Identifying Depressive Subtypes in a Large Cohort Study: Results From the Netherlands Study of Depression and Anxiety (NESDA)

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Objective: The heterogeneity of depression in the current classification system remains a point of discussion in the psychiatric field, despite previous efforts to subclassify depressive disorders. Data-driven techniques may help to come to a more empirically based classification. This study aimed to identify depressive subtypes within a large cohort of subjects with depression.

Method: Baseline data from 818 persons with a *DSM-IV* diagnosis of current major depressive disorder or minor depression who participated in the Netherlands Study of Depression and Anxiety were used. Respondents were recruited in the community, in primary care, and in specialized mental health care from September 2004 through February 2007. Latent classes were derived from latent class analysis using 16 depressive symptoms from the Composite International Diagnostic Interview and the Inventory of Depressive Symptomatology. Classes were characterized using demographic, clinical psychiatric, psychosocial, and physical health descriptors.

Results: Three classes were identified: a severe melancholic class (prevalence, 46.3%), a severe atypical class (prevalence, 24.6%), and a class of moderate severity (prevalence, 29.1%). Both severe classes were characterized by more neuroticism (melancholic OR = 1.05 [95% CI, 1.01–1.10]; atypical OR = 1.07 [95% CI, 1.03–1.12]), more disability (melancholic OR = 1.07 [95% CI, 1.05–1.09]; atypical OR = 1.06 [95% CI, 1.04–1.07]), and less extraversion (melancholic OR = 0.95 [95% CI, 0.92–0.99]; atypical OR = 0.95 [95% CI, 0.92–0.99]) than the moderate class. Comparing the melancholic class with the atypical class revealed that the melancholic class had more smokers (atypical OR = 0.57 [95% CI, 0.39–0.84]) and more childhood trauma (atypical OR = 0.86 [95% CI, 0.74–1.00]), whereas the atypical class had more women (atypical OR = 1.52 [95% CI, 0.99–2.32]), a higher body mass index (atypical OR = 1.13 [95% CI, 1.09–1.17]), and more metabolic syndrome (atypical OR = 2.17 [95% CI, 1.38–3.42]).

Conclusions: Both depression severity (moderate vs severe) and the nature of depressive symptoms (melancholic vs atypical) were found to be important differentiators between subtypes. Higher endorsement rates of somatic symptoms and more metabolic syndrome in the atypical class suggest the involvement of a metabolic component.

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Major depression is widely recognized as an important and universal public health issue. However, at the same time, it is probably the most widely criticized product of our current psychiatric nosology, mainly because of its heterogeneity.[1–5] Further refinement of the diagnostic classification of major depressive disorder is one of the great challenges ahead. Ideally, further classification of depressive disorders would be based on empirically validated symptom profiles, which are linked to etiologic subtypes and predict both the prognosis and response to treatment.

In the past, many attempts have been made to further subclassify major depressive disorder along 1 or more of the lines above. Examples of such specifiers—currently acknowledged in the *DSM-IV*—are melancholic depression and atypical depression. Especially classifying atypical depression may be important as it has shown to identify patients who are more responsive to monoamine oxidase inhibitors than to tricyclic antidepressants.[6,7] Nevertheless, the definition of atypical depression also receives critique since its underlying symptom profile has not been consistently confirmed in studies measuring all *DSM-IV* atypical symptom indicators.[8–10]

In order to come to a more empirically based classification, data-driven techniques that cluster persons on the basis of their endorsed symptom pattern seem very useful. Previous studies using such techniques have shown that severity of symptoms as well as the nature of symptoms (typical vs atypical) play an important role in distinguishing subtypes of depression.[11–13] However, these studies used a limited set of depressive symptoms for their classification. Furthermore, they did not examine profiles within a large cohort of depressed patients but included the entire range of the population (including the healthy), and they did not apply a large effort to characterize subtypes according to psychosocial and physical health indicators. Such further characterization, however, is essential for achieving valuable information on potential differential etiologic mechanisms underlying different symptom profiles.

Therefore, in the current study, our primary aim was to identify empirically valid subtypes of depressive disorder on the basis of depressive symptomatology in a large cohort of depressed subjects participating in the Netherlands Study of Depression and Anxiety (NESDA). The second aim was to

test whether these subtypes yield meaningful categories in terms of underlying risk factors, comorbidity patterns, and clinical characteristics.

METHOD

Sample

Data were derived from the baseline measurements of NESDA. The NESDA cohort (N = 2,981) consists of persons aged 18–65 years with a current or remitted depressive and/or anxiety disorder, persons at risk due to family history or subthreshold symptoms, and healthy controls. Participants were recruited in the general population, in primary care, and in specialized mental health care from September 2004 through February 2007. The research protocol was approved by the ethics committees of participating universities, and all respondents provided written informed consent. Exclusion criteria used were the following: (1) a primary clinical diagnosis of psychotic disorder, obsessive-compulsive disorder, bipolar disorder, or severe addiction disorder and (2) not being fluent in Dutch. A detailed description of the NESDA study design can be found elsewhere.[14] All patients with a current (1-month recency) diagnosis of major depressive disorder (n = 802) or minor depression (n = 84) were initially selected. Persons with complete data on depressive symptoms were included in the current analyses (total N = 818). Persons excluded from analyses because of incomplete data on depressive symptoms (n = 68) had attained a lower education level, had a lower depression severity, and were less often of North European descent.

Measures

Depressive symptoms. A total of 16 depressive symptoms were used as indicator variables to identify subtypes in a latent class analysis and were derived from 2 sources. The 9 key depression symptoms of the *DSM-IV* were based on the Composite International Diagnostic Interview (CIDI),[15] lifetime version 2.1, which was used to diagnose depressive and anxiety disorders according to *DSM-IV* criteria and was conducted by specially trained clinical research staff. The items were coded as "not present" or "present," except for the items regarding changes in appetite, weight, sleep, and psychomotor disturbances. For appetite and weight, 2 separate variables with 3 categories were constructed, namely "no change in appetite/weight," "decreased appetite/weight" and "increased appetite/weight," making up a total number of 10 CIDI symptoms. For sleep and psychomotor disturbances, variables were constructed in a similar way but with 1 extra category that indicated the presence of both insomnia and hypersomnia and both psychomotor agitation and retardation. This way, we would be able to distinguish symptom patterns while preventing violation of the latent class analysis assumption of local independence (correlation between variables in a class is accounted for by the latent variable), which could occur when separate variables would have been included for different expressions of symptoms.[16]

Further, 6 additional variables specific for atypical and melancholic features according to *DSM-IV* were derived from the 30-item Inventory of Depressive Symptomatology–Self-Report (IDS-SR) (www.ids-qids.org).[17,18] For atypical depression, the following symptoms were used: mood reactivity (item 8), leaden paralysis (item 30), and interpersonal rejection sensitivity (item 29). For melancholic depression, the following symptoms were derived: worse mood in the morning (diurnal variation, item 9a), early morning awakening (item 3), and quality of mood (item 10). Lack of reactivity was already captured in the atypical symptom of mood reactivity. The IDS-SR responses were dichotomized as 0 or 1 = absent and 2 or 3 = present.

Characteristics to describe identified latent classes. Four groups of variables were used to characterize identified latent classes, namely demographic, clinical psychiatric, psychosocial, and physical health indicators. These 4 groups of indicators encompass risk factors, comorbidity indicators, and other characteristics in 4 areas that may explain differences between classes and provide hints about the etiology of different subtypes.

Standard demographics included age, sex, and educational level (in years).

Clinical psychiatric indicators included key clinical characteristics of the depressive disorder such as age at onset and number of episodes as assessed in the CIDI psychiatric interview. The presence of 1-month comorbid anxiety (panic disorder with and without agoraphobia, agoraphobia, social phobia, generalized anxiety disorder) and alcohol dependence disorders was assessed using the CIDI as well. Family history of depression was assessed using the family tree method,[19] and a measure for duration of depressive disorder was derived from the life chart representing the number of months being depressed in the prior 4-year period.[20] Further, the presence of manic symptoms was assessed with the Mood Disorder Questionnaire (MDQ).[21]

Psychosocial characteristics comprised neuroticism and extraversion assessed using the NEO Personality Inventory.[22] Negative life events in the last year were assessed with the Brugha questionnaire, The List of Threatening Experiences,[23] and childhood trauma was assessed using the structured inventory from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) that constructs an index (range 0–4) incorporating the occurrence and frequency of 4 types of abuse before age 16 (emotional neglect, psychological abuse, physical abuse, and sexual abuse).[24] Overall functioning was measured with the World Health Organization Disability Assessment Schedule II (WHODAS).[25]

Physical health indicators included physical activity measured with the International Physical Activity Questionnaire (IPAQ)[26] and expressed per 1,000 metabolic equivalent minutes per week. Current smoking (yes/no) was assessed, and pain was measured using a count of pain locations (range, 0–7) mentioned on the Chronic Graded Pain Scale.[27] Further, objective and standardized assessments of weight and height were performed to calculate body mass index (kg/m^2). The presence of somatic conditions was assessed in the

baseline interview. A count of the number of somatic diseases (including lung disease, osteoarthritis, cancer, gastrointestinal disease, liver disease, epilepsy, thyroid disease) for which the subject was receiving medical treatment was constructed. Separate variables were used for cardiovascular disease and diabetes, since these may share biologic phenomena with depressive disorder (eg, HPA axis dysfunction, inflammation[28,29]) and have been specifically linked with somatic symptoms of depression.[30] Cardiovascular disease and diabetes were assessed using adjudicated information integrating medication use and self-report information. Subsequent analyses will also explore the role of metabolic syndrome—a clustering of cardiovascular risk factors—defined according to the Adult Treatment Panel-III (ATP-III) criteria.[31,32] The ATP-III criteria are as follows: (1) waist circumference >102 cm in men or >88 cm in women, (2) triglycerides ≥1.7 mmol/L (150 mg/dL), (3) high-density lipoprotein cholesterol <1.03 mmol/L (40 mg/dL) in men or <1.30 mmol/L (50 mg/dL) in women, (4) blood pressure ≥130/85 mm Hg or drug treatment for hypertension, and (5) fasting plasma glucose ≥6.1 mmol/L (110 mg/dL) or drug treatment for elevated glucose. Persons who score positive on 3 or more criteria are considered to have the metabolic syndrome.

Statistical Analysis

In the first phase of the analyses, we performed latent class analysis using Mplus,[16,33] version 5.1, to identify differential symptom profiles. Latent class analysis, often described as a "categorical equivalent" of factor analysis, assumes that an unobserved, latent categorical variable explains the association among a set of observed depressive symptoms. It computes 2 sets of parameters: (1) latent class probabilities or class prevalences and (2) conditional probabilities, ie, estimated probabilities of observed variables given that the individual is a member of that class (analog to factor loadings in factor analysis). Models with 1 class up to 5 classes were fitted. Latent class analysis output provides several statistical information criteria, like the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), but currently there is no consensus on which criterion identifies the best number of classes. The best-fitting number of classes was determined using these statistics—lowest value preferred for BIC and AIC—as well as interpretability of the classes.[34] The Cramer V statistic, a measure of association derived from the Pearson χ^2 ranging from 0 to 1, was calculated for each item in the latent class analysis as effect-size measure to express the discriminating capacity of each item.[35] Once the best-fitting number of classes was determined, respondents were assigned to their most likely class, and their distinct depressive symptomatology profile was described.

In a second phase of the analyses, we evaluated the characteristics of these classes in order to explore potential mechanisms underlying the classes. This was done by evaluating differences across the classes in demographic, psychopathological, psychosocial, and physical health indicators (using SPSS, version 15.0; SPSS Inc, Chicago, Illinois). χ^2 tests (for categorical variables), analysis of variance (for continuous variables), and Kruskal-Wallis tests (for nonparametric continuous variables) were used to test for differences in characteristics across classes. Additional pairwise comparisons were performed to test for differences between pairs of classes. Multinomial logistic regression analyses were conducted to examine multivariable determinants of identified depressive subclasses.

RESULTS

Latent Class Analysis Outcome

The best-fitting model, based on interpretability and BIC and AIC values, in a latent class analysis with 16 depressive symptoms was a 3-class model (Table 1) (BIC = 15,627; AIC = 15,307). The 2-class model had a comparable BIC value (15,616) but a higher AIC value (15,404) and was considered to be conceptually less meaningful, as it differentiated only in severity. Mean posterior probabilities for most likely class membership were 0.80 for class 1, 0.88 for class 2, and 0.84 for class 3, indicating acceptable classification quality.

Table 1 shows the probability of symptom endorsement in the 3 identified latent classes. The first class (prevalence, 46.3%) was characterized by overall high symptom endorsement. This class also had the highest proportions on most melancholic symptoms (decreased appetite, weight loss, psychomotor change, lack of responsiveness, diurnal variation, and early morning awakening) and, furthermore, had relatively high endorsement rates of leaden paralysis. The second class (prevalence, 24.6%) showed a more atypical symptom pattern with increased appetite, weight gain, and leaden paralysis and also had relatively high symptom endorsement. The third class (prevalence, 29.1%) had the lowest probabilities on all depressive symptoms, indicating moderate severity.

Characteristics of the Identified Classes

Table 2 shows the psychopathological characteristics of the identified latent classes. The moderate class (class 3) had a later onset, had shorter duration of depression, and had lower proportions of manic symptoms, positive family history, comorbid panic disorder with agoraphobia, social phobia, and generalized anxiety disorder than both severe classes.

Demographic, psychosocial, and physical health characteristics of classes are described in Table 3. Class 1 (severe melancholic) distinguished itself from the other 2 classes by a higher number of negative life events in the past year and by a higher proportion of smokers. Class 2 (severe atypical) showed a higher body mass index compared to classes 1 and 3. Class 3 (moderate) distinguished itself from both severe classes by more favorable scores on WHODAS functioning, neuroticism, and extraversion scales; a lower score on the childhood trauma index; and a lower number of pain locations.

Two things stood out in the latent class outcomes and the univariable characterization of classes. First, given that class 3, with moderate severity, appeared to have more favorable characteristics, it seems that severity of depression played a distinguishing role in differentiating classes 1 and 2 from

Table 1. Probabilities of Endorsing Depressive Symptoms Derived From Latent Class Analysis (N = 818)

Class Description	Class 1, Severe Melancholic	Class 2, Severe Atypical	Class 3, Moderate Severity	Cramer V Statistic	*P* Value
Prevalence, %	46.3	24.6	29.1		
DSM-IV criterion symptoms					
Depressed mood	1.000	0.977	0.800	0.363	<.001[a,b,c]
Loss of interest	0.976	0.964	0.896	0.182	<.001[a,b]
Weight				0.373	<.001[a,b,c]
No weight change	0.744	0.713	0.859		
Weight loss	0.256	0.017	0.105		
Weight gain	0.000	0.270	0.036		
Appetite				0.553	<.001[a,b,c]
No change in appetite	0.369	0.284	0.508		
Decreased appetite	0.631	0.055	0.267		
Increased appetite	0.000	0.660	0.226		
Sleep				0.236	<.001[a,b,c]
No change in sleep	0.049	0.034	0.154		
Less sleep	0.515	0.388	0.508		
More sleep	0.093	0.180	0.163		
Both less and more sleep	0.342	0.398	0.175		
Psychomotor				0.253	<.001[a,b]
No psychomotor change	0.364	0.405	0.675		
Psychomotor retardation	0.213	0.229	0.042		
Psychomotor agitation	0.207	0.176	0.225		
Both agitation and retardation	0.215	0.190	0.058		
Fatigue/energy loss	0.964	1.000	0.840	0.305	<.001[a,b,c]
Guilt/worthlessness	0.918	0.921	0.664	0.354	<.001[a,b]
Lack of concentration/indecisiveness	0.985	0.991	0.947	0.128	<.01[a,b]
Suicidal	0.774	0.705	0.404	0.359	<.001[a,b,c]
Additional atypical and melancholic symptoms					
Lack of responsiveness[d]	0.397	0.334	0.072	0.331	<.001[a,b]
Leaden paralysis	0.779	0.841	0.278	0.561	<.001[a,b]
Interpersonal sensitivity	0.496	0.535	0.144	0.347	<.001[a,b]
Quality of mood	0.569	0.629	0.367	0.243	<.001[a,b,c]
Diurnal variation, worse in morning	0.116	0.111	0.038	0.129	<.01[a,b]
Early morning awakening	0.338	0.230	0.163	0.187	<.001[a,b,c]

[a]Severe melancholic versus moderate severity was significantly different ($P < .05$).
[b]Severe atypical versus moderate severity was significantly different ($P < .05$).
[c]Severe atypical versus severe melancholic was significantly different ($P < .05$).
[d]Presence of responsiveness is an atypical feature, while lack of responsiveness is a melancholic feature.

Table 2. Clinical Psychiatric Characteristics of the Identified Latent Classes (N = 818)

Characteristic	Class 1, Severe Melancholic, n = 379	Class 2, Severe Atypical, n = 201	Class 3, Moderate Severity, n = 238	Overall *P* Value
Age at onset, median (IQR)	25 (19)	22 (16)	28 (22)	.002[a,b]
No. of episodes, median (IQR)	1 (4)	1 (4)	2 (3)	.629
No. of depressed months in last 4 years, median (IQR)	18.7 (25.2)	18.2 (21.3)	9.6 (14.4)	<.001[a,b]
Significant manic symptoms, %	10.3	9.5	4.6	.038[a,b]
First-degree family history, %	84.3	83.8	72.9	<.001[a,b]
Presence of comorbid anxiety disorder, %				
Panic disorder with agoraphobia	22.4	26.4	9.7	<.001[a,b]
Panic disorder without agoraphobia	8.7	10.9	7.1	.373
Social phobia	36.9	35.3	20.2	<.001[a,b]
Agoraphobia	7.1	6.5	5.9	.830
Generalized anxiety disorder	37.2	31.3	18.5	<.001[a,b]
Comorbid alcohol dependence, %	21.9	23.4	18.1	.353

[a]Severe melancholic versus moderate severity was significantly different ($P < .05$).
[b]Severe atypical versus moderate severity was significantly different ($P < .05$).
Abbreviation: IQR = interquartile range.

class 3. Second, within the more severe subtypes (classes 1 and 2), there were marked differences in symptom patterns and characteristics; class 1 appeared to represent melancholic depression, while class 2 endorsed reversed vegetative symptoms representing a more atypical pattern and was associated with a high body mass index, possibly indicating that this latter type is linked to metabolic abnormalities. To further explore the differences between classes, we performed multinomial logistic regression comparing the 2 severe classes with the moderate class and the severe classes with each other. All variables used in Tables 2 and 3 with an overall $P < .10$ were included as covariates.

Table 4 presents the results from the multivariable, multinomial logistic regression analyses. When compared to the

Table 3. Demographic, Psychosocial, and Physical Health Characteristics of the Identified Latent Classes (N = 818)

Characteristic	Class 1, Severe Melancholic, n = 379	Class 2, Severe Atypical, n = 201	Class 3, Moderate Severity, n = 238	Overall *P* Value
Demographic				
Age, mean (SD), y	41.5 (11.9)	40.6 (11.3)	42.8 (13.1)	.14
Sex, female, %	65.4	73.1	63.4	.08
Education, mean (SD), y	11.4 (3.3)	11.4 (3.3)	11.4 (2.9)	.99
Psychosocial				
WHODAS functioning score, mean (SD)	46.4 (15.3)	44.5 (14.7)	28.5 (14.7)	< .001[a,b]
Neuroticism score, mean (SD)	44.4 (6.1)	44.4 (5.9)	38.7 (6.8)	< .001[a,b]
Extraversion score, mean (SD)	31.1 (6.6)	31.4 (6.5)	35.7 (6.1)	< .001[a,b]
Childhood trauma index, median (IQR)	1 (2)	1 (2)	1 (2)	< .001[a,b]
No. of negative life events, median (IQR)	1 (1)	0 (1)	0 (1)	.04[a,c]
Physical health				
Physical activity as 1,000 metabolic-equivalent minutes/week, mean (SD)	3.2 (3.2)	3.6 (3.3)	3.4 (3.1)	.36
Current smoking, yes, %	52.8	36.8	37.4	< .001[a,c]
No. of pain locations, mean (SD)	4.0 (1.7)	4.2 (1.7)	3.5 (1.6)	.001[a,b]
No. of somatic diseases, mean (SD)	0.4 (0.7)	0.4 (0.7)	0.3 (0.7)	.35
Cardiovascular disease, yes, %	8.8	6.5	6.3	.44
Diabetes, yes, %	6.5	7.1	3.4	.19
Body mass index, mean (SD)	25.3 (5.0)	28.3 (5.7)	25.4 (4.8)	< .001[b,c]

[a]Severe melancholic versus moderate severity was significantly different ($P < .05$).
[b]Severe atypical versus moderate severity was significantly different ($P < .05$).
[c]Severe atypical versus severe melancholic was significantly different ($P < .05$).
Abbreviations: IQR = interquartile range, WHODAS = World Health Organization Disability Assessment Schedule II.

Table 4. Odds Ratios and 95% CIs for the Multivariable Comparison of the 3 Identified Latent Classes

Characteristic	Comparison of Severe Classes Versus Moderate Class[a]: Severe Melancholic Class, Odds Ratio (95% CI)	Comparison of Severe Classes Versus Moderate Class[a]: Severe Atypical Class, Odds Ratio (95% CI)	Comparison Subtypes: Atypical Class Versus Melancholic Class,[b] Odds Ratio (95% CI)
Clinical psychiatric			
Age at onset, per 10 years	0.98 (0.83–1.16)	0.83 (0.69–1.01)**	0.85 (0.72–0.99)*
Duration, per 6 depressed months	1.14 (1.04–1.25)*	1.12 (1.01–1.24)*	0.98 (0.91–1.06)
Significant manic symptoms	0.95 (0.41–2.20)	1.27 (0.51–3.15)	1.33 (0.71–2.52)
Family history of depressive disorder	1.69 (1.03–2.78)*	1.61 (0.92–2.82)**	0.95 (0.57–1.59)
Presence of comorbid anxiety disorder			
Panic disorder with agoraphobia	1.21 (0.68–2.18)	1.65 (0.89–3.08)	1.36 (0.86–2.16)
Social phobia	0.75 (0.47–1.21)	0.74 (0.44–1.25)	0.99 (0.65–1.50)
Generalized anxiety disorder	1.40 (0.88–2.25)	1.03 (0.61–1.73)	0.73 (0.49–1.09)
Demographic			
Sex, female	0.87 (0.56–1.36)	1.33 (0.81–2.19)	1.52 (0.99–2.32)**
Psychosocial			
WHODAS functioning score	1.07 (1.05–1.09)*	1.06 (1.04–1.07)*	0.99 (0.97–0.99)*
Neuroticism score	1.05 (1.01–1.10)*	1.07 (1.03–1.12)*	1.02 (0.98–1.05)
Extraversion score	0.95 (0.92–0.99)*	0.95 (0.92–0.99)*	1.00 (0.97–1.03)
Childhood trauma index	1.22 (1.02–1.45)*	1.05 (0.86–1.27)	0.86 (0.74–1.00)**
No. of negative life events	0.99 (0.83–1.19)	0.86 (0.70–1.07)	0.87 (0.73–1.04)
Physical health			
No. of pain locations	1.03 (0.91–1.16)	1.04 (0.91–1.20)	1.01 (0.90–1.14)
Current smoking	1.47 (0.98–2.21)**	0.84 (0.53–1.33)	0.57 (0.39–0.84)*
Body mass index	0.97 (0.93–1.01)	1.09 (1.04–1.14)*	1.13 (1.09–1.17)*

[a]Moderate class is the reference.
[b]Melancholic class is the reference.
*$P < .05$, **$P < .10$.
Abbreviation: WHODAS = World Health Organization Disability Assessment Schedule II.

moderate class, those in the severe melancholic class were more likely to report a positive family history of depression and a higher childhood trauma score, and those in the severe atypical class had a higher body mass index. Both severe classes were more likely to have longer duration, less favorable scores on WHODAS functioning, more neuroticism, and less extraversion than the moderate class. When we directly compared class 2 (severe atypical) with class 1 (severe melancholic), it was apparent that a younger age at onset, better functioning, and a higher body mass index were associated with a higher risk of having a severe atypical symptom pattern, whereas current smoking was significantly more prevalent in the class with the severe melancholic symptom pattern.

As body mass index was found to be a significant variable in 2 of 3 comparisons (see Table 4) and because we wanted to further explore potential metabolic abnormalities within classes, the prevalence of metabolic syndrome was compared

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Table 5. Odds Ratios and 95% CIs for Metabolic Syndrome and the Separate Criteria for Metabolic Syndrome[a]

Variable	Comparison Subtypes: Atypical Class Versus Melancholic Class,[b] Odds Ratio (95% CI)
Metabolic syndrome	2.17 (1.38–3.42)*
Separate criteria for metabolic syndrome	
Waist circumference (> 102 cm in men or > 88 cm in women)	2.30 (1.59–3.35)*
Triglycerides (≥ 1.7 mmol/L)	1.93 (1.25–2.99)*
HDL cholesterol (< 1.03 mmol/L in men or < 1.30 mmol/L in women)	1.45 (0.90–2.33)
Blood pressure (≥ 130/85 mm Hg or taking medication for hypertension)	1.21 (0.83–1.77)
Blood glucose (≥ 6.1 mmol/L or taking medication for elevated glucose)	1.03 (0.59–1.79)

[a]Models were corrected for all variables presented in Table 4 except body mass index; all criteria were entered into separate models.
[b]Melancholic class is the reference.
*$P < .05$.
Abbreviation: HDL = high-density lipoprotein.

between the severe melancholic and severe atypical classes. The prevalence of metabolic syndrome was significantly higher in the severe atypical class (25.5%) compared to the severe melancholic class (15.5%; $P = .004$). Also, in multivariate logistic regression analyses, the metabolic syndrome significantly predicted class membership (Table 5). Of the separate metabolic syndrome criteria—especially those representing the fat-related component, large waist circumference and high triglycerides, but not the other metabolic abnormalities, were more prevalent among the severe atypical class (Table 5).

DISCUSSION

The first aim of this study was to identify empirically valid subtypes of depression on the basis of symptomatology. We identified 3 subtypes. The first class (severe melancholic depression: prevalence, 46.3%) was characterized by weight loss, decreased appetite, insomnia, and relatively high probabilities on other melancholic symptoms such as lack of responsiveness, early morning awakening, and a worse mood in the morning. Class 2 (severe atypical depression: prevalence, 24.6%) was characterized by increased appetite, weight gain, and leaden paralysis. The third class (moderate depression: prevalence, 29.1%) had the lowest probabilities across all symptoms. Overall, classes were mainly differentiated by severity (moderate vs severe) and the nature of symptoms (melancholic vs atypical).

The second aim of the study was to test whether these classes yield meaningful categories in terms of comorbidity and underlying risk factors and characteristics (clinical psychiatric, psychosocial, and physical health factors). Classes were indeed found to have distinct characteristics. The severe melancholic class was characterized by relatively many smokers and a history of childhood trauma. The severe atypical class was associated with female gender, a higher body mass index, and more metabolic syndrome, suggesting that metabolic abnormalities play an important role in this subtype. The third class, of moderate severity, was characterized overall by more favorable characteristics (eg, better functioning, lower neuroticism, and higher extraversion scores) as compared to the first 2 classes.

Our findings are, in a certain respect, in line with an earlier latent-class-analysis study in the general population, which also identified a differentiation in subclasses on the basis of severity.[12] In addition, previous latent-class-analysis studies identified atypical subtypes, but these were generally based on the presence of increased appetite/weight and hypersomnia only and did not include all other *DSM-IV* criteria of atypical depression, such as mood reactivity, leaden paralysis, and interpersonal sensitivity.[11–13] Our latent class analysis, which did include all melancholic and atypical symptoms, did not consistently confirm the existence of an atypical depression class with all the symptoms defined in the *DSM-IV* specifier. This finding is in line with previous studies that called into question the current definition of atypical depression.[8–10] Certain symptoms, such as interpersonal sensitivity and responsiveness, were not much more likely in the severe atypical class (class 2). In fact, the driving symptoms in this class were mainly somatic or metabolic related, with a key role for appetite and weight increase.

The subtypes identified in our study had different symptom patterns but were also accompanied by distinct characteristics, which point to differential potential etiologic mechanisms. The severe melancholic class distinguished itself in having a higher proportion of smokers. Mechanisms involved may include a shared genetic vulnerability for both nicotine dependence and depression—and the use of smoking as a form of self-medication. According to this last theory, mood-altering properties of nicotine are especially reinforcing to depressed persons who are prone to experience negative affect.[36] Melancholic individuals further experienced more childhood trauma, which has been found to be associated with melancholic symptoms in 1 study[37] but not in others[38,39] and could result in an enhanced vulnerability for depression.[40]

As for the atypical class, not only did this class endorse the more somatic depressive symptoms, such as increased appetite and weight gain, but it was also associated with a higher body mass index and metabolic syndrome. This finding may suggest that this subtype involves a metabolic component. McIntyre and colleagues[28] previously suggested that metabolic abnormalities may be a defining component in depressive disorders. The relationship with the metabolic syndrome seemed to be driven by the fat-related indicators—abdominal obesity and triglycerides. It is well known that depression is associated with somatic diseases like cardiovascular disease and diabetes,[29,41,42] in which metabolic abnormalities may play a linking role. No differences in the prevalence of these somatic diseases were observed in our study, but this finding may be explained by the fact that our sample was relatively young, while these conditions most often occur later in life. If the specific subtype is indeed a metabolic form of depression, then several

pathways could be underlying, like those of increased inflammatory immune responses, increased HPA-axis activity, and leptin resistance.[43–45] We further observed a preponderance of women and an earlier age at onset in this class, which is in line with earlier observations[46–49] of samples with atypical symptoms (such as increased appetite and weight gain).

The third class found in this study, which represented a subtype of moderate severity, had much lower probabilities of endorsing depressive symptoms, revealing the important role of depression severity. Univariable analyses showed lower psychiatric comorbidity and better psychosocial functioning (better WHODAS functioning, lower neuroticism, and higher extraversion scores), and, in multivariable analyses, better psychosocial functioning remained significantly associated with the moderate class, confirming that this class represents a less severe form of depression in which functioning is less impaired.

We found that identified subtypes can be differentiated by severity and by the nature of symptoms and that these subtypes have distinct characteristics. What implications do these findings have? The differences in severity suggest that persons with a severe melancholic or severe atypical subtype most likely require more intensive treatment than persons with the moderate subtype. The higher frequency of metabolic abnormalities in the atypical subtype indicates that treatment of these cases should not only be aimed at psychiatric symptoms but should also consider somatic abnormalities.

The present study is one of the largest to date to investigate the existence of depressive subtypes in a large cohort of depressed subjects; however, some limitations should be noted. Classification of persons based on the most likely class membership may mean that, for some persons, classification is highly accurate (with 1 posterior probability close to 1 and the 2 other probabilities close to 0), while, for others, the posterior probabilities lie much closer to each other, making classification less accurate. In subsequent analyses of class differences, these differences between persons are not taken into account, which may lead to distorted estimates and standard errors. Multinomial logistic regression restricted to persons with a posterior probability > 0.80 showed that, with exception of the family history and extraversion findings, all significant findings in Tables 4 and 5 remained, indicating that classification inaccuracy had limited effect on the overall conclusions (data not shown). Further, by including only outpatients from the community we captured the largest and therefore most informative group of persons from a clinical point of view, but our results may not be generalizable to the most severe group of hospitalized patients. It further should be noted that discrepancies between CIDI and IDS items may exist due to a different administration mode. Also, our analyses were cross-sectional. Although the results of this study support the existence of a melancholic symptom pattern and an atypical symptom pattern, the stability of these patterns over time in different episodes and their value in predicting course and outcome of depression still need to be evaluated in longitudinal analyses. Finally, with respect to atypical depression and its metabolic abnormalities, we cannot infer causal relationships between these factors from these analyses.

To conclude, this study identified 3 subtypes of depression, each with a distinct symptom pattern and distinct characteristics. In addition to a moderate symptom class, we found 2 classes with more severe symptoms. The first of these severe classes had a melancholic symptom pattern, while the other had an atypical symptom pattern. The fact that the atypical class was characterized by somatic depressive symptoms and metabolic abnormalities indicates that there may be a metabolic component involved in this subtype. Thus, both severity (ie, severe vs moderate) as well as the nature of depressive symptoms (ie, melancholic vs atypical) were found to be important for the differentiation of subtypes. Distinguishing these subtypes may be useful for further etiologic as well as clinical longitudinal research.

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