

# Age-at-Onset of 648 Patients with Major Affective Disorders: Clinical and Prognostic Implications

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## ABSTRACT

### BACKGROUND AND OBJECTIVE

Onset-age reportedly differs among affective disorders and may be a simple, objective means of supporting diagnosis, prognosis, and treatment-selection. We compared onset-age in Argentine patients diagnosed with the *Diagnostic and Statistical Manual of Mental Disorders* 4th ed. (*DSM-IV*) major mood disorders (bipolar [BPD] types I, II, or unspecified [NOS], or unipolar-major depressive disorder [UP-MDD]).

### METHODS

Adult patients ( $n = 648$ ) were diagnosed with a *DSM-IV-TR* BPD (243 type-I, 199 type-II, and 88 NOS), or UP-MDD (118) and skewed onset-age distributions were compared nonparametrically. We also examined associations of onset-age with demographic and clinical characteristics, tested the ability of onset-age to distinguish BPD from UP-MDD patients, and predicted later morbidity or disability.

### RESULTS

By diagnosis, onset-age (median with interquartile range [IQR]) ranked: BP-I (25.0 [14.0]) = BP-II (25.0 [15.8]) < BPD-NOS (33.0 [21.5]) < UP-MDD (37.0 [17.0]) years;  $p < .0001$ . Median onset-age [IQR] across all 530 BPD cases was 26 [16], or 11 [6] years younger than MDD cases ( $p < .0001$ ). Onset-age was significantly older among ever-married and employed patients, not related to gender or educational level, and not significantly predictive of later recurrence rates (episodes/year). Onset-age separated BP-I + II from UP-MDD patients highly significantly but with only moderate sensitivity (73%) and poor specificity (18%) at optimized criterion ages of  $\leq 20$  years for BPD and  $\geq 40$  years for UP-MDD (59.5%, 18.8%).

### DISCUSSION

Onset was younger among BPD than UP-MDD patients, generally confirming recent findings in other world regions. Older onset was associated with some functional outcomes (marriage and work) but not an index of morbidity (recurrence rate), suggesting a complex relationship to later illness-course and disability.

Keywords: age-at-onset, bipolar disorders, unipolar major depressive disorder

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Major affective disorders are highly heterogeneous in their clinical presentations, longitudinal course, risk of disability and mortality, and responses to treatment. Age-at-onset is a relatively simple and objective indicator reported to vary among patients with specific types of mood disorders. Onset-age may have value as a correlate or predictor of particular clinical or biomedical features of specific types of mood disorders<sup>1-3</sup> and young onset-age has been proposed specifically as an indicator of relatively great familial or genetic risk and of adverse long-term outcome.<sup>4</sup>

Definitions of onset-age vary and may represent age at first manifestations of symptoms, major episodes, diagnosis, treatment, or hospitalization. Currently, onset is commonly defined as the age at a first major episode of illness meeting standard international diagnostic criteria,

usually *DSM-IV* or *ICD-10*, although it is likely that even earlier psychopathological manifestations occur in many cases but often pass undetected in retrospective assessments.<sup>1,3,5,6</sup>

Previous studies have estimated average onset-age for patients with various types of bipolar disorder (BPD) as usually occurring between 15 and 30 years.<sup>3,6,7</sup> Typically, unipolar major depressive disorder has been found to begin at somewhat later ages, peaking in the mid-to-late 30s.<sup>3,6,7</sup> There also appear to be differences in onset-age among particular types of BPD patients, especially type I starting younger than type II, anticipating other important clinical differences between the two groups.<sup>6,8,9</sup> BPD-II patients tend toward an intermediate onset-age, between those diagnosed with BPD-I and UP-MDD, to parallel their main morbidity in

depressive states. Those with unspecified forms of BPD have rarely been studied.

Within groups of patients with major affective disorder diagnoses, younger onset has been associated with specific characteristics. These have included: (1) diagnosis of BPD, (2) a relatively high rate of mood disorders among first-degree relatives, (3) more years of education, (4) being unmarried, and (5) being unemployed.<sup>6,10–17</sup> In addition, onset of BPD at a particularly young age has been associated with: (1) higher rates of comorbid conditions including substance abuse and panic or severe anxiety disorders, as well as juvenile attention or conduct disorders; (2) psychotic features during acute episodes of affective illness, perhaps particularly in women; and (3) a high risk of suicides and attempts.<sup>1,9,10,18–23</sup> These observations generally suggest that earlier onset-age may be associated with more severe or complex forms of BPD, perhaps with a greater familial or genetic contribution to risk.

At the other extreme, BPD first diagnosed relatively late in adult life (typically at age  $\geq 60$  years) is often associated with neuromedical disorders such as early dementia, strokes, infections, or head injuries; a particularly severe course; and high mortality rates.<sup>24–26</sup> Late-onset cases often tend to lack a family history of mood disorders or of substance abuse; inconsistent evidence also suggests a relatively high prevalence of mixed (agitated–dysphoric) manic-depressive episodes, as well as inferior treatment responses with geriatric onset.<sup>12,26–29</sup>

Differences in family history, early manifestations or precursor-states, clinical presentation of first major episodes, and subsequent illness-course, disability, risk of mortality, and treatment responses all have been proposed to vary with onset-age. This simple, objective, and relatively easily ascertained characteristic may therefore be of clinical and research importance that may include diagnostic and predictive value.<sup>6,30,32</sup> Notably, early-onset may help to identify cases of initial depression that are likely to have a future BPD course, despite substantial apparent overlap in onset-ages of BPD other than type I, with UP-MDD cases.<sup>6,32</sup> Moreover, earlier recognition and appropriate treatment of early-onset BPD patients may limit later morbidity, dysfunction, and mortality among such patients; as well as guiding prognosis and long-term planning of clinical management; and serving as an additional phenotype-defining characteristic with which to guide biomedical research.<sup>4,6,30–33</sup>

Given the importance of further quantifying onset-age among patients with particular types of major mood disorders, we assembled and analyzed clinical information and onset-age data for 648 Argentine mood-disorder patients with various forms of BPD or UP-MDD. The aim of the study was to characterize onset-ages in a previously rarely studied population and to correlate onset-age with various demographic, diagnostic, and other clinical measures. We aimed specifically to test the hypotheses that onset-age is younger among BPD—especially type I BPD patients than in UP-MDD patients—and that earlier onset may predict a more severe later illness-course.

## METHODS

### Patient Subjects

The study sample included 648 currently adult patients, diagnosed with a major affective disorder, based on DSM-IV-TR criteria. Patients included met DSM-IV criteria to support diagnosis of an adult major affective disorder. Onset-age was estimated from patient and family reports and medical records based on the presence of substantial functional impairment following a first-recognized, clinically significant, affective syndrome, and meeting DSM-IV diagnostic criteria as adults. Cases involving cyclothymia or dysthymia were not included. Participants provided written, informed consent for anonymous and aggregate analysis of their clinical data, following review of the study protocol by the human studies ethics committee of the University of Palermo in Buenos Aires, Argentina.

### Data Analysis

Owing to skewing of age distributions, onset-age data are shown as medians with interquartile range (IQR) or as frequencies (percentage); other data are presented as means  $\pm$  standard deviations (SD). Categorical comparisons were based on contingency tables ( $\chi^2$ ) and continuous data were compared with Mann–Whitney (z-statistic, with degrees of freedom [df] = 1) and Kruskal–Wallis tests (H-statistic; df  $\geq 2$ ). Correlations were based on nonparametric (Spearman-rank test [ $r_s$ ]) to avoid assumptions about mathematical relationships involved. Statistics employed standard, commercial software (SPSS-17; SPSS Corp., Chicago, IL; Statview-5, SAS Corp., Cary, NC; and Stata-8, Stata Corp., College Station, TX).

## RESULTS

### Subject Characteristics

Overall, among the 648 mood-disorder patients, current age averaged ( $\pm$ SD)  $46.2 \pm 13.0$  years and duration of illness from onset averaged  $16.7 \pm 12.2$  years (Table 1). The overall median [IQR] onset-age was 28.0 [18.0] years (mean [ $\pm$ SD] =  $29.7 \pm 12.2$ ), with moderate skewing toward younger ages: 54.4% of all illnesses started before age 30, especially in BPD (58.8% vs UP-MDD: 30.3%) and in women (67.5% vs men: 55.1%). Adult-onset ( $\geq 19$  years) involved 79.8% of cases, juvenile-onset (age  $\leq 18$  years) involved 20.2% of cases including 2.16% with childhood-onset ( $< 12$  years). Salient characteristics of patients in specific diagnostic subgroups including sex, education, marital, and employment status also are summarized (Table 1).

### Onset-Age Versus Diagnosis and Gender

By diagnosis, median [IQR] onset age ranked: BP-I (25.0 [14.0]) = BP-II (25.0 [15.8]) < BP-NOS (unspecified; 33.0 [21.5]), UP-MDD (37.0 [17.0] years). Onset-age differed little between men and women with either a BPD or UP-MDD (Table 2). Median onset-age among the 441 women was 28.0 [18.0] and 27.0 [19.5] years among the 207 men. Median

**Table 1.** Characteristics of 648 Major Affective Disorder Patients

Subgroup or Measure	Bipolar I	Bipolar II	Bipolar NOS	UP-MDD
Cases (n [%])	243 [37.5]	199 [30.7]	88 [13.6]	118 [18.2]
Women (%)	59.3	71.9	71.6	77.1
Marital status (%)				
Divorced or separated	34.9	37.8	46.2	56.9
Single	31.2	25.4	29.5	23.9
Married	21.6	21.2	16.7	10.1
Widowed	12.4	15.5	7.69	9.17
Ever married	68.8	74.6	70.5	76.1
Years of education (%)				
<12	5.79	1.53	0.00	1.69
12	16.1	15.3	14.8	17.8
>12	78.1	83.2	78.1	80.5
Employed (%)	78.4	84.3	97.5	96.4
Average onset-age (years)				
Mean $\pm$ SD	27.0 $\pm$ 10.8	27.5 $\pm$ 11.2	33.0 $\pm$ 13.6	36.7 $\pm$ 12.5
Median [IQR]				
All cases	25.0 [14.0]	25.0 [15.8]	33.0 [21.5]	37.0 [17.0]
Women	25.0 [14.0]	26.0 [14.8]	33.0 [21.0]	37.0 [18.0]
Men	24.0 [14.0]	24.0 [17.0]	35.0 [25.5]	38.0 [15.8]
Onset age-group (%)				
Child (<12)	1.09	1.40	0.78	0.31
Juvenile ( $\leq$ 19)	10.4	8.39	2.80	1.71
Adult ( $\geq$ 20)	27.2	22.1	10.4	16.6
Current age (years)	44.8 $\pm$ 13.0	45.4 $\pm$ 12.9	47.9 $\pm$ 11.6	49.3 $\pm$ 11.9
Years of illness	18.4 $\pm$ 11.8	13.3 $\pm$ 12.0	14.9 $\pm$ 11.43	12.6 $\pm$ 11.9

Note: BPD, bipolar disorder (types I, II, or not-otherwise-specified [NOS]); UP-MDD, unipolar major depressive disorder. Juveniles include adolescents and children. IQR, interquartile range for medians.

onset-age was markedly younger among all 530 BPD patients (26.0 [16.0]) than in the 118 UP-MDD patients (37.0 [17.0] years;  $z = 6.60$ ,  $p < .0001$ ), but similar among types I and II BPD patients (both 25.0 years; **Table 2**). Juvenile-onset (age  $\leq 17$  years) involved 15.3% of all cases including 2.20% with childhood (<12) onset and 84.7% of patients were of adult-onset ( $\geq 18$  years;  $\chi^2$  [ $df = 2$ ] = 15.8,  $p = .0004$ ).

### Onset Age and Long-Term Functional Status and Morbidity

We considered available demographic and clinical factors for comparison to onset-age, initially based on bivariate statistics, followed by multivariate linear regression modeling of selected factors (**Table 3**). Initial bivariate analyses found much younger onset-ages in association with never having married (unmarried vs married: 24.3  $\pm$  10.1 vs 31.7  $\pm$  12.2 years;  $F = 51.5$ ,  $p < .0001$ ) and being unemployed (24.5  $\pm$  9.64

vs 30.5  $\pm$  12.5 years;  $F = 17.2$ ,  $p < .0001$ ) but not with education or sex (not shown). There was a weak but significant, positive, nonparametric correlation between more years of education and older onset-age ( $r_s = +.101$ ,  $p = .011$ ; not shown). However, morbidity, as episodes/year at risk was not related to onset-age, overall ( $r_s = .054$ ,  $p = .180$ ), nor among patients diagnosed with BPD ( $r_s = .076$ ,  $p = .087$ ) or UP-MDD ( $r_s = .177$ ,  $p = .060$ ).

Multivariate modeling supported strong, positive, correlations of older onset-age with ever being married and being employed, as well as with UP-MDD versus BPD diagnoses but not with sex. Categorical educational achievement was not significantly associated with onset-age (**Table 2**). Moreover, morbidity as estimated by episodes/years-at-risk (from onset to present age) was significantly, though relatively weakly related to onset-age, however, as an unexpected direct correlation (older onset, greater morbidity; **Table 3**).

### Potential Value of Onset-Age to Differentiate Diagnoses

We also considered the distribution of onset-ages across diagnoses to see if a relatively early age-criterion might help to differentiate among specific diagnostic subgroups. Histograms of each diagnostic type (**Figure 1**: left panel) indicate close similarities of types I and II BPD, with a broad but somewhat older median among the relatively few BPD-NOS cases. All of these BPD patients were clearly younger-at-onset than UP-MDD patients (**Figure 1**: right panel). We then determined the proportions of BPD types I+II versus UP-MDD patients who were differentiated at defined onset age-levels using standard Bayesian definitions to determine sensitivity (younger-onset among BPD cases), specificity (older-onset among MDD cases), and positive predictive value (PPV; BPD cases among all cases with younger-onset). This procedure suggested that an onset-age criterion of <20 years (juvenile onset) was about the most favorable outcome (**Table 4**), and this impression was verified by an analysis of a receiver-operating function for age-criteria varied systematically from 10 to 50 years (not shown). However, the Bayesian characteristics of the proposed criterion age of <20 years yielded moderate sensitivity (72.9%) but poor specificity (17.6%; **Table 4**), suggesting that this approach would have limited clinical value as a diagnostic test. Similarly, using various older ages to identify cases of UP-MDD versus BPD, gained sensitivity as the onset-age-criterion increased from  $\geq 30$  to  $\geq 50$  years (from 29.7% to 84.8%), but specificity was only moderate and fell (from 40.3% to 7.22%). However, a criterion onset-age of 40 years was approximately optimal (sensitivity = 58.5%) but with very low specificity (18.8%).

## DISCUSSION

This study of age at first major episodes of DSM-IV bipolar and unipolar major mood disorders among patients in Argentina extends and generally supports recent findings from other countries.<sup>3,6,7</sup> Notably, the average age-at-onset of all three types of bipolar disorders was far younger than for unipolar depression, with a difference of 11 years between the median onset-age of BPD types I or II (25 years) and UP-MDD

(37 years). BPD patients not otherwise specified (NOS) have been little-studied, and their onset-age range overlapped that of other BPD patients and those diagnosed with UP-MDD (Tables 1 and 2). Their similarity in onset-age to the UP-MDD

**Table 2.** Factors Associated With Onset-Age in 648 Major Affective Disorder Patients

Factors	Onset Age [IQR]	Statistic	p-Value
<b>Diagnosis</b>			
Bipolar-I	25.0 [14.0]	57.6	<.0001
Bipolar-II	25.0 [15.8]		
Bipolar-NOS	33.0 [21.5]		
Unipolar	37.0 [17.0]		
All cases	28.0 [18.0]		
<b>Bipolar type</b>			
Bipolar-I	25.0 [14.0]	0.474	.635
Bipolar-II	25.0 [15.8]		
<b>Bipolar versus unipolar</b>			
Bipolar	26.0 [16.0]	6.60	<.0001
Unipolar	37.0 [17.0]		
<b>Marital status</b>			
Single	22.0 [10.0]	56.2	<.0001
Divorced/separated	31.5 [19.5]		
Widowed	31.5 [18.0]		
Married	29.0 [17.0]		
<b>Marital history</b>			
Ever married	30.0 [18.5]	7.38	<.0001
Never married	22.0 [10.0]		
<b>Employment</b>			
Employed	29.0 [19.2]	4.00	<.0001
Unemployed	23.0 [11.8]		
<b>Gender All diagnosis</b>			
Female	28.0 [18.0]	0.269	.788
Male	27.0 [19.5]		
<b>Bipolar</b>			
Female	26.0 [16.0]	0.278	.781
Male	25.0 [16.0]		
<b>Unipolar</b>			
Female	37.0 [18.0]	1.57	.118
Male	38.0 [15.8]		
<b>Education (years)</b>			
<12	30.0 [20.0]	2.25	.324
12	25.0 [14.5]		
>12	28.0 [18.0]		

**Table 2 (Continued)**

Factors	Onset Age [IQR]	Statistic	p-Value
Factors	$r_s$ [95% CI]	Statistic	p-Value
<b>Episodes/year</b>			
Overall	0.054 [-0.240 to 0.342]	1.34	.180
Unipolar	0.177 [-0.048 to 0.401]	1.88	.060
Bipolar	0.034 [-0.119 to 0.268]	1.71	.087

Note: Statistical comparisons of defined subgroups are based on nonparametric methods (Mann–Whitney [z-score], Kruskal–Wallis [H-score]), or Spearman) rank correlation ( $r_s$  [with 95% confidence interval] and z-statistic).

patients is not readily explained, but may reflect their relatively difficult distinction from UP-MDD cases, since BPD-NOS patients have variable features in mood episodes that may or may not meet DSM diagnostic criteria. We suspect that not meeting diagnostic criteria may be particularly likely with respect to mania and especially hypomania, even though most criteria for MDD may well be met among cases categorized as BPD-NOS. In contrast to some previous studies,<sup>34–39</sup> we found little difference of onset-ages between women and men (Table 2).

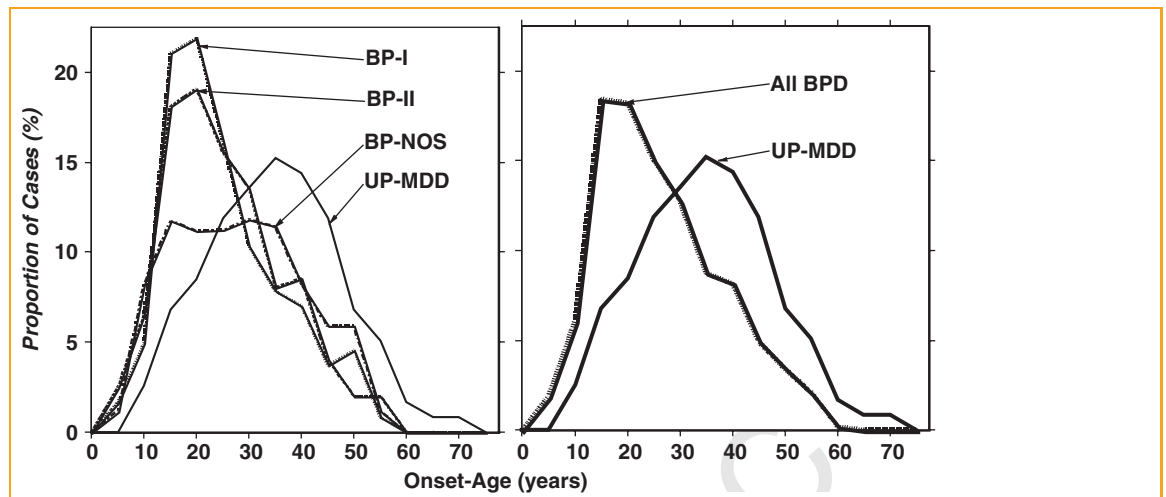
In addition to diagnostic subtype, several factors were strongly associated with onset-ages, notably later marital and occupational status. Older onset was associated with being or having been married and being employed including with multivariate modeling (Tables 2 and 3), probably because in some cases these attainments may have preceded illness-onset. Nevertheless, these observations suggest somewhat higher functional status in association with later onset, perhaps reflecting less severe illness or less impact of early morbidity at developmentally sensitive ages.<sup>4</sup> Consistent with this interpretation is that years of education were significantly and positively, though weakly, correlated with onset-age.

An unexpected finding was that morbidity as reflected in estimated episodes per years-at-risk was very weakly—and not negatively—associated with older onset-age in both BPD and UP-MDD patients (Table 2). This outcome may be influenced by some recall bias of events, including onset-

**Table 3.** Multivariate Linear Regression: Factors Associated With Younger Onset-Age

Factors	Slope ( $\beta$ ) [95% CI]	t-Score	p-Value
BPD > UP-MDD	8.45 [6.06–10.8]	6.95	<.0001
Never married	7.91 [5.85–9.96]	7.55	<.0001
Unemployed	5.19 [2.54–7.85]	3.85	<.0001
Fewer episodes/year	2.05 [0.69–3.40]	2.96	.003
Female sex	1.33 [0.62–3.28]	1.34	.182

Note: Factors shown are independently associated with older onset-age—all significantly so except for sex. BPD, bipolar disorder; UP-MDD, unipolar major depressive disorder. Slope functions ( $\beta$ -statistic) shown with 95% confidence intervals.



**Figure 1.** Histograms of distribution of onset-ages by diagnosis: (Left) Bipolar-I ( $n=243$ ; median [IQR] = 25.0 [14.0] years); Bipolar-II ( $n=199$ ; 25.0 [15.8]); Bipolar Not Otherwise Specified ( $n=88$ ; 33.0 [21.5]); Unipolar Major Depressive Disorder ( $n=118$ ; 37.0 [17.0]); (Right) All Bipolar Disorder cases ( $n=530$ ; 26.0 [16.0]) versus Unipolar Major Depressive Disorder cases ( $n=118$ ; 37.0 [17.0]).

age that occurred years previously. Nevertheless, several of these findings suggest possible disparity between measures of symptomatic affective morbidity (lack of more episodes/year with younger onset) and functional status reflected in social achievements including marriage and employment, which appeared to be less frequent with younger onset. This seeming inconsistency may reflect differences between possibly less onset-age-dependent or more chaotic symptomatic psychopathology and risk of recurrences of major mood disorders versus a more predictable impact of early illness on meeting developmental milestones. In turn, it remains to be defined whether important mediating variables may include subsyndromal mood fluctuations and sustained morbidity, especially depressive, dysthymic, and dysphoric morbidity. Such depressive morbidity dominates the long-term clinical picture in BPD patients, even with modern treatments, and appears to associate with

comorbidities including substance abuse as well as poor functional outcomes.<sup>40,41</sup>

An important component of this study was an effort to use onset-age to separate BPD from UP-MDD cases from the start of clinically manifested illness. We found large and highly significant differences between onset-age in BPD, especially types I and II, versus UP-MDD (Table 2; Figure 1). However, the diagnostic value of a range of specified ages, below which BPD was favored and above which MDD was favored, based on Bayesian principles was moderate and showed poor specificity (Table 4). Nevertheless, we recommend that onset of mood disorders among juveniles ( $\leq 18$  years old) or children ( $\leq 12$  years old) raise close consideration of potential BPD diagnoses that may not be apparent at onset if an illness presents initially with depression, whereas depressions starting at ages between 30 and 60 years are most likely unipolar.

**Table 4.** Bayesian Analysis: Distinguishing Bipolar I+II Disorder From Unipolar Major Depressive Disorder Patients by Onset-Age Criteria

Criterion (years)	Sensitivity (%)	Specificity (%)	PPV (%)	$\chi^2$	p-Value
<15 vs $\geq 15$	92.3	7.56	78.8	0.002	.968
<20 vs $\geq 20$	72.9	17.6	76.7	4.45	.035
<25 vs $\geq 25$	52.6	26.0	72.6	17.5	<.0001
<30 vs $\geq 30$	37.5	38.7	69.5	21.9	<.0001
<35 ca. $\geq 35$	24.4	57.1	67.9	15.8	<.0001
<40 vs $\geq 40$	16.9	68.9	67.0	11.7	.0006
<45 vs $\geq 45$	9.03	79.8	62.5	11.5	.0005
<50 vs $\geq 50$	5.87	86.6	61.9	7.79	.005

Note: Sensitivity = true positive/all bipolar; specificity = true negative/all unipolar; positive predictive value (PPV) = true positive/all positive, where "positive" means distinguishing bipolar I+II patients from unipolar depressive patients based on the stated onset-age criterion. A plausible criterion would be age <25 years, but this yields only moderate sensitivity (52.6%) and weak specificity (26.0%); this value also yields the maximum deviation from chance by receiver operating characteristic analysis (not shown).

This study has several limitations. A principal one is that ascertainment of onset-age depended heavily on post hoc recollection by patients, those who knew them well, or based on medical records, all of which can be inaccurate, perhaps randomly, but possibly more with longer illness and older current age. An additional limitation is that only a few clinical symptomatic and functional outcome measures were available for analysis. Also, the subjects in some categories were far fewer than the numbers of BPD I and II patients. Despite these limitations, this study adds to the international characterization of onset-age in a range of types of major mood disorders based on standardized diagnostic criteria. It supports the growing impression that BPD begins much earlier, on average, than UP-MDD and finds indications that early-onset predicts a worse functional outcome, although not necessarily a more severe clinical symptomatic course. We suggest that further research should consider possible explanations for the observed disparity between relationships of onset-age and functional versus symptomatic outcomes.

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