ORIGINAL ARTICLE

Heterogeneity of *DSM-IV* Major Depressive Disorder as a Consequence of Subthreshold Bipolarity

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Context: There is growing evidence that major depressive disorder (MDD) might be overdiagnosed at the expense of bipolar disorder (BPD).

Objectives: To identify a subgroup of subthreshold BPD among *DSM-IV* MDD, which is distinct from pure MDD regarding a range of validators of bipolarity, and to examine the pattern of these validators among different groups with affective disorders.

Design: Ten-year prospective longitudinal and family study including 3 follow-up waves. Data were assessed with the *DSM-IV* Munich Composite International Diagnostic Interview.

Setting: Community sample in Munich, Germany.

Participants: A total of 2210 subjects (aged 14-24 years at baseline) who completed the third follow-up.

Main Outcome Measures: Cumulative incidence of pure MDD, BPD, and subthreshold BPD (defined as fulfilling criteria for MDD plus having manic symptoms but never having met criteria for [hypo]mania).

Results: Among 488 respondents with MDD, 286 (58.6%) had pure MDD and 202 (41.4%) had subthreshold BPD (cumulative incidence, 9.3%). Compared with respondents who had pure MDD, respondents with subthreshold BPD were found to have a significantly increased family history of mania, considerably higher rates of nicotine dependence and alcohol use disorders, rates of panic disorder that were twice as high, and a tendency toward higher rates of criminal acts. Prospective analyses showed that subthreshold BPD converted more often into BPD during follow-up, with *DSM-IV* criterion D (symptoms observable by others) being of critical predictive relevance. With increasing severity of the manic component, rates for diverse validators accordingly increased (eg, alcohol use disorders, parental mania) or decreased (harm avoidance).

Conclusions: Data suggest that MDD is a heterogeneous concept including a large group with subthreshold BPD, which is clinically significant and shares similarities with BPD. Findings might support the need for a broader concept and a more comprehensive screening of bipolarity, which could be substantial for future research and adequate treatment of patients with bipolarity.

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THE DIAGNOSTIC CONCEPT OF major depressive disorder (MDD) was adopted in the *DSM-III*[1] in 1980 and subsequently refined in the *DSM-III-R*[2] and the *DSM-IV*.[3] Since then, MDD has been described as the most frequent mood disorder, with rates up to 16%, and as highly comorbid with anxiety and substance use disorders (SUDs).[4-6] In contrast as shown by large community studies, the prevalence of bipolar disorders (BPDs) is 2%, considerably lower.[7-10]

However, concerns about the reliability of the hypomania diagnosis were raised.[11,12] Several investigators noted that bipolarity might be underdiagnosed by the *DSM-IV* criteria as the diagnosis of bipolar II disorder (BP-II) requires the presence of a major depressive episode plus a hypomanic episode, and they also noted that some MDD cases might be better reclassified as bipolar.[13-18] This could particularly pertain to young adults, when the disorder is in its early stages. Additionally, it must be questioned whether the current *DSM-IV*–based instruments are sufficiently sensitive for detecting hypomania.[19,20] Support comes from epidemiological and clinical studies dealing with wider concepts of bipolarity, which showed that subthreshold BPD not recognized with the current *DSM-IV* criteria is common and clinically significant.[8,14,16,21,22] In the National Comorbidity Survey Replication, the overall prevalence of BPD increased from 2.1% to 4.4% if subthreshold BPD was considered, and the clinical validity of this subthreshold group was clearly demonstrated in terms of role impairment or comorbid-

ity.[8] In the small prospective Zurich Study,[14] a stepwise broadening of the criteria for hypomania allocated almost half of the subjects with major depressive episodes to a broadly defined bipolar group. The frequently reported association between alcohol use disorders (AUDs) and MDD disappeared in favor of a high association with BP-II.[14,23] Benazzi and Akiskal[19] found that 61% of 168 outpatients with MDD were classified as bipolar when the strict Structured Clinical Interview for *DSM* Disorders criteria for hypomania were broadened.

Overall, there is still a lack of large-scale epidemiological studies that systematically examine the question of whether *DSM-IV* MDD might be overdiagnosed at the expense of BPD owing to a too restrictive threshold for *DSM-IV* hypomania. Taking the considerable burden and clinical implications of BPD into account[9,10,24-26] as compared with MDD, the identification of cases with "hidden" bipolarity might be highly important.

Our investigation uses data from the prospective longitudinal Early Developmental Stages of Psychopathology (EDSP) study and has 3 goals. We examine how many cases previously classified as *DSM-IV* MDD would be reclassified as bipolar by broadening the criteria for mania/hypomania and to what degree such subthreshold BPD cases are distinct from pure MDD regarding a broad range of validators that were previously found to differentiate between BPD and unipolar depression.[14,27] Further, we examine the pattern of these validators among different groups of affective disorders with respect to clinical significance.

METHODS

DESIGN AND SAMPLE

Data come from the prospective longitudinal EDSP study[28,29] comprising a baseline investigation and 3 follow-up waves that cover an overall period of about 10 years. The baseline sample was drawn randomly from the 1994 government registries of all residents with German nationality aged 14 to 24 years in Munich and surrounding counties. The 14- to 15-year-olds were sampled at twice the probability of the individuals aged 16 to 21 years, and the 22- to 24-year-olds were sampled at half the probability of the individuals aged 16 to 21 years. A total of 3021 respondents were interviewed at baseline (response rate, 71.3%), of whom 36.2% were students at secondary level, 26.4% were students at university, and 21.7% were employed. Among the participants, 62.4% were living with their parents, 22.7% were living alone, and 12.1% were living with their partner or spouse.

The first follow-up (approximately 20 months after baseline) was conducted only for subjects aged 14 to 17 years at baseline, whereas the second and third follow-ups were conducted for all subjects (approximately 42 and 101 months after baseline, respectively; N=2210 participants at the third follow-up; response rate for baseline to the third follow-up, 73.2%). The most frequent reasons for nonresponse at baseline or the third follow-up were refusal or lack of time (21.5% at baseline; 17.7% at the third follow-up) and failure to contact (3.1% at baseline; 8.3% at the third follow-up). Changes in sociodemographic characteristics between baseline and the third follow-up occurred for school or employment status (at the third follow-up: secondary school, 0.3%; employed, 59.5%) and living arrangements (at the third follow-up: living with parents, 13.6%; living with partner or spouse, 43.7%). With the exception of nicotine dependence (odds ratio [OR]=1.60; 95% confidence interval [CI], 1.25-1.99) and any illegal SUD (OR=1.71; 95% CI, 1.10-2.47), there was no selective attrition between baseline and the third follow-up due to mental syndromes and disorders.

Our investigation is based on the 2210 respondents who completed the final 10-year follow-up (ie, the third follow-up). The EDSP study was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden and the Bayerische Landesärztekammer Munich. All participants provided informed consent.

DIAGNOSTIC ASSESSMENT

At each wave participants were interviewed with the computer-assisted Munich Composite International Diagnostic Interview (M-CIDI),[30] which allows for the standardized assessment of symptoms, syndromes, and diagnoses of *DSM-IV* disorders along with information about onset, duration, and severity.[3] It is supplemented by a respondents' booklet including disorder-specific questionnaires, symptom lists, and cognitive aids. Test-retest reliability and validity have been reported elsewhere.[31-33] The M-CIDI is highly sensitive for detecting any BPD and MDD (sensitivity, 93%-100%).[32] Clinical interviewers, mostly graduated psychologists, who had received the standardized M-CIDI training according to the World Health Organization protocol carried out face-to-face interviews mainly in the respondents' homes. All interviewers were regularly supervised. At baseline, lifetime and 12-month disorders were assessed. At the first through third follow-ups, the M-CIDI covered the interval since the respective last interview.

ASSESSMENT OF MENTAL DISORDERS

Depressive and manic symptoms, syndromes, and disorders were assessed using the *DSM-IV* M-CIDI sections E (depression) and F (mania). We built 8 mutually exclusive categories. According to the *DSM-IV* M-CIDI criteria, the spectrum of major mood disorders comprises threshold bipolar I disorder (BP-I), BP-II, and MDD. To establish a pure depression group, we split MDD into MDD without any manic features (pure MDD) and MDD with subthreshold hypomania (subthreshold BPD). Subthreshold hypomania means that the person reported a period of at least 4 days with the following: (1) elated or expansive mood that created troubles or was noticed by others as a change in functioning, but *DSM-IV* hypomania criterion B (meeting the required minimum number of symptoms) was not fulfilled, or (2) unusually irritable mood expressed as starting arguments, shouting at or hitting people, and having at least 3 manic symptoms, but criterion D (symptoms observable by others) was not met. Together these syndromes are labeled as the major affective spectrum because in each group *DSM-IV* criteria for major depressive episodes were fulfilled. The other categories incorporated a subthreshold definition of depressive disorders. Pure mild depression was defined as not meeting criteria for MDD but having any of the following *DSM-IV* M-CIDI diagnoses: dysthymia, minor depression, or recurrent brief depression. Correspondingly, subthreshold minor BPD was defined as having pure mild depression (no MDD but dysthymia, minor depression, or recurrent brief depression) accompanied by subthreshold hypomania as defined earlier. Minor BPD was defined as threshold *DSM-IV* hypomania with or without *DSM-IV* M-CIDI dysthymia, minor depression, or recurrent brief depression. These groups are summarized throughout the article as minor affective spectrum conditions.

The control group comprised the remaining respondents without any major or minor affective syndrome or disorder.

The number of episodes with manic or depressive features and the age at onset of the first episode were assessed in the

respective sections of the M-CIDI not only for respondents with full-threshold affective syndromes and disorders but also for respondents with subthreshold affective syndromes and disorders. Comorbid mental disorders (eg, anxiety disorders, eating disorders, SUDs) were also assessed with the M-CIDI according to the *DSM-IV*.

ASSESSMENT OF SOCIODEMOGRAPHIC CHARACTERISTICS AND CRIMINAL ACTS

Data on sociodemographic factors were derived from the M-CIDI section A at the third follow-up. Data on criminal acts were collected at the second follow-up using the German version of the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders[30,34] and derived from the following antisocial personality disorder item: "At an age of older than 15: have you ever done anything illegal (eg, theft, drug dealing, financial beguilement, or prostitution)—even if you were not caught—or have you ever been arrested?"

ASSESSMENT OF PARENTAL MENTAL DISORDERS

To determine parental mental disorders according to the *DSM-IV*, all available information on each parent from 2 sources was aggregated. First, at the first follow-up, direct interviews were conducted with mothers of the younger cohort or with fathers if mothers were not available (1026 mothers, 27 fathers; response rate, 86.0%).[35,36] At the third follow-up, parents of respondents with any affective syndrome or disorder who agreed to contact their parents and to DNA sampling were interviewed (248 mothers, 187 fathers; response rate, 75.8%). Interviewers were blind to the diagnostic findings from offspring. The parent M-CIDI additionally provides family history information for the noninterviewed parent.[35] Second, a modified version of the Family History Research Diagnostic Criteria[37] was applied to obtain family history information from respondents. At baseline, M-CIDI stem questions for *DSM-IV* diagnoses were used and respondents were additionally asked whether the relative had sought professional help because of the respective symptoms. At the second and third follow-ups, an extended family history module covering *DSM-IV* M-CIDI criteria was applied. We found low to moderate sensitivity (range, 0.2-0.5) but high specificity (range, 0.8-0.9) for family history information.

Consistent with our focus on threshold and subthreshold expressions, we report threshold diagnoses defined as meeting full *DSM-IV* M-CIDI criteria for the respective mental disorder and subthreshold diagnoses that additionally include cases falling short of just 1 of the required *DSM-IV* criteria.

ASSESSMENT OF PERSONALITY TRAITS

The Tridimensional Personality Questionnaire by Cloninger[38] containing 100 items was used to assess the following 3 higher-order personality dimensions at the third follow-up: novelty seeking, harm avoidance, and reward dependence. For each dimension, a continuous scale was created using Cloninger's scoring keys. Because only 0.1% of the total sample reported (hypo)manic episodes, and 1.8% of the total sample reported depressive episodes 2 weeks before the third follow-up, an influence on the Tridimensional Personality Questionnaire assessment should have been marginal. The Tridimensional Personality Questionnaire has good validity and good test-retest reliability.[38,39]

STATISTICAL ANALYSES

Cumulative incidences were calculated by aggregating all diagnostic information from baseline to the third follow-up. This corresponds to lifetime diagnostic findings up to ages 23 to 34 years depending on the respondent's age at the third follow-up. Associations with sociodemographic factors, comorbid mental disorders, and parental mental disorders were estimated with ORs from logistic regressions adjusted for age and sex. Standardized ORs were calculated to estimate associations with standardized continuous variables (disorder characteristics, personality traits) to allow comparisons regardless of measurement units. We did not adjust for multiple testing because we considered specific categories of the affective spectrum to be related to individual hypotheses and examined their pattern of associations with various validators.

A kernel density plot of the frequency of episodes with manic features according to the number of symptoms during the worst episode regarding all categories from the major affective spectrum (MDD to BP-I) was calculated. Following several studies,[17,40] a cluster of at least 2 manic symptoms of *DSM-IV* criteria A and B (without priority) was required. A multimodal distribution of the number of manic symptoms with zones of rarity would suggest different categorical disorder subtypes separated by natural boundaries; a unimodal distribution would indicate a dimensional nature of (hypo)mania.[40,41]

Data were weighted by age, sex, geographic location, and noncontact or nonresponse at baseline to account for the different sampling probabilities and to adjust the distribution to the original sampling frame.[29] Analyses were carried out with Stata version 9.0 statistical software (StataCorp LP, College Station, Texas). The Huber-White sandwich method for weighted data was used to adjust statistical inference for the weighting of the data.[42]

RESULTS

CUMULATIVE INCIDENCE OF AFFECTIVE SYNDROMES AND DISORDERS

Almost half of the respondents reported a lifetime history of any mood symptom (44.0%). Among the major spectrum, the cumulative incidence of *DSM-IV* MDD until the third follow-up was 23.2% and thus considerably higher than that of BP-II (1.4%) and BP-I (3.0%) (**Table 1**). Among respondents with MDD, 286 (58.6%) met the study criteria for pure MDD and 202 (41.4%) met the criteria for subthreshold BPD (MDD with subthreshold hypomania) (cumulative incidence, 9.3%). The rates for the minor spectrum were 8.4% for pure mild depression, 5.5% for subthreshold minor BPD, and 2.5% for minor BPD.

ASSOCIATIONS OF AFFECTIVE SYNDROMES AND DISORDERS WITH SOCIODEMOGRAPHIC FACTORS

Pure MDD, BP-II, BP-I, and pure mild depression were associated with lower social class, with rates ranging between 16.4% and 29.4% as compared with 10.8% of control respondents (**Table 2**; results for minor spectrum available on request). Furthermore, we found ORs consistently smaller than 1 for each major and minor affective group, indicating their overall poorer financial situation when compared with control respondents.

Respondents with subthreshold BPD were more frequently separated, divorced, or widowed than control respondents (8.3% vs 2.4%, respectively; OR=3.65; 95% CI=1.46-9.11); this rate for other groups ranged between 0.0% and 5.9%.

Table 1. Cumulative Incidence of *DSM-IV* Syndromes and Disorders of the Major and Minor Affective Spectrum at Third Follow-up

Syndrome or Disorder	Respondents, No. (Weighted %) Total (N=2210)	Women (n=1075)	Men[a] (n=1135)	Women vs Men, OR (95% CI)[b]
Major affective spectrum[c]				
Pure MDD	286 (13.9)	157 (16.1)	129 (11.6)	1.74 (1.30-2.33)[d]
Subthreshold BPD	202 (9.3)	135 (12.4)	67 (6.1)	2.55 (1.80-3.62)[d]
BP-II	33 (1.4)	22 (2.0)	11 (0.7)	3.47 (1.57-7.65)[d]
BP-I	65 (3.0)	32 (3.0)	33 (3.0)	1.25 (0.71-2.19)
Minor affective spectrum[e]				
Pure mild depression	171 (8.4)	85 (8.6)	86 (8.1)	1.35 (0.94-1.94)
Subthreshold minor BPD	125 (5.5)	58 (5.2)	67 (5.8)	1.14 (0.75-1.72)
Minor BPD	55 (2.5)	34 (3.1)	21 (2.0)	1.92 (1.04-3.54)[d]
Control respondents	1273 (56.0)	552 (49.6)	721 (62.7)	NA

Abbreviations: BP-I, bipolar I disorder; BP-II, bipolar II disorder; BPD, bipolar disorder; CI, confidence interval; MDD, major depressive disorder; NA, not applicable; OR, odds ratio.
[a] Reference group.
[b] The ORs are adjusted for age.
[c] Pure MDD indicates MDD without any (hypo)manic features. Subthreshold BPD indicates MDD with subthreshold hypomania.
[d] $P < .05$.
[e] Pure mild depression indicates dysthymia, minor depression, or recurrent brief depression. Subthreshold minor BPD indicates dysthymia, minor depression, or recurrent brief depression with subthreshold hypomania. Minor BPD indicates hypomania with or without dysthymia, minor depression, or recurrent brief depression.

Table 2. Associations Between Sociodemographic Factors and Major Affective Disorders[a]

Characteristic	Control, Weighted % (n=1273)	MDD: Pure MDD (n=286) Weighted %	Pure MDD OR (95% CI)[b]	Subthreshold BPD (n=202) Weighted %	Subthreshold BPD OR (95% CI)[b]	BP-II (n=33) Weighted %	BP-II OR (95% CI)[b]	BP-I (n=65) Weighted %	BP-I OR (95% CI)[b]	Subthreshold BPD vs Pure MDD, OR (95% CI)[c]
Educational level[d]										
Hauptschule[e]	9.9	10.3	1 [Reference]	7.7	1 [Reference]	18.6	1 [Reference]	10.2	1 [Reference]	1 [Reference]
No degree	0.5	1.1	1.98 (0.48-8.11)	0.8	2.04 (0.44-9.30)	1.8	1.99 (0.16-23.88)	0.0	NA	0.78 (0.13-4.52)
Realschule or *Fachschule*	19.9	23.5	1.07 (0.61-1.84)	30.4	1.80 (0.95-3.39)	15.5	0.34 (0.09-1.30)	25.3	1.22 (0.45-3.32)	1.66 (0.78-3.49)
Gymnasium	69.8	65.1	0.89 (0.54-1.45)	61.2	1.11 (0.62-1.99)	64.1	0.46 (0.15-1.31)	64.5	0.89 (0.37-2.17)	1.22 (0.62-2.42)
Social class										
Lower[e]	10.8	16.4	1 [Reference]	15.3	1 [Reference]	26.2	1 [Reference]	29.4	1 [Reference]	1 [Reference]
Middle	60.4	60.1	0.65 (0.42-0.98)[f]	54.6	0.65 (0.39-1.06)	41.3	0.30 (0.10-0.80)[f]	42.4	0.26 (0.12-0.53)[f]	0.97 (0.54-1.72)
Upper	28.9	23.5	0.54 (0.33-0.88)[f]	30.1	0.80 (0.46-1.40)	32.5	0.54 (0.19-1.51)	28.2	0.36 (0.16-0.81)[f]	1.42 (0.73-2.76)
Financial situation										
Low[e]	7.4	14.1	1 [Reference]	12.3	1 [Reference]	16.2	1 [Reference]	15.8	1 [Reference]	1 [Reference]
Intermediate	27.7	30.8	0.60 (0.36-0.98)[f]	33.6	0.77 (0.42-1.37)	32.6	0.56 (0.16-1.86)	30.7	0.53 (0.21-1.35)	1.26 (0.65-2.40)
High	53.6	47.0	0.45 (0.28-0.72)[f]	43.5	0.49 (0.28-0.86)[f]	43.3	0.37 (0.12-1.07)	36.9	0.32 (0.12-0.78)[f]	1.08 (0.57-2.01)
Very high	11.3	8.0	0.40 (0.21-0.76)[f]	10.6	0.65 (0.31-1.33)	7.9	0.38 (0.08-1.70)	16.5	0.71 (0.26-1.95)	1.61 (0.68-3.78)
Marital status										
Married[e]	22.8	21.3	1 [Reference]	23.5	1 [Reference]	20.3	1 [Reference]	26.7	1 [Reference]	1 [Reference]
Separated, divorced, or widowed	2.4	3.8	1.81 (0.69-4.68)	8.3	3.65 (1.46-9.11)[f]	0.0	NA	5.9	2.20 (0.44-10.82)	1.98 (0.64-6.02)
Unmarried	74.9	74.9	1.46 (0.95-2.34)	68.2	1.09 (0.68-1.75)	79.7	1.56 (0.50-4.79)	67.4	0.93 (0.43-2.00)	0.74 (0.42-1.28)
Criminal acts										
No[e]	81.8	81.1	1 [Reference]	74.9	1 [Reference]	70.6	1 [Reference]	67.8	1 [Reference]	1 [Reference]
Yes	18.2	18.9	1.21 (0.81-1.81)	25.1	2.10 (1.41-3.13)[f]	29.4	2.73 (1.22-6.09)[f]	32.2	2.38 (1.25-4.52)[f]	1.68 (0.99-2.83)

Abbreviations: BP-I, bipolar I disorder; BP-II, bipolar II disorder; BPD, bipolar disorder; CI, confidence interval; MDD, major depressive disorder; NA, not applicable; OR, odds ratio.
[a] Cumulative incidences at the third follow-up.
[b] The ORs are adjusted for age and sex. The control group is the reference group.
[c] The ORs are adjusted for age and sex. The pure MDD group is the reference group.
[d] *Hauptschule* is secondary general school; *Realschule* or *Fachschule*, intermediate secondary school; and *Gymnasium*, grammar school.
[e] Reference group.
[f] $P < .05$.

Table 3. Disorder Characteristics of Major Affective Disorders[a]

	MDD						
	Pure MDD[b] (n=268)	Subthreshold BPD (n=202)		BP-II (n=33)		BP-I (n=65)	
Characteristic	Median (IQR)	Median (IQR)	OR (95% CI)[c]	Median (IQR)	OR (95% CI)[c]	Median (IQR)	OR (95% CI)[c]
Depressive features							
Episodes, No.	2 (1-5)	2 (1-5)	0.90 (0.78-1.04)	3 (1-7)	1.13 (0.90-1.42)	3 (2-8)	1.07 (0.92-1.23)
Age at onset, y	18 (15-21)	17 (14-20)	0.96 (0.75-1.22)	16 (12-19)	0.58 (0.33-1.03)	16 (14-19)	0.57 (0.41-0.80)[d]
Manic features							
Episodes, No.	NA	3 (1-10)	NA	8 (1-20)	NA	8 (3-20)	NA
Age at onset, y	NA	16 (13-19)	NA	16 (12-18)	NA	15 (13-17)	NA

Abbreviations: BP-I, bipolar I disorder; BP-II, bipolar II disorder; BPD, bipolar disorder; CI, confidence interval; IQR, interquartile range; MDD, major depressive disorder; NA, not applicable; OR, odds ratio.

[a] Cumulative incidences at the third follow-up.

[b] Reference group.

[c] The ORs are adjusted for age and sex.

[d] $P < .05$.

Rates of criminal acts were similar for respondents with pure MDD and control respondents (18.9% vs 18.2%, respectively). The probability of criminal acts, however, increased with higher levels of manic features, from 25.1% for subthreshold BPD to 32.2% for BP-I. Rates also tended to increase for those with subthreshold BPD compared with those with pure MDD (OR=1.68; 95% CI=0.99-2.83; $P=.05$).

DISORDER CHARACTERISTICS OF AFFECTIVE SYNDROMES AND DISORDERS

Among the major spectrum, a decreased age at depression onset was shown in BP-I compared with pure MDD (median, 16 vs 18 years, respectively; OR=0.57; 95% CI, 0.41-0.80) (**Table 3**). Among the minor spectrum, we did not find differences for the number of episodes with depressive features (pure mild depression: median, 1 episode; subthreshold minor BPD: median, 2 episodes; minor BPD: median, 1 episode) or for the age at depression onset (pure mild depression: median, 20 years; subthreshold minor BPD: median, 19 years; minor BPD: median, 18 years) (further results for the minor spectrum are available on request).

Regarding manic features, Table 3 shows a median of 3 episodes for subthreshold BPD and 8 episodes for both BP-II and BP-I, and the median age at onset ranged between 15 years for BP-I and 16 years for both subthreshold BPD and BP-II. Among the minor spectrum, the median number of episodes with manic features and the median age at onset were 1 episode and 17 years, respectively, for subthreshold minor BPD and 8 episodes and 16 years, respectively, for minor BPD. Among both the major and minor spectrum, the median age at onset for the first episode with depressive or manic features tended to be younger with an increasing level of mania.

In the entire major affective spectrum, the kernel density plot of the frequency of episodes with manic features according to the number of symptoms during the worst episode showed a unimodal distribution between MDD and BP-I without zones of rarity (**Figure**).

In prospective analyses excluding cases with onset of BP-I or BP-II before and/or at baseline, cases with lifetime subthreshold BPD at baseline as compared with pure MDD tended to convert more often into any BPD, especially BP-I, during follow-up (7.2% vs 1.7%, respectively; OR=4.57; 95% CI, 0.86-24.01; $P=.07$). In particular, criterion D (mood disturbances and change in functioning observable by others) seemed to be the strongest indicator of conversion: subthreshold BPD cases meeting this criterion as compared with the rest of the MDD group revealed a significantly higher risk of conversion to any BPD (13.2% vs 3.3%, respectively; OR=4.25; 95% CI, 1.13-15.92; $P=.03$) and specifically to BP-I (11.0% vs 1.5%, respectively; OR=8.32; 95% CI, 1.49-46.41; $P=.02$).

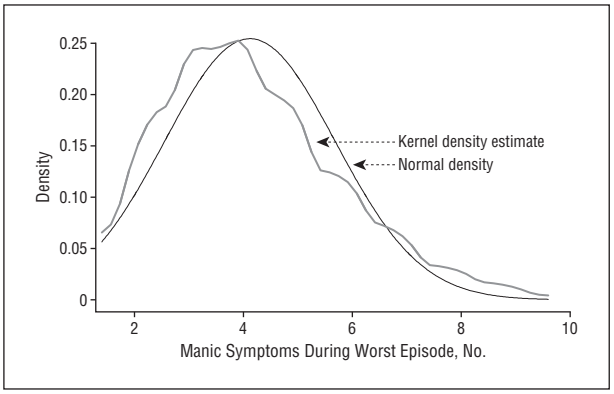

Figure. Kernel density plot of the frequency of episodes with manic features according to the number of symptoms during the worst episode including the entire major affective spectrum.

COMORBIDITY OF AFFECTIVE SYNDROMES AND DISORDERS WITH OTHER MENTAL DISORDERS

All major spectrum disorders were associated with almost all anxiety disorders; only 2 comparisons were not significant in the BP-II group (**Table 4**). The rate of panic disorder was more than twice as high for subthreshold BPD (12.3%) than for pure MDD (4.7%). Among the minor spectrum, the highest degree of comorbidity with anxiety disorders was observed for pure mild depression, with 7 of 9 possible associations being significant (**Table 5**).

Table 4. Comorbidity of Major Affective Disorders With Other Mental Disorders[a]

Other Mental Disorder	Control, Weighted % (n=1273)	MDD: Pure MDD (n=286) Weighted %	MDD: Pure MDD (n=286) OR (95% CI)[b]	MDD: Subthreshold BPD (n=202) Weighted %	MDD: Subthreshold BPD (n=202) OR (95% CI)[b]	BP-II (n=33) Weighted %	BP-II (n=33) OR (95% CI)[b]	BP-I (n=65) Weighted %	BP-I (n=65) OR (95% CI)[b]	Subthreshold BPD vs Pure MDD, OR (95% CI)[c]
Any anxiety disorder	19.6	44.6	3.07 (2.23-4.21)[d]	53.0	3.96 (2.78-5.64)[d]	59.0	4.76 (2.03-11.14)[d]	55.4	5.59 (3.12-10.03)[d]	1.31 (0.87-1.98)
PD with or without agoraphobia	1.7	4.7	2.48 (1.14-5.34)[d]	12.3	6.55 (3.24-13.19)[d]	3.5	1.65 (0.20-13.50)	9.9	5.78 (2.07-16.16)[d]	2.59 (1.26-5.30)[d]
Agoraphobia without PD	1.5	7.4	4.51 (2.05-9.92)[d]	4.7	2.50 (1.01-6.13)[d]	10.3	5.37 (1.48-19.46)[d]	15.9	11.67 (4.49-30.29)[d]	0.62 (0.27-1.40)
Social phobia	2.8	9.1	3.15 (1.72-5.77)[d]	13.6	4.54 (2.53-8.11)[d]	13.9	4.45 (1.03-19.21)[d]	16.0	6.77 (2.94-15.53)[d]	1.55 (0.82-2.89)
Any specific phobia	8.9	17.9	2.01 (1.33-3.02)[d]	23.4	2.62 (1.71-4.01)[d]	37.8	5.02 (2.08-12.14)[d]	19.1	2.41 (1.14-5.11)[d]	1.28 (0.77-2.12)
Phobia NOS	6.8	11.4	1.66 (1.01-2.75)[d]	13.6	1.80 (1.06-3.06)[d]	20.1	2.74 (1.01-7.43)[d]	20.3	3.67 (1.76-7.62)[d]	1.22 (0.65-2.25)
GAD	1.1	10.0	9.08 (4.21-19.55)[d]	9.9	7.92 (3.67-17.05)[d]	8.4	6.47 (0.82-50.80)	17.6	19.48 (7.74-49.00)[d]	0.96 (0.50-1.86)
OCD	0.4	3.8	10.21 (3.57-29.15)[d]	2.9	6.76 (2.35-19.43)[d]	12.8	35.31 (7.17-173.77)[d]	15.6	52.83 (18.02-154.88)[d]	0.66 (0.23-1.86)
PTSD	1.0	6.6	6.58 (3.01-14.39)[d]	10.9	9.69 (4.39-21.39)[d]	9.1	7.94 (2.01-31.28)[d]	11.4	13.50 (4.53-40.21)[d]	1.57 (0.75-3.28)
Any SUD	41.7	48.1	1.49 (1.10-2.01)[d]	56.5	2.33 (1.64-3.32)[d]	65.5	3.63 (1.45-9.08)[d]	70.7	3.78 (2.01-7.10)[d]	1.53 (1.01-2.33)[d]
Nicotine dependence	21.3	32.7	1.84 (1.34-2.53)[d]	43.6	3.12 (2.20-4.44)[d]	54.5	4.79 (2.14-10.70)[d]	53.4	4.31 (2.44-7.59)[d]	1.62 (1.06-2.45)[d]
Alcohol abuse	24.8	24.2	1.19 (0.84-1.69)	29.6	1.91 (1.29-2.84)[d]	22.2	1.39 (0.55-3.49)	43.7	2.82 (1.54-5.15)[d]	1.62 (1.01-2.63)[d]
Alcohol dependence	9.3	9.9	1.39 (0.84-2.28)	17.9	3.39 (2.08-5.54)[d]	20.5	5.27 (1.82-15.27)[d]	24.7	3.94 (1.92-8.07)[d]	2.37 (1.31-4.25)[d]
Any illegal SUD	8.2	12.9	2.15 (1.39-3.32)[d]	12.8	2.41 (1.48-3.91)[d]	27.9	7.76 (3.20-18.78)[d]	26.4	5.35 (2.76-10.36)[d]	1.02 (0.58-1.79)
Any eating disorder[e]	2.5	10.9	3.80 (2.05-7.05)[d]	10.4	3.31 (1.68-6.49)[d]	18.2	6.54 (1.79-23.84)[d]	6.5	2.40 (0.78-7.36)	0.83 (0.41-1.66)
Suicide attempt	1.0	5.8	6.04 (2.56-14.21)[d]	7.2	6.83 (2.82-16.48)[d]	31.5	43.17 (14.17-131.50)[d]	17.3	21.40 (7.76-58.94)[d]	1.17 (0.52-2.60)

Abbreviations: BP-I, bipolar I disorder; BP-II, bipolar II disorder; BPD, bipolar disorder; CI, confidence interval; GAD, generalized anxiety disorder; MDD, major depressive disorder; NOS, not otherwise specified; OCD, obsessive-compulsive disorder; OR, odds ratio; PD, panic disorder; PTSD, posttraumatic stress disorder; SUD, substance use disorder.

[a] Cumulative incidences at the third follow-up.

[b] The ORs are adjusted for age and sex. The control group is the reference group.

[c] The ORs are adjusted for age and sex. The pure MDD group is the reference group.

[d] $P < .05$.

[e] Any eating disorder indicates anorexia nervosa, bulimia nervosa, atypical anorexia nervosa, or atypical bulimia nervosa.

Rates of any SUD, nicotine dependence, and any illegal SUD were elevated among all major spectrum disorders when compared with control respondents. In contrast, pure MDD was associated with neither alcohol abuse nor alcohol dependence, whereas rates were increased for bipolar groups. Rates for alcohol dependence increased from 17.9% in subthreshold BPD to 24.7% in BP-I and decreased to 9.9% in respondents with pure MDD and 9.3% in control respondents. Among the minor spectrum, the strongest comorbidity with SUDs was revealed for subthreshold minor BPD, which was associated with all SUD categories. Compared with the pure depression groups, the respective groups with subthreshold hypomania showed an increased risk for any of the analyzed SUDs except for any illegal SUD.

While associations with eating disorders were found only for major affective disorders, associations with suicide attempts were demonstrated for the major and minor spectrum. The highest rate was in respondents with BP-II (31.5%) as compared with control respondents (1.0%).

MENTAL DISORDERS IN FAMILIES OF INDIVIDUALS WITH AFFECTIVE SYNDROMES AND DISORDERS

With the exception of minor BPD, respondents from all groups had a family history of depression more frequently than control respondents. Increased rates for parental mania, however, were exclusively observed for affective groups with a manic component (**Table 6** and **Table 7**). Rates for parental subthreshold and threshold mania were highest among respondents with BP-II (20.4% and 8.1%, respectively) and BP-I (20.0% and 14.4%, respectively) but were also increased in respondents with subthreshold BPD (9.1% and 5.9%, respectively) as compared with control respondents (4.4% and 2.5%, respec-

Table 5. Comorbidity of Minor Affective Syndromes and Disorders With Other Mental Disorders[a]

Other Mental Disorder	Control, Weighted % (n=1273)	Pure Mild Depression[b] (n=171) Weighted %	Pure Mild Depression[b] (n=171) OR (95% CI)[c]	Subthreshold Minor BPD[b] (n=125) Weighted %	Subthreshold Minor BPD[b] (n=125) OR (95% CI)[c]	Minor BPD[b] (n=55) Weighted %	Minor BPD[b] (n=55) OR (95% CI)[c]	Subthreshold Minor BPD vs Pure Mild Depression, OR (95% CI)[d]
Any anxiety disorder	19.6	36.9	2.34 (1.56-3.51)[e]	29.0	1.67 (1.02-2.72)[e]	29.7	1.48 (0.76-2.87)	0.71 (0.40-1.24)
PD with or without agoraphobia	1.7	5.8	3.14 (1.28-7.67)[e]	1.1	0.61 (0.12-2.94)	6.0	3.27 (0.83-12.86)	0.19 (0.03-0.98)[e]
Agoraphobia without PD	1.5	3.5	2.08 (0.61-7.03)	2.7	1.70 (0.46-6.13)	8.0	4.69 (1.47-14.89)[e]	0.82 (0.16-4.04)
Social phobia	2.8	8.9	3.26 (1.60-6.63)[e]	4.5	1.62 (0.59-4.38)	4.3	1.36 (0.32-5.70)	0.50 (0.16-1.51)
Any specific phobia	8.9	18.3	2.23 (1.34-3.69)[e]	10.9	1.24 (0.64-2.37)	8.7	0.82 (0.31-2.16)	0.55 (0.26-1.14)
Phobia NOS	6.8	10.9	1.66 (0.92-3.00)	11.4	1.77 (0.88-3.55)	12.9	1.74 (0.64-4.68)	1.03 (0.44-2.38)
GAD	1.1	4.8	4.08 (1.42-11.66)[e]	3.9	3.54 (0.90-13.79)	4.3	3.61 (0.83-15.55)	0.90 (0.19-4.15)
OCD	0.4	2.4	6.32 (1.54-25.87)[e]	3.0	8.35 (1.79-38.75)[e]	1.9	4.64 (0.58-36.80)	1.35 (0.22-8.17)
PTSD	1.0	6.2	6.26 (2.32-16.89)[e]	3.4	3.59 (1.10-11.65)[e]	3.5	3.07 (0.56-16.73)	0.58 (0.15-2.14)
Any SUD	41.7	43.1	1.14 (0.78-1.65)	61.7	2.40 (1.55-3.71)[e]	62.9	2.89 (1.55-5.38)[e]	2.09 (1.22-3.57)[e]
Nicotine dependence	21.3	27.0	1.38 (0.91-2.09)	39.3	2.41 (1.56-3.71)[e]	38.2	2.40 (1.26-4.53)[e]	1.77 (1.01-3.09)[e]
Alcohol abuse	24.8	21.1	0.88 (0.55-1.38)	38.5	2.12 (1.34-3.37)[e]	26.3	1.42 (0.69-2.90)	2.42 (1.31-4.44)[e]
Alcohol dependence	9.3	8.4	0.98 (0.48-1.99)	20.2	2.79 (1.57-4.93)[e]	13.5	2.16 (0.85-5.46)	2.78 (1.22-6.35)[e]
Any illegal SUD	8.2	13.9	2.18 (1.28-3.72)[e]	21.9	3.68 (2.14-6.32)[e]	11.8	1.91 (0.78-4.62)	1.66 (0.84-3.29)
Any eating disorder[f]	2.5	3.2	1.11 (0.41-3.03)	4.0	1.50 (0.46-4.82)	1.9	0.60 (0.07-4.62)	1.28 (0.31-5.20)
Suicide attempt	1.0	5.3	5.83 (2.17-15.63)[e]	4.7	5.00 (1.45-17.24)[e]	2.2	2.21 (0.25-19.55)	0.86 (0.23-3.12)

Abbreviations: BPD, bipolar disorder; CI, confidence interval; GAD, generalized anxiety disorder; NOS, not otherwise specified; OCD, obsessive-compulsive disorder; OR, odds ratio; PD, panic disorder; PTSD, posttraumatic stress disorder; SUD, substance use disorder.

[a] Cumulative incidences at the third follow-up.

[b] Pure mild depression indicates dysthymia, minor depression, or recurrent brief depression. Subthreshold minor BPD indicates dysthymia, minor depression, or recurrent brief depression with subthreshold hypomania. Minor BPD indicates hypomania with or without dysthymia, minor depression, or recurrent brief depression.

[c] The ORs are adjusted for age and sex. The control group is the reference group.

[d] The ORs are adjusted for age and sex. The pure mild depression group is the reference group.

[e] $P<.05$.

[f] Any eating disorder indicates anorexia nervosa, bulimia nervosa, atypical anorexia nervosa, or atypical bulimia nervosa.

tively). When compared with the respective pure depression groups, significant differences were found for those with subthreshold BPD (subthreshold mania: OR=2.22; 95% CI, 1.10-4.65; threshold mania: OR=3.08; 95% CI, 1.09-8.68) and subthreshold minor BPD (subthreshold mania: OR=3.02; 95% CI, 1.21-7.47).

Parental anxiety disorders and AUDs were associated with the entire major spectrum. For the minor spectrum, associations were observed for pure mild depression and subthreshold minor BPD.

PERSONALITY TRAITS AMONG INDIVIDUALS WITH AFFECTIVE SYNDROMES AND DISORDERS

Scores for novelty seeking increased with higher levels of manic features (**Table 8**) (minor spectrum: pure mild depression: mean score, 16.2; subthreshold minor BPD: mean score, 16.6; minor BPD: mean score, 17.1; further results for the minor spectrum are available on request). Compared with control respondents, higher scores were shown for respondents with subthreshold BPD (OR=1.30; 95% CI, 1.07-1.58) and BP-I (OR=1.41; 95% CI, 1.07-1.87). Scores for reward dependence also increased with a growing manic component, whereas those for harm avoidance decreased toward bipolarity. Associations were revealed for preponderantly depressed groups (pure MDD, subthreshold BPD, and pure mild depression).

Comparing groups with pure depression and groups with subthreshold hypomania, respondents with subthreshold minor BPD reported being less harm avoidant than the mildly depressed group (OR=0.69; 95% CI, 0.51-0.94).

COMMENT

Against the background of indications that MDD might be overdiagnosed at the expense of BPD, the aims of our investigation were to identify and examine a subgroup of subthreshold BPD among cases with threshold *DSM-IV* MDD regarding a range of validators for bipolarity and to explore patterns of these validators across various affective spectrum conditions. Using prospective longitudinal community data from a large sample of 2210 subjects, we replicated and extended the preliminary results of a smaller study.[14]

Five main results support the heterogeneity of MDD and the current underestimation of bipolar phenomena. First and most importantly, family data demonstrated increased rates of parental mania among respondents with subthreshold bipolarity but not among those with pure MDD. Explorative analyses of minor affective spectrum conditions confirmed these findings by revealing similar associations. Second, respondents with subthreshold hypomania in the major and minor affective spectrum had essentially higher rates of nicotine dependence and AUDs compared with the pure depression groups. Contrarily, among respondents with pure depression, the rates for AUDs were within the range of those observed

Table 6. Mental Disorders in Families of Individuals With Major Affective Disorders[a]

DSM-IV Mental Disorder Among Parents	Control, Weighted % (n=1273)	MDD: Pure MDD (n=286) Weighted %	MDD: Pure MDD (n=286) OR (95% CI)[b]	MDD: Subthreshold BPD (n=202) Weighted %	MDD: Subthreshold BPD (n=202) OR (95% CI)[b]	BP-II (n=33) Weighted %	BP-II (n=33) OR (95% CI)[b]	BP-I (n=65) Weighted %	BP-I (n=65) OR (95% CI)[b]	Subthreshold BPD vs Pure MDD, OR (95% CI)[c]
Depression										
Subthreshold	46.1	68.8	2.54 (1.85-3.42)[d]	76.5	3.70 (2.53-5.42)[d]	78.0	3.99 (1.54-10.30)[d]	77.2	3.91 (2.01-7.57)[d]	1.46 (0.93-2.30)
Threshold	22.0	41.0	2.50 (1.83-3.40)[d]	46.5	3.04 (2.14-4.30)[d]	52.9	3.73 (1.66-8.36)[d]	63.5	6.41 (3.52-11.65)[d]	1.23 (0.81-1.84)
Mania										
Subthreshold	4.4	4.3	1.02 (0.53-1.96)	9.1	2.31 (1.30-4.10)[d]	20.4	5.89 (2.42-14.27)[d]	20.0	5.60 (2.70-11.57)[d]	2.22 (1.10-4.65)[d]
Threshold	2.5	1.9	0.76 (0.28-1.99)	5.9	2.36 (1.14-4.87)[d]	8.1	3.41 (0.99-11.63)	14.4	6.44 (2.69-15.37)[d]	3.08 (1.09-8.68)[d]
Any anxiety disorder										
Subthreshold	36.7	55.3	2.38 (1.75-3.22)[d]	58.8	2.62 (1.84-3.73)[d]	67.3	3.72 (1.58-8.71)[d]	77.5	6.70 (3.33-13.45)[d]	1.11 (0.73-1.69)
Threshold	17.3	31.7	2.38 (1.72-3.29)[d]	40.9	3.41 (2.38-4.87)[d]	47.3	4.25 (1.89-9.51)[d]	47.4	4.75 (2.60-8.65)[d]	1.44 (0.95-2.19)
Any alcohol use disorder										
Subthreshold	28.0	39.7	1.68 (1.24-2.27)[d]	47.7	2.31 (1.63-3.26)[d]	62.5	4.00 (1.79-8.94)[d]	49.8	2.63 (1.47-4.69)[d]	1.34 (0.89-2.02)
Threshold	12.9	21.1	1.74 (1.20-2.51)[d]	27.8	2.55 (1.72-3.77)[d]	34.7	3.56 (1.58-8.00)[d]	27.6	2.58 (1.36-4.88)[d]	1.37 (0.84-2.22)

Abbreviations: BP-I, bipolar I disorder; BP-II, bipolar II disorder; BPD, bipolar disorder; CI, confidence interval; MDD, major depressive disorder; OR, odds ratio.
[a] Cumulative incidences at the third follow-up.
[b] The ORs are adjusted for age and sex. The control group is the reference group.
[c] The ORs are adjusted for age and sex. The pure MDD group is the reference group.
[d] $P < .05$.

Table 7. Mental Disorders in Families of Individuals With Minor Affective Syndromes and Disorders[a]

DSM-IV Mental Disorder Among Parents	Control, Weighted % (n=1273)	Pure Mild Depression[b] (n=171) Weighted %	Pure Mild Depression[b] (n=171) OR (95% CI)[c]	Subthreshold Minor BPD[b] (n=125) Weighted %	Subthreshold Minor BPD[b] (n=125) OR (95% CI)[c]	Minor BPD[b] (n=55) Weighted %	Minor BPD[b] (n=55) OR (95% CI)[c]	Subthreshold Minor BPD vs Pure Mild Depression, OR (95% CI)[d]
Depression								
Subthreshold	46.1	65.8	2.22 (1.53-3.21)[e]	73.4	3.22 (2.00-5.16)[e]	54.5	1.38 (0.74-2.55)	1.43 (0.80-2.54)
Threshold	22.0	30.0	1.56 (1.04-2.33)[e]	35.9	2.04 (1.32-3.14)[e]	31.6	1.58 (0.79-3.12)	1.28 (0.73-2.21)
Mania								
Subthreshold	4.4	5.4	1.27 (0.58-2.76)	14.6	3.81 (2.02-7.18)[e]	10.8	2.72 (1.02-7.20)[e]	3.02 (1.21-7.47)[e]
Threshold	2.5	3.1	1.22 (0.43-3.46)	5.7	2.34 (0.92-5.95)	4.8	1.90 (0.52-6.94)	1.82 (0.51-6.43)
Any anxiety disorder								
Subthreshold	36.7	46.6	1.66 (1.14-2.40)[e]	63.1	3.19 (2.04-4.98)[e]	47.1	1.53 (0.81-2.90)	1.92 (1.12-3.30)[e]
Threshold	17.3	21.8	1.42 (0.91-2.20)	29.2	2.09 (1.32-3.28)[e]	24.2	1.48 (0.69-3.17)	1.44 (0.80-2.60)
Any alcohol use disorder								
Subthreshold	28.0	36.2	1.48 (1.01-2.17)[e]	42.7	1.95 (1.27-2.97)[e]	26.8	0.90 (0.47-1.72)	1.28 (0.75-2.17)
Threshold	12.9	21.1	1.80 (1.12-2.87)[e]	22.2	1.94 (1.19-3.18)[e]	17.0	1.38 (0.64-2.97)	1.05 (0.56-1.94)

Abbreviations: BPD, bipolar disorder; CI, confidence interval; OR, odds ratio.
[a] Cumulative incidences at the third follow-up.
[b] Pure mild depression indicates dysthymia, minor depression, or recurrent brief depression. Subthreshold minor BPD indicates dysthymia, minor depression, or recurrent brief depression with subthreshold hypomania. Minor BPD indicates hypomania with or without dysthymia, minor depression, or recurrent brief depression.
[c] The ORs are adjusted for age and sex. The control group is the reference group.
[d] The ORs are adjusted for age and sex. The pure mild depression group is the reference group.
[e] $P < .05$.

for control respondents. Third, although pure MDD was associated with panic disorder, the association was substantially stronger among cases with subthreshold BPD. Fourth, the major and minor groups with subthreshold hypomania were more likely to engage in criminal acts than control respondents, whereas rates of criminal acts were not elevated among purely depressed respondents. Finally, prospective analyses revealed that sub-

Table 8. Personality Trait Scores on the Tridimensional Personality Questionnaire Among Individuals With Major Affective Disorders[a]

Personality Trait	Control, Mean (SE) (n=1273)	MDD								Subthreshold BPD vs Pure MDD, OR (95% CI)[c]
		Pure MDD (n=286)		Subthreshold BPD (n=202)		BP-II (n33)		BP-I (n=65)		
		Score, Mean (SE)	OR (95% CI)[b]	Score, Mean (SE)	OR (95% CI)[b]	Score, Mean (SE)	OR (95% CI)[b]	Score, Mean (SE)	OR (95% CI)[b]	
Novelty seeking	16.3 (0.2)	16.4 (0.3)	1.03 (0.89-1.20)	17.5 (0.4)	1.30 (1.07-1.58)[d]	17.9 (1.1)	1.46 (0.88-2.41)	17.9 (0.6)	1.41 (1.07-1.87)[d]	1.18 (0.96-1.46)
Harm avoidance	11.7 (0.2)	14.6 (0.4)	1.57 (1.34-1.84)[d]	14.1 (0.5)	1.38 (1.15-1.65)[d]	14.2 (1.5)	1.33 (0.77-2.28)	12.0 (1.0)	1.02 (0.72-1.46)	0.89 (0.73-1.08)
Reward dependence	17.2 (0.1)	18.2 (0.3)	1.21 (1.02-1.42)[d]	18.9 (0.4)	1.37 (1.12-1.68)[d]	19.0 (0.9)	1.33 (0.83-2.11)	19.2 (0.6)	1.68 (1.20-2.37)[d]	1.11 (0.90-1.39)

Abbreviations: BP-I, bipolar I disorder; BP-II, bipolar II disorder; BPD, bipolar disorder; CI, confidence interval; MDD, major depressive disorder; OR, odds ratio.
[a] Cumulative incidences at the third follow-up.
[b] The ORs are adjusted for age and sex. The control group is the reference group.
[c] The ORs are adjusted for age and sex. The pure MDD group is the reference group.
[d] $P < .05$.

threshold BPD tended to convert more often into any BPD, especially BP-I, than pure MDD. Criterion D (symptoms observable by others) was of critical predictive relevance because it was significantly associated with the subsequent first onset of BPD.

Of the 488 subjects with *DSM-IV* MDD, 286 (58.6%) were found to have pure MDD; 202 (41.4%) had additional subthreshold hypomania symptoms and were reclassified according to the study criteria as having subthreshold BPD. This figure is supported by Benazzi,[43] who found that among 111 depression-remitted outpatients interviewed with the modified Structured Clinical Interview for *DSM* Disorders–Clinician Version, 39.5% of respondents had subsyndromal hypomania.[19] In our study, the observed cumulative incidence of 23.2% for *DSM-IV* MDD would decrease to 13.9% if cases with subthreshold BPD (9.3%) were deducted. Correspondingly, the rate of any BPD would increase to 13.7%, thus being equal to the rate of pure MDD. This is consistent with reports from the Zurich Study showing a lifetime prevalence of 11.0% for softly defined BP-II vs 11.4% for pure MDD[14] and with clinical investigations.[19,44]

In accordance with results from the National Comorbidity Survey Replication reported by Merikangas et al,[8] our data provide further evidence for the underlying dimensional nature of the diagnostic spectrum of BPD as suggested by several investigators.[16,17,44,45] We found that with increasing severity of the manic component, depression and mania onset tended to be earlier, rates of criminal acts and comorbid alcohol dependence continuously increased, and rates of parental depression and mania continuously increased. Conclusive confirmation also comes from analyses on personality traits revealing that the stronger the manic component is, the higher the mean values are for novelty seeking and reward dependence but the lower they are for harm avoidance. The kernel density plot showed a unimodal distribution (no zones of rarity) of episodes of manic symptoms between MDD and BP-I, which strongly supports the dimensional view.[40,41] Consistently, human genetic studies had recently underscored common genetic variations increasing susceptibility for the entire affective spectrum.[46]

Overall, cumulative incidences of 1.4% for BP-II and 3.0% for BP-I from the EDSP study appear to be rather high compared with other European studies[9] or the American National Comorbidity Survey Replication with rates of approximately 1.0% for both BP-I and BP-II. This is most likely owing to the prospective longitudinal design and timing of our study because the first 3 decades of life are a high-incidence phase for bipolar symptoms,[9,10] which could be forgotten later. Nevertheless, rates are comparable to those of a large US national survey of 43 093 subjects with 3.3% for BP-I[7] and to those of the Zurich study with 6.0% for the overall bipolar spectrum and 4.4% for mania.[47] The higher rates for BP-I compared with BP-II in the EDSP study are consistent with findings of studies from Italy and Ireland reporting 12-month prevalence rates of 0.2% and 0.1% for BP-II, respectively, vs 1.3% and 0.3% for BP-I, respectively.[48,49]

Consistent with other studies,[8,50,51] our data show high comorbidity rates for anxiety disorders and BPD, which are as high as those for MDD and considerably higher for BP-I compared with those for MDD. Our findings on SUDs are concordant with results from the Zurich Study[23] documenting that comorbidity of MDD with AUDs became nonsignificant after exclusion of subthreshold BPD. Prospective analyses of the Zurich Study data illustrated that MDD was related to subsequent benzodiazepine abuse or dependence only, whereas manic symptoms below the diagnostic threshold for BPD were powerful predictors for all levels of the substances investigated.[22] Importantly, preliminary analyses of the EDSP study data revealed that subthreshold BPD at baseline predicted the subsequent first onset of an AUD, particularly alcohol dependence during follow-up (OR=4.21; 95% CI, 1.36-12.78; $P=.01$), whereas pure MDD had no predictive value. This suggests that subthreshold bipolarity might increase alcohol problems and contradicts the assumption that it could solely be the consequence of increased alcohol use among depressed individuals.

LIMITATIONS

Several limitations should be considered. First, by using the M-CIDI, even more comprehensive data collection on the bipolar spectrum as proposed in several studies[13,14,17] was not possible. Individuals characterized by overactivity only were found to have a clinical profile similar to that of individuals with bipolarity,[14] and overactivity was shown to be highly sensitive for predicting BP-II diagnosis.[43] Because overactivity is not a stem criterion within the M-CIDI, we may have lost these individuals for our subthreshold BPD group. Second, respondents with episodes shorter than 4 days could not be included even though clinical significance of brief episodes (1-3 days) was shown[14] and a 2-day limit was recommended.[13] Third, no information on cyclothymia, rapid cycling, or mixed episodes was available, although these cases might be covered by our subthreshold definitions. Fourth, good concordance of the CIDI diagnoses with blinded clinical diagnoses based on the Structured Clinical Interview for *DSM* Disorders was reported.[20] Nevertheless, the CIDI–Structured Clinical Interview for *DSM* Disorders concordance was higher for lifetime BP-I than for BP-II and subthreshold BPD.[20] Fifth, estimates of parental psychopathology could be biased by the inclusion of family history information, which might be influenced by respondents' diagnostic status. Additional analyses exclusively based on direct parent interviews supported an association between threshold parental mania and subthreshold BPD but not pure MDD in offspring (OR=15.92; 95% CI, 2.07-122.36; $P=.01$). Sixth, because the median age at onset of the first major depressive episode is earlier in BPD than in MDD,[52] we could have missed pure MDD cases beginning later than the age range of our young sample. Seventh, despite the fairly large sample, prospective analyses were still based on relatively small case numbers.

Despite these limitations, our data support that subthreshold BPD is common and appears to be sufficiently distinct from pure MDD to deserve separate attention. Because our current diagnostic manuals do not provide specific guidance and criteria to identify subthreshold bipolar cases, there is reason for concern regarding at least 2 domains. First, with respect to basic research, underdiagnosing BPDs could decrease the power to detect causal components. Within molecular genetic studies, correct phenotyping and identification of homogeneous disorder subtypes are essential. Second, consequences with respect to treatment should be considered: National Comorbidity Survey Replication data indicate that with a decreasing manic component, the proportion of individuals getting the appropriate medication (combination of antidepressants and antimanic agents) declines.[8] This matters because beyond the burden of MDD,[6,53,54] a range of additional significant impairments for subthreshold BPD comparable to those of full-threshold BPD[9,10,22,24-26] should be recognized as, for example, higher rates for suicide attempts, comorbid obsessive-compulsive disorder and SUD, or an earlier onset of disorders.[9,14,27,55] We also broadly found the same differences for subthreshold BPD, with significantly increased problems related to nicotine and alcohol use, markedly elevated rates for comorbid panic disorder, and a more pronounced tendency to behave illegally when compared with individuals with pure MDD. Taking episodes with depressive and manic features together, respondents with subthreshold BPD as compared with those who are purely depressed had an earlier onset of their disorder (median, 17 vs 18 years, respectively) and had more episodes (median, 5 vs 2 episodes, respectively), which might cause additional stress.

Our findings could be relevant with regard to the upcoming *DSM-V*. They indicate a need to broaden the concept of bipolarity in the current *DSM-IV* criteria by introducing a specifier for bipolarity into the MDD concept or by softening some criteria for hypomania and to adapt the *DSM*-based instruments. Identifying the true threshold separating MDD from BPD is difficult as there is strong evidence for a bipolar spectrum, with hypomania as a continuous factor between MDD and BP-II. Therefore, the splitting of BP-II and MDD based on hypomania has been questioned.[40] However, categories are useful for clinical practice in identifying cases and matching the right patient with the right treatment. Regarding our definition of subthreshold BPD, this study might add information to determine an adequate threshold for bipolarity, which is currently too strict. At a later stage this threshold could be refined by genetic information and biomarkers.[56] Furthermore, our prospective data along with those of other studies[57,58] identified putative indicators (eg, symptoms observable by others, early onset, mood liability) for an increased risk of conversion from MDD to BPD, which could be valuable for clinicians to apply the appropriate treatment early.

CONCLUSIONS

This study might be seen as additional evidence that MDD is a heterogeneous phenotype that is overdiagnosed at the expense of BPD. A broadening of the concept of bipolarity and a more comprehensive screening of bipolarity might be substantial not only for future research but also for providing adequate treatment to patients with a serious mental disorder characterized by a considerably increased risk of a chronic course with a debilitating decrease in functioning. Considering that the disorder frequently starts in adolescence, a critical developmental stage, early identification and treatment are highly important.

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