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Bipolar symptoms, somatic burden and functioning in older-age bipolar disorder: A replication study from the global aging & geriatric experiments in bipolar disorder database (GAGE-BD) project

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Abstract

Objectives: The Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) project pools archival datasets on older age bipolar disorder (OABD). An initial Wave 1 (W1; $n = 1369$) analysis found both manic and depressive symptoms reduced among older patients. To replicate this finding, we gathered an independent Wave 2 (W2; $n = 1232$, mean $\pm$ standard deviation age 47.2 ± 13.5, 65% women, 49% aged over 50) dataset.

Design/Methods: Using mixed models with random effects for cohort, we examined associations between BD symptoms, somatic burden and age and the contribution of these to functioning in W2 and the combined W1 + W2 sample (n = 2601).

Results: Compared to W1, the W2 sample was younger ($p < 0.001$), less educated ($p < 0.001$), more symptomatic ($p < 0.001$), lower functioning ($p < 0.001$) and had fewer somatic conditions ($p < 0.001$). In the full W2, older individuals had reduced manic symptom severity, but age was not associated with depression severity. Age was not associated with functioning in W2. More severe BD symptoms (mania $p \leq 0.001$, depression $p \leq 0.001$) were associated with worse functioning. Older age was

significantly associated with higher somatic burden in the W2 and the W1 + W2 samples, but this burden was not associated with poorer functioning.

Conclusions: In a large, independent sample, older age was associated with less severe mania and more somatic burden (consistent with previous findings), but there was no association of depression with age (different from previous findings). Similar to previous findings, worse BD symptom severity was associated with worse functioning, emphasizing the need for symptom relief in OABD to promote better functioning.

KEYWORDS

aging, bipolar disorder, depression, functioning, mania, medical burden

Key points

- With the global population of older adults increasing rapidly, it is important to understand how older adults with bipolar disorder (BD) differ from younger adults.
- This replication analysis using a large global dataset focused on older-age bipolar disorder (OABD) and examined associations of older age, BD symptoms, somatic burden and functioning.
- Older age was associated with less severe mania and more somatic burden but there was no association of depression with age.
- Worse BD symptom severity was associated with worse functioning, emphasizing the need for symptom relief in OABD to promote better functioning.

1 | INTRODUCTION

With the rapidly growing global population of older adults, there is an urgent need for specific data on bipolar disorder (BD) in this age-group.[1] Unfortunately, there continues to be a dearth of research about the aging process in BD.[2,3] The Global Aging & Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) project pools archival datasets to advance knowledge on older age BD (OABD).[4–10] Key goals of the GAGE-BD project are to examine patterns of BD mood trajectory with age and to characterize the associations between BD symptoms, somatic comorbidities, and functional status.

Results from an initial Wave 1 (W1; $n = 1369$) analysis suggested that both BD manic and depressive symptoms are less severe in older age.[5] Education moderated this effect, such that those with lower education showed more diminished symptoms with age; there was no evidence of moderation by sex.[5] Worse BD symptom severity was associated with poorer functioning, and the relationship of depression with functioning was more severe among older patients.[5] Somatic comorbidity was high, but not significantly associated with poorer functioning. While findings from this large, global sample are intriguing, being able to replicate them using data from independent research samples would enhance validity and generalizability.

This is a replication analysis of GAGE-BD using a new, independent Wave 2 (W2; $n = 1232$; 15 studies from 10 sites) dataset and the same outcome variables and methods. The first aim was to examine associations between BD symptoms, somatic burden, and advancing age. We hypothesized that both manic and depressive symptoms

would be less severe in older participants, particularly among those with lower education, while somatic burden would be greater with older age. We also explored possible moderation of these relationships by sex. The second aim was to examine the contribution of symptom severity and somatic burden to functioning. We expected that individuals with more severe symptoms and greater somatic burden would have poorer functioning, and that these relationships would be particularly strong among older participants. As in our previous analysis of W1 data, we included BD participants of all ages in our primary W2 analyses to increase our power to observe relationships with age. However, because we are specifically interested in OABD, and because individuals who were ≥50 years old were less represented in the W2 dataset (48.8% of sample) compared to W1 (86.6% of the sample), we also explored findings on the subset of OABD in W2. Finally, we explored findings in the combined W1 and W2 dataset ($n = 2601$). We expected that similar findings would be evident in the full W2 sample, the W2 OABD subset, and in the combined W1 + W2 dataset. Through these replication and extension analyses, we hoped to provide a solid foundation for future work by GAGE-BD and in OABD more generally.

2 | METHODS

2.1 | Datasets and data aggregation

GAGE-BD comprises pooled data from multiple archival studies contributed by a team of international investigators. The

overarching approach and methods of GAGE-BD have been described elsewhere.[4,5] As the GAGE-BD dataset is intended to facilitate secondary analyses on diverse topics and shed insights on general aging-related issues in people with BD, there were no specific inclusion criteria for W2 dataset inclusion other than that they would focus primarily on BD and have reasonable representation of people with BD who were over the age of 50 years. The W2 sample is a completely independent set of 1232 BD participants from 15 studies from 10 sites as of March 2022. Results from the original W1 sample ($n = 1369$; data lock March 2021) helped inform hypotheses for this replication study, and are included in exploratory analyses here. The aggregate W1 + W2 sample was derived from 33 studies from 18 sites across the globe reporting data.

Supplemental Tables S1 and S2, and Supplemental Figure S1, show sites that contributed W1 and W2 data and selected meta-data information provided by sites such as where the study was conducted, study inclusion and exclusion criteria, sample size and study design. Approval to contribute coded data with no private health information was obtained by originating site institutional review boards or ethics committees and a data use agreement was executed between each contributing site and the project coordinating center (Case Western Reserve University School of Medicine, Cleveland, Ohio, USA).

2.2 | Measures

Data domains were aggregated 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)[11] total score. While many variables were used "as is" without any need for data harmonization or re-coding to create uniform variable categories, it should be noted that studies may have had differing methods of measuring or defining a given domain. For example, studies may have used different methods of defining age of BD onset (e.g., first manic episode vs. first mood episode regardless of polarity).

Select variables required harmonization or re-coding based on meta-data or other variables, such as BD subtype (e.g., Type I vs. Type II). Relevant to this analysis, depressive symptom severity using different rating scales (the Hamilton Depression Rating Scale),[12] Montgomery-Asberg Depression Rating Scale,[13] Inventory of Depressive Symptoms[14] and Center for Epidemiologic Studies—Depression[15] were categorized into a single ordinal variable by converting individual scores into severity bands (no/minimal, mild, moderate and severe) following procedures established in preliminary work on dataset integration.[16] For this analysis we used baseline BD symptom data for all datasets, regardless of the study methodology.

Functional status was assessed using the Global Assessment of Functioning (GAF)[17]; however, GAF was only collected in 8 out of 15 studies ($n = 540$) in W2 and 17 out of 33 studies ($n = 1209$) in the combined W1 +W2 dataset. We were not able to consistently identify if sites were using versions of the GAF that may have

included psychiatric symptom severity anchors within the GAF score calculation. Somatic comorbidity was assessed across studies using a variety of methods, including the Cumulative Illness Rating Scale[18] and the Charlson Comorbidity Index[19] or clinical determination of selected comorbidity categories based on self-report, charts, or examination. Somatic comorbidity was harmonized into 8 binary variables (absence vs. presence of cardiovascular, respiratory, gastrointestinal, liver, renal, genitourinary, musculoskeletal, and endocrine disorders).[20] A cumulative somatic comorbidity burden was derived by summing the total number of positively endorsed comorbidity domains.

2.3 | Data analysis

All variables were examined for distributional characteristics, and descriptive comparisons of W1 and W2 samples were conducted for continuous and categorical variables. YMRS was left-skewed (low manic symptom severity) and therefore log transformed to meet normality assumptions for all analyses. The transformation resulted in a distribution that was near Gaussian and reductions in skewness (0.06), and kurtosis (−0.57). For the first aim, linear and ordered logistic mixed models were used with a random effect for study cohort for mania severity, depression symptom severity, and somatic comorbidity as the respective dependent variables. The independent variable of interest was age; sex and education were included as covariates. We iteratively examined if the association for age with each outcome was moderated by education or by sex through the inclusion of interaction terms.

For the second aim, level of functioning as measured by GAF was the dependent variable and age was an independent variable of interest with sex and education as covariates. In this linear mixed model with a random effect for study cohort, we iteratively included other independent variables of interest: mania severity, depression severity, and number of affected somatic domains. We subsequently included interaction terms for age and mania severity, age and depression symptom severity, and age and comorbidity burden.

For each aim, we also conducted exploratory analyses with a W2 sub-group of individuals ≥50 years (W2 OABD sub-group, $n = 601$), given that this is the suggested age threshold for OABD (2) and the original W1 analysis had a larger proportion of OABD than the new W2 sample. Finally, we explored findings in the combined sample of W1 + W2 for the same research questions given the greater power afforded. For all analyses, a two-sided alpha of 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Overall sample description

Table 1 shows descriptive summaries for the W1 ($n = 1369$), W2 ($n = 1232$), W2 OABD subsample ($n = 601$), and combined W1 + W2

($n = 2601$) samples. The W2 replication sample had a mean age of 47.2 years (standard deviation (SD) 13.5), 800 women (64.9%) and 601 individuals [(48.8%) $\geq$ age 50. Compared to W1, the W2 sample was younger ($t[2484.8] = 26.6$, $p < 0.001$), more predominantly female ($\chi^2[1] = 21.49$, $p < 0.0001$), less educated ($t[2009] = 3.66$, $p < 0.001$), had more severe BD symptoms ($\chi^2[3] = 29.26$, $p < 0.001$), had poorer functioning ($t[949.08] = 5.53$, $p < 0.001$) and had comorbidities across fewer somatic domains ($t[2121.3] = 16.54$, $p < 0.001$). Manic symptom severity in the W2 replication sample was low, and most had no or only minimal depression. The most common somatic comorbidities in W2, among participants with available data, were cardiovascular (26.3%, $n = 229$), endocrine (21.5%, $n = 173$), musculoskeletal (19.1%, $n = 129$), and respiratory conditions (13.2%, $n = 94$). Figure 1 shows the distribution of subject age in the W1 and W2 data sets.

3.2 | Age relationships to BD symptoms and somatic burden

With respect to the hypothesis that both BD manic symptoms would be attenuated in older age, in the full W2, older individuals had reduced manic symptom severity, even adjusting for sex and education (Table 2, Figure 2). The finding was moderated by education, but not sex (data not shown), such that those with fewer years of education had a stronger association of lower mania symptoms with older age (Supplemental Table S3a). In exploratory analyses, there was no relationship of age with mania severity in the W2 OABD subgroup, whether unadjusted or adjusted for sex and education (Supplemental Table S3b), and no moderation by either education or sex (data not shown). In the combined W1 + W2 sample, similar to the W2 sample, older individuals had lower manic symptom severity, even with adjustment for sex and education (Supplemental Table S3c; Supplemental Figure S2). There was no moderation of age relationships with mania by education or sex in the combined sample (data not shown).

In contrast to our hypothesis about attenuated depression severity with age, older age was not associated with lower depression severity in the full W2 (Table 3). The same was true in the W2 OABD subgroup analysis. In fact, when sex, education and age x sex were included in the model (Supplemental Table S4a); the model showed that older OABD and OABD women had *more* depression. This was in the context of an interaction of sex and age such that the positive relationship of age and depression was only significant among OABD men (Supplemental Table S4b)—however, this subgroup analysis consisted of only 171 OABD men. In the combined W1 + W2 sample, age also was not associated with depression severity (Supplemental Table S4c), even with adjustment for sex and education, and there was no moderation by either education or sex (data not shown).

Older age was significantly associated with an increased number of somatic conditions in the W2 (Supplemental Table S5a) and the W1 + W2 sample (Supplemental Table S5c) but not in the W2 OABD subgroup (Supplemental Table S5b).

3.3 | Functioning—Relationship to age and symptom severity

GAF scores were available in 8 contributing W2 studies ($N = 540$) and the mean GAF was 57.6 (SD 18.1), which is consistent with individuals having some difficulty with social, occupational, and school functioning, but generally functioning relatively well. Age was not associated with GAF in W2 (Table 4) or W2 OABD (Supplemental Table S6a). In the W1 + W2 sample, increasing age was associated with decreased GAF, however this relationship did not persist in models that also included BD symptoms (Supplemental Table S6b). As predicted, we found that more severe BD symptoms (mania $p \leq 0.001$, depression $p \leq 0.001$) were associated with worse functioning in W2 (Table 4), W1 + W2 (Table S4b), and in the W2 OABD (Supplemental Table S6), in age, sex, and education adjusted models.

With respect to our hypothesis that age would moderate the associations of BD symptoms with functioning, in W2, the relationship of depression severity to GAF was stronger in younger individuals ($p = 0.02$, Supplemental Table S7a). There was no evidence of moderation of the relationship of GAF to mania severity in W2, W2 OABD, or W1 + W2 (Supplemental Tables S7a, b, c) or to depression symptom severity in W2 OABD or W1 + W2 (Supplemental Tables S7b, c).

3.4 | Functioning—Relationship to somatic comorbidity

Greater comorbidity was not associated with poorer functioning in W2 (Table 4), W2 OABD (Supplemental Table S6a), or W1 + W2 (Supplemental Table S6b), in age, sex, and education adjusted models. Further, age did not moderate the relationship of somatic burden with GAF in any of the samples (Supplemental Tables S7a,b,c).

4 | DISCUSSION

With the global population of older adults increasing rapidly, it is important to understand how older people with BD differ from younger adults with the disorder.[21] An incremental approach towards data acquisition, used by this international team of experts in OABD, allowed for a unique opportunity to confirm or refute our previous observations on a large and novel dataset with adequate sampling of older individuals. This first-ever replication analysis of GAGE-BD confirmed some of our initial findings,[5] but also showed differences both when only examining W2 and when analyzing the larger and more diverse W1 + W2 combined sample. Our analyses of both the replication and combined samples suggest that older age is significantly associated with slightly less severe symptoms of mania and somewhat greater somatic comorbidity (consistent with previous findings in W1[5]), but there was no association of depression with age in either W2 or the combined sample (in contrast to previous findings in W1[5]). Interestingly, when we examined only OABD within W2, we

TABLE 1 Descriptive statistics for GAGE-BD W1 (n = 1369), W2 (n = 1232), W2 OABD subsample (n = 601) and W1 + W2 samples (n = 2601).

| Descriptive variables | # Studies | # Participants | | | | Mean (SD) or % | | | | p value[a] |
		W1	W2	W2-OABD	W1 + W2	W1	W2	W2-OABD	W1 + W2	
Age, years	33	1369	1232	601	2601	60.7 (12.1)	47.2 (13.5)	58.4 (7.1)	54.3 (14.5)	<0.0001
Age range, years		1369	1232	601	2601	18–95	17–85	50–85	17–95	
Age ≥50 years	33	1185	601	601	1786	86.6%	48.8%	100%	68.7%	<0.0001
Sex	33	1369	1232	601	2601					<0.0001
Male		602	432	222	1034	44.0%	35.1%	36.9%	39.8%	
Female		767	800	379	1567	56.0%	64.9%	63.1%	60.3%	
Diagnosis	31	1279	1232	601	2511					0.1818
Bipolar I		952	921	471	1873	74.4%	74.8%	78.4%	74.6%	
Bipolar II		275	277	116	552	21.5%	22.5%	19.3%	22.0%	
Other bipolar		52	34	14	86	4.1%	2.8%	2.3%	3.4%	
Age of onset, years	30	1106	987	494	2093	31.9 (15.7)	30.8 (12.8)	34.9 (14.4)	31.4 (14.4)	0.0764
Years of education	29	1041	970	495	2011	12.7 (4.0)	12.0 (3.9)	11.1 (4.4)	12.3 (4.0)	0.0003
Currently working	22	776	694	348	1470					<0.0001
Yes		183	260	115	443	23.6%	37.5%	33.1%	30.1%	
No		593	434	233	1027	76.4%	62.5%	66.9%	69.9%	
GAF total[b]	17	669	540	202	1209	62.8 (13.0)	57.6 (18.1)	51.7 (23.8)	60.5 (15.7)	<0.0001
Depression band	25	817	878	477	1695					<0.0001
Absent		405	432	286	837	49.6%	49.2%	60.0%	49.4%	
Mild		234	183	77	417	28.6%	20.8%	16.1%	24.6%	
Moderate		155	200	71	355	19.0%	22.8%	14.9%	21.0%	
Severe		23	63	43	86	2.8%	7.2%	9.0%	5.1%	
YMRS total	29	1147	816	438	1963	4.2 (5.4)	6.2 (9.5)	5.6 (10.5)	5.1 (7.4)	<0.0001
BPRS total	8	228	286	150	514	28.6 (14.5)	32.9 (9.9)	35.5 (9.5)	31.0 (12.3)	0.0002
Somatic comorbidity										
Total comorbidity	29	1274	872	470	2146	1.8 (1.7)	0.8 (1.0)	1.1 (1.0)	1.4 (1.5)	<0.0001
Cardiovascular comorbidity	29	553/1270	229/871	186/469	782/2141	43.5%	26.3%	39.7%	36.5%	<0.0001
Respiratory comorbidity	26	408/1144	94/712	55/354	502/1856	35.7%	13.2%	15.5%	27.0%	<0.0001
GI comorbidity	23	235/958	58/674	36/316	293/1632	24.5%	8.6%	11.4%	18.0%	<0.0001
Hepatic/pancreatic comorbidity	22	71/942	14/602	10/244	85/1544	7.5%	2.3%	4.1%	5.5%	<0.0001
Renal comorbidity	21	57/883	11/674	7/316	68/1557	6.5%	1.6%	2.2%	4.4%	<0.0001
GU comorbidity	17	148/699	11/537	11/232	159/1236	21.2%	2.0%	4.7%	12.9%	<0.0001
Musculoskeletal comorbidity	24	402/998	129/674	87/316	531/1672	40.3%	19.1%	27.5%	31.8%	<0.0001
Endocrine comorbidity	28	424/1272	173/803	140/427	597/2075	33.3%	21.5%	32.8%	28.8%	<0.0001

Note: Of the 2601 BD participants represented in the total sample, there was some missing data for all measures, so sample size for each measure noted separately. OABD: Age ≥50 years.

Abbreviations: BPRS, 18-item Brief Psychiatric Rating Scale, score range 18–26 with higher scores indicating more severe psychiatric symptoms; GAF, Global Assessment of Functioning score range 0–100 with higher scores indicating better functioning; GI, gastro-intestinal; GU, genito-urinary; OABD, older-age bipolar disorder; SD, standard deviation; W1, Wave 1 sample, data lock March 2021; W2, Wave 2 sample, data lock March 2022. YMRS, Young Mania Rating Scale, score range 0–60 with higher scores indicating more severe manic symptoms.

[a]Statistically significance comparing W1 and W2 samples.

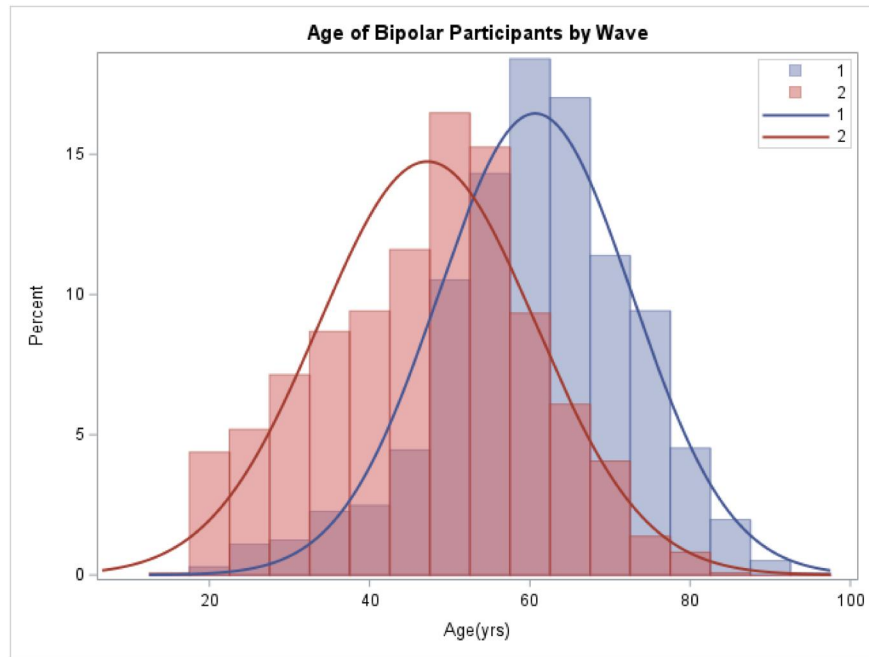[b]Date derived from 8 studies from wave 2 (3 from Texas site-Houston, San Antonio and UNC data).

FIGURE 1 Distribution of subject mean age in W1 and W2 GAGE-BD samples.

TABLE 2 Associations of age with YMRS symptoms and moderation by education in W2.

Predictor	Model[a] = 557		Model[a] N = 514		Model[a] N = 514	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Age	−0.014 (−0.02, −0.01)	**<0.001**	−0.014 (−0.02, −0.01)	**<0.001**	−0.04 (−0.06,−0.02)	**<0.001**
Sex			0.02 (−0.14, 0.18)	0.819	0.03 (−0.13, 0.19)	0.742
Education			−0.01 (−0.03, 0.02)	0.525	−0.10 (−0.18, −0.02)	0.012
Age x education					0.002 (0.000, 0.003)	**0.015**

Note: Young Mania Rating Scale (YRMS) was log transformed. Sex reference group is men. Bold values indicate $p < 0.05$.

Abbreviation: CI, confidence interval.

[a]Linear regression model with a random effect for study cohort.

observed a relationship in this subsample such that older age was associated with more depression, but only among men. Thus, the pattern of age associations with depression severity was mixed and varied by which sample was examined.

In our previous work in W1, individuals with lower education had a stronger negative association of age and depression severity, but not mania severity; in the current study, this moderation was observed for mania but not depression, in both W2 and W1 + W2. There was some limited evidence for sex moderation in the present analysis (different from previous findings in W1), as OABD men had a stronger *positive* relationship of age with depression than OABD women. Our findings also confirm our original W1 results that functioning is relatively stable across adulthood and that worse BD symptom severity levels, but not somatic comorbidities, are associated with worse functioning in OABD, regardless of sex. In the W2 sample, like in W1, age moderated the relationship of depression severity with functioning, but in the opposite direction (W1: older had stronger relationship; W2: younger had stronger relationship); consistent with this, the opposing effects appeared to cancel each

other out in the combined W1+W2 sample, where there was no significant age moderation.

A recent literature review[22] concluded that the existing research data regarding whether OABD has a better, equal or worse course and prognosis than working-age BD is inconclusive. Older reports suggest that the polarity of BD may shift in older age, with a greater amount of time in depressive episodes and less time in manic or mixed states.[23] While our cross-sectional analysis of samples who had relatively low severity of mania symptoms was not able to examine shifts in polarity, the fact that manic severity appears attenuated with age may support the notion that time in manic states may be reduced in OABD. It is also possible that those with lower mania symptoms are more likely to survive into later life; longitudinal studies are needed to examine this possibility. Conclusions regarding depressive severity and age remain unclear, although neither the W1 or W2 findings suggest that depressive symptoms are generally worse in older people with BD. Although, among the W2 OABD subsample, the oldest men seemed to have greater depression than men nearer to age 50, this should be interpreted with caution due to
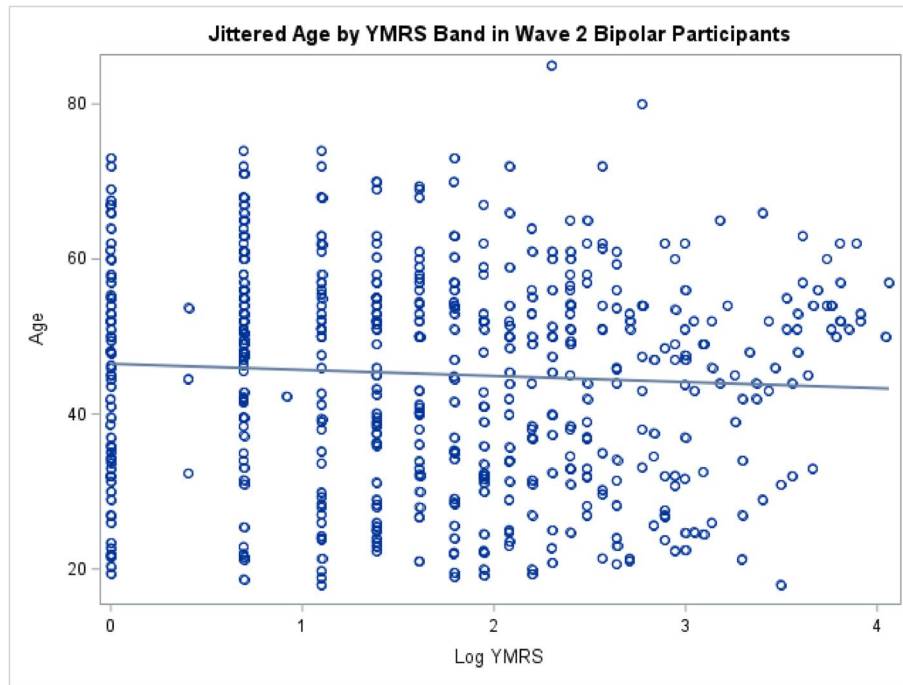
FIGURE 2 Linear relationship between age and manic symptom severity demonstrating a lower manic symptom severity with age in the W2 sample.

TABLE 3 Association of age with depression symptom bands (no depression, mild, moderate, severe) in W2.

	Model[a] N = 878		Model[a] N = 811	
Predictor	OR (95% CI)	p	OR (95% CI)	p
Age	1.00 (0.99, 1.02)	0.713	1.01 (0.99, 1.02)	0.451
Sex			1.27 (0.93, 1.72)	0.128
Education			0.94 (0.90, 0.98)	**0.002**

Note: Sex reference is men. Depression band reference is no depression (reverse coded for logistic models). Bold values indicate p < 0.05.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Ordered logistic model with a random effect for study cohort.

the sex imbalance [67% women] of this subsample. W2 may have demonstrated less attenuation of depression with age compared to W1 because the overall depression severity of the sample was greater; more severe cases may not resolve as easily over time compared to milder cases, but this would need confirmation with longitudinal study. Although the W2 sample was younger than W1 on average, there was comparable variance in age in the two samples, which should have allowed us to observe similarly strong associations between depression and age if they existed.

Our finding that lower levels of education may enhance the negative relationship of manic symptoms with age is somewhat counter-intuitive. It is possible that individuals with more education, and perhaps jobs that require more cognitive focus, could have had additional stress during their working years, leading to less resolution of mania symptoms later in life. Alternatively, there could be less of a survivor bias among more highly educated people if they are better able to access care despite mania symptoms and thus live longer.

In this sample, the GAF, used to assess functional status, demonstrated mean total scores consistent with some difficulty with social and occupational functioning, but still generally functioning relatively well. Functioning was not associated with age or comorbidity, but in models that controlled for age and education, more severe manic *and* depressive symptoms were significant drivers of reduced functioning. Contrary to expectations, the association of functioning and depression was stronger among younger individuals in the replication sample, but not age-dependent in the combined sample. Our replicated findings are consistent with a recent review[24] which found that residual BD symptoms, particularly depression, are a driver of worse functioning. Our findings also support the notion that treatment of residual or subclinical mood symptoms across the lifespan is critical. Still, some versions of the GAF include severity of psychiatric symptoms as part of the rating assignment and thus any conclusions regarding functioning and BD symptoms needs to be tempered by these potential methodological limitations.

TABLE 4 Associations from multivariate linear mixed models for GAF in W2.

Predictor	Model[a] N = 502 β (95% CI)	p	Model[a] N = 345 β (95% CI)	p	Model[a] N = 498 β (95% CI)	p	Model[a] N = 502 β (95% CI)	p
Age	−0.07 (−0.17, 0.04)	0.213	−0.06 (−0.18, 0.07)	0.364	−0.05 (−0.14, 0.05)	0.362	−0.07 (−0.17, 0.04)	0.226
Sex	0.99 (−1.35, 3.32)	0.406	1.13 (−1.53, 3.79)	0.402	1.37 (−0.82, 3.55)	0.220	1.00 (−1.34, 3.34)	0.403
Education	0.40 (0.05, 0.76)	**0.026**	0.15 (−0.26, 0.56)	0.470	0.24 (−0.09, 0.57)	0.157	0.40 (0.05, 0.76)	**0.026**
YMRS			−2.48 (−3.90, −1.06)	**<0.001**				
Depression symptom severity					−5.31 (−6.53, −4.10)	**<0.001**		
Comorbidity burden (# of affected domains)							−0.09 (−1.53, 1.35)	0.902

Note: Sex reference: men (0). Depression severity (increasing values = increasing severity). Bold values indicate $p < 0.05$.

Abbreviations: CI, confidence interval; GAF, global assessment of functioning; YMRS, Young Mania Rating Scale (log transformed).

[a]Linear regression models with a random effect for study cohort.

In common with some other reports,[25] somatic comorbidity in the GAGE-BD sample is highly prevalent, particularly cardiovascular disease, which occurred in just over a third of the combined W1 + W2 sample. Most individuals had multiple comorbid conditions with a mean of 1.4 (SD 1.5) conditions in the combined W1 + W2 sample, and older individuals were likely to have more somatic co-morbid conditions. We replicated the lack of an association of so-matic comorbidities with functioning, although this may reflect the strong focus of the GAF on mental versus physical health. In addition, an important caveat to interpretation of our findings is that somatic conditions were grouped into 8 broad categories and our data harmonization methods did not allow for counting of multiple con-ditions within a given category, for example, hypertension and heart failure. Thus, it seems likely that our somatic burden count repre-sents a lower boundary of what might be identified where more specific and finer-grained evaluations of somatic comorbidity are assessed, and that we might observe stronger relationships to everyday functioning measures that incorporate physical limitations.

This study had a number of limitations inherent in an analysis of archival data and use of an aggregate sample from diverse sources and a W2 sample that differed in some demographic characteristics from the W1 sample. Meta-data was heterogeneous with differing study designs and outcomes assessments. Some studies enrolled exclusively or mainly older people with BD and some included healthy controls (not analyzed in this report). For a few sites that had multiple studies, all study meta-data was not available for every study. To facilitate data analysis, variables had to be harmonized or collapsed into binary or ordinal categories, which limited finer-grained assessments of symptoms and somatic burden. A further limitation is the use of the GAF as a measure of functioning, which is not ideal as it mixes functionality and clinical severity and has been surpassed by scales like the Functioning Assessment Short Test, FAST[26,27] that was adjusted for use with older adults (FAST-O)[28];

however, only GAF was available across multiple sites in GAGE-BD. We also lacked a measure of cognitive reserve, which is a more powerful mediator of functioning than education.[29] Offsetting these limitations, the GAGE-BD project represents the largest dataset with good representation of adults >50 years old and an international geographic representation. In addition, to our knowledge, this anal-ysis is the first to attempt to directly replicate age-related findings in BD with an independent sample; our ongoing efforts will also allow for further replication studies based on data being contributed to Wave 3. Other publications from the GAGE-BD project have included investigation of somatic comorbidity among men and women,[6] BD subtypes,[30] mixed symptoms in OABD[8–10] and clinical characteristics of individuals prescribed lithium and prescribed antipsychotic drugs. Our group of international scientists is in the process of attempting to replicate these other findings, which, if confirmed, can optimize generalizability of results and inform a better and much-needed understanding of clinical presentation of BD in the 2nd half of life.[31]

In conclusion, this first replication analysis from the GAGE-BD project provides additional insight into OABD outcomes with respect to BD symptom presentation, functional status and somatic comor-bidity burden. It also sheds light on the importance of large, diverse samples and how findings can vary depending on the features of each sample. Future work will aim to expand knowledge on additional nu-ances of BD symptoms, somatic burden and medication treatments.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Data is 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.

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REFERENCES
1. Carvalho AF, Firth J, Vieta E. Bipolar disorder. *N Engl J Med.* 2020;383(1):58-66. https://doi.org/10.1056/nejmra1906193. PMID: 32609982.
2. Sajatovic M, Strejilevich SA, Gildengers AG, et al. A report on older-age bipolar disorder from the international society for bipolar disorders task force. *Bipolar Disord.* 2015;17(7):689-704. https://doi.org/10.1111/bdi.12331
3. Dols A, Kessing LV, Strejilevich SA, et al. Do current national and international guidelines have specific recommendations for older

adults with bipolar disorder? A brief report. *Int J Geriatr Psychiatry.* 2016;21(12):1295-1300. https://doi.org/10.1002/gps.4534

4. Sajatovic M, Eyler LT, Rej S, et al. The global aging & geriatric experiments in bipolar disorder database (GAGE-BD) project: understanding older-age bipolar disorder by combining multiple datasets. *Bipolar Disord.* 2019;21(7):642-649. https://doi.org/10.1111/bdi.12795

5. Sajatovic M, Dols A, Rej S, et al. Bipolar symptoms, somatic burden, and functioning in older-age bipolar disorder: analyses from the global aging & geriatric experiments in bipolar disorder database project. *Bipolar Disord.* 2021;24(2):195-206. https://doi.org/10.1111/bdi.13119

6. Almeida OP, Dols A, Blanked MAJ, et al. Physical health burden among older men and women with bipolar disorder: results from the Gage-Bd Collaboration. *Am J Geriatr Psychiatr.* 2022;30(6):727-732. https://doi.org/10.1016/j.jagp.2021.12.006

7. Burdick KE, Millet 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;24(7):709-719. https://doi.org/10.1111/bdi.13208

8. Eyler LT, Briggs FBS, Dols A, et al. Symptom severity mixity in older-age bipolar disorder: analyses from the global aging and geriatric experiments in bipolar disorder database (GAGE-BD). *Am J Geriatr Psychiatr.* 2022;30(10):1096-1107. https://doi.org/10.1016/j.jagp.2022.03.007

9. Arndt S. An example of an elegant report on a complex issue: mixity in bipolar disorder. *Am J Geriatr Psychiatr.* 2022;30(10):1108-1109. https://doi.org/10.1016/j.jagp.2022.04.005

10. Chen P, Eyler LT, Gildengers A, et al. Demographic and clinical characteristics of antipsychotic drug-treated older adults with bipolar disorder from the global aging and geriatric experiments in bipolar disorder database (GAGE-BD). *Psychopharmacol Bull.* 2022;52(2):8-33.

11. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry.* 1978;133(5):429-435. https://doi.org/10.1192/bjp.133.5.429

12. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56-62. https://doi.org/10.1136/jnnp.23.1.56

13. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134(4):382-389. https://doi.org/10.1192/bjp.134.4.382

14. Rush AJ, Giles DE, Schlesser MA, et al. The inventory for depressive symptomatology (IDS): preliminary findings. *Psychiatr Res.* 1986;134:382-389.

15. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977;1(3):385-401. https://doi.org/10.1177/014662167700100306

16. Orhan M, Millett C, Klaus F, et al. GAGE-BD consortium. Comparing continuous and harmonized measures of depression severity in older adults with bipolar disorder: relationship to functioning. *J Affect Disord.* 2022;314:44-49. https://doi.org/10.1016/j.jad.2022.06.074

17. Spitzer RL, Gibbon M, Williams JBW, et al. Global assessment of functioning (GAF) scale. *Outcome Assess Clin Pract.* 1996;1.

18. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc.* 1968;16(5):622-626. https://doi.org/10.1111/j.1532-5415.1968.tb02103.x

19. Chaudhry S, Jin L, Meltzer D. Use of a self-report-generated Charlson comorbidity Index for predicting mortality. *Med Care.* 2005;43(6):607-615. https://doi.org/10.1097/01.mlr.0000163658.65008.ec

20. Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatr Res.* 1992;41(3):237-248. https://doi.org/10.1016/0165-1781(92)90005-n

21. *World Population Ageing 2019.* : Department of Economic and Social Affairs. 2020.

22. Arnold I, Dehning J, Grunze A, Hausmann A. Old age bipolar disorder-epidemiology, aetiology and treatment. *Medicina.* 2021;57(6):587. https://doi.org/10.3390/medicina57060587

23. Coryell W, Fiedorowicz J, Solomon D, Endicott J. Age transitions in the course of bipolar I disorder. *Psychol Med.* 2009;39(8):1247-1252. https://doi.org/10.1017/s0033291709005534

24. del Mar Bonnín CDM, Reinares M, Martínez-Arán A, et al. Improving functioning, quality of life, and well-being in patients with bipolar disorder. *Int J Neuropsychopharmacol.* 2019;22(8):467-477. https://doi.org/10.1093/ijnp/pyz018

25. Warner A, Holland C, Loban F, et al. Physical health comorbidities in older adults with bipolar disorder: a systematic review. *J Affect Disord.* 2023;326:232-242. https://doi.org/10.1016/j.jad.2023.01.083

26. Rosa AR, Sánchez-Moreno J, Martínez-Aran A, et al. Validity and reliability of the functioning assessment Short test (FAST) in bipolar disorder. *Clin Pract Epidemiol Ment Health.* 2007;3(1):5. https://doi.org/10.1186/1745-0179-3-5

27. Rabelo-da-Ponte FD, Veroldini N, Goularte JF, et al. Identifying pathways between psychiatric symptoms and psychosocial functioning in the general population. *Eur Neuropsychopharmacol.* 2023;67:86-94. https://doi.org/10.1016/j.euroneuro.2022.11.005

28. Orhan M, Korten N, Stek M, Comijs H, Schouws S, Dols A. The relationship between cognitive and social functioning in older patients with bipolar disorder. *J Affect Disord.* 2018;240:177-182. https://doi.org/10.1016/j.jad.2018.07.055

29. Amoretti S, Ramos-Quiroga JA. Cognitive reserve in mental disorders. *Eur Neuropsychopharmacol.* 2021;49:113-115. https://doi.org/10.1016/j.euroneuro.2021.04.011

30. Beudners AJ, Klaus F, Kok AA, et al. Bipolar I and bipolar II subtypes in older age: results from the global aging and geriatric experiments in bipolar disorder (GAGE-BD) project. *Bipolar Disord.* 2023;25(1):43-55. https://doi.org/10.1111/bdi.13271

31. Lavin P, Rej S, Olagunju AT, et al. *Essential Data Dimensions for Prospective International Data Collection in Older Age Bipolar Disorder (OABD): Recommendations from the GAGE-BD Group.* Bipolar Discord; 2023.

SUPPORTING INFORMATION

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