adherence Enhancement in Bipolar Disorder"; McLean Hospital's "Geriatric Mood Disorders Research Database"; University of California San Diego's "Dynamic Inflammatory and Mood Predictors of Cognitive Aging in Bipolar Disorder"; University of Sao Paulo's "Cognitive impairment and dementia in late life bipolar disorder"; University of Barcelona's " University of Barcelona Bipolar Disorder Program Cohort"; Yale School of Medicine's "Mood Disorders Research Program Database"; and GGZ inGeest's "Dutch Older Bipolar Cohort" wave 2012 and wave 2017–2018. Inclusion and exclusion criteria from these 11 studies are noted in Table S2. Not all cases from each study were included in the analyses if a key variable was missing (such as employment status). Among the 11 included studies, 4 (36.3%) were interventional trials, with the remainder being observational studies. A majority of the studies ($N=7$, 63.6%) were conducted in the United States, involving 448 participants (60.7% of the sample). Studies done outside of the United States comprised two from the Netherlands, one from Brazil and one from Spain.

2.2 | Outcome of Interest

Employment status was dichotomized as "employed" versus "unemployed." Different datasets had differing categories of individuals who were not employed, some with clearly defined retired subgroups versus other datasets that had broader/nonspecific categories. Our overall dataset did not provide information of sufficient granularity to be able to consistently parse out reasons for nonworking status, for example, people who took early retirement due to the effects of BD and/or retirement because of excessive job demands. Harmonization of categories within these dichotomous groupings results in further loss of granularity. For example, a classification of retired (when available) was classified in the unemployed category, as was unemployment due to disability (when available). Individuals classified as part-time employed were classified as employed.

2.3 | Predictors of Interest

Demographic predictors were age and gender. Education was analyzed as a continuous variable (years of education). BD age of onset was also a continuous variable (in years). Data on the number of lifetime psychiatric hospitalizations, excluding admissions for substance use or dependence, were extracted. Information on comorbid substance use disorders and anxiety disorders were categorized as lifetime or current.

Psychiatric symptom measures included the Young Mania Rating Scale (YMRS) and harmonized ordinal depression severity categories. For this analysis, we focused on manic and depressive symptoms, given the greater availability of these variables in the dataset. The YMRS is an 11-item self-report rating scale used to assess the severity of manic symptoms over the preceding 48 h.[19] Each item on the scale is rated out of 0–4 or 0–8 points, producing a score out of 60, where a higher total score denotes a higher severity of symptoms.

The process for categorizing depressive symptoms from the GAGE-BD collaboration into depression symptom severity bands has been described elsewhere.[20,22] Briefly, symptoms of depression severity derived from the Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), and Center for Epidemiological Studies-Depression (CES-D) were combined to create a severity score corresponding to mild–moderate and severe depression based on established cut-off scores and the distribution of scores in the dataset. The HAM-D is a clinician-rated scale consisting of 17 items, measuring somatic and affective symptoms of depression.[23] Each item is scored for

severity on a scale of 0–2 or 0–5 points, where a higher score reflects higher symptom severity. The MADRS is a 10-item clinician-rated scale that assesses the severity of depressive symptoms in the past week, each rated from 0 to 6, where a higher score reflects higher depressive symptom severity.[24] The CES-D is a 20-item self-report scale that measures depressive symptoms during the previous week, with scores ranging from 0 to 60.[25] Scores 0–16 represent no depression, scores over 16 indicate clinically relevant depression, scores 16–27 represent mild to moderate depression, and scores over 28 represent severe depression. In our harmonized categories, no depression corresponded to HAM-D total score of 0–7, MADRS total score of 0–6, or CES-D total score of 0–15. Mild–moderate depression corresponded to HAM-D total score of 8–23, MADRS total score of 7–34 or CES-D total score of 16–27. Severe depression corresponded to HAM-D total score of ≥24, MADRS ≥35, or CES-D total score of ≥28.

Somatic comorbidities were extracted from standardized evaluations, such as the Charlson Comorbidity Index,[26] the Cumulative Illness Rating Scale for Geriatrics,[27] and/or medical comorbidity categories derived from the assessments of study participants. The extracted data were then categorized into eight dichotomous variables (somatic comorbidity present vs. absent) in the following systems: cardiovascular, respiratory, gastrointestinal, hepatic/pancreatic, renal, genitourinary, musculoskeletal, and endocrine. For the analysis, we focused on the total number of systems with somatic comorbidities.

2.4 | Statistical analysis

To examine the relationship between demographic and clinical characteristics and employment, multivariable logistic mixed models were completed using generalized linear mixed models with the cohort/study as a random intercept. The baseline model included age, gender, education, and age of onset. Since complete data were not available across all observations, we iteratively examined the relationships for the following variables, adjusting for baseline predictors: number of psychiatric hospitalizations, psychiatric comorbidity, somatic comorbidity, and psychiatric illness severity (based on YMRS and a 3-category depression band). Models were repeated, restricting them to those <65 years of age (excluding those who were at typical retirement ages). The significance is defined by a two-sided alpha of 5%. Statistical analyses were completed in SAS Version 9.4 and Stata SE v17.0.

3 | RESULTS

3.1 | Demographic and clinical variables

Participant characteristics are described in Table 1. Out of the 738 participants included, 23.6% were employed ($n=174$) while 76.4% were unemployed ($n=564$). The mean (SD) age of the sample was 57.4 (11.9) years. The sample was predominantly high school educated (73.7%) or greater, with a mean (SD) years of education of 13.1 (3.7). Women made up 58% ($n=428$) of the overall sample. The majority of individuals ($n=543$, 74.1%) had Type 1 BD, and the sample had a mean age of BD onset of 28.0 (14.2) years. BD symptom severity was relatively mild in this sample, with approximately 40% of the sample presenting no depressive symptoms and one-half having mild–moderate depressive symptoms. The mean YMRS score of 5.6 (6.0) suggests absent or mild manic symptom severity.

Noteworthy descriptive differences by employment status were a later mean age of onset, a lower proportion of at least a high school education, a higher proportion with mild to severe depression, a higher burden of cardiovascular disease, a greater history of psychiatric hospitalizations, and comorbidity for both anxiety and substance/alcohol use disorders in those who were unemployed. Table 2 shows descriptive data (demographics and selected clinical variables) in the U.S. and non-U.S. subgroups. The proportion of individuals who were unemployed was similar between the U.S. (23.9%) and non-U.S. (23.1%) subgroups.

3.2 | Associations with employment status

In multivariable logistic regression models (Table 3), older age and fewer years of education were consistently associated with greater odds of unemployment across models. In iterative models, the number of psychiatric hospitalizations (OR = 1.09, $p=0.046$), history of both anxiety and substance/alcohol use disorder comorbidity (OR = 2.74, $p=0.028$), number of somatic comorbidity domains (OR = 1.27, $p=0.027$), and mild–moderate (OR = 2.17, $p=0.003$) and severe depression (OR = 3.56, $p=0.023$) were significantly associated with unemployment. Individuals with at least mild depression and both anxiety and substance/alcohol use disorders had a two-fold increased odds of being unemployed, and these associations persisted when both variables were included in a multivariable model (data not shown). These associations largely persisted when restricted to those <65 years of age (Table 4); a key difference was that the effect of severe depression substantially increased (OR = 7.3, $p=0.018$). No significant association between manic symptoms, gender, or age of onset and employment status was observed.

4 | DISCUSSION

In this large, heterogeneous, cross-sectional sample of patients with BD that adjusted for relevant demographic and clinical variables and aligned with our initial hypotheses, we found that lower educational attainment, older age, more severe depressive symptoms, more prior psychiatric hospitalizations, and more comorbidity (particularly the dual comorbidity of having substance use disorder and anxiety) were associated with greater odds of unemployment. While being unemployed or having a work disability has been linked to lower education in the general population,[28,29] our findings contribute to a

TABLE 1 Descriptive statistics for GAGE-BD total sample by employment status ($n = 738$).

Descriptive variables	All cases ($n = 738$)	Employed ($n = 174$)	Unemployed ($n = 564$)
Age, years (mean [SD])	57.4 (11.9)	55.5 (10.9)	58.0 (12.1)
Age range, years	18–90	18–85	19–90
Age by decade (*N*/%)			
18–30 years	14 (1.9%)	4 (2.3%)	10 (1.8%)
30–40 years	47 (6.4%)	15 (8.6%)	32 (5.7%)
40–50 years	74 (10.0%)	8 (4.6%)	66 (11.7%)
50–60 years	260 (35.2%)	81 (46.6%)	179 (31.7%)
60–70 years	243 (32.9%)	58 (33.3%)	185 (32.8%)
70–80 years	83 (11.3%)	6 (3.5%)	77 (13.7%)
80+ years	17 (2.3%)	2 (1.2%)	15 (2.7%)
Age ≥ 50	603 (81.7%)	147 (84.5%)	456 (80.9%)
Sex			
Male	310 (42.0%)	86 (49.4%)	224 (39.7%)
Female	428 (58.0%)	88 (50.6%)	340 (60.3%)
Diagnosis ($n = 733$)			
Bipolar I	543 (74.1%)	132 (75.9%)	411 (73.5%)
Bipolar II	186 (25.4%)	41 (23.6%)	145 (25.9%)
Other bipolar	4 (0.6%)	1 (0.6%)	3 (0.5%)
Age of onset, years ($n = 679$; mean [SD])	28.0 (14.2)	25.1 (12.8)	28.9 (14.5)
Years of education (mean [SD])	13.1 (3.7)	14.8 (3.2)	12.6 (3.7)
≥12 years education (*N*/%)	544 (73.7%)	152 (87.4%)	392 (69.5%)
Depression Band ($n = 672$)			
No depression	274 (40.8%)	96 (57.1%)	178 (35.3%)
Mild to moderate	358 (53.3%)	66 (39.3%)	292 (57.9%)
Severe	40 (5.9%)	6 (3.6%)	34 (6.8%)
YMRS total ($n = 707$)	5.6 (6.0)	5.0 (5.7)	5.8 (6.1)
Somatic Comorbidity			
Cardiovascular ($n = 705$)	257 (36.5%)	43 (25.0%)	214 (40.2%)
Respiratory ($n = 665$)	210 (31.6%)	48 (27.9%)	162 (32.9%)
GI ($n = 666$)	121 (18.2%)	23 (13.4%)	98 (19.8%)
Hepatic/pancreatic ($n = 664$)	34 (5.1%)	10 (5.9%)	24 (4.9%)
Renal ($n = 524$)	25 (4.8%)	8 (5.8%)	17 (4.4%)
GU ($n = 344$)	44 (12.8%)	6 (5.0%)	38 (17.0%)
Musculoskeletal ($n = 706$)	256 (36.3%)	50 (29.1%)	206 (38.6%)
Endocrine ($n = 706$)	188 (26.6%)	35 (20.2%)	153 (28.7%)
Number of somatic comorbidities ($n = 344$)	1.7 (1.3)	1.3 (1.5)	2.0 (1.8)
Psychiatric comorbidity			
Number of psychiatric hospitalizations[a] ($n = 489$)	3.5 (5.9)	2.0 (3.5)	3.9 (6.4)
Lifetime nonbipolar psychiatric diagnosis ($n = 580$)			
None	232 (40.0%)	67 (50.4%)	165 (36.9%)
Lifetime Anxiety Disorder	123 (21.2%)	35 (26.3%)	88 (19.7%)
Lifetime substance/alcohol use disorder	102 (17.6%)	18 (13.5%)	84 (18.8%)
Lifetime anxiety & substance/alcohol use disorders	123 (21.2%)	13 (9.8%)	110 (24.6%)

Note: Of the 738 BD participants represented in the total sample, there was some missing data for all measures, so sample size for each measure is given separately.

Abbreviations: GI, gastro-intestinal; GU, genito-urinary; SD, standard deviation; YMRS, Young Mania Rating Scale, score range 0–60 with higher scores indicating more severe manic symptoms.

[a]Excluding substance use/dependence.

pool of mixed results in the BD literature, which have reported both a positive association[8,12,30–32] and no association between education and employment.[6,33–37]

Educational attainment is often used as a proxy for "cognitive reserve," a theoretical construct that aims to explain the differences in individual susceptibility toward cognitive impairment due to brain

TABLE 2 Descriptive characterization of U.S. vs. Non-U.S. samples.

Descriptive variables	U.S. studies (*N* = 7)	Non-U.S. studies (*N* = 4)
N	448 (60.7%)	290 (39.3%)
Age, years (mean [SD])	53.7 (12.3)	63.2 (8.4)
Age ≥ 50	313 (60.0%)	290 (100%)
Sex		
Male	182 (40.6%)	128 (44.1%)
Female	266 (59.4%)	162 (55.9%)
Diagnosis (*n* = 733)		
Bipolar I	362 (81.7%)	181 (62.4%)
Bipolar II	77 (17.4%)	109 (37.6%)
Other bipolar	4 (0.9%)	0
Age of onset, years (mean [SD]; *n* = 679)	24.5 (12.9)	32.7 (14.5)
Years of education (mean [SD])	13.8 (2.9)	12.0 (4.5)
≥ 12 years education (*N*/%)	368 (82.1%)	176 (60.7%)
Employed (*N*/%)	107 (23.9%)	67 (23.1%)
Depression band (*n* = 672)		
No depression	98 (22.6%)	176 (73.6%)
Mild to moderate	313 (72.3%)	45 (18.8%)
Severe	22 (5.1%)	18 (7.5%)
YMRS total (*n* = 707)	7.0 (6.0)	3.4 (5.5)
Comorbidity		
Number of somatic comorbidities (*n* = 344)	2.2 (1.9)	0.7 (0.5)
Number of psychiatric hospitalizations* (*n* = 489)	4.8 (7.5)	1.9 (2.5)
Lifetime nonbipolar psychiatric diagnosis (*n* = 580)		
None	77 (22.0%)	155 (67.4%)
Lifetime anxiety disorder	102 (29.1%)	21 (9.1%)
Lifetime substance/alcohol use disorder	58 (16.6%)	44 (19.1%)
Lifetime Anxiety & Substance/Alcohol Use Disorders	113 (32.3%)	10 (4.4%)

*excluding psychiatric admissions for substance use or dependence.

pathology and aging.[38] In BD, cognitive impairment is observed even during remission[39]; people with BD who have lower cognitive reserve also have worse performance on cognitive measures[40] and experience greater cognitive decline after illness onset.[41] Since cognitive deficits have been found to be predictive of diminished occupational functioning in BD[42] and OABD,[43,44] it is possible that those with higher education would have greater cognitive reserve and less decline in cognitive performance, making it easier to maintain employment.

Consistent with Kleinman et al.,[17] more severe BD symptoms are associated with a reduced likelihood of employment. It is possible that the greater severity of BD symptoms could also have contributed to the finding of greater number of prior psychiatric hospitalizations among those who were unemployed. We additionally found that older age was associated with unemployment in all tested models, and this appeared to be independent from the associations with education and depressive symptoms in a model including all significant predictors from previous models. The associations persisted even when examining a preretirement-aged subsample (≤64 years), suggesting that retirement of previously employed individuals is not a major explanatory contributor to our findings. Overall, our finding indicating that older age is associated with a greater likelihood of unemployed status is consistent with prior studies.[36,45–48] Our findings extend on these previous studies, most of which drew their conclusions by means of comparisons between employed versus unemployed individuals' baseline characteristics without adjusting for potentially confounding factors. In addition, there is a possibility that the presence of cognitive impairment or a lower cognitive reserve may explain the link between age and employment status. For example, ageism or stigma related to BD could make it harder for older people with BD to enter or re-enter the workforce after an interrupted period of work due to illness concerns.

With respect to comorbidity, we found that greater somatic burden and being comorbid for both substance use disorder and anxiety were associated with being unemployed. It has been reported that BD has a higher prevalence of substance-use disorders than any other psychiatric illness[49,50] and that those with both BD and substance disorders have more complications, including more anxiety- and stress-related disorders, as well as impulsivity and poor modulation of motivation[51] - all factors that could potentially contribute to difficulty in sustaining employment. This contrasts with Arvilommi et al. who suggested that psychiatric comorbidity did not predict being on employment disability in the long term.[52] Konno et al. also found no difference in the proportions of individuals with psychiatric comorbidity among those with continuous employment vs. those who lost their jobs.[10]

Contrary to our initial hypotheses and adjusted models, we did not find a significant relationship between gender, BD age of onset, manic symptoms, and employment status. These findings are largely consistent with prior studies that have failed to establish a robust relationship between these variables and employment. Although Konno et al. noted a gender difference in employment status relative to comorbidity, suggesting that this finding was reflective of national gender differences in employment.[10] Our finding is also in line with Zimmerman et al.,[7] who found no gender differences, and Holm et al. study,[8] who pointed out that gender differences in employment rate were reflective of the general population, despite the gender difference being greater in BD samples versus samples with schizophrenia.

The strengths of these analyses include the utilization of harmonized data from a large, multisite, and global sample. As with the strengths, the limitations of this paper are also primarily attributable to the diverse sample collected from multiple centers across different countries, as well as the different focus of each study and differing study designs. Some of the variables, such as comorbidities, were available to a limited number of participants, hence our iterative modeling approach. However, we tried to

TABLE 3 Multivariable logistic regression associations for unemployment.

	Baseline Model 1		Model 2		Model 3		Model 4		Model 5	
Predictor	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age	1.06 (1.03, 1.09)	**<0.001**	1.06 (1.03, 1.10)	**<0.001**	1.05 (1.02, 1.08)	**0.003**	1.04 (1.00, 1.08)	**0.027**	1.05 (1.02, 1.08)	**0.001**
Female	1.41 (0.95, 2.11)	0.091	1.51 (0.92, 2.46)	0.103	1.61 (1.02, 2.54)	**0.041**	1.14 (0.68, 1.91)	0.615	1.33 (0.87, 2.02)	0.190
Education (years)	0.87 (0.81, 0.92)	**<0.001**	0.89 (0.82, 0.96)	**0.002**	0.89 (0.83, 0.95)	**0.001**	0.91 (0.84, 0.98)	**0.009**	0.88 (0.82, 0.94)	**<0.001**
Age of onset	1.00 (0.98, 1.02)	0.852	1.00 (0.98, 1.02)	0.739	1.01 (0.99, 1.03)	0.609	1.01 (0.98, 1.03)	0.676	1.01 (0.99, 1.03)	0.469
Number of Psychiatric hospitalizations			1.09 (1.00, 1.18)	**0.046**						
Psychiatric comorbidity (reference = None)										
Lifetime anxiety disorder (current or past)					1.43 (0.75, 2.73)	0.274				
Lifetime substance/alcohol use disorder (current or past)					1.88 (0.88, 4.03)	0.103				
Lifetime anxiety & substance/alcohol use disorders					2.74 (1.11, 6.73)	**0.028**				
Number of medical comorbidities							1.27 (1.03, 1.57)	**0.027**		
Current symptoms										
YMRS total score									1.01 (0.98, 1.05)	0.456
Mild–moderate depression (vs. low)									2.17 (1.30, 3.61)	**0.003**
Severe depression (vs. low)									3.56 (1.19, 10.65)	**0.023**

Note: Generalized Linear Mixed Model with a random intercept for study cohort. Model 1: $N = 679$; Model 2: $N = 484$; Model 3: $N = 530$; Model 4: $N = 289$; Model 5: $N = 601$.

Abbreviations: CI, confidence interval; YMRS, Young Mania Rating Scale.

The bolded values indicated *p* values that were <0.05.

TABLE 4 Multivariable logistic regression associations for unemployment in those <65 years of age.

	Baseline Model 1		Model 2		Model 3		Model 4		Model 5	
Predictor	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age	1.06 (1.02, 1.09)	**0.001**	1.60 (1.02, 1.10)	**0.004**	1.05 (1.01, 1.09)	**0.018**	1.05 (1.00, 1.10)	**0.031**	1.05 (1.01, 1.09)	**0.006**
Female	1.26 (0.81, 1.95)	0.310	1.47 (0.87, 2.49)	0.146	1.44 (0.88, 2.36)	**0.146**	1.06 (0.61, 1.84)	0.842	1.16 (0.73, 1.84)	0.534
Education (years)	0.88 (0.82, 0.94)	**<0.001**	0.90 (0.83, 0.97)	**0.007**	0.90 (0.84, 0.97)	**0.009**	0.93 (0.85, 1.01)	0.069	0.88 (0.81, 0.94)	**<0.001**
Age of onset	0.99 (0.97, 1.01)	0.440	0.99 (0.97, 1.01)	0.396	0.99 (0.97, 1.01)	0.358	1.00 (0.97, 1.03)	0.860	1.01 (0.97, 1.05)	0.728
Number of Psychiatric hospitalizations			1.10 (1.00, 1.20)	**0.041**						
Psychiatric comorbidity (reference = None)										
Lifetime anxiety disorder (current or past)					1.34 (0.66, 2.72)	0.418				
Lifetime substance/alcohol use disorder (current or past)					1.70 (0.73, 3.95)	0.214				
Lifetime anxiety & substance/alcohol use disorders					2.67 (1.02, 6.96)	**0.045**				
Number of medical comorbidities							1.12 (0.89, 1.41)	0.335		
Current symptoms										
YMRS total score									1.01 (0.98, 1.05)	0.549
Mild–moderate depression (vs. low)									2.17 (1.30, 3.61)	**0.001**
Severe depression (vs. low)									3.56 (1.19, 10.65)	**0.005**

Note: Generalized Linear Mixed Model with a random intercept for study cohort. Model 1: $N = 516$; Model 2: $N = 406$; Model 3: $N = 431$; Model 4: $N = 234$; Model 5: $N = 490$.

Abbreviations: CI, confidence interval, YMRS, Young Mania Rating Scale.

The bolded values indicated *p* values that were <0.05.

address these limitations by treating each study site as a random effect across models. Null findings in our covariate models may have been due to modest sample sizes (e.g., psychiatric comorbidities were only available in a subset of participants). The inability to analyze working and nonworking subgroups (such as retired vs. those on early disability) is another limitation of the analysis. Having only four countries represented is a limitation that hinders country-specific comparisons. Additionally, because our participants were recruited from different sites, local employment rates may affect our findings. Prior studies have cautioned against analyzing employment rates isolated from local employment rates, as this could potentially jeopardize identification of the real extent of BD's involvement in unemployment.[8,15] Similarly, given the aggregate nature of the data, it is difficult to ascertain whether differences in employment due to demographic factors, such as age, are reflective of the general population across sites. We did not have sufficient sample sizes of non-BD participants from each study to compare rates between those with and without BD in our dataset. Additionally, individual or regional-specific factors, such as stressful life events or regional economic downturns, which may also contribute to unemployment,[53] were not considered in our analyses. It is important to note that all of our data were collected prior to the onset of the COVID pandemic and thus may not generalize to the COVID or post-COVID world. While we did address age of onset, we did not measure time spent in the symptomatic stage, which may have additional implications for employment status. Finally, not having reliable/consistent data on the number of past episodes, predominant polarity, or presence of psychosis across the datasets are additional limitations of our report.

In conclusion, our results suggest an association between lower levels of education, older age, psychiatric severity, comorbidity, and a greater likelihood of unemployment in BD. Greater BD depressive symptoms are associated with a greater likelihood of unemployment. Our findings come with clinical, public health, and socioeconomic implications, such as tailoring educational access to people with BD and supporting those who have had breaks in employment with skills training in order to re-enter the workforce. It is important for treatment to address occupational status in OABD to both reduce economic burden and increase quality of life for patients.[54,55] Optimizing BD symptom management, particularly depressive symptoms, throughout the life-span would positively impact multiple daily-life domains, including occupational status. Overall, more research is needed on factors affecting educational attainment in BD across the lifespan.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data are available as part of the GAGE-BD project and subject to the completion of appropriate data use agreements. Qualified scientists who wish to access the data should contact the study lead author.

ETHICS STATEMENT

Approval to contribute data was obtained by each site's institutional review boards or ethics committees and by the GAGE-BD coordinating center (Case Western Reserve University School of Medicine, Cleveland, Ohio, USA).

PATIENT CONSENT STATEMENT

Patients provided consent to participate in research studies at each individual site as required by the local institutional review board (IRB) or ethics committee.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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