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Sex Differences Among Older Adults With Bipolar Disorder: Results From the Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD) Project

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ABSTRACT

Objective: *Sex-specific research in adult bipolar disorder (BD) is sparse and even more so among those with older age bipolar disorder (OABD). Knowledge about sex differences across the bipolar lifespan is urgently needed to target and improve treatment. To address this gap, the current study examined sex differences in the domains of clinical presentation, general functioning, and mood symptoms among individuals with OABD.* ***Methods:*** *This Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD) study used data from 19 international studies including BD patients aged ≥50 years (N = 1,185: 645 women, 540 men).A comparison of mood symptoms between women and men was conducted initially using two-tailed t tests and then accounting for systematic differences between the contributing cohorts by performing generalized linear mixed models (GLMMs). Associations between sex and other clinical characteristics were examined using GLMM including: age, BD subtype, rapid cycling, psychiatric hospitalization, lifetime psychiatric comorbidity, and physical health comorbidity, with study cohort as a random intercept.* ***Results:*** *Regarding depressive mood symptoms, women had higher scores on anxiety and hypochondriasis items. Female sex was associated with more psychiatric hospitalizations and male sex with lifetime substance abuse disorders.* ***Conclusion:*** *Our findings show important clinical sex differences and provide support that older age women experience a more severe course of BD, with higher rates of psychiatric hospitalization. The reasons for this may be biological, psychological, or social. These differences as well as underlying mechanisms should be a focus for healthcare professionals and need to be studied further.* (Am J Geriatr Psychiatry 2024; 32:326–338)

Highlights

- **What is the primary question addressed by this study?**
  Are there sex differences in clinical presentation, general functioning and mood symptoms among older adults with bipolar disorder?
- **What is the main finding of this study?**
  Female sex was associated with psychiatric hospitalization and male sex with higher rates of lifetime substance abuse disorders.
- **What is the meaning of the finding?**
  Older aged women with bipolar disorder experience a more severe course of illness, emphasizing the importance of addressing sex-specific disparities in healthcare.

INTRODUCTION

Bipolar disorder (BD) is a complex and chronic mood disorder that affects a significant portion of the population, with a lifetime prevalence estimated at around 2.5%.[1] Sex differences in adult BD are documented in the literature and summarized in a review containing studies before 2010[2] and an analysis containing studies published between 2010 and 2020.[3] Although age at first mood episode does not apparently differ between women and men,[2] men more often debut with a manic episode, whereas women seem more likely to present with depression[3] and

experience depressive episodes more frequently than men.[4] In women, a higher occurrence of BD type II[4,5] and rapid cycling was seen in hospitalized patients,[5,6] but not in community samples of people with BD.[7] Women diagnosed with BD suffer more from comorbid internalizing disorders (e.g., PTSD and eating disorders), while men have higher rates of externalizing disorders (e.g., substance use disorders (SUD) and conduct disorders.[2] Women are also at increased risk of hypothyroidism and migraine compared with men.[2,8] Psychiatric hospitalization of adults with BD has been associated with many factors, including female sex.[9,10] A recent systematic review and meta-analysis[11] showed that studies reported poorer functional scores for women. Women have been shown to have higher psychosocial functioning than men in two studies,[12,13] and similar psychosocial functioning in another study.[14] Limited evidence is available about sex differences in the clinical presentation of BD during depressive and manic episodes, with some studies suggesting that women more often report somatic symptoms (e.g., a change in appetite, weight change) during depressive episodes than men,[15] but findings lack consistency for manic episodes.[2] A recent study found higher severity of manic symptoms among women.[16]

While research on BD has primarily focused on younger adults, a recent study[17] highlighted the importance of studying older adults with BD (OABD; defined as age ≥50 years). Aging is characterized by significant changes in biological, psychological, and social domains. Biologically, the important role of gonadal steroid hormones and their widespread effects on the brain has become increasingly evident.[18,19] In contrast to the endogenous fluctuations in hormone levels during perimenopause, estrogen levels decline to remain persistently low after menopause.[19,20] In schizophrenia, this decline is considered a trigger for worsening symptoms and disease course.[21] Psychologically and socially, a new set of stressors arises in older age with varying impact among men and women, including widowhood/living alone, poor health/chronic illness, cognitive decline, and other challenges.[22] Older adults with a severe mental illness may face additional challenges, such as medication side effects and difficulty accessing appropriate care.[23] A previous analysis of the Global Aging and Geriatric Experiments in Bipolar Disorder Database (GAGE-BD) in an overlapping sample showed a higher proportion of men with OABD with cardiovascular, renal and endocrinological morbidities, as compared to healthy controls, although physical health morbidities affected more women than men with OABD.[24]

The present study aims to explore sex differences in OABD and their impact on clinical presentation, general functioning, and mood symptoms. The previous studies in adults have been relatively small, ad-hoc, and yielded findings that are difficult to generalize to older patients. Therefore, investigating these aspects in OABD is important because sex differences may have implications for general functioning, morbidity, and treatment. More knowledge on sex differences will facilitate optimal care of people with BD across the full lifespan.

To address this gap in knowledge, we conducted a study on sex differences in OABD using a large international dataset. We hypothesize that OABD women are more likely to have BD type II and rapid cycling,[2,4] suffer more from internalizing psychiatric comorbidities,[2] have a higher number of physical health comorbidities,[24] have higher rates of psychiatric hospitalization,[9,10] have worse general functioning[11] and report changes in appetite and weight during depressive episodes.[15]

METHODS

Study Population

The current study analyzed cross-sectional data from the Global Aging & Geriatric Experiments in Bipolar Disorder (GAGE-BD) project. The GAGE-BD database comprises data from a consortium of investigators involved in OABD research.[27] The overarching approach and methods have been described elsewhere[17,25] including sample characteristics and meta-data of contributing studies. For the current analyses data from Wave 1 (as of July 2021) were used. A total of 19 study cohorts from 12 sites contributed to the current analyses (Tables S1 and S2). Table S2 shows the inclusion/exclusion criteria for the contributing studies. In the present analyses, participants aged ≥50 years were included, totaling 1,185 patients. The participating studies determined the diagnosis based on the Structured Clinical Interview for DSM Disorders for DSM-IV (SCID-IV), the Mini-International Neuropsychiatric Interview (MINI) for DSM-IV, or clinical evaluation (Table S2).

Sociodemographic and Clinical Variables

Demographic variables (e.g., age, sex) and clinical variables (e.g., age of onset of initial symptoms), illness duration, number of affective episodes, depression severity, rapid cycling and psychiatric hospitalizations) were harmonized across studies (for details, see ref. 17).

Comorbidities and General Functioning

The GAGE-BD project harmonized the data for psychiatric comorbidities across studies into one variable for lifetime psychiatric diagnosis: 0 = None, 1 = Lifetime Anxiety Disorder (current or past), 2 = Lifetime Substance/Alcohol Use Disorder (current or past), 3 = Both, 4 = Not clear. For the current analysis, this variable was transformed into two binary variables: lifetime anxiety disorder 1 = Yes, 0 = No, and/or lifetime substance use disorder (SUD) (including alcohol disorder and/or other substances) 1 = Yes, 0 = No. Presence of physical diseases was categorized (yes/no). Across studies, physical comorbidity was extracted from standardized evaluations such as the Charlson Comorbidity Index (CCI), the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), and/or physical health comorbidity categories derived from the assessment of study participants (e.g., clinical determination of selected comorbidity categories based on self-report, charts, or examination). The harmonization of physical conditions followed CIRS-G guidelines into eight binary variables.[26] The resulting variables were defined based on having at least one comorbidity within the cardiovascular, respiratory, gastrointestinal, liver, renal, genitourinary, musculoskeletal, and endocrine system. The count number of physical health domains with comorbidities was created by summing the eight binary variables (present or not present), for those participants with complete data on all eight disease domains.[17,24]

General functional status was assessed using the Global Assessment of Functioning (GAF) score by the treating psychiatrist.[27] The score represents a global rating of current global functioning ranging from 1 to 100, with lower scores indicating lower functioning and scores >90 suggesting no functional impairment.

Mood symptoms

Current depressive symptoms were measured with either the Hamilton Depression Rating Scale (HAM-D),[28] Montgomery-Äsberg Depression Rating Scale (MADRS)[29] or the Center for Epidemiologic Studies Depression Scale (CES-D).[30] In order to harmonize depression severity across the total sample, the continuous total scores of the rating scales were transformed into a three-level categorical variable (depression band) (none, mild-moderate, or severe depression) that were calculated as follows: no depression (HAM-D: 0−7, MADRS: 0−6, CES-D: 0−15); mild-moderate depression (HAM-D: 8−23, MADRS: 7−34, CES-D: 16−27); and severe depression (HAM-D ≥ 24, MADRS ≥ 35, CES-D ≥ 28).[31]

In all contributing sites, current mania severity was assessed with the Young Mania Rating Scale (YMRS).[32] A categorical variable was created: Absent manic symptoms (YMRS 0−7), mild manic symptoms (YMRS 8−19), and moderate manic symptoms (YMRS ≥ 20).[31]

In addition to the assessment of the categorical variables, BD mood symptoms were also assessed using the total scores on the YMRS, MADRS, and HAM-D scales separately as well as the individual scale items for each of these scales. The CES-D scale was not included in these separate analyses because the CES-D is an instrument used for screening.

Statistical Methods

First, clinical characteristics and demographics were reported as means with standard deviations or percentages. An initial comparison of clinical characteristics between women and men with BD was conducted using two-tailed t tests for continuous variables and $\chi 2$ tests for categorical variables, without correcting for site differences.

A comparison of mood symptoms (YMRS, MADRS, HAM-D: total scores as well as individual scale items) between women and men was initially conducted using a two-tailed t test. We also accounted for systematic differences between the contributing studies by performing generalized linear mixed models (GLMMs) using a normal distribution with an identity link function and random intercept for study cohort and a significance level set at $p < 0.01$.

Next, to examine the effects of female sex on several variables that were selected based on previous literature (e.g., BD subtype, rapid cycling, lifetime psychiatric comorbidity, psychiatric hospitalization, and number of physical health comorbidities) while

controlling for differences among study cohorts, we performed generalized linear mixed models (GLMM). In these models, female sex was entered as independent variable (with male sex as the reference group), sociodemographic or clinical variables as outcome variables, and study cohort as random intercept to account for meta-data differences between the contributing studies.

For the dependent variables BD subtype and rapid cycling, we used a logistic regression since these were binary variables. For the outcome variables number of psychiatric hospitalizations and number of physical health comorbidities, we chose a negative binomial regression, since there was no clear indication of these variables being zero inflated. In the GLMMs for outcome variable number of psychiatric hospitalizations two studies were excluded (DOBI-1 and TMU) as these studies did not have sufficient data on number of psychiatric hospitalizations.

The GLMM models that tested sex differences for each dependent variable were adjusted for potential confounders (age, BD subtype, rapid cycling, number of psychiatric hospitalizations, lifetime psychiatric comorbidity and number of physical health comorbidities). Each model included all other examined variables to test for the unique relationships of each dependent variable while controlling for the others.

The significance level was set at two-sided $p < 0.05$. For statistical analysis, SAS 9.4 and SPSS version 28 were used.

Ethical Issues

All individual research studies were approved by local research site Ethics or Institutional Review Board (IRB), conducted in accordance with the Helsinki Declaration as revised 1989 and proceeded after informed consent was obtained. A Data Use Agreement (DUA) was executed between each contributing site and the study coordinating center (Case Western Reserve University School of Medicine, Cleveland, OH).

RESULTS

Sample Characteristics

The sample consisted of 1,185 OABD patients, with a slightly higher proportion of women in the sample (n = 645, 54.4%). Women were younger than men (Table 1).

Clinical Variables: Univariate Analyses

In univariate analyses not controlling for the effect of site (Table 1), distribution of BD subtype differed amongst sexes. No difference in distribution amongst sexes was seen for rapid cycling. Sex differences were seen in age at onset (Fig. 1), with women debuting at an earlier age. Women had a longer mean duration of diagnosed bipolar illness than men and the number of psychiatric hospitalizations was higher in women. Physical health burden also was higher in women (Fig. 2). Regarding psychiatric comorbidity, a difference was only seen in SUD, which was diagnosed more frequently in men than women. No difference was seen in general functioning.

BD Mood Symptoms

Depressive Mood Symptoms

Clinically significant depressive symptoms were absent in 60.7%, mild to moderate in 35.4%% and severe in 3.9% of participants. The distribution of depressive symptoms was similar for men and women (Table 1). Individual MADRS scores were available for 151 women (23.4%) and 107 men (19.8%) (Table 2). Controlled for study cohort, there was no difference in total scores between the sexes, nor was there any sex difference in individual scale items. HAM-D items were available for 187 women (29.0%) and 110 men (20.4%). Controlled for study cohort, no difference between the sexes was seen in total HAM-D scores, though women had higher scores on anxiety and hypochondriasis items (Table 2).

Manic Mood Symptoms

Manic mood symptoms were absent in 85.8%, mild in 12.3%, and moderate in 1.9 % of all patients and were equally divided in the sexes (Table 1). Individual YMRS scores were available for 347 women (53.8%) and 247 men (45.7%). After controlling for study cohort (Table 2), no sex differences were seen.

TABLE 1. Demographic and Clinical Characteristics

	Total Sample n = 1,185	Women (n = 645, 54.4%)	Men (n = 540, 45.6%)	$\chi 2$/ t[a]	p-Value
Age, mean (SD), range	n = 118,564.0 (9.0), 50−95	n = 64,563.4 (9.2), 50−95	n = 54,064.7 (8.6), 50−89	t = 2.4, df = 1,183	**0.02**
Clinical variables					
BD subtype (N,%)	n = 1,103	n = 634	n = 469	$\chi 2$ = 6.1, df =2	**<0.05**
BD-I	714 (64.7%)	400 (63.1%)	314 (67.0%)		
BD-II	249 (22.6%)	140 (22.1%)	109 (23.2%)		
BD other	140 (12.7%)	94 (14.8%)	46 (9.8%)		
Rapid cycling (N,%)	n = 518	n = 281	n = 237	$\chi 2$ =1.5,df =1	0.22
History (current or past)	88 (17.0%)	53 (18.9%)	35 (14.8%)		
Age at onset, mean (SD), range	n = 95,434.0 (15.7), 5−77	n = 50,832.2 (15.0), 5−77	n = 44,635.1 (16.3), 5−76	t = −3.8, df = 952	**<0.01**
Duration of BD in years, mean (SD), range	n = 106,030.5 (13.9), 0−65	n = 57,931.6 (13.9), 0−65	n = 48,129.0 (13.9), 0−65	t = 3.0, df = 1058	**<0.01**
Number of psychiatric hospitalizations, mean (SD), range	n = 658 3.4 (5.0), 0−50	n = 368 4.0 (5.9), 0−50	n = 2902.8 (3.4), 0−21	t = −3.2, df = 605	**<0.01**
Current episode					
Depression band[b](n,%)	n = 921	n = 511	n = 410	$\chi 2$ = 0.0, df = 2	1.0
Absent	559 (60.7%)	310 (60.7%)	249 (60.7%)		
Mild to moderate	326 (35.4%)	181 (35.4%)	145 (35.4%)		
Severe	36 (3.9%)	20 (3.9%)	16 (3.9%)		
CES-D	n = 257 12.8 (9.1), 0−49	n = 134 13.0 (9.5), 0−49	n = 123 12.6 (8.6), 0−41	t = −0.3, df = 255	0.8
Mania band(N,%)	n = 1,122	n = 607	n = 416	$\chi 2$ =3.2, df =2	0.2
Absent	963 (85.8%)	531 (87.5%)	432 (83.9%)		
Mild	138 (12.3%)	67 (11.0%)	71 (13.8%)		
Moderate	21 (1.9%)	9 (1.5%)	12 (2.3%)		
Physical health comorbidity[c]	n = 1112	n = 598	n = 514		
Number of physical health domains with a comorbidity, mean (SD), range	1.92 (1.74), 0−8	2.19 (1.84), 0−8	1.61 (1.56), 0−8	t = −5.6, df = 1110	**<0.01**
				$\chi 2$=34.1, df = 8	**<0.01**
0	227 (20.4%)	101 (16.9%)	126 (24.5%)		
1	357 (32.1%)	174 (29.05%)	183 (35.6%)		
2	199 (17.9%)	113 (18.86%)	86(16.7%)		
3	128 (11.5%)	71 (11.9%)	57 (11.1%)		
4	79 (7.1%)	52 (8.7%)	27(5.3%)		
5	74 (6.7%)	51 (8.5%)	23 (4.47%)		
6	28 (2.5%)	23 (3.9%)	5 (1.0%)		
7	16 (1.4%)	10 (1.7%)	6 (1.2%)		
8	4 (0.4%)	3 (0.5%)	1 (0.2%)		
Lifetime psychiatric comorbidity[d] (N, %)	n = 660	n = 352	n = 308	$\chi 2$=9.3, df =3	**0.03**
None	282 (42.7%)	152 (43.2%)	130 (42.2%)	$\chi 2$=0.1, df = 1	0.80
Anxiety disorder	145 (22.0%)	87 (24.7%)	58 (18.8%)	$\chi 2$=3.3, df = 1	0.07
Substance use disorder[e]	132 (20.0%)	56 (15.9%)	76 (24.7%)	$\chi 2$=7.9, df = 1	**<0.01**
General functioning					
GAF score, mean (SD), range	n = 436 63.7 (14.0), 9−100	n = 259 64.0 (14.8), 9−100	n = 177 63.2 (12.7), 25−100	t = −0.7, df = 412	0.51

Notes: Of the 1,185 BD participants represented in the total sample, there was some missing data for all measures, so sample size for each measure are given separately. M: mean; SD: standard deviation; BD: bipolar disorder; BD-I: bipolar I disorder; BD-II: bipolar II disorder; CES-D: Center for Epidemiologic Studies Depression Scale; GAF: Global Assessment of Functioning; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale; df: degree of freedom.

Bold values statistically significant items ($p < 0.05$).

[a] Two-tailed t tests for continuous variables and $\chi 2$ tests for categorical variables.

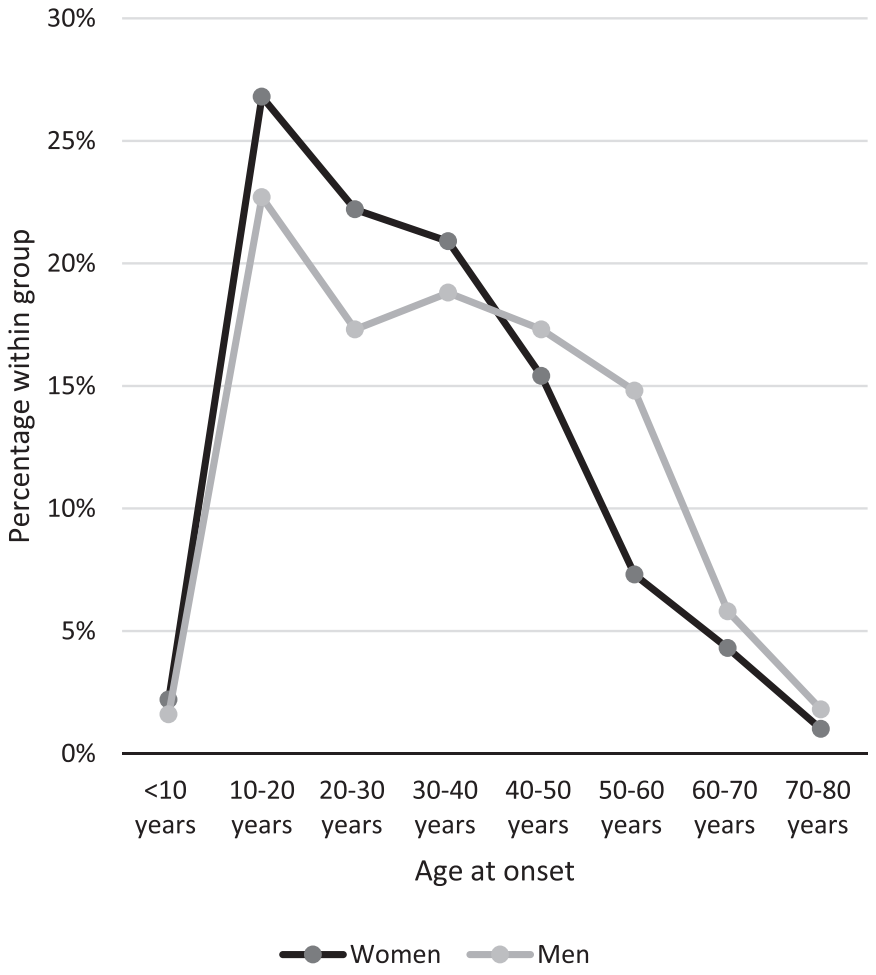
[b] The depression severity band was harmonized from MADRS, HAMD, and CES-D, see text for cut-offs.

[c] Number of physical health domains with a comorbidity: total number of physical health diseases, out of 8 disease categories. Only calculated for participants with available data for all of the 8 disease categories (N = 1,112).

[d] Current and past psychiatric comorbidity.

[e] Substance use disorder (SUD): substance/alcohol use disorder.

FIGURE 1. Age at onset of BD. Note: Age of onset was defined as the age of first symptoms in years. Women had a mean age at onset of 32.2 years (SD = 15.0) versus 35.1 years in men, (SD=16.3),(t = −3.8, df = 952, p <0.01) analyzed with a t test.



The Effects of Female Sex on the Selected Variables Using GLMM Controlling for Site and Other a priori Variables

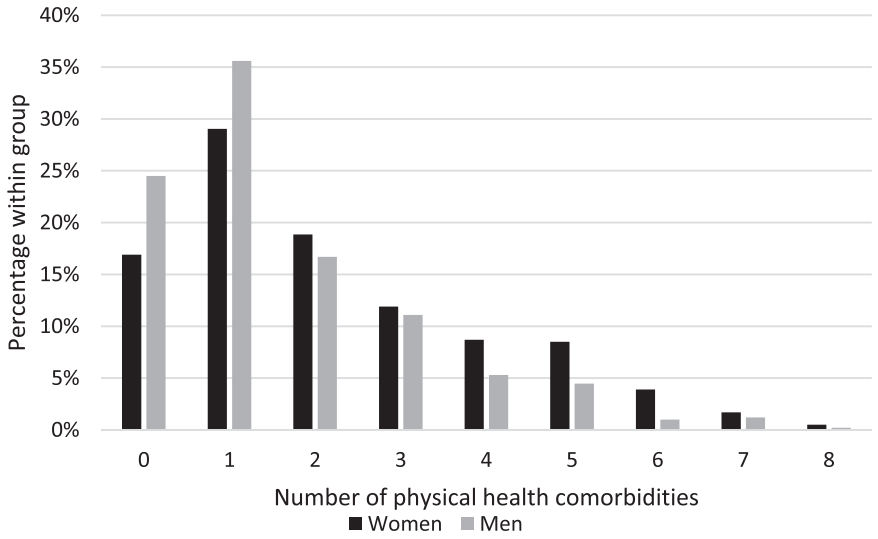
Sex was not statistically associated with BD diagnosis or rapid cycling (Table 3). Female sex was associated with higher numbers of psychiatric hospitalizations, but not physical health burden or lifetime anxiety disorder. Women were less likely to have lifetime SUD.

DISCUSSION

The present study investigated sex differences in 1,185 patients with OABD in the GAGE-BD dataset. The results showed that regarding depressed mood symptoms, women had higher scores on psychological anxiety, somatic anxiety, and hypochondriasis items. Regarding manic mood symptoms, women showed lower scores on the content item and higher scores on the insight item. In addition, after correcting for confounders, female sex was associated with more psychiatric hospitalizations and fewer lifetime SUDs.

In accordance with an earlier study,[15] results of the current study show that women present with an earlier age of onset of BD. This may be due to hormonal and sociocultural factors, since estrogen fluctuations during the menstrual cycle may trigger mood episodes and may increase their risk for BD at a younger age.[15,33]

FIGURE 2. Number of physical health comorbidities Note: Number of physical health comorbidities was defined based on co-morbidity within the following domains: cardiovascular, respiratory, gastrointestinal, liver, renal, genitourinary, musculoskeletal, and endocrine. Summing across these eight categories was used to construct a cumulative physical comorbidity burden variable. Physical health burden was higher in women (2.2 in women SD = 1.8 versus1.6 in men SD = 1.6), (t = −5.6, df = 1,109, p <0.01) analyzed with a $\chi 2$ test.



Contrary to our hypothesis, we did not find an increased occurrence of BD II and rapid cycling in older women, which has previously been observed in adult BD.[2,4] The current study evaluated mostly non-hospitalized patients, which may have resulted in an equal distribution of subtypes and rapid cycling between sexes, as seen in other studies evaluating nonhospitalized adult patients with BD.[7] The pathogenesis of rapid cycling BD is not known. However, different biological correlates of rapid cycling bipolar disorder have been identified in adults (e.g., inheritability, SSRI use, increased susceptibility to DNA damage, hypothyroidism, insulin resistance, or more severe brain changes in frontal areas);[34] it is not clear whether these findings represent etiologic causes or consequences of the disorder.

Women had higher rates of psychiatric hospitalizations. This finding is in line with studies in youth or younger adult BD.[9,10] There are several factors that may contribute to higher rates of psychiatric hospitalization in women, such as that women might experience more severe and frequent mood episodes during certain phases of the menstrual cycle (particularly the premenstrual phase) which can lead to a greater need for hospitalization.[35] However, it may also be due to sociocultural factors or it may reflect a greater tendency for women to seek and obtain hospitalized treatment and the limited abilities of their partner/spouse to provide care at home.[36]

Compared to the general population, BD patients are more likely to experience SUDs and are at an increased risk of relapse and poorer treatment outcomes.[37] In line with adult BD, men have higher rates of SUDs.[2] As women with BD are at particular high risk for SUDs compared to women in the general community.[38] interventions to avoid or reduce substance should be considered for both women and men.

Contrary to our hypothesis, no difference was observed in general functioning between men and women. An important caveat is that the scale to measure functioning in our analyses (GAF) consists of several items that capture occupational functioning, making it less suitable for a study in older adults. The Functional Assessment Short Test for Older Adults (FAST-O), modified for OABD, may be a more appropriate instrument to measure all domains of psychosocial functioning in older adults.[39]

The current study did not identify any sex differences in the current severity of depression or mania, which is not surprising given the characteristics of

TABLE 2. Sex Differences in Mood Symptoms

	Women (n = 645)	Men (n = 540)	t	p-Value	Controlled for Study Cohort, t-Value, p-Value[a]
YMRS	Female (n = 347)	Male (n = 247)			
Total YMRS score, mean (SD), range	4.5 (5.2), 0–32	5.1 (5.5), 0–33	t = 1.4, df = 592	0.16	t = 0.2, p = 0.81
Elevated mood	0.3 (0.7), 0–4	0.4 (0.8), 0–3	t = 1.8, df = 475	0.08	t = 1.4, p = 0.16
Increased motor activity-energy	0.3 (0.6), 0–3	0.4 (0.7), 0–4	t = 1.8, df = 487	0.08	t = 1.4, p = 0.16
Sexual interest	0.1 (0.5), 0–3	0.2 (0.6), 0–3	t = 1.9, df = 460	0.06	t = 1.7, p = 0.08
Sleep	0.6 (0.9), 0–4	0.7 (1.0), 0–3	t = 1.4, df = 590	0.17	t = 0.8, p = 0.45
Irritability	1.0 (1.6), 0–8	0.9 (1.5), 0–8	t = −0.7, df = 592	0.50	t = −1.8, p = 0.08
Speech	0.8 (1.6), 0–8	0.9 (1.7), 0–8	t = 0.8, df = 585	0.41	t = 0.0, p = 1.0
Language—thought disorder	0.5 (0.8), 0–3	0.6 (0.8), 0–3	t = 0.5, df = 591	0.63	t = −0.4, p = 0.67
Content	0.3 (1.2), 0–8	0.6 (1.9), 0–8	t = 2.3, df = 383	0.02	t = 2.3, p = 0.02
Disruptive—aggressive behavior	0.3 (1.0), 0–8	0.2 (0.8), 0–4	t = −0.9, df = 585	0.37	t = −1.1, p = 0.26
Appearance	0.1 (0.4), 0–3	0.1 (0.4), 0–2	t = 0.7, df = 591	0.46	t = 0.5, p = 0.60
Insight	0.2 (0.6), 0–4	0.1 (0.4), 0–3	t = −2.5, df = 563	0.01	t = −2.3, p = 0.03
MADRS	Women (n = 151)	Men (n = 107)			
Total MADRS score, mean (SD), range	16.4 (10.9), 0–40	16.9 (11.0) 0–40	t = 0.4, df = 256	0.72	t = 0.2, p = 0.84
Apparent sadness	1.9 (1.7), 0–6	1.9 (1.5), 0–5	t = 0.2, df = 256	0.83	t = 0.1, p = 0.95
Reported sadness	1.7 (1.6), 0–5	2.0 (1.6), 0–5	t = 1.4, df = 256	0.16	t = 1.4, p = 0.16
Inner tension	2.1 (1.4), 0–5	2.1 (1.5), 0–5	t = 0.2, df = 256	0.85	t = 0.0, p = 0.97
Reduced sleep	2.3 (2.0), 0–6	1.9 (2.1), 0–6	t = −1.4, df = 256	0.17	t = −1.6, p = 0.12
Reduced appetite	1.0 (1.5), 0–5	1.3 (1.7), 0–6	t = 1.4, df = 256	0.18	t = 1.2, p = 0.21
Concentration difficulties	2.2 (1.7), 0–6	2.2 (1.6), 0–6	t = 0.0, df = 256	1.0	t = −0.2, p = 0.86
Lassitude	1.6 (1.6), 0–5	1.8 (1.6), 0–5	t = 0.7, df = 256	0.46	t = 0.6, p = 0.57
Inability to feel	1.6 (1.6), 0–5	1.6 (1.7), 0–6	t = 0.2, df = 256	0.81	t = 0.2, p = 0.87
Pessimistic thoughts	1.5 (1.5), 0–5	1.5 (1.5), 0–5	t = 0.0, df = 256	0.99	t = 0.1, p = 0.91
Suicidal thoughts	0.5 (1.0), 0–5	0.5 (0.9), 0–4	t = 0.2, df = 256	0.86	t = 0.1, p = 0.91
HAMD	Women (n = 187)	Men (n = 110)			
Total HAMD 17 score, mean (SD), range	7.31 (7.65), 0–32	8.7 (8.38), 0.30.0	t = 1.48, df = 295	0.14	t = −1.7, p = 0.10
Depressed mood	0.72 (1.08), 0–4.0	1.22 (1.35), 0–4.0	t = 3.32, df = 191	<0.01	t = 1.2, p = 0.23
Feelings of guilt	0.66 (0.96), 0–4.0	0.72 (1.08), 0–3.0	t = 0.47, df = 294	0.64	t = −1.7, p = 0.09
Suicide	0.19 (0.54), 0–4.0	0.22 (0.61), 0–3.0	t = 0.45, df = 295	0.65	t = −0.4, p = 0.67
Insomnia early	0.56 (0.80), 0–2.0	0.61 (0.88), 0–2.0	t = 0.48, df = 295	0.63	t = −0.5, p = 0.59
Insomnia middle	0.40 (0.69), 0–2.0	0.53 (0.80), 0–2.0	t = 1.43, df = 295	0.15	t = 0.7, p = 0.50
Insomnia late	0.27 (0.61), 0–2.0	0.41 (0.73), 0–2.0	t = 1.64, df = 197	0.10	t = 0.8, p = 0.40
Work and activities	0.65 (1.14), 0–2.0	1.13 (1.47), 0–4.0	t = 2.92, df = 187	<0.01	t = 0.3, p = 0.76
Retardation psychomotor	0.21 (0.55), 0–3.0	0.22 (0.58), 0–3.0	t = 0.06, df = 295	0.95	t = −0.9, p = 0.39
Agitation	0.16 (0.45), 0–3.0	0.26 (0.67), 0–4.0	t = 1.43, df = 166	0.15	t = 0.8, p = 0.41
Anxiety (psychological)	1.00 (1.19), 0–4.0	0.95 (1.22), 0–4.0	t = −0.32, df = 295	0.75	t = −2.5, p = 0.01
Anxiety somatic	0.89 (1.10), 0–4.0	0.69 (0.97), 0–4.0	t = −1.55, df = 295	0.12	t = −3.1, **p <0.01**
Somatic symptoms (gastrointestinal)	0.29 (0.59), 0–2.0	0.32 (0.62), 0–2.0	t = 0.33, df = 295	0.74	t = −1.5, p = 0.15
Somatic symptoms general	0.49 (0.73), 0–2.0	0.70 (0.84), 0–2.0	t = 2.30, df = 295	0.02	t = 0.2, p = 0.83
Genital symptoms	0.13 (0.43), 0–2.0	0.31 (0.67), 0–2.0	t = 2.52, df = 163	0.01	t = 2.0, p = 0.05
Hypochondriasis	0.43 (0.86), 0–3.0	0.22 (0.56), 0–2.0	t = −2.53, df = 292	0.01	t = −3.1, **p <0.01**
Loss of weight	0.17 (0.48), 0–2.0	0.16 (0.50), 0–2.0	t = −0.13, df = 295	0.90	t = −1.4, p = 0.17
Insight[b]	0.09 (0.34), 0–2.0	0.05 (0.27), 0–2.0	t = −1.03, df = 272	0.31	t = −1.3, p = 0.21

Notes: Of the 1,185 BD participants represented in the total sample, there was some missing data for all measures, so sample size for each measure are given separately. M: mean; SD: standard deviation; CES-D: Center for Epidemiologic Studies Depression Scale; GAF: Global Assessment of Functioning; HAMD: Hamilton Depression Rating Scale; MDRS: Montgomery-Asberg Depression Rating Scale; YMRS: Young Mania Rating Scale.

[a] Generalized linear mixed model (GLMM) using a normal distribution with an identity link function and random intercept for study cohort with threshold set at p <0.01.

[b] In the GLMM for HAMD 17 subitem Insight three studies were excluded (GERISA, Inflam, and OPT-BD) as these studies did not have sufficient data on this subitem.

our sample. Regarding individual item scores, after correcting for study cohort, women had higher item scores on anxiety, and hypochondriasis. This finding of increased anxiety in women is clinically important and may increase treatment of anxiety with psychotherapy, such as cognitive based therapy (CBT) in women with BD. Also, we hypothesize that anxiety may lead to increased hospitalization of women, and therefore the focus of treatment should include the anxiety symptoms.

TABLE 3. Generalized Linear Mixed Models Examining the Association of Female Sex on Variables

Model	Dependent Variable	Beta (95% CI)[a]	Std. Error	t	p-Value
BD subtype	BD-II[b]	0.56 (−0.19 to 1.31)	0.38	1.48	0.14
Rapid cycling	Rapid cycling[c]	−0.32 (−1.29 to 0.65)	0.49	−0.64	0.52
Number of psychiatric hospitalizations	Number of psychiatric hospitalizations[d]	0.63 (0.20−1.07)	0.22	2.87	**<0.01**
Lifetime psychiatric comorbidity	Lifetime anxiety disorder[4]	0.56 (−0.93 to 2.04)	0.75	0.74	0.46
	Lifetime SUD[e] disorder	−1.38 (−2.52 to −0.25)	0.58	−2.40	**0.02**
Physical health comorbidities	Physical health comorbidities[f]	0.19 (−0.12 to 0.50)	0.16	1.20	0.23

Notes: Generalized linear mixed model with a random intercept for study cohort.
Bold values statistically significant items ($p < 0.05$).
[a] Unstandardized estimates of Beta.
[b] Corrected for age, rapid cycling, number of psychiatric hospitalizations, lifetime psychiatric comorbidity and number of physical health comorbidities.
[c] Corrected for age, BD diagnoses, number of psychiatric hospitalizations, lifetime psychiatric comorbidity and number of physical health comorbidities.
[d] Corrected for age, BD diagnoses, rapid cycling, lifetime psychiatric comorbidity and number of physical health comorbidities.
[e] Corrected for age, BD diagnoses, rapid cycling, number of psychiatric hospitalizations, and number of physical health comorbidities.
[f] Corrected for age, BD diagnoses, rapid cycling, number of psychiatric hospitalizations, and lifetime psychiatric comorbidity.

Strengths, Limitations, and Suggestions for Future Research

Our findings are strengthened by the large and international GAGE-BD database, which is well suited for investigating sex differences among OABD. However, we have to interpret our results in light of several limitations. Data on clinical variables such as menopausal state, personality disorders, history of trauma, use of medication such as mood stabilizers or antipsychotics, and help-seeking behavior were absent or limited, thereby impeding further statistical analyses. Multiple testing can also be seen as a limitation in the current study, especially in the analyses of the mood symptoms. However, we changed the threshold to $p < 0.01$ when analyzing the subitems of the different mood scales lowering the chance of a type I error.

It would be valuable for future studies to examine extensively the care needs and health resources of both sexes, with special attention for prevention and physical health needs in women. As we did not differentiate sex at birth as a biological variable versus gender, this limits our ability to make any conclusions regarding gender minorities. Lastly, the variability of sex differences across BD lifespan highlights the importance for future longitudinal research to incorporate neurobiological data (e.g., sex hormones, neuroimaging) in order to offer insight into underlying mechanisms and the development and persistence of sex differences from youth to old age.

CONCLUSION

Clinical Interpretation and Implications

Knowledge about sex differences across the bipolar lifespan is urgently needed in the era of precision medicine in order to develop targeted therapies and improve treatment outcomes. In this GAGE-BD study, after correcting for confounders, important clinical sex differences were seen. Higher rates of SUDs were observed in older aged men. Our findings provide support that older women experience a more severe course of BD than older men, with higher rates of psychiatric hospitalization and more anxiety and hypochondriasis symptoms. The reasons for these differences may be biological, psychological, or social. The observed sex differences as well as underlying mechanisms should be a focus by healthcare professionals in diagnosing and treating BD and warrants further investigation.

AUTHOR CONTRIBUTIONS

Machteld A.J.T. Blanken contributed to the concept, performed analyses, and wrote and completed the manuscript. Mardien L. Oudega contributed to the concept, data analysis and writing of the manuscript. Osvaldo P Almeida contributed data and critically reviewed drafts of the manuscript. Sigfried N. T. M. Schouws contributed to

the data collection and reviewed the manuscript. Melis Orhan contributed to the data collection and reviewed the manuscript, Alexandra J. M. Beunders contributed to the data collection and reviewed the manuscript, Ursula M.H. Klumpers contributed to the interpretation of data. Caroline Sonnenberg contributed to the conception and design, revising the manuscript critically for important intellectual content. Hilary P. Blumberg contributed data and contributed to the interpretation of the results and editing of the manuscript. Lisa T. Eyler designed and led GAGE-BD, contributed data, and reviewed the manuscript critically. Brent P. Forester contributed to the original data, manuscript review and editing. Orestes V. Forlenza contributed to the GAGE-BD database and reviewed the manuscript, Ariel Gildengers contributed to the data collection and reviewed the manuscript. Benoit H. Mulsant contributed to funding for part of the data and critically reviewed the manuscript, Tarek Rajji critically reviewed the manuscript, Soham Rej contributed to the Conception of GAGE-BD and reviewed the manuscript, Kaylee Sarna contributed to the database creation, harmonized data, and reviewed the manuscript. Ashley Sutherland contributed to data analysis, data collection, and manuscript editing. Joy Yala contributed to the data harmonization. Eduard Vieta contributed to the data collection, gave input on the manuscript and supervision. Farren Briggs contributed to the study design, analytical guidance, interpretation of results, and manuscript editing and review. Martha Sajatovic developed the overall GAGE BD proposal, interpreted analysis and assisted with manuscript development, and Annemiek Dols contributed to the design of the study, supervision of data collection and writing of manuscript. All authors are in agreement with this manuscript.

DATA 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.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2023.10.008.

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