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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In the small prospective Zurich Study, 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 Akiskal19 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 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 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, 59.3%) and living arrangements (at the third follow-up: living with parents, 13.6%; living with partner or spouse, 43.7%).

### 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 antiso- 
cial personality disorder item: “At an age of older than 15, have you ever been 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%).33,36 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.19,37,38 Second, a modified version of the Fam- 
ily History Research Diagnostic Criteria37 was applied to obtain family history information from respondents. At baseline, M- 
CIDI stem questions for DSM-IV diagnoses were used and re- 
spondents 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 specific- 
ity (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 dis- order 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 Cloninger39 con- taining 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. Be- cause only 0.1% of the total sample reported (hypo)manic epi- sodes, and 1.8% of the total sample reported depressive episodes 2 weeks before the third follow-up, an influence on the Tridi- mensional Personality Questionnaire assessment should have been marginal. The Tridimensional Personality Questionnaire has good validity and good test-retest reliability.39,40

**STATISTICAL ANALYSES**

Cumulative incidences were calculated by aggregating all di- agnostic 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 stan- 
dardized continuous variables (disorder characteristics, per- sonality traits) to allow comparisons regardless of measurement units. We did not adjust for multiple testing because we con- sidered specific categories of the affective spectrum to be re- 
lated 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 spec- trum (MDD to BP-I) was calculated. Following several stud- ies,17,41 a cluster of at least 2 manic symptoms of DSM-IV cri- teria 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 sepa- 
rated by natural boundaries; a unimodal distribution would in- 
dicate a dimensional nature of (hypo)mania.42,43

Data were weighted by age, sex, geographic location, and non- 
contact or nonresponse at baseline to account for the different sampling probabilities and to adjust the distribution to the origi- 
nal sampling frame.30 Analyses were carried out with Stata ver- 
sion 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 spec- trum, 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 mi- nor 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 be- 
tween 16.4% and 29.4% as compared with 10.8% of control re- 
spondents (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

<table>
<thead>
<tr>
<th>Syndrome or Disorder</th>
<th>Total (N=2210)</th>
<th>Women (n=1075)</th>
<th>Men (n=1135)</th>
<th>Women vs Men, OR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major affective spectrum</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure MDD</td>
<td>286 (13.9)</td>
<td>157 (16.1)</td>
<td>129 (11.6)</td>
<td>1.74 (1.30-2.33)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Subthreshold BPD</td>
<td>202 (9.3)</td>
<td>135 (12.4)</td>
<td>67 (6.1)</td>
<td>2.55 (1.80-3.62)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>BP-II</td>
<td>33 (1.4)</td>
<td>22 (2.0)</td>
<td>11 (0.7)</td>
<td>3.47 (1.57-7.65)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>BP-I</td>
<td>65 (3.0)</td>
<td>32 (3.0)</td>
<td>33 (3.0)</td>
<td>1.25 (0.71-2.19)</td>
</tr>
<tr>
<td><strong>Minor affective spectrum</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pure mild depression</td>
<td>171 (8.4)</td>
<td>85 (8.6)</td>
<td>86 (8.1)</td>
<td>1.35 (0.94-1.94)</td>
</tr>
<tr>
<td>Subthreshold minor BPD</td>
<td>125 (5.5)</td>
<td>58 (5.2)</td>
<td>67 (5.8)</td>
<td>1.14 (0.75-1.72)</td>
</tr>
<tr>
<td>Minor BPD</td>
<td>55 (2.5)</td>
<td>34 (3.1)</td>
<td>21 (2.0)</td>
<td>1.92 (1.04-3.54)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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.

<sup>a</sup> Reference group.
<sup>b</sup> The ORs are adjusted for age.
<sup>c</sup> Pure MDD indicates MDD without any (hypo)manic features. Subthreshold BPD indicates MDD with subthreshold hypomania.
<sup>d</sup> P<.05.
<sup>e</sup> 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.

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Table 2. Associations Between Sociodemographic Factors and Major Affective Disorders<sup>a</sup>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control, Weighted % (n=1273)</th>
<th>Pure MDD (n=286)</th>
<th>Subthreshold BPD (n=202)</th>
<th>BP-II (n=33)</th>
<th>BP-I (n=65)</th>
<th>Subthreshold BPD vs Pure MDD, OR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Educational level</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td>Hauptschule&lt;sup&gt;e&lt;/sup&gt;</td>
<td>9.9</td>
<td>10.3</td>
<td>7.7</td>
<td>18.6</td>
<td>10.2</td>
<td>1</td>
</tr>
<tr>
<td>No degree</td>
<td>0.5</td>
<td>1.1</td>
<td>0.8</td>
<td>1.8</td>
<td>1.96 (0.95-4.03)</td>
<td></td>
</tr>
<tr>
<td>Realschule or Fachschule&lt;sup&gt;g&lt;/sup&gt;</td>
<td>19.9</td>
<td>23.5</td>
<td>10.7 (0.61-1.84)</td>
<td>30.4</td>
<td>1.80 (0.95-3.39)</td>
<td>15.5</td>
</tr>
<tr>
<td>Gymnasium</td>
<td>69.8</td>
<td>65.1</td>
<td>0.89 (0.54-1.45)</td>
<td>61.2</td>
<td>1.11 (0.62-1.99)</td>
<td>64.1</td>
</tr>
<tr>
<td><strong>Social class</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Low</td>
<td>10.8</td>
<td>16.4</td>
<td>1</td>
<td>Reference</td>
<td>26.2</td>
<td>1</td>
</tr>
<tr>
<td>Middle</td>
<td>60.4</td>
<td>60.1</td>
<td>0.65 (0.42-0.98)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>54.6</td>
<td>0.65 (0.39-1.06)</td>
<td>41.3</td>
</tr>
<tr>
<td>Upper</td>
<td>28.9</td>
<td>23.5</td>
<td>0.54 (0.33-0.88)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>30.1</td>
<td>0.80 (0.46-1.40)</td>
<td>32.5</td>
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<tr>
<td><strong>Financial situation</strong></td>
<td></td>
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<tr>
<td>Low</td>
<td>7.4</td>
<td>14.1</td>
<td>1</td>
<td>Reference</td>
<td>12.3</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>27.7</td>
<td>30.8</td>
<td>0.60 (0.36-0.98)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>33.6</td>
<td>0.77 (0.42-1.37)</td>
<td>32.6</td>
</tr>
<tr>
<td>High</td>
<td>53.6</td>
<td>47.0</td>
<td>0.45 (0.28-0.72)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>43.5</td>
<td>0.49 (0.28-0.86)</td>
<td>43.3</td>
</tr>
<tr>
<td>Very high</td>
<td>11.3</td>
<td>8.0</td>
<td>0.40 (0.21-0.76)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>10.6</td>
<td>0.65 (0.31-1.33)</td>
<td>7.9</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
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<tr>
<td>Married&lt;sup&gt;e&lt;/sup&gt;</td>
<td>22.8</td>
<td>21.3</td>
<td>1</td>
<td>Reference</td>
<td>23.5</td>
<td>1</td>
</tr>
<tr>
<td>Separated, divorced, or widowed</td>
<td>2.4</td>
<td>3.8</td>
<td>1.81 (0.69-4.68)</td>
<td>8.3</td>
<td>3.65 (1.46-9.11)</td>
<td>0.0</td>
</tr>
<tr>
<td>Unmarried</td>
<td>74.9</td>
<td>74.9</td>
<td>1.46 (0.95-2.34)</td>
<td>68.2</td>
<td>1.09 (0.68-1.75)</td>
<td>79.7</td>
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<tr>
<td>Criminal acts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No&lt;sup&gt;e&lt;/sup&gt;</td>
<td>81.8</td>
<td>81.1</td>
<td>1</td>
<td>Reference</td>
<td>74.9</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>18.2</td>
<td>18.9</td>
<td>1.21 (0.81-1.81)</td>
<td>25.1</td>
<td>2.10 (1.41-3.13)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>29.4</td>
</tr>
</tbody>
</table>

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.

<sup>a</sup>Cumulative incidences at the third follow-up.
<sup>b</sup>The ORs are adjusted for age and sex. The control group is the reference group.
<sup>c</sup>The ORs are adjusted for age and sex. The pure MDD group is the reference group.
<sup>d</sup>Hauptschule is secondary general school; Realschule or Fachschule, intermediate secondary school; and Gymnasium, grammar school.
<sup>e</sup>Reference group.
<sup>f</sup>P<.05.

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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; \( P = .02 \)).

**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).

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**Table 3. Disorder Characteristics of Major Affective Disorders**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MDD</th>
<th>Subthreshold BPD</th>
<th>BP-II</th>
<th>BP-I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pure MDD(b) ((n=268))</td>
<td>Subthreshold BPD ((n=202))</td>
<td>BP-II ((n=33))</td>
<td>BP-I ((n=65))</td>
</tr>
<tr>
<td>Depressive features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes, No.</td>
<td>2 (1-5)</td>
<td>2 (1-5)</td>
<td>2 (1-7)</td>
<td>3 (2-8)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>18 (15-21)</td>
<td>17 (14-20)</td>
<td>16 (12-19)</td>
<td>16 (14-19)</td>
</tr>
<tr>
<td>Manic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes, No.</td>
<td>NA</td>
<td>3 (1-10)</td>
<td>8 (1-20)</td>
<td>8 (3-20)</td>
</tr>
<tr>
<td>Age at onset, y</td>
<td>NA</td>
<td>16 (13-19)</td>
<td>16 (12-18)</td>
<td>15 (13-17)</td>
</tr>
</tbody>
</table>

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 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 major 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%).

**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%, respectively).
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 (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).

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).

### Table 5. Comorbidity of Minor Affective Syndromes and Disorders With Other Mental Disorders

<table>
<thead>
<tr>
<th>Other Mental Disorder</th>
<th>Control, Weighted % (n=1273)</th>
<th>Pure Mild Depressionb (n=171)</th>
<th>Subthreshold Minor BPDb (n=125)</th>
<th>Minor BPDb (n=55)</th>
<th>Subthreshold Minor BPD vs Pure Mild Depression, OR (95% CI)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any anxiety disorder</td>
<td>19.6</td>
<td>36.9</td>
<td>2.34 (1.56-3.51)</td>
<td>29.0</td>
<td>1.67 (1.02-2.72)</td>
</tr>
<tr>
<td>PD with or without agoraphobia</td>
<td>1.7</td>
<td>5.8</td>
<td>3.14 (1.28-7.67)</td>
<td>1.1</td>
<td>0.61 (0.12-2.94)</td>
</tr>
<tr>
<td>Agoraphobia without PD</td>
<td>1.5</td>
<td>3.5</td>
<td>2.08 (0.61-7.03)</td>
<td>2.7</td>
<td>1.70 (0.46-6.13)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>2.8</td>
<td>8.9</td>
<td>3.26 (1.60-6.63)</td>
<td>4.5</td>
<td>1.62 (0.59-4.38)</td>
</tr>
<tr>
<td>Any specific phobia</td>
<td>8.9</td>
<td>18.3</td>
<td>2.23 (1.34-3.69)</td>
<td>10.9</td>
<td>1.24 (0.64-2.37)</td>
</tr>
<tr>
<td>Phobia NOS</td>
<td>6.8</td>
<td>10.9</td>
<td>1.66 (0.92-2.30)</td>
<td>11.4</td>
<td>1.77 (0.88-3.55)</td>
</tr>
<tr>
<td>GAD</td>
<td>1.1</td>
<td>4.8</td>
<td>4.08 (1.42-11.66)</td>
<td>3.9</td>
<td>3.54 (0.90-13.79)</td>
</tr>
<tr>
<td>OCD</td>
<td>0.4</td>
<td>2.4</td>
<td>6.32 (1.54-25.87)</td>
<td>3.0</td>
<td>8.35 (1.79-38.75)</td>
</tr>
<tr>
<td>PTSD</td>
<td>1.0</td>
<td>6.2</td>
<td>6.26 (2.32-16.89)</td>
<td>3.4</td>
<td>3.59 (1.10-11.65)</td>
</tr>
<tr>
<td>Any SUD</td>
<td>41.7</td>
<td>43.1</td>
<td>1.14 (0.78-1.65)</td>
<td>61.7</td>
<td>2.40 (1.55-3.71)</td>
</tr>
<tr>
<td>Nicotine dependence</td>
<td>21.3</td>
<td>27.0</td>
<td>1.38 (0.91-2.09)</td>
<td>39.3</td>
<td>2.41 (1.56-3.71)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>24.8</td>
<td>21.1</td>
<td>0.88 (0.55-1.38)</td>
<td>38.5</td>
<td>2.12 (1.34-3.37)</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>9.3</td>
<td>8.4</td>
<td>0.98 (0.48-1.99)</td>
<td>20.2</td>
<td>2.79 (1.57-4.93)</td>
</tr>
<tr>
<td>Any illegal SUD</td>
<td>8.2</td>
<td>13.9</td>
<td>2.18 (1.29-3.72)</td>
<td>21.9</td>
<td>3.68 (2.14-6.32)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>2.5</td>
<td>3.2</td>
<td>1.11 (0.41-3.03)</td>
<td>4.0</td>
<td>1.50 (0.46-4.82)</td>
</tr>
</tbody>
</table>

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.

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### 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.
Fourth, the major and minor groups with subthreshold BPD were substantially stronger among cases with subthreshold BPD. For control respondents, the association was sub-stantially stronger among cases with subthreshold MDD. Although pure MDD was associated with panic disorder, the association was sub-stantially 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-
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-remitting outpatients interviewed with the modified Structured Clinical Interview for DSM Disorders—Clinician Version, 39.5% of respondents had subsyndromal hypomania.49 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 approximately 1% 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-I7 and to those of the Zurich study with 6.0% for the entire 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,8,9,50,51 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.

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

<table>
<thead>
<tr>
<th>Personality Trait</th>
<th>MDD</th>
<th>Pure MDD</th>
<th>Subthreshold BPD</th>
<th>BP-II</th>
<th>BP-I</th>
<th>Subthreshold BPD vs Pure MDD, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control, ME (n=1273)</td>
<td>Score, ME (95% CI)</td>
<td>Score, ME (95% CI)</td>
<td>Score, ME (95% CI)</td>
<td>Score, ME (95% CI)</td>
<td>Score, ME (95% CI)</td>
</tr>
<tr>
<td>Novelty seeking</td>
<td>16.3 (0.2)</td>
<td>16.4 (0.3)</td>
<td>1.03 (0.89-1.20)</td>
<td>17.5 (0.4)</td>
<td>1.30 (1.07-1.58)</td>
<td>17.9 (1.1)</td>
</tr>
<tr>
<td>Harm avoidance</td>
<td>11.7 (0.2)</td>
<td>14.6 (0.4)</td>
<td>1.57 (1.34-1.84)</td>
<td>14.1 (0.5)</td>
<td>1.38 (1.15-1.65)</td>
<td>14.2 (1.5)</td>
</tr>
<tr>
<td>Reward dependence</td>
<td>17.2 (0.1)</td>
<td>18.2 (0.3)</td>
<td>1.21 (1.02-1.42)</td>
<td>18.9 (0.4)</td>
<td>1.37 (1.12-1.68)</td>
<td>19.0 (0.9)</td>
</tr>
</tbody>
</table>

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.
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\(^\text{13,14,17}\) was not possible. Individuals characterized by overactivity only were found to have a clinical profile similar to that of individuals with bipolarity,\(^\text{14}\) and overactivity was shown to be highly sensitive for predicting BP-II diagnosis.\(^\text{15}\) 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\(^\text{14}\) and a 2-day limit was recommended.\(^\text{13}\) 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.\(^\text{20}\) Nevertheless, the CIDI–Structured Clinical Interview for DSM Disorders concordance was higher for lifetime BP-I than for BP-II and subthreshold BPD.\(^\text{25}\) 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,\(^\text{52}\) 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.\(^\text{8}\) This matters because beyond the burden of MDD,\(^\text{6,33,35}\) a range of additional significant impairments for subthreshold BPD comparable to those of full-threshold BPD\(^\text{20,22,24,26}\) should be recognized as, for example, higher rates for suicide attempts, comorbid obsessive-compulsive disorder and SUD, or an earlier onset of disorders.\(^\text{9,14,27,35}\) 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.\(^\text{40}\) 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.\(^\text{56}\) Furthermore, our prospective data along with those of other studies\(^\text{27,38}\) 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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Author Contributions: Drs Zimmermann, Lieb, and Wittchen take responsibility for the integrity of the data. All of the authors had full access to all of the data in the study and take responsibility for the accuracy of the data analysis.

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Lilly and Company, Novartis, Pfizer, and Schering-Plough, has served as a consultant to Eli Lilly and Company, GlaxoSmithKline, Hoffmann-La Roche, Novartis, Pfizer, and Wyeth, and has served on the speakers’ bureau for Novartis, Schering-Plough, Pfizer, and Wyeth. Dr Holzboer is founder and shareholder of Afectis Pharmaceuticals AG and is the owner of several patents related to depression. Dr Angst has served on the advisory board for Eli Lilly and Company, Janssen-Cilag, Lundbeck, and Sanofi-Aventis and has served on the speakers’ bureau for Eli Lilly and Company and AstraZeneca.

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