The Identification and Validation of Distinct Depressive Syndromes in a Population-Based Sample of Female Twins

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Background: Depression, a clinically heterogeneous syndrome, may also be etiologically heterogeneous. Using a prospective, epidemiologic, and genetically informative sample of adult female twins, we identify and validate a typology of depressive syndromes.

Methods: Latent class analysis was applied to 14 disaggregated DSM-III-R symptoms for major depression reported over the last year by members of 1029 female-female twin pairs.

Results: Seven classes were identified, of which 3 represented clinically significant depressive syndromes: (1) mild typical depression, (2) atypical depression, and (3) severe typical depression. Severe typical depression was characterized by comorbid anxiety and panic, long episodes, impairment, and help seeking. Atypical depression was similar in severity to mild typical depression, but was characterized by increased eating, hypersomnia, frequent, relatively short episodes, and a proclivity to obesity. Individuals with recurrent episodes tended to have the same syndrome on each occasion. The members of twin pairs concordant for depression had the same depressive syndrome more often than expected by chance and this resemblance was greater in monozygotic than in dizygotic pairs.

Conclusion: In an epidemiologic sample of female twins, depression is not etiologically homogeneous, but is instead made up of several syndromes that are at least partially distinct from a clinical, longitudinal, and familial/genetic perspective.

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Despite decades of research, it is still uncertain whether depression is a homogeneous clinical syndrome and, if not, whether it is possible to identify meaningful and valid subtypes. From a methodologic perspective, typologic studies of depression can be characterized in 4 ways. First, a wide array of the statistical methods have been used including factor analysis, discriminant function analysis, cluster analysis, grade of membership analysis, latent trait analysis, and latent class analysis. Second, samples have been ascertained in varying settings, including psychiatric hospitals, outpatient clinics, primary care practices, and the general population. Third, different assessment tools have been used including self-report checklists, clinician-completed rating scales, and structured psychiatric interviews. Fourth, efforts to validate the proposed typology have varied widely, from the examination of treatment response, relapse rate, pattern of psychiatric illness in relatives to replication in a second sample.

A small proportion of individuals affected with major depression (MD) are in specialist care, and of these, few are hospitalized. Those seen in psychiatric treatment settings are not a random sample of those affected in the population, as they are more severely affected and more likely to demonstrate certain symptoms such as suicidal ideation. Therefore, a "natural" typology of depressive syndromes may more likely emerge from epidemiologic samples.

In this study, we examine a typology of depression based on an LCA of all depressive symptoms from the DSM-III-R criteria for MD as they occurred over the last year in a large sample of female twins from a population-based registry. We then attempt to empirically validate this typology.

See Methods on next page
METHODS
SAMPLE AND ASSESSMENT METHODS

Data for the LCA analysis were collected from 2163 white female same-sex twins ascertained through a population-based twin registry in the state of Virginia.25 Zygosity diagnoses were based on a series of standard questions, photographs, and in cases of uncertainty, DNA polymorphisms. In this report, we examine twins from the 1029 pairs of known zygosity (589 monozygotic [MZ] and 440 dizygotic [DZ]) where both twins had been personally interviewed and had responded to all symptom questions. The mean (±SD) age of this sample at initial interview was 30.1±7.5 years.

Information was collected from respondents on the occurrence during the year prior to interview of 20 individual symptoms. Fourteen of these symptoms were the disaggregated 9 “A Criteria” for MD in DSM-III-R26 (Table 1) and were used in the latent class analysis. Six of the 9 criteria were represented by a single item. Two criteria were disaggregated into 2 items: criterion A4, insomnia and hypervigilance and criterion A5, psychomotor retardation and agitation. One criterion, A2, was disaggregated into 4 items: decreased appetite, increased appetite, decreased weight, and increased weight. The 6 remaining items reflected hopelessness, irritability, and the cognitive and somatic aspects of generalized anxiety and panic.

Symptoms were required to have a duration of at least 5 days. For each symptom that was reported as present, interviewers probed to determine if it was due to physical illness or medication. If this was the case, which occurred an average of 17.4% of the time across all symptoms, then the symptom was considered not present.

If only 1 symptom was reported, that single symptom was analyzed. If 2 or more symptoms were reported, the respondent was asked whether any of the symptoms co-occurred. If no, then the single more severe symptom determined by the twin was analyzed. If 2 or more symptoms co-occurred, this defined a syndrome. If only 1 syndrome was present in the last year, then this was analyzed. If 2 or more syndromes were present in the last year (which occurred in 14.6% of the sample), then we examined the syndrome with more symptoms, giving greater weight to depressive symptoms.

For the most prominent symptom or syndrome, respondents were asked a series of further questions including number of occurrences during the last year, longest duration, degree of impairment, and help seeking.

If twins responded to either of the 2 questions for generalized anxiety disorder (GAD) or panic, they were then asked, for the last year, questions assessing DSM-III-R criteria for GAD and panic disorder.

TABLE 1

<table>
<thead>
<tr>
<th>Class</th>
<th>Symptom Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increased appetite</td>
<td>32%</td>
</tr>
<tr>
<td>2</td>
<td>Decreased appetite</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>Insomnia</td>
<td>18%</td>
</tr>
<tr>
<td>4</td>
<td>Hypervigilance</td>
<td>16%</td>
</tr>
<tr>
<td>5</td>
<td>Psychomotor retardation</td>
<td>15%</td>
</tr>
<tr>
<td>6</td>
<td>Agitation</td>
<td>12%</td>
</tr>
<tr>
<td>7</td>
<td>Decreased weight</td>
<td>10%</td>
</tr>
<tr>
<td>8</td>
<td>Increased weight</td>
<td>8%</td>
</tr>
<tr>
<td>9</td>
<td>Hopelessness</td>
<td>7%</td>
</tr>
<tr>
<td>10</td>
<td>Irritability</td>
<td>6%</td>
</tr>
<tr>
<td>11</td>
<td>Cognitive aspects</td>
<td>5%</td>
</tr>
<tr>
<td>12</td>
<td>Somatic aspects</td>
<td>4%</td>
</tr>
<tr>
<td>13</td>
<td>Generalized anxiety</td>
<td>3%</td>
</tr>
<tr>
<td>14</td>
<td>Panic</td>
<td>2%</td>
</tr>
</tbody>
</table>

POTENTIAL VALIDATORS

In a separate section of the interview, respondents were asked about any history of MD, GAD, or panic disorder prior to the last year, as well as any lifetime history of phobia, bulimia, and alcoholism. The interview booklet was blindly reviewed by one of us (K.S.K.) and diagnoses were assigned using DSM-III-R criteria for the last year and prior to the last year. The GAD criteria were modified in 2 ways. First, the DSM-III27 1-month rather than 6-month minimum duration was used. Second, the diagnostic hierarchy, in which GAD could not be diagnosed if only present during a depressive episode, was dropped. Four phobia subtypes were examined.

Body mass index (BMI represents a measure of weight in kilograms divided by the square of the height in meters) was calculated using self-report data. Significantly overweight and obese in this female population were defined, respectively, as a BMI of more than 23.8 and 28.6 or more.29 Personality was assessed using an adapted version of the short form of Eysenck's Personality Questionnaire.30,31 obtained by mailed questionnaire at least 1 year prior to the interview at which depressive symptoms were reported.

RESULTS

THE CLASSES: ENDORSED SYMPTOMS

Table 1 depicts the observed class membership and endorsement frequencies for all 14 depressive symptoms in the best fitting LCA model. Class 1 was the largest class, constituting 52.2% of the sample. Of the individuals in this class, two thirds denied any depressive symptoms in the last year and the remaining one third endorsed 1 symptom—most commonly depressed mood, feeling tired, or gaining weight.

Members of class 2—4.6% of the sample—endorsed on average (mean±SD) 2.3±1.0 individual symptoms. All reported increased appetite, the only other symptoms commonly endorsed being weight gain and depressed mood. None of these twins met DSM-III-R criteria for MD.

The individuals in class 3, who made up 21.6% of the sample, endorsed 2.8±1.0 co-occurring symptoms, most commonly the “core” depressive symptoms of depressed mood or loss of interest and/or pleasure. Vegetative symptoms, except for tiredness, were rare. Only 3.8% of the individuals in this class met criteria for MD.

Members of class 4, who consisted of 7.2% of the sample, endorsed a mean (±SD) of 3.1±1.3 individual depressive symptoms. More than half of these twins endorsed decreased appetite and depressed mood, other commonly reported symptoms being weight loss, trouble sleeping, and feeling of tiredness. A diagnosis of MD was made for 2% of these twins.

Twins in class 5 made up 8.9% of the sample and reported a mean (±SD) of 6.3±1.3 co-occurring depressive symptoms. Nearly all twins in this class reported depressed mood and more than half described loss of interest and/or pleasure, decreased appetite, trouble sleeping, feelings of tiredness, and psychomotor agitation. More than 30% endorsed weight loss, guilt, and trouble concentrating. However, almost none of the twins in this class reported increased appetite or weight gain, and hypervigilance was also rare. Of the twins in this class, 66.1% met DSM-III-R criteria for MD.

Individuals in class 6, who constituted 3.9% of the sample, reported a mean (±SD) of 6.2±1.5 co-occurring depressive symptoms. Ninety-seven percent of these twins endorsed depressed mood and 80% loss of interest and/or pleasure. In contrast to class 5, these twins commonly re-
We also asked about the occurrence and dating of 9 "personal" and 22 "network" stressful life events (SLEs) over the month of the interview and the 12 preceding months. To assess the relationships between SLEs and the depressive syndromes, we examined the frequency of "severe" SLEs in the month preceding or the month of onset of the depressive syndrome, severe events being defined as those 4 events that increased the risk of onset of DSM-III-R MD by at least 10-fold: assault, serious marital problems, divorce or break-up, and death of a close relative.

In addition, an average (mean ± SD) of 17 ± 3.7 months after their initial interview, twins were reinterviewed by telephone with a 92.5% cooperation rate. This telephone interview contained the same assessment of last year symptoms used in their initial face-to-face interview.

STATISTICAL ANALYSIS

Typically, multivariate analyses in psychiatric genetics have been confined to linear structural modeling, as implemented by programs such as LISREL [11] and Mx. Although these approaches have been fruitful, they emphasize a "dimensional" approach to psychiatric disorders. By contrast, LCA assumes that psychiatric syndromes are, by their nature, "categorical." Latent class analysis, which can probably be best characterized as a "categorical analog" of factor analysis, is based on the following major assumptions:

- There exist m (≥1, to be determined) mutually exclusive and exhaustive classes of subjects within the population.
- The distribution of responses to each item is entirely determined by class membership.
- Within each class, responses to individual items are independent.

Using a FORTRAN program written by 1 of us (L.J.E.), we applied LCA to a 2058×14 data matrix (individual twins × symptoms of the disaggregated 9 "A Criteria" for MD in DSM-III-R) and identified 7 classes (details available on request). Individual twins were then assigned class membership based on the likelihood of their particular response profiles. The median likelihood ratio between the most and next most likely class was 12.4; 75.1% of the sample was assigned to a class with a likelihood ratio of more than 3.0. This computer program, including the algorithm for class assignment, is available to interested researchers. The purpose of our study is to present these results for clinical and research considerations, and to test the validity of the classes so identified.

Data concerning the occurrence of symptoms in the 12 months after the initial interview were also available on a slightly smaller sample (n = 1874) obtained from a follow-up interview conducted by telephone 1 year later. The solution for the first year of interview was imposed on the data from the second year to examine changes in class membership over time.

Exploratory analyses were then performed to examine characteristics of the classes of depressive episodes (eg, level of impairment, average duration, frequency), as well as comorbidity of the classes with other disorders. Comparisons of mean values of these descriptive variables among classes were performed using generalized linear models in SAS. Multiple comparison tests using the GT2 method of Hochberg were performed to more closely examine the differences among the means when the overall F-test of the means was significant. Complete tables of these pairwise comparisons can be obtained from the senior author. Discussion of comparisons among classes is limited to 3 classes which, on examination, appeared to describe MD-like syndromes. In addition, classes were examined across twin pairs to examine possible familiality of class membership. To maximize our sample size of twin pairs concordant for a depressive syndrome, we examined class membership either at the first or second personal interview. If an individual had a depressive syndrome at each assessment, she was classified on the basis of her first episode.

ported increased appetite and weight gain, only rarely endorsing decreased appetite or weight loss. While insomnia was endorsed by over twice as many twins in class 5 as in class 6, hypersonnia was reported by over 3 times as many twins in class 6 as in class 5. While psychomotor agitation was considerably more common in members of class 5 compared with class 6, retardation was endorsed more frequently by twins in class 6 than in class 5. Forty-six percent of the twins in class 6 met DSM-III-R criteria for MD.

Individuals in class 7, who constituted only 1.6% of the sample, were far and away the most symptomatic, endorsing on average (mean ± SD) 9.9 ± 1.2 co-occurring depressive symptoms. All individuals in this class endorsed depressed mood, loss of interest and/or pleasure, psychomotor agitation, tiredness, and insomnia. Seventy percent or more also reported psychomotor retardation, trouble concentrating, and feelings of guilt. Decreased appetite, weight loss, and insomnia were reported considerably more frequently than increased appetite, weight gain, and hypersonnia. Nearly all individuals in this class (96.9%) met DSM-III-R criteria for MD.

Pairwise comparisons of all classes indicate that classes 5 through 7 are significantly different from all other classes for the percentage diagnosed with MD, while classes 2 through 4 did not differ. In addition, on average individuals in class 7 endorsed significantly more symptoms than subjects in any other class. Classes 5 and 6 did not significantly differ from each other in the average number of symptoms endorsed, but both had greater symptom frequencies than classes 1 through 4. Thus, classes 5 through 7 represent potential "clinical" depressive syndromes and we will refer to them as follows: class 5 "mild typical depression," class 6 "atypical depression," and class 7 "severe typical depression." While some of the subsequent analyses will examine all classes, others will be restricted to these 3 clinical classes.

THE CLASSES: OTHER CLINICAL CHARACTERISTICS

Table 2 examines clinical characteristics of the 7 classes as delineated by LCA. Age at interview differed significantly across all classes, largely due to a younger age of those in class 4. However, age did not differ in the 3 clinical classes. All classes, as well as the 3 clinical classes,
Table 1. Observed Class Membership and Endorsement Frequencies of 14 Depressive Symptoms in the Best Fitting Latent Class Model

<table>
<thead>
<tr>
<th>Symptom</th>
<th>DSM-III-R*</th>
<th>Prevalence by Class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Felt depressed</td>
<td>A1</td>
<td>0.15</td>
</tr>
<tr>
<td>Loss of interest and/or pleasure</td>
<td>A2</td>
<td>0.00</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>A3</td>
<td>0.00</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>A3</td>
<td>0.00</td>
</tr>
<tr>
<td>Weight loss</td>
<td>A3</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight gain</td>
<td>A3</td>
<td>0.06</td>
</tr>
<tr>
<td>Insomnia</td>
<td>A4</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>A4</td>
<td>0.00</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>A5</td>
<td>0.03</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>A5</td>
<td>0.00</td>
</tr>
<tr>
<td>Tired</td>
<td>A6</td>
<td>0.06</td>
</tr>
<tr>
<td>Guilt</td>
<td>A7</td>
<td>0.00</td>
</tr>
<tr>
<td>Trouble concentrating</td>
<td>A8</td>
<td>0.00</td>
</tr>
<tr>
<td>Suicide</td>
<td>A9</td>
<td>0.00</td>
</tr>
</tbody>
</table>

| Observed class membership, %    | 52.2       | 4.6     | 21.6    | 7.2     | 8.9     | 3.9     | 1.6     |
| N                                | 1075       | 95      | 445     | 148     | 183     | 66      | 32      |

| % Diagnosed MD by DSM-III-R      | 0.0        | 0.0     | 3.8     | 2.0     | 6.1     | 46.3    | 96.9    |
| No. of symptoms, mean           | 0.4        | 2.3     | 2.8     | 3.1     | 6.3     | 6.2     | 9.9     |
| No. of symptoms, ±SD            | 0.5        | 1.0     | 1.0     | 1.3     | 1.3     | 1.5     | 1.2     |

*The DSM-III-R "A Criteria" for major depression (MD) reflected by the individual symptoms.

significantly differed for the other 4 characteristics. The typical clinical classes had a syndrome of longer duration than the nonclinical classes, while the class representing atypical depression did not differ in duration from the nonclinical classes. Among the clinical classes, severe typical depression had significantly longer episodes than either mild typical or atypical depression.

For number of episodes in the last year, the most deviant class was that with atypical depression, which had significantly more frequent episodes than mild typical depression but not severe typical depression. Both severe impairment and treatment seeking were reported significantly more frequently by the clinical than by the nonclinical classes and were significantly more common in those with severe typical depression than in those with mild typical or atypical depression, which did not, in turn, differ significantly from each other.

Endorsement rates for the 6 co-occurring additional symptoms, inquired of in all twins, are seen for all 7 classes in Table 3. The endorsement rates for all of these 6 symptoms differed significantly both across all 7 classes and within the 3 clinical classes. Those with severe typical depression endorsed all 6 of these symptoms significantly more frequently than those with mild typical or atypical depression. Cases with mild typical depression reported all of these symptoms more frequently than those with atypical depression, and this difference was significant for 3 of the 6 symptoms: hopeless, anxious, and tense. Of the 4 remaining classes, class 1 reported significantly lower rates of irritability, hopelessness, and anxiety than all other classes. Among classes 2 through 4, no consistent pattern of differences in the 6 symptoms was detected.

Table 3 also depicts the frequency with which members of the 7 clinical classes had GAD or a panic disorder, diagnosed by DSM-III-R criteria, in the last year that co-occurred with their depressive syndrome. These rates differed significantly both across all 7 classes and within the 3 clinical classes. The results were particularly striking for GAD. While 78.1% of those with severe typical depression also met criteria for GAD during the depressive episode, the comparable figures for mild typical and atypical depression were 32% and 13%, respectively—all significantly different from one another.

THE CLASSES: LIFETIME PREVALENCE OF OTHER DISORDERS

Lifetime prevalence rates for alcoholism in the 3 clinical classes were similar: mild typical depression, 28.1%; atypical depression, 26.3%; and severe typical depression, 24.6%. For phobias, severe typical depression had substantially higher rates (59.4%) than either mild typical depression (42.6%) or atypical depression (48.8%). The difference between mild and severe typical depression approached significance (odds ratio [OR]=1.97, P<.08). We then examined specific phobic subtypes and found that the rates of neither animal nor social phobia distinguished the 3 clinical classes. However, compared with those with mild typical or atypical depression, individuals with severe typical depression had significantly higher lifetime prevalences of agoraphobia and situational phobia. Twins with atypical depression had the highest lifetime prevalence of bulimia (19.0%), followed by those with severe typical (15.6%) and mild typical depression (6.6%). Compared with those with mild typical depression, twins with atypical depression were at a significantly increased risk for bulimia (OR=3.34, P<.01).
Table 2. Clinical Characteristics of the 7 Classes Delineated by Latent Class Analysis

<table>
<thead>
<tr>
<th>Class</th>
<th>Longest Duration, d*</th>
<th>No. of Episodes, Last Year*</th>
<th>Age at Interview, y*</th>
<th>% Severe Impairment</th>
<th>% Seeking Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>...</td>
<td>...</td>
<td>30.2 (7.7)</td>
<td>4.4†</td>
<td>7.2†</td>
</tr>
<tr>
<td>2</td>
<td>29.4 (55.6)</td>
<td>2.7 (2.8)</td>
<td>31.7 (7.5)</td>
<td>5.1†</td>
<td>13.7</td>
</tr>
<tr>
<td>3</td>
<td>23.4 (45.0)</td>
<td>2.7 (3.3)</td>
<td>29.8 (7.4)</td>
<td>11.1†</td>
<td>17.3</td>
</tr>
<tr>
<td>4</td>
<td>27.7 (37.1)</td>
<td>1.7 (1.4)</td>
<td>27.2 (6.9)</td>
<td>5.8†</td>
<td>12.2</td>
</tr>
<tr>
<td>5</td>
<td>25.7 (79.8)</td>
<td>2.7 (2.7)</td>
<td>30.8 (7.2)</td>
<td>22.4</td>
<td>31.7</td>
</tr>
<tr>
<td>6</td>
<td>42.6 (72.6)</td>
<td>2.6 (3.2)</td>
<td>31.1 (7.4)</td>
<td>16.3</td>
<td>25.6</td>
</tr>
<tr>
<td>7</td>
<td>111.5 (13.4)</td>
<td>2.3 (2.4)</td>
<td>30.8 (6.8)</td>
<td>43.8</td>
<td>56.3</td>
</tr>
</tbody>
</table>

F (df)§ 20.0± (5, 977) 4.7± (5, 977) 5.1± (6, 2051) ...
F (df)‖ 8.1l (2, 289) 3.6k (2, 252) 0.1 (2, 292) ...
χ²§ 71.1
χ²‖ 10.3# 9.9f

*Mean± SD
†N smaller than class total, only those with 2 or more concurrent symptoms queried.
‡N smaller than class total, only those with 1 or more symptoms queried.
§Test over all 7 categories.
‖Test only over the 3 categories representing "clinical" depression: classes 5, 6, and 7.
#P<.05

BMI AND PERSONALITY

Because the typical and atypical depressive syndromes were most clearly distinguished by a different pattern of appetite and weight change, we investigated BMI. Body mass index differed significantly both across all 7 classes (F=15.65, df=6/2043, P=.000) and across the 3 clinical classes (F=17.79, df=2/289, P=.000). Body mass index was highly significantly greater in women with atypical depression (mean±SE: 26.0±0.6) than in either those with mild or severe typical depression (22.3±0.3 and 21.9±0.6, respectively). Of those with atypical depression, 60.0% were significantly overweight compared with 22.4% of those with mild and 18.8% of those with severe typical depression (χ²=39.01, df=2, P=.000). Criteria for obesity were met by 28.9% of women with atypical depression and only 6.0% and 3.1% of those with mild and severe typical depression, respectively (χ²=30.15, df=2, P=.000).

Although increased above those without major depressive symptoms, the levels of neuroticism did not differentiate between the 3 depressive classes (F=0.44, df=2/230, P=.not significant). By contrast, of all 7 classes, those with atypical depression had the lowest level of extraversion, with scores on this dimension significantly differentiating the 3 clinical classes (F=3.85, df=2/230, P=.02).

THE CLASSES: PRIOR STRESSFUL LIFE EVENTS

The occurrence of severe SLEs was examined in the month prior to and the month of the onset of the depressive episode. In a random 2-month period in twins without clinical depressive syndromes, severe SLEs occurred 5.5% of the time. Severe SLEs were associated with the onset of mild typical, atypical, and severe typical depression at 20.4%, 20.0%, and 28.3% of the time, respectively. While the frequency of severe SLEs was increased above chance expectation in all of these 3 groups (χ²=65.6, 40.0, and 40.7, respectively, all with df=1 and P=.000), they did not differ significantly from one another (χ²=1.59, df=2, P=not significant).

THE CLASSES: LONGITUDINAL ANALYSES

We first examined whether the kind of depressive syndrome experienced in the year preceding the first interview predicted having any of the 3 clinical depressive syndromes in the year prior to the second interview. Compared with those in the "nonclinical classes" (1 through 4) at the first interview, the ORs for the clinical classes were mild typical depression, 3.89 (P=.000); atypical depression, 8.29 (P=.000); and severe typical depression, 6.06 (P=.000).

We next examined the 106 individuals who reported a syndrome in 1 of the 3 depressive classes in both the year prior to the first interview and the year prior to the second interview. As seen in Table 4 (which shows the observed, expected, and χ² value for each of the 9 cells), the proportion of twins who had the same depressive syndrome during both periods of assessment substantially exceeded chance expectation (χ²=17.69, df=4, P=.001). Examining only those twins with depressive syndromes during both years, the OR for having the same depressive class on both occasions was similar for mild typical depression (3.39) and atypical depression (5.78), but lower for severe typical depression (1.56).

THE CLASSES: LIFETIME HISTORY OF PSYCHIATRIC DISORDERS AND BMI IN CO-TWINS

Table 5 presents the ORs for the lifetime risk for psychiatric disorders in the co-twin of a twin in 1 depressive class compared with the co-twin of a twin in another depressive class. Compared with co-twins of twins with mild typical depression, co-twins of twins with severe typical depression were at increased lifetime risk for all the psychiatric disorders examined. The increase, however, did not reach significance for any disorder. Compared with co-twins of twins with atypical depression, co-twins of twins with severe typical depression were at increased risk for MD, alcoholism, panic disorder, pho...
bias, and GAD but at decreased risk for bulimia. Again, there was no significant difference for any disorder. Compared with co-twins of twins with mild typical depression, co-twins of twins with atypical depression had a relatively similar risk for the psychiatric disorders examined, except for bulimia, where their risk was nearly tripled. This difference was statistically significant.

Compared with co-twins of twins in the nonclinical classes, BMI was significantly elevated in co-twins of twins with atypical depression (b=2.17, t=4.98, P=.000). The BMI was also significantly elevated in the co-twins of twins with mild typical depression, but the associated increase was about half as large as that seen in co-twins of twins with atypical depression (b=1.17, t=2.60, P=.01). By contrast, BMI was not elevated in co-twins of twins with severe typical depression (b=0.16, t=0.24, P=not significant).

**CONCORDANCE OF SPECIFIC DEPRESSIVE SYNDROMES IN TWIN PAIRS**

Including both years of assessment, the sample contained 92 twin pairs where both twins had had a mild typical, atypical, or severe typical depressive episode, 54 of whom were MZ and 38 DZ (Table 6). The MZ pairs demonstrated a much more significant concordance for class membership ($\chi^2=16.08, df=4, P=.001; \kappa=+0.55$, reference 39) than did the DZ twins ($\chi^2=5.10, df=4, P=.28, \kappa=+0.37$). Substantial concordances were found for all 3 clinical syndromes in the MZ twin pairs: mild typical OR, 5.9; atypical OR, 5.4; and severe typical OR, 15.7. The degree of twin similarity was less striking in the DZ pairs: mild typical OR, 1.3; atypical OR, 1.0; and severe typical OR, 5.4.

Table 7 presents a summary of the findings associated with the 3 clinical classes of mild typical, atypical, and severe typical depression.

**COMMENT**

**SUBTYPES OF DEPRESSION AS IDENTIFIED BY LATENT CLASS ANALYSIS**

Examining the pattern of symptom endorsement in the last year for the 14 disaggregated *DSM-III-R* criteria for MD in our epidemiologic sample of female twins, LCA identified 7 classes. The first 2 classes, which demonstrated few if any depressive symptoms, bore no apparent relationship to clinical depression.
### Table 5. Odds Ratio for Lifetime Risk of Disease in Co-twin of Twin in Depressive Class (A) Compared With Risk to Co-twin of Twin in Depressive Class (B)*

<table>
<thead>
<tr>
<th>Class A/B</th>
<th>MD</th>
<th>ALC</th>
<th>Panic</th>
<th>Phobia</th>
<th>Bulimia</th>
<th>GAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical/mild typical</td>
<td>1.01</td>
<td>1.01</td>
<td>1.23</td>
<td>0.89</td>
<td>2.80†</td>
<td>0.66</td>
</tr>
<tr>
<td>Severe typical/mild typical</td>
<td>1.26</td>
<td>1.05</td>
<td>1.62</td>
<td>1.62</td>
<td>1.65</td>
<td>2.20</td>
</tr>
<tr>
<td>Severe typical/atypical</td>
<td>1.22</td>
<td>1.03</td>
<td>1.36</td>
<td>2.03</td>
<td>0.59</td>
<td>3.21</td>
</tr>
</tbody>
</table>

*MD indicates major depression; ALC, alcoholism; and GAD, generalized anxiety disorder.
†Significant at P<.01.

### Table 6. Similarity for Specific Depressive Syndromes in Twin Pairs Where Both Members Reported a ‘Clinical’ Depression*

#### Monozygotic Twin Pairs, Twin 2

<table>
<thead>
<tr>
<th>Twin 1</th>
<th>Mild Typical</th>
<th>Atypical</th>
<th>Severe Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild typical</td>
<td>25 (20.0)</td>
<td>4 (7.8)</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Atypical</td>
<td>1.3</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Severe typical</td>
<td>9 (12.7)</td>
<td>9 (4.9)</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

#### Dizygotic Twin Pairs, Twin 2

<table>
<thead>
<tr>
<th>Twin 1</th>
<th>Mild Typical</th>
<th>Atypical</th>
<th>Severe Typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild typical</td>
<td>12 (12.5)</td>
<td>4 (3.5)</td>
<td>3 (3.6)</td>
</tr>
<tr>
<td>Atypical</td>
<td>0.0</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Severe typical</td>
<td>4 (5.3)</td>
<td>1 (1.5)</td>
<td>3 (1.3)</td>
</tr>
</tbody>
</table>

*For each cell, the observed number is given, followed within parentheses by the expected value; beneath these, is the χ2 value for that cell.

The third and fourth classes, which together constituted 30% of the sample, reported depressive syndromes with 2 to 4 individual symptoms. Although almost none of these twins met criteria for MD, 10% reported incapacitation, 45% moderate impairment, and 15% sought professional help. These conditions were recurrent, typically lasting 3 to 4 weeks. We know relatively little about these syndromes of "minor depression disorder."

All the 3 remaining classes, 5 through 7, bore some resemblance to clinical depression. With respect to severity, classes 5 and 6 were similar and reflected a depressive syndrome of mild to moderate intensity. By contrast, class 7 was substantially more severe. However, the pattern of symptoms revealed a different grouping. While classes 5 and 7 were characterized by decreases in the vegetative functions of eating and sleeping, class 6 was characterized by increases.

### VALIDATION OF THESE PUTATIVE SUBTYPES

We attempted to validate our putative typology of depression in several ways, the results of 5 of which are particularly noteworthy. First, we examined their co-occurrence with anxiety symptoms, which strongly discriminated all 7 classes and the 3 clinical classes. Uniformly, individuals with severe typical depression endorsed anxiety and panic symptoms at rates 2 to 4 times higher than the other 2 clinical classes. A similar pattern was seen with anxiety disorders. More than 75% of twins with severe typical depression had, at the same time, an anxiety syndrome diagnosable as either GAD or panic disorder. In this epidemiologic sample of women, severe depression rarely occurred without major symptoms of anxiety.

Second, we examined lifetime prevalence of other psychiatric disorders. Some differences were found. Severe typical depression had the highest prevalence rates of phobia, while the risk of bulimia was highest in atypical depression.

Third, the association between BMI and depressive class was particularly striking. On average, twins with atypical depression weighed 9 kg more than those with mild typical depression and 7.2 kg more than those with severe typical depression. Along with the association with bulimia, these findings suggest that individuals with atypical depression may have a vulnerability to excess eating under stress. Our results replicate the previous findings of Stunkard et al90 that weight change during a depressive episode is strongly related to basal BMI. Body mass index was also substantially elevated in the co-twins of twins with atypical depression. These results suggest the intriguing hypothesis that familial/genetic factors that influence the vulnerability to atypical depression also influence the vulnerability to obesity. Alternatively, the liability to obesity may not be itself directly related to the risk for broadly
defined depression. However, given that depression is manifest, then the clinical form of the disorder (i.e., typical vs atypical vegetative features) may be influenced by the familial/genetic vulnerability to obesity.

Fourth, in a re-interview with the same twin sample, among twins with depressive syndromes at both assessments, a moderate and highly statistically significant concordance for depressive class was revealed. These results are consistent with previous findings that the direction of weight change is stable across depressive episodes.30

Fifth, among all twin pairs where both members had a clinical depressive syndrome, there was a highly significant concordance for class membership. Furthermore, resemblance for depressive class was substantially greater in concordant MZ twin pairs than in concordant DZ twin pairs. These results suggest that the familial factors that influence the kind of depressive syndrome displayed by an affected individual are at least in part genetic. Given that these twins were assessed blindly by different interviewers, this result provides strong validation for our typology. Our findings suggest that, from a familial/genetic perspective, the syndrome of major depression is not etiologically homogeneous.

We are aware of only 1 previous study31 that has addressed the familial/genetic relationship between typical and atypical depression. In a family history study of 330 patients with unipolar depression, Stewart et al32 found that compared with relatives of probands with melancholia, relatives of probands with atypical depression had a significantly lower rate of typical MD and a significantly higher rate of atypical depression. These same authors also present results from a pilot family study showing a similar pattern of results. Also, since atypical depression has been previously characterized by selective antidepressant response to monoamine oxidase inhibitors,43 it is of interest to note that Pare and Mack42 suggest that response to monoamine oxidase inhibitors vs tricyclic antidepressants is correlated in pairs of relatives with MD.

‘NEUROTIC’ DEPRESSION

Previous work33 suggests that, in this large epidemiologic sample of women, we should have found a syndrome of neurotic depression characterized by non-endogenous clinical features, personality abnormalities, life events prior to onset, and a personal and family history of alcoholism. Neuroticism was not increased in our twins with atypical depression, although they were more introverted. Stressful life events were slightly more common in those with severe typical depression—the syndrome with the most endogenous features. Neither alcoholism in the twin nor in her co-twin discriminated among the 3 clinical depressive syndromes. These results suggest that our typology of depression bears little resemblance to that proposed by Winokur.43,44

ATYPICAL DEPRESSION

The most striking result of these analyses was the identification, in an epidemiologic sample, of a class of patients characterized by atypical (i.e., reverse) vegetative symptoms. More important, this class was both relatively stable over time and familial. The term “atypical depression” was first applied by West and Dally45 to patients with nonendogenous clinical features and emotional reactivity whose depression responded to the monoamine oxidase inhibitor iproniazid. Since then, the term has been used to describe a variety of related syndromes. In addition to responsiveness to monoamine oxidase inhibitors, such patients are often characterized by reverse vegetative features, prominent anxiety, mood reactivity, rejection sensitivity, and intense lethargy.46 We are aware of only 1 epidemiologic study of this syndrome based on the Epidemiologic Catchment Area study.47 Defining atypical depression solely by overeating and oversleeping, Horwath and colleagues48 found that it constituted 16% of all lifetime cases of MD and was associated with psychomotor slowing and comorbid panic disorder, drug abuse, and somatization disorder. Like us, Horwath et al found no significant association between atypical depression and alcoholism. The syndrome labeled here as “atypical depression” shares some but not all features with those described previously. Most important, it is characterized by the reverse vegetative features of overeating and oversleeping. There is also modest evidence that, at least compared with cases with mild typical depression that are of similar overall severity, those with atypical depression more frequently report tiredness and psychomotor retardation.

Two features of atypical depression as found in this sample, however, were not consistent with previous formulations of this diagnostic category or with the results of the 1 previous epidemiologic study.49 First, atypical depression in this sample was not characterized by prominent anxiety symptoms or disorders. In fact, anxiety symptoms were less common in atypical depressive cases than in those with either mild or severe typical depression. Second, several previous descriptions of atypical depression emphasized the stress-related nature of the syndrome. However, those with atypical depression in our sample were the least likely depressive class to have their episode preceded by an SLE.

LIMITATIONS

These results should be interpreted in the context of 4 potential methodologic limitations. First, the sample is solely women, mostly in early to middle adult life. Whether depressive symptoms in an epidemiologic sample of men, or an older sample of women, would yield similar classes is unknown.

Second, observations in twin pairs were not statistically independent as assumed by our LCA model. Previous simulations have suggested that this situation produces little bias in parameter estimation, but underestimates sampling error.47

Third, latent class membership is not an “all or none” phenomenon. The LCA program calculates, for all individuals, the likelihood of membership in each class. For some twins, 1 class was far and away the most likely, while for others, the difference in likelihood across 2 or more classes was small. We have conducted preliminary analy-
ses including only those twins whose class could be assigned with confidence. While the stability of class assignment over time changed little, concordance for the clinical classes in MZ twin pairs increased. It may be useful to incorporate the confidence of class assignment in future LCA analyses.

Finally, while LCA can indicate whether a pattern of observed symptoms in a population is consistent with the existence of discrete latent classes, it cannot prove that such discrete classes exist. For example, although we consider it unlikely, especially for mild typical and atypical depression, it is possible that the classes of depression observed in this sample reflect only differing points on a single underlying continuum of severity.

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