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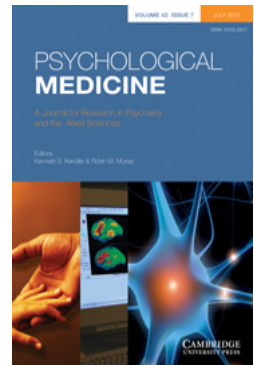
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Course trajectories of unipolar depressive disorders identified by latent class growth analysis

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Background. Current classification of unipolar depression reflects the idea that prognosis is essential. However, do DSM categories of major depressive disorder (MDD), dysthymic disorder (Dysth) and double depression (DD = MDD + Dysth) indeed adequately represent clinically relevant course trajectories of unipolar depression? Our aim was to test DSM categories (MDD, Dysth and DD) in comparison with empirically derived prognostic categories, using a prospectively followed cohort of depressed patients.

Method. A large sample ($n=804$) of out-patients with unipolar depression were derived from a prospective cohort study, the Netherlands Study of Depression and Anxiety (NESDA). Using latent class growth analysis (LCGA), empirically derived 2-year course trajectories were constructed. These were compared with DSM diagnoses and a wider set of putative predictors for class membership.

Results. Five course trajectories were identified, ranging from mild severity and rapid remission to high severity and chronic course trajectory. Contrary to expectations, more than 50% of Dysth and DD were allocated to classes with favorable course trajectories, suggesting that current DSM categories do not adequately represent course trajectories. The class with the most favorable course trajectory differed on several characteristics from other classes (younger age, more females, less childhood adversity, less somatic illnesses, lower neuroticism, higher extraversion). Older age, earlier age of onset and lower extraversion predicted poorest course trajectory.

Conclusions. MDD, Dysth and DD did not adequately match empirically derived course trajectories for unipolar depression. For the future classification of unipolar depression, it may be wise to retain the larger, heterogeneous category of unipolar depression, adopting cross-cutting dimensions of severity and duration to further characterize patients.

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Key words: Course, depressive disorders, latent class growth analysis.

Introduction

From Kraepelin to modern times, the course trajectory has been an important criterion for validating psychiatric syndromes. In 1980, course was incorporated into the diagnostic criteria of various subtypes of depressive disorders of the *Diagnostic and Statistical Manual* (DSM), resulting in the diagnostic categories of major depressive disorder (MDD) and dysthymic disorder (Dysth). Over the years, various other unipolar depressive syndromes or subtypes have been defined, including double depression (DD: the co-occurrence of MDD and Dysth).

This diversity among depressive disorders has been the topic of debate, with much of the controversy focusing on whether MDD and Dysth are qualitatively distinct disorders or represent different ends of a severity continuum (Shankman & Klein, 2002). The enormous overlap in diagnoses between MDD and Dysth (Klein *et al.* 2006) and the failure to demonstrate differences between MDD and Dysth on a broad range of demographic, clinical, psychosocial, family history and treatment response variables (Keller & Lavori, 1984; Angst & Wicki, 1991; McCullough *et al.* 2003) fuelled this debate. Judd *et al.* (2002) concluded that Dysth is an integral component of the longitudinal structure of MDD, with each symptom level representing a different phase of illness intensity, activity and severity (Judd & Akiskal, 2000). By contrast, there is evidence to support the existence of specific diagnostic subtypes within the larger group of affective

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disorders, such as chronic depression (McCullough *et al.* 2003).

To study the validity of various depressive subtypes, statistical methods designed to cluster heterogeneous outcomes naturally occurring in the data can be helpful. Free from any *a priori* assumptions, data-driven techniques, such as latent class growth analysis (LCGA), that cluster persons based on their trajectories of a given outcome may thus result in a more empirically based classification that can then be compared with the DSM classification of unipolar affective disorders. This method can be used to determine whether different depressive subtypes based on course trajectories can be distinguished and to what extent this corresponds with the current diagnostic categories. To date, several studies have used this approach to assess course trajectories in depressive disorders across adolescence (Stoolmiller *et al.* 2005; Olino *et al.* 2010) and among mothers throughout the childrearing phase (Campbell *et al.* 2009; Skipstein *et al.* 2010), or among bereaved caregivers (Li 2005; Taylor *et al.* 2008). Colman *et al.* (2007) examined course trajectories over the life course among the general population. However, some of these studies were limited by the inclusion of men only (Stoolmiller *et al.* 2005), use of different measures or informants over time (Stoolmiller *et al.* 2005; Colman *et al.* 2007), or combined depressive and anxiety symptoms (Colman *et al.* 2007). Hence, comparison of latent course trajectories with current DSM categories for depressive subtypes is lacking.

In this study we aimed to identify clinically relevant course trajectories, derived from LCGA, in a large cohort of currently depressed subjects participating in the Netherlands Study of Depression and Anxiety (NESDA). To determine whether the identified classes represent different course trajectories, we briefly validated the classes by means of some external validators. Next, we compared the identified course trajectories with the current diagnostic categories of MDD, Dysth and DD. If DSM categories identify clinical course trajectories sufficiently, we would expect MDD to be the prominent diagnosis in a class with best course trajectory and, additionally, most persons with MDD should be allocated to the class with the best course trajectory. Likewise, Dysth should be the most prominent diagnosis in the class with a chronic course, albeit of moderate severity, and most persons with Dysth should be allocated to this class. Finally, we expected DD to be the most prominent diagnosis in the class, representing a chronic and severe course trajectory, and most persons with DD to be allocated to this particular class. In addition, because DSM categories suggest particular course trajectories, we examined to what extent DSM

categories predict course trajectories. Finally, we explored the characteristics of each identified class and examined putative predictors of class membership, and hence course trajectory. In previous studies, sociodemographics, co-morbid anxiety disorders (Hayden & Klein, 2001), age of onset of depressive symptoms (Klein *et al.* 1999; Angst *et al.* 2009), childhood adversity (Hayden & Klein, 2001; Rhebergen *et al.* 2011), somatic co-morbidity (Angst *et al.* 2009), neuroticism (Hayden & Klein, 2001; Rhebergen *et al.* 2011) and a family history of depression (Klein *et al.* 1999; Stoolmiller *et al.* 2005; Olino *et al.* 2010) have been demonstrated to predict course trajectories. However, some inconsistencies exist. In this study, we examine the predictive value of sociodemographics (age, gender, level of education), co-morbid anxiety disorder, age of onset, childhood adversity, number of somatic illnesses, neuroticism, extraversion, and the presence of a family member with depression for class membership.

Method

Study sample

The NESDA is designed to investigate the course and consequences of depressive and anxiety disorders. It is a multisite naturalistic cohort study of adults (aged 18–65 years) recruited from the general population, general practices, and mental health organizations. The method of recruitment was extensively described elsewhere (Penninx *et al.* 2008). The study protocol was approved by the Ethical Review Board of the VU University Medical Center and written informed consent was obtained from all participants. For the present analysis, we selected respondents from the NESDA baseline assessment with a 6-month MDD ($n=1115$) and/or a 6-month Dysth ($n=305$) (total $n=1158$). Of the 1158 persons at baseline, 946 (81.7%) could be followed up after 2 years. Attrition in the study population was higher among those with younger age [odds ratio (OR) 1.02], lower educational level (OR 1.08) and those with DD (OR 1.47), but was not associated with sex, MDD or Dysth. Attrition for the NESDA has been described more extensively elsewhere (Lamers *et al.* 2011). To exclude persons already in remission, we restricted the sample to 804 subjects with a 6-month depressive diagnosis who confirmed symptoms in the month prior to baseline at either the Composite Interview Diagnostic Instrument (CIDI) recency questions or the Life Chart Interview (LCI; Lyketsos & Nestadt, 1994) recorded at baseline. Of this final sample, 65.4% were female, with a mean age of 42.0 ± 12.2 years and 11.6 ± 3.3 years of education. Diagnoses were established using CIDI version

2.1, according to DSM-IV criteria (WHO, 1998). The CIDI is a structured interview with acceptable reliability and validity (Wittchen, 1994; Wittchen *et al.* 1996). It was administered by specially trained research staff.

Measurements

Symptoms of depression

The LCGA was based on depressive symptoms derived from the LCI (Lyketsos & Nestadt, 1994). The LCI was assessed both at baseline and after 2 years of follow-up by a trained interviewer. Baseline LCI served to compute a measure of duration of depressive symptomatology. LCI at the 2-year follow-up provided the data for the LCGA. First, the occurrence of life events in a particular period was explored to refresh memory and then the presence of depressive symptoms was assessed during each month of the successive years. In addition, for each month with reported depressive symptoms, the self-reported burden of the symptoms was assessed on a five-point scale, ranging from no or minimal severity, to mild, moderate, severe, or very severe. As the LCI at follow-up retrospectively assessed the burden of depressive symptoms over 2 years, this resulted in 24 scores of perceived burden of depressive symptoms. None of the 804 respondents had missing data on the LCI at follow-up.

External validators

To assess the validity of the identified course trajectories, we examined the distribution of various putative validators across the identified classes. We examined the total scores on the 30-item Inventory of Depressive Symptomatology – Self Report version (IDS-SR, www.ids-qids.org; Rush *et al.* 1986, 1996), both at baseline and after 2 years. In addition, the percentage of decline in IDS score during 2 years of follow-up was calculated. Next, level of functioning was measured by total scores on the World Health Organization Disability Assessment Schedule II (WHO-DAS; Chwastiak & Von Korff, 2003), both at baseline and after 2 years of follow-up. Again the percentage of improvement on the WHO-DAS over 2 years of follow-up was calculated. The WHO-DAS queries difficulties in various domains of life during the past 30 days. We computed total scores based on five domains of the WHO-DAS (cognition, mobility, self-care, interpersonal interactions, participation in society). Finally, we examined the presence of a 6-month CIDI diagnosis of depression and/or Dysth at follow-up.

Depressive categories

To compare the identified course trajectories with DSM-IV categories and also to examine the predictive value of DSM-IV categories on class membership, we examined the relative distribution of depressive disorders at baseline per class and across classes (i.e. the percentages of baseline disorders across the rows). A depressive disorder at baseline consisted of a 6-month CIDI MDD and/or Dysth at baseline. Three depression groups were defined: major depressive disorder (MDD) ($n=573$) consisted of those fulfilling an MDD and no Dysth diagnosis; dysthymic disorder only (Dysth) ($n=34$) consisted of those with a dysthymic disorder but not an MDD diagnosis; and DD ($n=197$) was defined as Dysth with a co-morbid MDD, ignoring the sequence of onset of Dysth and MDD.

Putative predictors of class membership

Although DSM-IV depressive categories are partly based on course and severity measures, we examined additional course and severity markers. This enabled us to perform multivariate multinomial logistic regression analyses to test whether DSM-IV categories have some additional value in the prediction of class membership over other baseline severity and duration measures. As a measure of severity, we used IDS-SR at baseline. This measure was also used as a putative external validator for the identified course trajectories. As a measure of duration, we calculated the number of months with depressive symptoms prior to baseline, using LCI data from the past 5 years prior to baseline, recorded at baseline. Next, we examined the distribution of several other characteristics across the identified course trajectories and their predictive value on class membership (age, gender, level of education, co-morbid anxiety disorder, age of onset, childhood adversity, number of somatic illnesses, neuroticism, extraversion, and the presence of a family member with depression). Age was included as a continuous variable. Level of education was measured by years of education. Co-morbid anxiety disorder included a 6-month diagnosis of panic disorder (with or without agoraphobia); agoraphobia without history of panic disorder; social phobia and/or generalized anxiety disorder, as recorded by the CIDI. Age of onset of the index disorder was assessed in the CIDI. Earliest age was used for those with co-morbid disorders. Childhood adversity was assessed using a structured interview from the Netherlands Mental Health Survey and Incidence Study (NEMESIS; Bijl *et al.* 1998), in which respondents were asked to retrospectively recall whether they had experienced emotional neglect, psychological abuse, physical abuse or sexual abuse before the age of 16 years. A childhood index was

computed (range 0–4), as used previously (Wiersma *et al.* 2009). The presence of somatic conditions was assessed in the baseline interview. A count of the number of somatic diseases (including cardiovascular disease, diabetes, lung disease, osteoarthritis, cancer, gastrointestinal disease, liver disease, epilepsy, thyroid disease) for which medical treatment is received was constructed. Neuroticism and extraversion were assessed by means of the neuroticism and extraversion dimension of the NEO (Neuroticism–Extroversion–Openness) personality questionnaire, a 60-item questionnaire measuring five personality domains (Costa & McCrae, 1995). The presence of a depressive disorder in first-degree family members was assessed using the family tree method (Fyer & Weissman, 1999).

Statistical analyses

To identify distinct classes based on different course trajectories, we performed LCGA, which is used to identify different classes of persons showing a comparable course of symptoms (Nylund *et al.* 2007). It starts with one class, suggesting one type of course fitting for all persons. Then successively more classes are added to determine the best-fitting model. Because LCGAs and other mixture models are susceptible to converging on local rather than global solutions (Nylund *et al.* 2007), we used multiple random starting values for the estimated models (500 repeats with 20 final optimizations). We increased the number of random starting values when necessary to avoid local solutions. We first fitted standard LCGA with intercept and linear effect of time. Then we successively added a quadratic and cubic slope factor to allow for curved trajectories. These additional growth factors will add computational burden and may add to convergence problems and model instability. Therefore, we fixed the variance and covariance estimates in all models to zero to aid convergence (Jung & Wickrama, 2008). The LCI score was treated in the LCGA as a continuous variable. The LCGAs were conducted using M-plus version 5 (Muthén & Muthén, 2007).

To determine which model best fitted the data, we combined the smallest Bayesian information criterion (BIC), the Lo–Mendell–Rubin (LMR) likelihood ratio test, entropy and proportions of the classes with interpretability and clinical relevance of the latent trajectory classes. Of the traditionally used information criteria, such as Akaike’s Information Criterion (AIC) and BIC, the latter performs best (Nylund *et al.* 2007). The accuracy of the AIC decreases as the sample size increases because there is no adjustment for sample size (Nylund *et al.* 2007). Lower BIC values indicate better model fit. The LMR test provides a

p value that indicates whether the $k-1$ class model is rejected in favor of the k class model. Finally, entropy, as a measure of the quality of classification, is presented for models with more than one class, in addition to the proportions of individuals in each class. To identify clinically relevant classes, we only considered models with classes greater than 5%.

After the identification of the classes, persons were assigned to their most likely class based on model probabilities. Then, we examined the validity of the identified classes by testing the distribution of the potential validators across classes, and we compared the characteristics of participants across the identified classes using two-tailed χ^2 statistics for categorical variables and one-way analysis of variance (ANOVA) statistics for continuous variables. Additional pairwise comparisons were performed to test for differences between pairs of classes. Multivariate, multinomial logistic regression analyses were conducted to examine determinants of class membership. First, the association between DSM categories and class membership was examined (model 1). Second, the association between severity and duration measures and class membership was examined (model 2). Third, both DSM categories and severity and duration measures were combined in one model to test any additional predictive value of DSM categories above measures of severity and duration in predicting class membership (model 3). Fourth, the association between other characteristics and class membership was examined. All comparisons were conducted using SPSS version 15.0 (SPSS Inc., USA).

Results

In Table 1 the maximum likelihood values, the BIC, the entropy, the LMR likelihood ratio tests and the proportion of individuals in each class of each LCGA model are presented. The standard linear model provided a good representation of the various course trajectories. Addition of cubic and quadratic growth factors resulted in non-fitting models (data not shown). Non-convergence and solutions with inadmissible estimates occurred. Therefore, we altered the random starts to 2000/750, but this still did not yield adequate estimates. To test the assumption that cubic or quadratic slopes might be present in some but not all classes, we tried to constrain each respective class to follow a linear model, while allowing the other classes cubic or quadratic trajectories. This also did not yield fitting models. Hence, both cubic and quadratic models were considered as non-fitting. Although the BIC values continued to diminish in the linear model, the LMR test failed to reach significance, from the

Table 1. Parameters of fit of latent class growth analysis (LCGA)

Linear model	Class	Maximum likelihood	BIC	Entropy	LMR test		Proportion of individuals in class						
					2LL	<i>p</i>	1	2	3	4	5	6	
1.1	1												
1.2	2	-27123.643	54441.248	0.96	7895.32	<0.001	0.58	0.42	-	-	-	-	-
1.3	3	-25956.525	52127.077	0.96	2334.24	0.04	0.16	0.50	0.34	-	-	-	-
1.4	4	-25267.652	50769.397	0.96	1377.75	0.03	0.10	0.49	0.15	0.26	-	-	-
1.5	5	-24752.198	49758.553	0.97	1030.90	0.01	0.44	0.24	0.10	0.15	0.07		
1.6	6	-24438.526	49151.274	0.97	627.344	0.42	0.23	0.09	0.43	0.09	0.05	0.12	

BIC, Bayesian Information Criterion; LMR, Lo-Mendell-Rubin; LL, log likelihood.

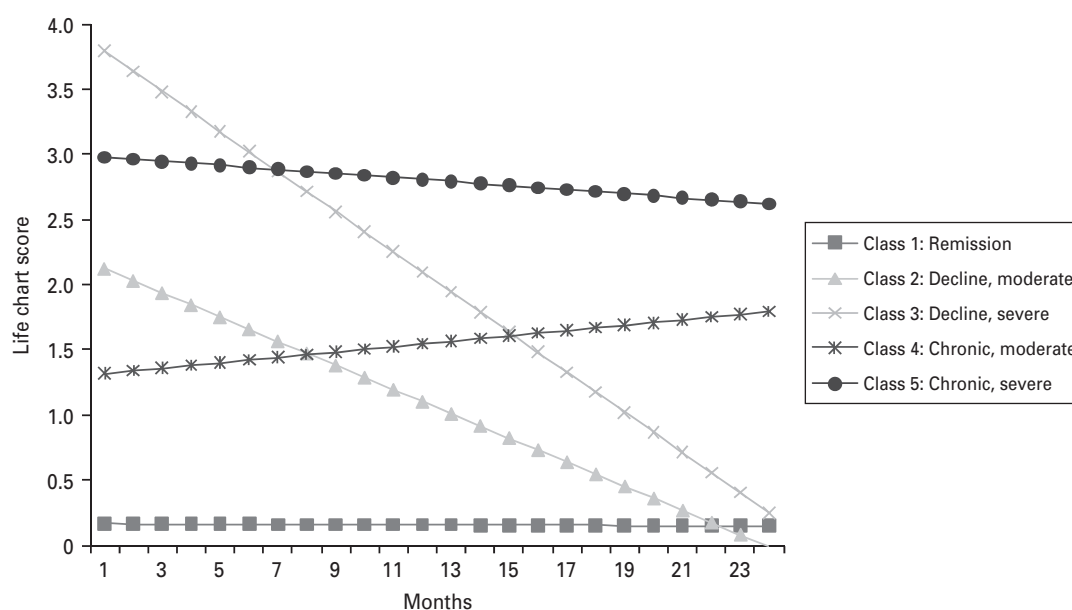


Fig. 1. Identified course trajectories, derived from latent class growth analysis (LCGA). To facilitate interpretation, class numbering corresponds to increasing severity and/or duration of depressive symptoms.

six-class model onwards. Hence, the five-class linear model provided the best fit for the observed data.

Figure 1 shows the course trajectories of the five latent classes identified. The first class (prevalence 44.3%) was characterized by a rapid remission of symptoms. The second class (prevalence 24.1%) showed a decline of symptoms, albeit slower than class 1. In addition, the burden of depressive symptoms at baseline was higher compared to the first class. The third class (prevalence 9.8%) showed a gradual decline of symptoms, but initial depression severity was higher than both previous classes. The fourth class (prevalence 15.0%) had a chronic course trajectory, of moderate depression severity. Finally, the fifth class (prevalence 6.7%) had a chronic course trajectory, with the highest burden of depressive symptoms.

Validation of the course trajectories

We tested the validity of the five-class model by examining the distribution of severity measures (IDS score, level of functioning) and measures of change (decline in IDS score, improvement in functioning) across the course trajectory classes identified (Table 2). As expected, both extremes, class 1 (remission) and class 5 (chronic severe), were markedly distinct from each other on all parameters. Next, we expected that classes of similar severity at baseline (classes 2 and 4, classes 3 and 5) would not differ on baseline severity measures but would differ on measures of change. This was confirmed. In addition, we expected no differences between chronic course trajectories (classes 4 and 5) on measures of change (decline in IDS score,

Table 2. Distribution of putative validators across the identified latent course trajectories

	Class 1 (remission, mild severity) <i>n</i> = 356 (44.3%)	Class 2 (decline, moderate severity) <i>n</i> = 194 (24.1%)	Class 3 (decline, severe) <i>n</i> = 79 (9.8%)	Class 4 (chronic, moderate severity) <i>n</i> = 121 (15.0%)	Class 5 (chronic, severe) <i>n</i> = 54 (6.7%)	Overall statistics χ^2 (df)/ <i>F</i> (df) <i>p</i> value
IDS at baseline, mean (s.d.)	30.3 (10.8)	35.6 (10.4)	38.6 (10.5)	35.7 (11.5)	41.1 (9.9)	21.9 (4) <0.001
IDS at 2-year follow-up, mean (s.d.)	18.1 (9.8)	25.3 (12.1)	28.8 (13.4)	28.0 (13.0)	33.4 (11.6)	40.5 (4) <0.001
Percentage decline in IDS score during 2-year follow-up	36.2 (34.6)	27.4 (32.8)	23.3 (35.2)	19.1 (32.5)	17.2 (25.8)	9.1 (4) <0.001
Functioning (high score = low functioning) at baseline, mean (s.d.)	67.7 (17.7)	75.4 (17.5)	80.0 (19.5)	73.9 (17.5)	81.3 (15.2)	15.0 (4) <0.001
Functioning (high score = low functioning) after 2-year follow-up, mean (s.d.)	25.2 (18.1)	34.7 (21.3)	41.1 (21.3)	37.9 (21.9)	51.4 (23.1)	29.9 (4) <0.001
Percentage improvement in functioning during 2-year follow-up	63.5 (25.6)	54.8 (24.8)	48.1 (26.3)	50.1 (24.0)	37.1 (25.4)	19.1 (4) <0.001
Current CIDI diagnosis of depression after 2-year follow-up, %	24.5	60.3	62.0	73.6	100	185.8 (4) <0.001

IDS, Inventory of Depressive Symptomatology; s.d., standard deviation; df, degrees of freedom.

Significant differences across classes ($p < 0.05$): Class 1 *versus* 2: all parameters significantly different; Class 1 *versus* 3: all parameters significantly different; Class 1 *versus* 4: all parameters significantly different; Class 1 *versus* 5: all parameters significantly different; Class 2 *versus* 3: IDS at baseline, IDS at 2 years (functioning baseline $p = 0.06$), functioning 2 years, improvement in functioning; Class 2 *versus* 4: decline in IDS, CIDI disorder after 2 years (IDS at 2 years $p = 0.06$); Class 2 *versus* 5: all parameters significantly different; Class 3 *versus* 4: (IDS at baseline $p = 0.07$), functioning baseline; Class 3 *versus* 5: IDS at 2 years, functioning at 2 years, improvement in functioning, CIDI disorder after 2 years; Class 4 *versus* 5: all parameters significantly different, except change in IDS.

improvement in functioning), whereas difference in severity measures were expected. This was also confirmed. The course trajectory over 2 years of class 3 (decline, severe) could only partly be confirmed by external validators. Despite expectations that class 3 (decline, severe) would improve over time, severity measures of class 3 after 2 years were more like those of class 4 (chronic, moderate) (no significant differences, except baseline severity measures) than class 2 (decline, moderate). In addition, we expected classes 3 (decline, severe) and 4 (chronic, moderate) to differ on all parameters. However, they only differed significantly in baseline functioning. To conclude, our LCGA-identified model could largely be confirmed by external validators.

Depressive diagnoses

As presented in Table 3, we tested the distribution of the baseline DSM-IV categories of MDD, Dysth and DD across the trajectory classes identified. As expected, comparisons of the relative distribution of depressive disorders per class showed that the percentage of MDD gradually and significantly declined when course trajectories worsened, whereas the percentage of DD gradually rose. In addition, the fourth class (chronic, moderate) had the highest relative percentage of persons with Dysth (9.1%) and the fifth class (chronic, severe) had a relatively high percentage of persons with DD (44.4%). However, when DSM categories represent clinically relevant course types, persons with MDD should mainly be allocated to the most favorable course trajectory, whereas persons with Dysth and DD should mainly be allocated to the chronic classes. To examine this assumption, we compared the distribution of baseline depressive disorders across classes (i.e. the percentages of baseline disorders across the rows). As expected, MDD was most prevalent among the rapidly improving, mild class (class 1, 50%). However, almost two-thirds (61.7%) of the persons with Dysth at baseline were allocated to the best course trajectory classes (38.2% class 1; 23.5% class 2). Similarly, more than half of the persons with DD were allocated to the best course trajectory classes (28.4% class 1; 26.4% class 2), a significantly higher percentage compared to other classes. This is in contrast to our *a priori* assumptions.

To further test the association between DSM categories and course trajectories, we conducted multinomial multivariate logistic regression analyses. First, the association between DSM categories and class membership was examined (model 1) (reference class 1; rapid remission and mild severity). As shown in Table 4, the association between DD and class membership showed an increase in ORs across the

classes. Dysth was associated with class 4 (chronic, moderate) only. Next, the association between severity and duration measures and class membership was examined (model 2). IDS score was associated with class membership, with the highest odds for the severe classes [class 3: OR 2.03, 95% confidence interval (CI) 1.56–2.65; class 5: OR 2.56, 95% CI 1.86–3.52]. Number of months was associated with classes 3, 4 and 5, with similar ORs. Finally, both DSM categories and severity and duration measures were examined in one multivariate, multinomial, logistic regression model to test whether DSM categories would have additional predictive value over duration and severity measures only, in predicting class membership (model 3). Whereas the IDS score continued to predict class membership, DD was only associated with class 5 (chronic, severe). Dysth still predicted class membership for class 4.

Characteristics of the classes and their predictive value on course trajectories

Whereas class 1 significantly differed on a broad range of characteristics (lower age, more females, less childhood adversity, less somatic illnesses, lower neuroticism, higher extraversion) from the other classes, differences among the other four classes were less profound (Table 3). The fourth class (chronic, moderate) was significantly older than classes 1 and 3 and had a significantly higher number of somatic illnesses compared to classes 1 and 2. In addition, the fifth class (chronic, severe) had a lower age of onset compared to classes 1, 3 and 4, and a higher number of family members with depression compared to classes 2 and 4.

In multinomial multivariate logistic regression analyses (reference class 1; rapid remission and mild severity), lower extraversion was associated with class 2 (decline, severe) (OR 1.33, 95% CI 1.08–1.67) (Table 4). Higher neuroticism was associated with class 3 (decline, severe). For the two chronic classes more predictors could be identified. A chronic course trajectory of moderate severity (class 4) was associated with being male (OR 1.59, 95% CI 1.01–2.63), having more somatic illnesses (OR 1.26, 95% CI 1.02–1.55) and a higher level of neuroticism (OR 1.40, 95% CI 1.05–1.86). Similarly, a higher age (OR 1.45, 95% CI 1.03–2.04), an earlier age of onset (OR 1.79, 95% CI 1.23–2.63) and a lower level of extraversion (OR 1.49, 95% CI 1.04–2.13) predicted poorest course trajectory (chronic, severe). First-degree family members with depression resulted in high odds for the poorest course trajectory (class 5) (OR 2.57, 95% CI 0.75–8.76), albeit not reaching significance. In a *post-hoc* analysis comparing both chronic classes, a family history of depression was significantly associated with class 5

Table 3. Distribution of putative risk factors across the identified latent course trajectories

	Class 1 (remission, mild severity) <i>n</i> = 356 (44.3%)	Class 2 (decline, moderate severity) <i>n</i> = 194 (24.1%)	Class 3 (decline, severe) <i>n</i> = 79 (9.8%)	Class 4 (chronic, moderate severity) <i>n</i> = 121 (15.0%)	Class 5 (chronic, severe) <i>n</i> = 54 (6.7%)	Overall statistics χ^2 (df)/ <i>F</i> (df), <i>p</i> value
Baseline DSM diagnosis						
Depressive disorders in each class						
MDD	80.6	69.1	67.1	58.7	51.9	46.0 (8), <0.001
Dysth	3.7	4.1	0	9.1	3.7	
DD	15.8	26.8	32.9	32.2	44.4	
Depressive disorders across classes						
MDD (% of MDD at baseline, <i>n</i> = 573)	50.0	23.4	9.3	12.4	4.9	35.4 (4), <0.001
Dysth (% of Dysth at baseline, <i>n</i> = 34)	38.2	23.5	0	32.4	5.9	10.9 (4), 0.03
DD (% of DD at baseline, <i>n</i> = 197)	28.4	26.4	13.2	19.8	12.2	33.7 (4), <0.001
Severity/duration						
IDS at baseline, mean (s.d.)	30.3 (10.8)	35.6 (10.4)	38.6 (10.5)	35.7 (11.5)	41.1 (9.9)	21.9 (4), <0.001
Depressed months prior to baseline, mean (s.d.)	18.0 (15.6)	21.6 (16.7)	26.4 (17.9)	28.0 (18.8)	28.0 (16.8)	12.2 (4), <0.001
Other characteristics						
Age (years), mean (s.d.)	40.7 (12.5)	42.8 (12.5)	41.2 (11.8)	44.4 (10.9)	43.5 (11.6)	2.8 (4), 0.03
Gender, % female	69.3	63.4	67.1	59.5	57.4	6.2 (4), 0.18
Education, mean (s.d.)	11.7 (3.2)	11.5 (3.3)	11.2 (3.1)	11.3 (3.5)	11.9 (3.8)	0.7 (4), 0.59
Co-morbid anxiety disorder (any disorder), % yes	61.1	66.0	67.1	63.6	74.1	4.3 (4), 0.37
Age of onset of depression (years), mean (s.d.)	27.8 (12.2)	28.1 (13.1)	27.6 (13.8)	28.1 (12.7)	22.4 (11.6)	2.4 (4), 0.05
Childhood trauma, mean (s.d.)	1.1 (1.1)	1.3 (1.2)	1.4 (1.3)	1.4 (1.3)	1.4 (1.3)	2.6 (4), 0.04
No. of somatic illnesses, mean (s.d.)	0.6 (0.9)	0.7 (0.9)	0.8 (1.0)	1.0 (1.2)	0.8 (0.8)	3.14 (4), 0.01
Neuroticism, mean (s.d.)	41.5 (6.8)	43.3 (6.4)	44.5 (5.7)	43.6 (6.3)	44.3 (4.9)	6.6 (4), <0.001
Extraversion, mean (s.d.)	34.2 (6.6)	31.8 (6.1)	31.4 (7.2)	31.9 (5.8)	30.5 (7.0)	8.8 (4), <0.001
Family history of depression, % yes	85.1	84.0	87.3	79.3	94.4	7.2 (4), 0.13

MDD, Major depressive disorder; Dysth, dysthymia; DD, double depression (=MDD + Dysth); IDS, Inventory of Depressive Symptomatology; s.d., standard deviation; df, degrees of freedom.

Significant differences across classes ($p < 0.05$): Class 1 *versus* 2: MDD, DD, IDS baseline, months depressed, age, neuroticism, extraversion; Class 1 *versus* 3: MDD, DD, IDS baseline, months depressed, childhood adversity, neuroticism, extraversion; Class 1 *versus* 4: MDD, Dysth, DD, IDS baseline, months depressed, age, gender, childhood adversity, somatic illnesses, neuroticism, extraversion; Class 1 *versus* 5: MDD, DD, IDS baseline, months depressed, age of onset, childhood adversity, neuroticism, extraversion; Class 2 *versus* 3: (Dysth $p = 0.07$), IDS baseline, months depressed; Class 2 *versus* 4: MDD (Dysth $p = 0.07$), months depressed, somatic illnesses; Class 2 *versus* 5: MDD, DD, IDS baseline, months depressed, family with depression; Class 3 *versus* 4: Dysth, age; Class 3 *versus* 5: Age of onset; Class 4 *versus* 5: IDS baseline, age of onset, family with depression.

Table 4. Results from multivariate, multinomial, logistic regression analyses associating baseline diagnosis, severity and duration and other characteristics with the identified course trajectories, compared to the most favorable course trajectory (class 1: remission, mild severity; reference)

	Class 2 (decline, moderate severity)	Class 3 (decline, severe)	Class 4 (chronic, moderate severity)	Class 5 (chronic, severe)
Model 1: Baseline DSM diagnosis				
Depressive disorder				
MDD	Reference	Reference	Reference	Reference
Dysth	1.31 (0.53–3.24)	No dysth in class 3	3.41 (1.47–7.93)	1.57(0.34–7.32)
DD	1.98 (1.29–3.05)	2.51 (1.45–4.34)	2.81 (1.73–4.55)	4.38 (2.37–8.10)
Model 2: Severity/duration				
IDS score at baseline ^a	1.61 (1.33–1.95)	2.03 (1.56–2.65)	1.49 (1.19–1.87)	2.56 (1.86–3.52)
No. of months depressed prior to baseline ^a	1.13 (0.93–1.37)	1.40 (1.09–1.80)	1.62 (1.32–2.00)	1.46 (1.09–1.95)
Model 3: Baseline DSM diagnosis, severity and duration				
Depressive disorder				
MDD	Reference	Reference	Reference	Reference
Dysth	1.35 (0.54–3.41)	No dysth in class 3	2.80 (1.16–6.76)	1.58 (0.33–7.70)
DD	1.53 (0.93–2.54)	1.31 (0.68–2.52)	1.44 (0.81–2.56)	2.35 (1.13–4.88)
IDS score at baseline ^a	1.59 (1.31–1.93)	1.99 (1.52–2.60)	1.50 (1.20–1.89)	2.48 (1.80–3.42)
No. of months depressed prior to baseline ^a	1.03 (0.83–1.29)	1.33 (1.00–1.78)	1.48 (1.16–1.88)	1.21 (0.87–1.69)
Model 4: Characteristics (full adjustment)				
Higher age ^a	1.20 (0.96–1.50)	0.97 (0.71–1.33)	1.29 (0.99–1.68)	1.45 (1.03–2.04)
Female	0.78 (0.53–1.16)	0.84 (0.49–1.46)	0.63 (0.38–0.99)	0.55 (0.30–1.04)
Higher education ^a	0.97 (0.82–1.15)	0.92 (0.73–1.17)	0.96 (0.79–1.17)	1.06 (0.81–1.38)
Co-morbid anxiety	1.01 (0.68–1.49)	0.92 (0.53–1.59)	0.85 (0.54–1.35)	1.44 (0.72–2.88)
Earlier age of onset	1.51 (0.81–1.27)	0.92 (0.66–1.27)	1.10 (0.85–1.43)	1.79 (1.23–2.63)
Childhood adversity ^a	1.08 (0.93–1.26)	1.15 (0.93–1.42)	1.19 (0.99–1.43)	1.08 (0.84–1.39)
Somatic illnesses ^a	0.97 (0.79–1.19)	1.15 (0.89–1.50)	1.26 (1.02–1.55)	1.16 (0.84–1.59)
Higher neuroticism ^a	1.25 (0.98–1.58)	1.50 (1.08–2.10)	1.40 (1.05–1.86)	1.28 (0.86–1.91)
Lower extraversion ^a	1.33 (1.08–1.67)	1.35 (0.99–1.81)	1.20 (0.93–1.56)	1.49 (1.04–2.13)
Family history of depression	0.90 (0.54–1.48)	1.17 (0.56–2.47)	0.64 (0.37–1.12)	2.57 (0.75–8.76)

MDD, Major depressive disorder; Dysth, dysthymia; DD, double depression (=MDD + Dysth); IDS, Inventory of Depressive Symptomatology; s.d., standard deviation.

^a Reported per s.d. increase: IDS score at baseline s.d. = 11; months depressed s.d. = 17; age s.d. = 12; education s.d. = 3; childhood adversity s.d. = 1; somatic illnesses s.d. = 1; neuroticism s.d. = 7; extraversion s.d. = 7.

Values given as odds ratio (95% confidence interval).

Bold is significant association ($p < 0.05$).

(chronic severe) membership (OR 4.00, 95% CI 1.14–14.29) in addition to an earlier age of onset (reference class 4).

Discussion

The aim of our study was to identify clinically relevant course trajectories in a large cohort of depressed subjects participating in the NESDA and to compare these with DSM categories of MDD, Dysth and DD. By implementing data-driven techniques, we identified five different course trajectories, ranging from mild severity and rapid remission to high severity and chronic course trajectory. LCGA enabled classification of course trajectories beyond the scope of DSM and produced detailed course trajectories, in which heterogeneity during course trajectories was taken into account.

More than 40% of the respondents had a rapid remission of the depressive symptoms (class 1) and differed significantly on a broad range of characteristics from the other classes, whereas 20% of the respondents had a chronic course trajectory (classes 4 and 5) that was associated with specific putative predictors of course. Spijker *et al.* (2002) found similar percentages of chronic course trajectories of depressed persons in a large 3-year follow-up population-based study, although they did not use a data-driven technique. A review by Nandi *et al.* (2009) described studies that identified distinct course trajectories of depressive symptoms in the general population and their determinants, based on data-driven techniques; whereas most studies included children, adolescents or young adults, six studies assessed depressive trajectories among adults, including specific samples, such as mothers (Campbell *et al.* 2009) or bereaved caregivers (Li, 2005; Taylor *et al.* 2008). Despite differences in sample and design, most studies identified several distinct course trajectories, with the most prevalent classes differing in severity of symptoms and often classifying a chronic course trajectory. Some studies also identified classes with increasing symptoms over time (Colman *et al.* 2007; Olino *et al.* 2010; Skipstein *et al.* 2010). As can be seen in Fig. 1, a worsening class is lacking in our model. As we limited our model to clinically relevant classes, representing at least 5% of the respondents, this class was not identified. In a higher-class model we indeed identified a small worsening class of less than 5% (data not shown).

Whereas in clinical practice depressive disorders are classified by DSM-IV categories, we now present a more empirically based classification of course trajectories, identified by data-driven techniques. The question is raised: are the DSM-IV depressive

categories associated with meaningful clinical course trajectories, or are the course trajectories derived from LCGA, based on severity and duration measures, clinically more relevant? Our aim was to compare DSM categories with the identified classes. Although the distribution of MDD across classes was largely as expected, considerable numbers of Dysth (61.7%) and DD (54.8%) were allocated to the two most favorable classes (classes 1 and 2). These results are in line with our previous results on course trajectories of depressive disorders in a large population-based study (Rhebergen *et al.* 2009). In that study, we found that 50.0% of persons with Dysth at baseline were free from any diagnosis after 1 year, rising to 70.8% after 3 years. Similarly, 46.4% of persons with DD were free from any depressive diagnosis after 1 year, rising to 69.1% after 3 years. These results indicate that the current diagnostic categories do not accurately distinguish or predict clinically relevant course trajectories. Although Dysth and DD are by definition chronic disorders, both our previous work and the current results suggest heterogeneous course trajectories within these diagnostic DSM categories. To our knowledge, previous comparisons of identified course trajectories with DSM categories are limited. Olino *et al.* (2010) investigated the prevalence of lifetime DSM diagnoses in the identified course trajectories of depression and anxiety from adolescence to adulthood in a general population sample. They found a high percentage of persons with Dysth in the persistent depressed class. All persons in this class had a lifetime diagnosis of MDD and half had a lifetime diagnosis of Dysth. They concluded that this class represents chronic or DD. We found a similar number of persons with Dysth in our chronic, severe class: Dysth was present in 48.1% of the respondents. However, although percentages of Dysth and DD within classes were as expected, the division of baseline disorders across classes differed from expectations. The majority of persons with Dysth or DD at baseline were allocated to the milder classes. Because Olino *et al.* (2010) recruited high school students with a history of psychopathology and controls without psychopathology, they did not investigate whether persons with Dysth were allocated as expected to the chronic classes or not. In addition, they did not find a class with decreasing probability of depressive disorder. Comparison to our decreasing symptom classes is therefore hampered. Likewise, probably due to limited follow-up, we did not identify a class with increasing depressive symptoms. In the class with increasing probability of depressive disorder, Olino *et al.* (2010) identified only a small minority with dysthymia. They suggest that this class represents persons with brief, recurrent depressive episodes. A more extended

follow-up would enable us to investigate the prevalence of Dysth in other course trajectories. Stoolmiller *et al.* (2005) investigated lifetime depressive diagnoses in the identified classes. None in the very low group, 5.7% in the moderate-decreasing group, 20.0% in the high-decreasing group and 29.2% in the high-persistent group were diagnosed with a lifetime depressive disorder. No distinction was made between MDD, Dysth or DD. In addition, this study only included men, hence limiting generalizability to the general population.

Comparison of DSM categories with measures of severity and duration, by means of multivariate, multinomial, logistic regression analyses, revealed that the IDS score was persistently identified as a predictor for class membership, duration was associated with class 3 and 4 membership, whereas the predictive value of DSM categories was only marginal. Dysth only predicted class 4 membership (chronic, moderate) and DD only predicted class 5 membership (chronic, severe). These results suggest the importance of a combination of severity and duration measures in predicting course trajectories. However, both Dysth and DD additionally predicted chronic course trajectories (class 1 reference), which suggests that these DSM-IV categories do have some additional predictive power above severity and duration measures only. In *post-hoc* analyses, comparing both chronic classes (class 4 reference), DSM-IV categories were no longer associated with course. We may conclude that DSM-IV categories predict chronic depression, compared to non-chronic depression, but they do not differentiate between chronic depressions. These findings are in line with previous research (Spijker *et al.* 2002; Ormel *et al.* 2004; Vuorilehto *et al.* 2009). An earlier (albeit non-longitudinal) latent class analysis (LCA) study in the general population also identified a differentiation in subclasses based on severity (Sullivan *et al.* 1998). In this context, McCullough *et al.* (2000, 2003) and Klein *et al.* (2006) suggested that the chronic *versus* non-chronic distinction with a cross-cutting dimension of severity constitutes an important source of heterogeneity in depression. Our results, based on data-driven techniques, support the suggestion of McCullough *et al.* (2003) to characterize depressive disorders on cross-cutting categories or dimensions, based on chronicity and severity of the index disorder. Continuous measurements, such as the LCI, might contribute to a more thorough classification of depressive disorders that better reflects clinical course trajectories.

The final aim was to examine the association between various characteristics and class membership. In multinomial regression analyses, we observed a preponderance of males, somatic illnesses and a

higher level of neuroticism in class 4 (chronic, moderate), and a higher age, an earlier age of onset and lower extraversion in class 5 (chronic, severe) (class 1 reference). Of note, we found male sex to be associated with the poorest course trajectory. Previously, this was also demonstrated by Olino *et al.* (2010) in a sample of adolescents and young adults. They suggested that being female was more associated with transient and episodic forms of internalizing psychopathology. Both somatic co-morbidity (Angst *et al.* 2009) and an earlier age of onset of depression were previously associated with chronic depressions, compared to non-chronic depressions (Mondimore *et al.* 2006; Angst *et al.* 2009). Although most studies to date have not used data-driven techniques, Olino *et al.* (2010) did use LCGA and concluded that the persistent depression class they identified may reflect an early-onset chronic form of depression (>70% chance of being depressed at each time interval), whereas the second depression class they identified may reflect an adult-onset, episodic form of depression with <25% chance of being depressed at each time interval. Because Olino *et al.* (2010) included adolescents, comparison with our results is hampered. However, a considerable number of persons in our study reported the onset of their depressive episodes prior to 18 years (29.4%). The mean age of onset was 27.5 ± 12.7 years (median = 25.0 years). Hence, many persons had their first depressive episode in adolescence. Klein *et al.* (1999) also demonstrated that the early-onset subtype was associated with a poorer course trajectory and also greater family history of mood disorders. In our model, family history of depression showed high odds (OR 2.57, 95% CI 0.75–8.76) for the poorest course trajectory (class 5; class 1 reference), but this did not reach significance. Similarly, Angst *et al.* (2009) could not demonstrate significant differences between chronic and non-chronic depressions related to family history of depression. Some other studies based on data-driven techniques identified family history of depressive symptomatology as a predictor for poor course trajectories. Stoolmiller *et al.* (2005) found that parental depressive symptoms contributed to class discrimination, discriminating the high-persistent class from the other three classes. This finding was replicated by Olino *et al.* (2010), who concluded that this pattern suggests that persistent depression may represent a more familial form of the disorder.

Our findings on personality dimensions are in line with previous reports. Both high neuroticism and low extraversion were previously found to be associated with chronicity (Robison *et al.* 2009; Wiersma *et al.* 2011).

Previous studies failed to demonstrate significant differences between various chronic depressions on a

variety of characteristics (Yang & Dunner, 2001; McCullough et al. 2003). Klein et al. (2006) suggested that the nature of chronic depression varies over time within individuals, indicating that the various manifestations of chronic depression in DSM-IV do not represent distinct disorders. In *post-hoc* analyses, comparing both chronic classes (class 4, chronic, moderate and class 5, chronic severe) we found that age of onset and a family history of depression differentiated between the two chronic classes (4 and 5). Lyons et al. (1998) and, more recently, Kendler et al. (2009) suggested that early age of onset does typify a subtype of depressive disorders, with poorer course trajectories. Hence, our fifth class (chronic, severe), characterized by greater severity, an early age of onset and a higher familial loading, may typify a distinct subtype and may be informative for etiological research.

Strengths and limitations

The present study is one of the largest to date to longitudinally investigate the existence of depressive course types in a large cohort of depressed subjects by data-driven methods. Furthermore, a wide range of putative predictors was tested. However, it should be noted that LCGAs draw upon mathematical models that cannot account for a great variety of fluctuations in symptom levels. As Judd and colleagues (Judd & Akiskal, 2000; Judd et al. 2002) state, there is strong evidence during the long-term course of illness that major, minor, dysthymic and subsyndromal symptoms wax and wane within the same patient and that these symptomatic periods are interspersed in the overall course within times when patients are in remission and symptom free. This pleiomorphic course cannot be described completely by LCGA. In addition, by excluding persons with a remitted depression, insight into the course trajectories of probable recurrent depression is not provided. This requires further research but falls outside the scope of this study. Likewise, LCI assessment over a more extended time period might identify course trajectories that could not be captured in the rather short timeframe of the current study, for example relapse symptomatology. Furthermore, it should be noted that classification of persons based on the most likely class membership may mean that for some persons classification is highly accurate, whereas 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. However, in our model, mean posterior probabilities ranged from

0.96 to 0.97 across classes, indicating that assigning individuals to their class was performed with precision. Finally, LCIs retrospectively assess depressive symptoms and perceived burden, which is prone to recall bias.

To conclude, MDD, Dysth and DD did not adequately match empirically derived course trajectories for unipolar depression. For the future classification of unipolar depression, it may be wise to retain the larger, heterogeneous category of unipolar depression, adopting cross-cutting dimensions of severity and duration to further characterize patients. LCI information may be helpful in clinical practice because it combines both severity and course information. In addition, the identified putative predictors facilitate identification of persons at risk for chronic course trajectories in clinical care.

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Declaration of Interest

None.

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