Sex Differences in the Longitudinal Course and Outcome of Bipolar Disorder in Youth

Rachel H. B. Mitchell, MD, MSc, FRCPC[a,*]; Heather Hower, MSW[b,c,d]; Boris Birmaher, MD[e]; Michael Strober, PhD[f]; John Merranko, MA[e]; Brian Rooks, PhD[e]; Tina R. Goldstein, PhD[e]; Jeffrey I. Hunt, MD[b,g]; Daniel P. Dickstein, MD[b,g]; Rasim S. Diler, MD[e]; Neal D. Ryan, MD[e]; Mary Kay Gill, MSN[e]; David Axelson, MD[h]; Martin B. Keller, MD[b,i]; Shirley Yen, PhD[b,j]; and Benjamin I. Goldstein, MD, PhD, FRCPC[a]

ABSTRACT

Objective: Despite substantial literature on sex differences in adults with bipolar disorder (BD), little is known about this topic in youth; this study examines sex differences in mood symptomatology and psychiatric comorbidity in prospectively followed youth with BD.

Methods: A subsample of the Course and Outcome of Bipolar Youth study (N = 370; female n = 199, male n = 171) enrolled October 2000–July 2006 (age at intake = 7–17.11 years) who met *DSM-IV* criteria for bipolar I disorder (BD-I; n = 221), bipolar II disorder (BD-II; n = 26), or operationalized BD not otherwise specified (BD-NOS; n = 123) with ≥ 4 years follow-up was included. Analyses examined sex differences at intake and, prospectively, in mood symptomatology and psychiatric comorbidity for a mean ± SD follow-up of 10.5 ± 1.72 years.

Results: Females were older than males at intake (mean ± SD age = 13.33 ± 3.32 vs 12.04 ± 3.16 years; $P = .0002$) and at age at mood onset (9.33 ± 4.22 vs 7.53 ± 3.74 years; $P < .0001$). After adjustment for confounders, males spent more time with syndromal ADHD ($P_{adjusted} = .001$) and females spent more time with syndromal anxiety ($P_{adjusted} = .02$). There were trends toward males spending more time with substance use disorder and females having more non-suicidal self-injurious behavior ($P_{adjusted} = .07$ and .09, respectively). There were no sex differences on outcome variables, including rate of or time to recovery and recurrence.

Conclusions: Contrasting with adult literature, this study identified minimal sex differences in the course of youth with BD. Longer-term studies are needed to clarify if youth-onset BD remains a "sex neutral" subtype of BD or diverges according to sex in adulthood.

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[a]Department of Psychiatry, Sunnybrook Health Sciences Centre, University of Toronto Faculty of Medicine, Toronto, Ontario, Canada

[b]Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, Rhode Island

[c]Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, Rhode Island

[d]Department of Psychiatry, School of Medicine, University of California at San Diego, San Diego, California

[e]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

[f]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

[g]Bradley Hospital, East Providence, Rhode Island

[h]Department of Psychiatry, Nationwide Children's Hospital and The Ohio State College of Medicine, Columbus, Ohio

[i]Butler Hospital, Providence, Rhode Island

[j]Massachusetts Mental Health Center and the Department of Psychiatry, Harvard Medical School at Beth Israel Deaconess Medical Center, Boston, Massachusetts

**Corresponding author:* Rachel H. B. Mitchell, MD, MSc, FRCPC, Department of Psychiatry, Sunnybrook Health Sciences Centre, EG-47, 2075 Bayview Ave, Toronto, ON M4N 3M5 (Rachel.mitchell@sunnybrook.ca).

Bipolar disorder (BD) is approximately twice as prevalent among female as among male adolescents in epidemiologic and clinical studies,[1–7] the only developmental epoch with female predominance in BD.[1,2] Despite substantial literature regarding sex differences in adults with BD,[8] little is known regarding sex differences in youth (ie, children or adolescents) with BD.[9–11] Sex differences in adult BD include more manic episodes[12,13] and comorbid substance use disorders (SUD) in males[12–15] versus more rapid cycling,[12,13,16] mixed and depressive episodes,[12,13,17–19] and comorbid anxiety disorders[16] and eating disorders[20] in females.

In a cross-sectional clinical study of 760 youth with BD,[9] males more frequently presented with mania and females more frequently presented with depression, whereas other studies[10,11] found no such differences. In terms of comorbidity, there is evidence of higher rates of disruptive behavioral disorders (DBDs)[9,11] and attention-deficit/hyperactivity disorder (ADHD)[9–11] in males and higher rates of anxiety disorders and eating disorders in females, in some,[10] but not all[9,11] studies. Initial data from the Course and Outcome of Bipolar Youth (COBY) study (N = 263) reported that female sex predicted more follow-up time spent with mania or depression as well as higher rates of conversion from BD-II to BD-I or BD-NOS to BD-I/BD-II over 2 years,[21] but not over 4 years,[22] and did not examine sex differences per se. To date, there have been no longitudinal studies of sufficient sample size and duration that have stratified the analyses by sex with the specific aim to investigate sex differences in the clinical phenotype of youth BD.

Sex differences in BD may inform sex-specific diagnostic and treatment strategies and guide research on neurobiological mechanisms that may underlie these differences.[23] We utilized the large COBY study cohort (N = 446) to examine sex differences in

Clinical Points

- Despite substantial literature on sex differences in adults with bipolar disorder, little is known about this topic in youth.
- With only a few exceptions, female and male youth with bipolar disorder had a similar course and outcome of illness.
- In contrast to bipolar disorder in adults, youth-onset bipolar disorder may be a "sex neutral" subtype of the disorder.

the course and outcome of youth with BD over an average of 10 years, hypothesizing that females will have a greater burden of depression and mixed episodes, more polarity changes, longer time to recovery, less time asymptomatic, more comorbid anxiety disorders,[10] and fewer comorbid DBDs and SUD as compared to males.[9,11,17–19]

METHODS

Subjects

The COBY study methods have been described elsewhere.[21,24] Briefly, the sample was comprised of 446 youth (BD-I, n = 260; BD-II, n = 32; BD not otherwise specified [BD-NOS], n = 154). This analysis restricted the sample to 370 subjects (199 males, 171 females) with a minimum of 4 years of follow-up. Subjects (aged 7–17.11 years at intake, enrolled October 2000–July 2006) met *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition (*DSM-IV*)[25] criteria for BD-I (n = 221; 110 males, 111 females), BD-II (n = 26; 12 males, 14 females), or a COBY-operationalized BD-NOS, as defined in the next paragraph (n = 123; 77 males, 46 females). Follow-up ranged from 4.10 to 14.11 years (mean ± SD=10.5 ± 1.72 years).

BD-NOS was defined according to the COBY study operationalized criteria.[21,26] Subjects were required to have a minimum of elated mood plus 2 *DSM-IV* symptoms or irritable mood plus 3 *DSM-IV* symptoms and change in the level of functioning for a minimum of 4 hours within a 24-hour period duration and have at least 4 cumulative lifetime days meeting the criteria.

Subjects were recruited through outpatient clinical referrals from 3 academic medical centers (University of Pittsburgh Medical Center, Brown University, and University of California at Los Angeles).[26,27] To date, subjects have been prospectively interviewed on average every 39.5 weeks for a mean of 547.5 weeks. The sample retention rate is at present 77%. The Institutional Review Board for each study site reviewed and approved the study protocol before enrollment of subjects. Informed consent and assent were obtained from the subjects and their parents/guardians at intake.

Procedures

At intake, youth and parents/guardians were interviewed about the youth's current and lifetime (prior to intake) psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL).[28] The KSADS Depression Rating Scale (DRS)[29] and the K-SADS Mania Rating Scale (MRS)[30] were used in place of the standard mood sections of the K-SADS-PL.

Parents were interviewed at intake about their psychiatric history using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID),[31] and a modified Family History Screen (FHS)[32] was used for first- and second-degree psychiatric family history. Socioeconomic status (SES) was measured using the Hollingshead 4-factor scale.[33] Functional impairment was assessed using the Children's Global Assessment Scale (CGAS).[34] Pubertal status and Tanner stage were assessed with the Petersen Pubertal Developmental Scale (PDS).[35]

Index episode was defined as the most recent mood episode at intake. Episode duration and time to recovery were calculated from the onset of the index episode; therefore, the duration of episode may exceed the length of follow-up for some subjects. Age at onset was calculated as the age at onset of any *DSM* mood episode or episode meeting criteria for operationalized BD-NOS. The duration of BD was calculated from age at onset.

A suicide attempt was defined as any self-injurious act that exceeded an operationalized threshold of lethal intent and/or medical lethality and was assessed via the K-SADS-P depression section suicidal acts item (current or most severe past episodes) and/or the K-SADS Summary Lifetime Diagnostic Checklist suicide attempt item.[36] Suicidal ideation was positive with K-SADS-P depression suicidal ideation scores ≥ 3.[36] Non-suicidal self-injury (NSSI) was positive with K-SADS-P non-suicidal self-damaging acts item ≥ 3.[36]

The Longitudinal Interval Follow-up Evaluation (LIFE)[37] measured change in psychiatric symptoms and treatment exposure between follow-up visits by identifying change points (eg, birthdays). The severity of symptoms, onset of new symptoms, and episode of polarity were tracked using weekly LIFE Psychiatric Status Rating (PSR) scores. Overlapping symptoms were not double counted. For mood disorders, the PSR scores ranged from 1 (no symptoms) to 2–4 (subthreshold symptoms and impairment) to 5 or 6 (full criteria with increasing levels of severity or impairment).[22] Comorbid conditions were scored from 1 to 3 (1 = minimal or no symptoms, 2 = subthreshold, 3 = threshold) or from 1 to 6 (1 or 2 = minimal or no symptoms, 3 or 4 = subthreshold, 5 or 6 = threshold). Clinically relevant psychotic symptoms were assigned a PSR score of 3.[22] Comorbid conditions included SUD, ADHD, DBDs, eating disorders (per *DSM-IV* criteria), and any anxiety disorder. Past and current pharmacologic treatment was ascertained using the Psychotropic Treatment Record of the LIFE.

The percentage of weeks spent asymptomatic or symptomatic in the mood symptom categories were based on the PSR score. Full recovery was defined as 8 consecutive weeks with PSR scores ≤ 2, reflecting minimal or no symptoms.[22] Time to recovery from the index episode was

measured from the onset of the index episode. A recurrence was defined as PSR score ≥ 5 for 1 week for mania/hypomania and for 2 weeks for depression.[22] Mixed episodes were defined according to *DSM-IV* criteria.[22]

Trained research assistants conducted the interviews, and results were presented to a child psychiatrist or psychologist for consensus.[22] Research assistants, psychiatrists, and psychologists were not blinded to diagnostic groups.

Statistical Analyses

Statistical analyses were performed using SAS version 9.4 (2013; SAS Institute Inc; Cary, North Carolina). Potential demographic/clinical confounders were identified as exhibiting significant between-group differences at the .10 level. Age and pubertal status (Spearman $r = 0.82$), intake DRS score and most severe lifetime DRS score ($r = 0.55$), and age at mood onset and duration of BD were moderately to highly correlated; therefore, age, intake DRS score, and duration of BD were selected for the final analyses. Rates of recovery and recurrence after the index episode were compared via χ^2 tests and logistic regression models, controlling for potential confounders. Times to recovery and recurrence after the index mood episode were compared between groups using log rank tests and Cox proportional hazards models, controlling for confounders. Satterthwaite *t* tests and weighted least-squares regression models were used to analyze the percentage of follow-up time spent asymptomatic and with syndromal and subsyndromal symptomatology, psychosis, and comorbidities. All *P* values are 2-sided at .05.

RESULTS

See Table 1 for sex differences in demographics and clinical characteristics.

Prevalence and Demographics

Of 370 youth with BD, 53.8% (n = 171) were male and 46.2% (n = 199) were female. Females were older than males (mean ± SD = 13.33 ± 3.32 vs 12.04 ± 3.16 years; $P = .0002$), and of more advanced pubertal status (Tanner stage IV or V, 67.4% vs 27.0%; $P < .0001$). There were no sex differences in other demographic variables.

Clinical Characteristics at Intake

As compared to males, females had older mean ± SD age at mood onset (9.33 ± 4.22 vs 7.53 ± 3.74 years, $P < .0001$) and shorter mean ± SD duration of BD (4.04 ± 3.01 vs 4.65 ± 2.96 years, $P = .04$). There was no sex difference in BD subtypes.

Females had more severe depressive symptoms at intake ($P = .01$) and lifetime ($P = .03$) as compared to males. There were no sex differences in manic symptoms. Males had higher rates of lifetime ADHD (70.4% vs 45.0%, $P < .0001$) and stimulant use (71.9% vs 36.3%, $P < .0001$). Lifetime pharmacologic treatment was otherwise similar. There were no sex differences at intake in lifetime history of DBDs, SUD, suicide attempts, suicidal ideation, physical or sexual abuse history, or global functioning. Females were nominally more likely than males to have a history of anxiety ($P = .12$), eating disorder ($P = .10$), and NSSI ($P = .10$). There were no significant sex differences in family history, although family history of anxiety was nominally more common in females ($P = .08$).

The following intake variables were entered as covariates in the prospective analyses: age, duration of BD, DRS scores, lifetime ADHD, and lifetime family history of anxiety disorders.

Recovery and Recurrence

There were no sex differences in rates of recovery, time to recovery, rates of recurrence, and time to recurrence of depression or mania/hypomania (see Table 2 and Figures 1 and 2).

Weekly Symptomatic Status

See Table 3 for data on weekly symptomatic status. Females spent more follow-up time with anxiety ($P_{adjusted} = .02$), and males spent more follow-up time with ADHD ($P_{adjusted} = .001$). There was a trend toward males' having more time with SUD ($P_{adjusted} = .07$) that became significant when age was the only covariate in the model ($P = .04$). Prior to adjustment, females spent more follow-up time with major depressive disorder (MDD) ($P = .03$) and in a subsyndromal mixed state ($P = .04$) and with NSSI (approached significance, $P = .06$). Prior to adjustment, males spent more follow-up time with DBDs ($P = .008$), in inpatient/residential treatment ($P = .03$), and receiving specialized psychosocial services ($P = .01$).

After adjustment, however, there were no sex differences in these or other variables.

Exploratory Analysis for the Effect of Age

To explore the effect of age on sex differences in the course of BD in youth, we tested the age-by-sex interaction for rates and time to recovery and recurrence; no interaction effects were found.

We also tested the age-by-sex interaction for weekly symptomatic status for mood states, NSSI, suicide attempts, and comorbidities; older females spent more time with any syndromal symptoms ($F = 6.24$; $P = .01$), syndromal depression ($F = 5.98$; $P = .01$), and anxiety ($F = 3.90$; $P = .04$) (data not shown).

DISCUSSION

In this sample of 370 youth with BD, there were no sex differences in the 10-year course of BD on core domains, including rate of and time to recovery or recurrence, or in time spent asymptomatic, in manic, mixed, or depressive episodes. However, independent of confounds, females spent more time with anxiety, whereas males spent more time with ADHD. Thus, our hypotheses regarding comorbidity were supported, whereas our hypotheses about the course of mood symptoms were not. Exploratory analyses evaluating the effect of age on sex differences in the course and outcome of BD revealed that older female adolescents with BD

Table 1. Sex Differences in Demographic and Clinical Characteristics Among Youth With Bipolar Disorder[a]

Characteristic	Males With BD (n = 199)	Females With BD (n = 171)	Statistic	*P* Value
Demographic				
Age, mean ± SD, y	12.04 ± 3.16	13.33 ± 3.32	$t = 3.8$	.0002
Race/ethnicity, white	83.42	81.33	$\chi^2 = 0.29$	.59
SES, mean ± SD	3.34 ± 1.21[b]	3.50 ± 1.18[b]	$t = 1.3$	.19
Living with both natural parents	42.23	41.50	$\chi^2 = 0.02$	.89
Pubertal status				
I	38.42	14.43	$\chi^2 = 48.15$	< .0001
II or III	34.64	18.21		
IV or V	27.01	67.43		
Follow-up, mean ± SD, wk	553.81 ± 89.06	540.01 ± 90.32	$t = 1.47$	.14
Clinical				
BD subtype				
BD-I	55.33	64.94	$\chi^2 = 5.88$	.05
BD-II	6.01	8.23		
BD-NOS	38.73	26.94		
Age at mood onset, mean ± SD, y[c]	7.53 ± 3.74	9.33 ± 4.22	$t = 4.32$	< .0001
Duration of BD, mean ± SD, y[d]	4.65 ± 2.96	4.04 ± 3.01	$t = 1.97$	.04
Mania Rating Scale score, mean ± SD				
Intake	22.69 ± 12.17	23.38 ± 12.34	$t = 0.54$	.58
Most severe lifetime	33.43 ± 7.69	34.70 ± 8.07	$t = 1.38$	.16
K-SADS DRS score, mean ± SD				
Intake	13.35 ± 9.33	15.98 ± 10.98	$t = 2.44$	.01
Most severe lifetime	20.98 ± 9.64	23.70 ± 11.88	$t = 2.15$	.03
Any anxiety	41.74	33.92	$\chi^2 = 2.37$	.12
Eating disorder	0.50	2.91	Fisher	.10
ADHD	70.40	45.00	$\chi^2 = 24.32$	< .0001
ODD	43.20	35.70	$\chi^2 = 2.19$	.13
CD	10.60	12.90	$\chi^2 = 0.48$	.49
SUD	6.50	9.90	$\chi^2 = 1.43$	.23
Suicide attempt	28.60	29.20	$\chi^2 = 0.02$	.89
Suicidal ideation	73.40	74.30	$\chi^2 = 0.04$	.84
Self-injurious behavior	32.70	40.90	$\chi^2 = 2.72$	.10
History of physical/sexual abuse	18.10	21.60	$\chi^2 = 0.73$	.39
Psychotic symptoms	22.60	21.60	$\chi^2 = 0.05$	.82
CGAS score, mean ± SD				
Intake	55.73 ± 11.75	53.85 ± 12.59	$t = 1.47$	.14
Most severe lifetime	38.26 ± 9.91	36.71 ± 11.54	$t = 1.35$	.17
Lifetime pharmacologic treatment, yes				
Any psychotropics	95.54	95.33	$\chi^2 = 0.01$	.94
Antimanics	82.93	81.32	$\chi^2 = 0.17$	.68
Antidepressants	55.31	53.22	$\chi^2 = 0.16$	.69
Stimulants	71.92	36.33	$\chi^2 = 47.18$	< .0001
Psychiatric family history[e]				
Mania/hypomania	57.80	54.00	$\chi^2 = 0.50$	.47
Depression	87.10	85.70	$\chi^2 = 0.14$	.70
Anxiety disorder	73.60	65.00	$\chi^2 = 2.99$	.08
Any substance use disorder	68.80	75.90	$\chi^2 = 2.21$	.13
Suicide attempt	44.60	40.30	$\chi^2 = 0.65$	.42

[a]Values shown as % unless otherwise noted.
[b]Equivalent to middle class. The Hollingshead SES categories are as follows: upper class: social index V; score range, 66–55; upper middle class: social index IV; score range, 54–40; middle class: social index III; score range, 39–30; lower middle class: social indez II; score range, 29–20; lower class: social index I; score range, 19–8.
[c]Age 4 years was set as the minimum value.
[d]Calculated from age at onset of any *DSM* mood episode.
[e]Having at least 1 first- or second-degree relative with history of psychiatric illness.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BD = bipolar disorder, BD-I = bipolar I disorder, BD-II = bipolar II disorder, BD-NOS = bipolar disorder not otherwise specified, CD = conduct disorder, CGAS = Children's Global Assessment Scale, Fisher = Fisher exact test, K-SADS DRS = Schedule for Affective Disorders and Schizophrenia for School-Age Children Depression Rating Scale, ODD = oppositional defiant disorder, SES = socioeconomic status, SUD = substance use disorder.

experienced more anxiety and depression compared to their male counterparts.

That the course of BD was not characterized by more mixed episodes in female versus male youth, and more manic episodes in male versus female youth, contrasts with the adult literature, although it converges with previous cross-sectional findings,[9–11] with the exception that males presented more often with mania in one study.[9] Females had significantly more depressive symptoms than males at intake, which is consistent with the research on adults with BD,[12,13,38] youth and adults with MDD,[39] and some[9] but not all[10,11] of the research on youth with BD. Over

Table 2. Sex Differences in Recovery and Recurrence Among Youth With Bipolar Disorder

Variable	Males With BD (n = 199)	Females With BD (n = 171)	Statistics	Unadjusted *P* Value	Adjusted *P* Value[a]
Rate of recovery, n/total n (%)	192/199 (96.51)	164/171 (95.93)	$\chi^2 = 0.08$	.77	.52
Rate of recurrence,[b] n/total n (%)	149/192 (77.64)	131/164 (79.92)	$\chi^2 = 0.27$	.60	.89
Estimated time to recovery/recurrence, median (95% CI), wk					
Time to recovery from the index episode[c]	130.30 (104.30–175.60)	112.43 (76.31–149.64)	$\chi^2 = 0.40$[d]	.53	.99
Time to recurrence[e]	93.00 (68.00–132.70)	73.00 (51.01–100.02)	$\chi^2 = 0.90$[d]	.34	.39

[a]Analyses adjusted for between-group demographic and clinical differences.
[b]Recurrence required either 1 week of Psychiatric Status Rating (PSR) scores ≥ 5 for mania/hypomania or 2 consecutive weeks of PSR scores ≥ 5 for depression.
[c]Index episode was defined as the current or most recent episode assessed at intake. To ascertain the episode duration, time to recovery was calculated from the onset of the index episode. Therefore, the duration of episode exceeds the length of prospective follow-up for some subjects.
[d]Log rank.
[e]Time to recurrence was calculated from the time participants fulfilled criteria for recovery until they met full criteria for a new episode.
Abbreviation: BD = bipolar disorder.

the course of follow-up, however, there were no sex differences in depressive symptoms in multivariate analyses. The finding that older female youth with BD have more syndromal symptoms of depression and anxiety compared to same-age male counterparts is consistent with the robust epidemiologic literature demonstrating higher prevalence of depression and anxiety in females after puberty.[40]

The absence of sex differences in youth with BD over an average of 10 years converges with findings from 4 years of follow-up[22] but not the first 2 years.[21] This discordance could relate to the implementation of effective treatments over time that mitigated initial sex differences, or to the natural course of illness.

One explanation for the absence of consistent sex specificity in the course of BD in youth is that the clinical phenotype of BD in youth invokes a "ceiling effect" of mixed symptom burden that limits the potential for sex differences.[9,10] That is, youth-onset BD may not be phenotypically distinct in males and females, as it is in adult-onset BD, despite being more prevalent in females. Longer-term studies are needed to clarify if youth-onset BD remains a "sex neutral" subtype of BD or diverges according to sex in adulthood.

Despite the lack of prospective differences in mood course, we found a younger age at mood onset in male youth with BD. Findings regarding sex differences in age at mood symptom onset in BD are inconsistent, with studies both supporting[41–43] and rejecting[44,45] a difference. Holtzman et al[46] recently evaluated the course of BD retrospectively in 500 adult subjects with BD stratified by sex according to pre-, peri-, and postpubertal age at onset. While the authors did not find a sex difference in age at mood onset, females with pre- and peripubertal onset had the least favorable course of BD illness.[46]

The greater burden of anxiety in female youth with BD is consistent with the adult BD

Figure 1. Recovery From Index Episode, by Sex, Among Youth With Bipolar Disorder

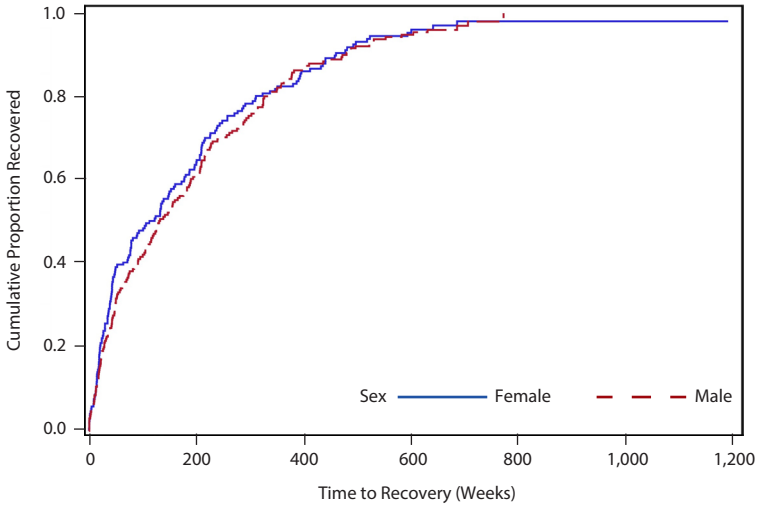

Figure 2. Recurrence After Recovery From Index Episode, by Sex, Among Youth With Bipolar Disorder

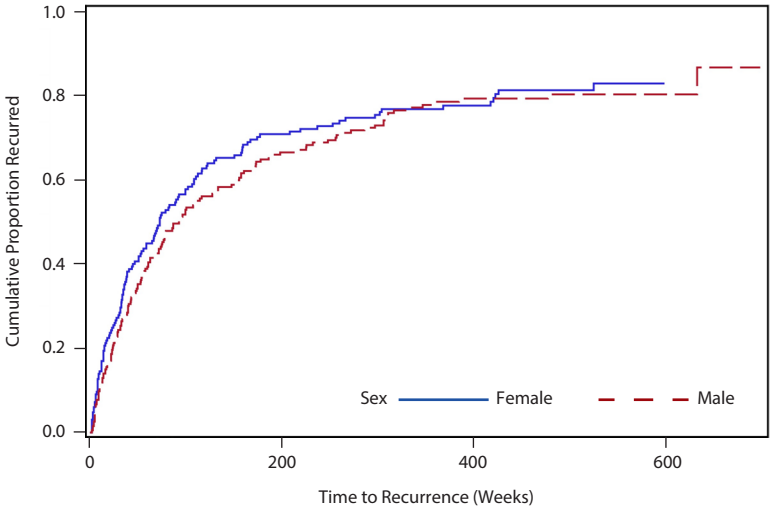

Table 3. Sex Differences in Weekly Symptomatic Status Among Youth With Bipolar Disorder[a]

Variable	Males With BD (n = 199)	Females With BD (n = 171)	*t*	Unadjusted *P* Value	*F*[b]	Adjusted *P* Value[b]
% of Weeks in Mood State During Follow-Up, Mean ± SD						
Asymptomatic	37.79 ± 25.54	37.79 ± 33.82	0	1	1.42	.36
Syndromal	12.78 ± 14.49	15.26 ± 16.94	1.50	.13	0.84	.41
Hypomanic/manic	1.76 ± 3.75	1.68 ± 3.56	0.21	.83	0.82	.52
Mixed	5.92 ± 9.58	6.46 ± 8.41	0.58	.56	0.28	.61
MDD	5.09 ± 8.01	7.12 ± 10.08	2.12	.03[b]	2.15	.22
Subsyndromal, %	49.43 ± 23.60	46.95 ± 22.80	1.03	.30	0.50	.63
Hypomanic/manic	10.64 ± 14.32	10.13 ± 14.31	0.34	.73	0	.82
Mixed	21.20 ± 21.41	16.97 ± 18.40	2.04	.04	0	.99
MDD	17.59 ± 15.67	19.85 ± 16.27	1.35	.18	1.26	.51
Suicidal ideation	3.03 ± 8.11	2.90 ± 6.32	0.17	.86	…	.99
Psychosis (delusions and/or hallucinations)	3.44 ± 12.42	4.24 ± 14.77	0.56	.58	0.03	.97
			χ^2	Unadjusted *P* Value	Wald χ^2	Adjusted *P* Value
% With Any Occurrence During Follow-Up						
Any non-suicidal self-injurious behavior	30.2	21.64	3.45	.06	2.84	.09
Any suicide attempts	30.2	33.3	0.43	.51	0.24	.62
Variable			*t*	Unadjusted *P* Value	*F*[b]	Adjusted *P* Value[b]
% of Weeks During Follow-Up Meeting Full Diagnostic Criteria for Comorbid Disorders, Mean ± SD						
Any comorbid disorder	65.59 ± 31.66	56.48 ± 37.19	2.51	.01	…	.96
SUD	13.59 ± 21.88	12.14 ± 20.76	0.65	.52	3.16	.07
ADHD	47.98 ± 36.00	31.18 ± 38.48	4.31	< .0001	0.13	.001
CD/ODD	29.14 ± 32.06	20.56 ± 30.03	2.66	.008	0.02	.25
Any Anxiety	20.79 ± 25.87	28.13 ± 32.80	2.36	.01	…	.02
% of Weeks Receiving Treatment During Follow-Up, Mean ± SD						
Any psychosocial	35.49 ± 25.91	30.15 ± 23.18	2.09	.04	…	.61
Inpatient/residential treatment	5.33 ± 10.44	3.32 ± 7.63	2.13	.03	…	.16
Specialized psychosocial services	11.62 ± 17.43	7.07 ± 14.00	2.78	.01	…	.14
Outpatient services	25.57 ± 20.27	23.76 ± 18.91	0.89	.37	…	.85

[a]Data obtained via the Longitudinal Interval Follow-up Evaluation (LIFE) Psychiatric Rating Scale (PSR).
[b]Analyses adjusted for between-group demographic and clinical differences.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BD = bipolar disorder, CD = conduct disorder, MDD = major depressive disorder, ODD = oppositional defiant disorder, SUD = substance use disorder.

literature[16] and some,[10] but not all[9] prior findings in youth with BD. The observed pattern aligns with the epidemiology of anxiety disorders in youth in general.[47,48] A previous COBY study[27] suggested that anxiety disorders increase mood symptom burden; however, greater anxiety in females in the current study did not translate into greater mood symptom burden. Our finding of male predominance in ADHD is also expected[49,50] and converges with the literature on children[9–11] and adults[51] with BD.

Although reduced to a trend after adjustment, males with BD also had a greater burden of SUD than females, which is in keeping with the adult BD[52] and the general SUD literature.[53,54] A prior COBY study[55] found that males and females were at an equivalent risk of new-onset SUD. Although beyond the scope of the current study, prior findings from adults indicate that there are sex differences in treatment in those with comorbid BD and SUD.[56]

There were no sex differences in suicidal ideation, suicide attempts, or NSSI. This finding is in contrast to the literature showing females of any age have more suicide attempts[57,58] and NSSI in community samples[59–61] and across many psychiatric disorders[55,56.] In youth with BD, however, the female predominance of suicide-related behavior may be an age-related phenomenon. According to the initial COBY sample, there were no sex differences in lifetime suicide attempts in late childhood or early adolescence (mean ± SD age = 12.7 ± 3.2 years).[62] In the same COBY cohort, there were more females than males who made a prospectively ascertained suicide attempt within 5 years.[36] Now, using this same COBY cohort, we found no sex differences in suicide-related behavior over 10 years. Thus, in female youth with BD, the increased risk of suicide attempt coincides with the highest-risk period of new-onset suicidal behavior between 16 and 18 years.[63]

Findings of the present study must be interpreted in the context of methodological limitations. First, despite efforts to obtain precise information, data collected through the LIFE (via a method similar to Timeline Follow Back [TLFB]) are subject to retrospective recall bias.[22] Nevertheless, we would not expect recall bias to differ between females and males, and the TLFB has been used extensively for more than 30 years in clinical and nonclinical research studies.[64] Second, to optimize power, we examined COBY subjects with child-onset and adolescent-onset BD together and therefore cannot rule out different sex-related findings in one of these subgroups. This said, the average age of the COBY sample was older than in previous studies examining sex differences in youth with BD,[9–11] and the current study was the only one offering detailed prospective information. Furthermore, with the exception of more anxiety and depression in older females, there were no age-specific sex differences in the prospective course of BD. Third, the examination of sex

differences in treatment effects was beyond the scope of the current study. Fourth, the subjects were self-reported White and were recruited from clinical settings, which may limit the generalizability of results. Nonetheless, course and morbidity in non–clinically referred BD youth have been shown to be similar to those in referred populations.[5] Fifth, the possibility of "overadjustment" leading to type II error cannot be ruled out.[65] However, covariates were conservatively chosen[65,66] and limited to variables with sex differences at intake. Moreover, post hoc analyses with only age as a covariate did not change the findings (data not shown). Sixth, while we were interested in studying the effects of both sex and gender, the statistical design of this study focused only on sex differences. Finally, it is important to note that we cannot rule out the possibility of nuanced sex differences such as within BD subtypes, nor did we evaluate for symptom-specific sex differences.

Despite these limitations, this study is the largest on this topic to date and the first longitudinal study with the specific aim of investigating sex differences among youth with BD. With the exception of psychiatric comorbidities that follow the expected sex patterns, female and male youth with BD had a similar course of illness. Therefore, youth-onset BD may not be phenotypically distinct in females versus males as it is in adult-onset BD. Longer-term studies are needed to clarify if youth-onset BD remains a "sex neutral" subtype of BD or diverges according to sex in adulthood. Finally, future studies are warranted to better understand the female predominance of BD in adolescence. As clinical characteristics do not provide strong signals, findings underscore the importance of incorporating neurobiological data (eg, sex hormones, neuroimaging phenotypes) to offer insight into plausible underlying mechanisms.

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