Insight into the heterogeneity of depressive disorders

Rhebergen, D.

2012

document version
Publisher's PDF, also known as Version of record

Chapter 6

Course trajectories of unipolar depressive disorders identified by Latent Class Growth Analysis

ABSTRACT

Background Current classification of unipolar depression reflects the idea that prognosis is essential. However, do DSM-categories of Major Depressive Disorder (MDD), Dysthymic Disorder and Double Depression indeed adequately represent clinically relevant course trajectories of unipolar depression? Our aim was to test DSM-categories (MDD, Dysthymic Disorder and Double Depression) in comparison with empirically derived prognostic categories, using a prospectively followed cohort of depressed patients.

Methods A large sample (n=804) of outpatients with unipolar depression were derived from a prospective cohort study (NESDA). Using Latent Class Growth Analysis (LCGA) empirically derived two-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, over 50% of Dysthymia and Double Depression 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 a number of 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.

Conclusion MDD, Dysthymia and Double Depression 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.

Didi Rhebergen
Femke Lamers
Jan Spijker
Ron de Graaf
Aartjan TF Beekman
Brenda WJH Penninx

Published in: Psychological Medicine 2011; 7: 1-14.

INTRODUCTION

From Kraepelin to modern times, course trajectories are an important criterion to validate 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. Over the years, various other unipolar depressive syndromes or subtypes were defined, including Double Depression (the co-occurrence of MDD and Dysthymic Disorder).

This diversity among depressive disorders has been topic of debate, with much of the controversy focusing on whether MDD and Dysthymic Disorder are qualitatively distinct disorders or represent different ends of a severity continuum (Shankman and Klein, 2002). The enormous overlap in diagnoses between MDD and Dysthymic Disorder (Klein et al., 2006) and failure to demonstrate differences between MDD and Dysthymic Disorder on a broad range of demographic, clinical, psychosocial, family history, and treatment response variables (Angst and Wicki 1991; McCullough et al., 2000, 2003) fuelled this debate. Judd et al. (2002) concluded that Dysthymic Disorder 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 and Akiskal, 2000). On the other hand, there is evidence to support the existence of specific diagnostic subtypes within the larger group of affective disorders, such as chronic depression (McCullough et al., 2000, 2003).

In order 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 like Latent Class (Growth) Analysis (LC(G)A), that cluster persons based on their trajectories of a given outcome, may thus result in a more empirically based classification, which can then be compared with the DSM classification of unipolar affective disorders. This way, it can be examined whether different depressive subtypes based on course trajectories can be distinguished and to what extent this corresponds with the current diagnostic categories. To date a number of studies employed 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 (Skipstein et al., 2010, Campbell et al., 2009) 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 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.

This study aims 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 see whether the identified classes actually represent different course trajectories, we briefly validate the classes by means of some external validators. Next, we compare the identified course trajectories with the current diagnostic categories of MDD, Dysthymic Disorder and Double Depression. If DSM-categories sufficiently identify clinical course trajectories, we 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 best course trajectory. Likewise, Dysthymic Disorder should be the most prominent diagnosis in the class with a chronic course, albeit of moderate severity, and most persons with Dysthymia should be allocated to this class. Finally, we expect Double Depression to be the most prominent diagnosis in the class, representing a chronic and severe course trajectory and most persons with Double Depression to be allocated to this particular class. In addition, since DSM-categories suggest particular course trajectories, we examine to what extent DSM-categories predict course trajectories. Finally, we explore the characteristics of each identified class and examine putative predictors of class membership, and hence course trajectory. Besides sociodemographics, comorbid anxiety disorders (Hayden and Klein, 2011), age of onset of depressive symptoms (Klein et al., 1999, Angst et al., 2009), childhood adversity (Hayden and Klein, 2001; Rhebergen et al., 2011), somatic comorbidity (Angst et al., 2009), neuroticism (Rhebergen et al., 2011; Hayden and Klein, 2011) and a family history of depression (Klein et al., 1999, Stoolmiller et al., 2005, Olino et al., 2010) have previously been demonstrated to predict course trajectories. However, some inconsistencies exist. In this study, we examine the predictive value of socio-demographics (age, gender, level of education), comorbid 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.

METHODS

Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is designed to investigate the course and consequences of depressive and anxiety disorders. It is a multi-site naturalistic cohort study of adults (18 to 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 Major Depressive Disorder (n=1115) and/or a 6-month Dysthymic Disorder (n=305) (Total n=1158). Of the 1158 persons at baseline, 946 (81.7%) could be followed-up after two years. Attrition in the study population was higher among those with younger age (OR 1.02), lower educational level (OR 1.08) and those with Double Depression (OR 1.47), but was not associated with sex, MDD or Dysthymic Disorder.

Attrition for the NESDA-study was described more extensively elsewhere (Lamers et al., 2012). In order 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 CIDI recency questions or the Life Chart Interview (LCI) (Lyketsos and Nestadt, 1994) (see below) 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 the Composite Interview Diagnostic Instrument (CIDI) version 2.1, according to DSM-IV criteria (World Health Organization, 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 Life Chart interview (LCI) (Lyketsos and Nestadt, 1994). The LCI was assessed both at baseline and after two years of follow-up by a trained interviewer. Baseline LCI served to compute a measure of duration of depressive symptomatology (see below). LCI at 2-year follow-up provided the data for the LCGA. First, the occurrence of life events in a particular period is explored to re-fresh memory and then presence of depressive symptoms is 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 ranging from no or minimal severity, mild, moderate, severe, or very severe (five point scale). Since the LCI at follow-up retrospectively assessed the burden of depressive symptoms during two 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 two years. In addition, the percentage of decline in IDS-score during two years follow-up was calculated. Next, level of functioning was measured by total scores on the WHO Disability Assessment Schedule II (WHO-DAS) (Chwastiak and Von Korff, 2003), both at baseline and after two years of follow-up. Again the percentage of improvement on the WHO-DAS during two years of follow-up was calculated. The WHO-DAS queries difficulties in various domains of life during the last 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 Dysthymic Disorder at follow-up.

Depressive categories

To compare the identified course trajectories with DSM-IV-categories as well as 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 Major Depressive Disorder (MDD) and/or Dysthymic Disorder at baseline. Various depression groups were defined: Major Depressive Disorder (MDD) (n=573) consisted of those with a MDD and no Dysthymic Disorder. Dysthymic Disorder only (n=34) consisted of those with a Dysthymic Disorder but not a MDD diagnosis. Double Depression (n=197) was defined as Dysthymic Disorder with a comorbid MDD, ignoring the sequence of onset of Dysthymia and MDD.

Putative predictors of class membership

Although DSM-IV depressive categories are also partly based on course and severity measures, we examined additional course and severity markers. This enables 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 (see above). 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 of the last 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, comorbid 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. Comorbid 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 interview. Earliest age was used for those with comorbid disorders. Childhood adversity was assessed using a structured interview from the NEMESIS study (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. A childhood index was computed (range 0-4), as previously used (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 one receives medical treatment was constructed. Neuroticism and extraversion were assessed by means of the neuroticism and extraversion dimension of the NEO personality questionnaire, a 60-item questionnaire measuring five

personality domains (Costa and McCrae, 1995). The presence of a depressive disorder in first degree family members was assessed using the family tree method (Fyer and Weissman, 1999).

Statistical analyses

To identify distinct classes based on different course trajectories, we performed Latent Class Growth Analysis (LCGA). LCGA 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. Since 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 and Wickrama, 2008). The LCI score was treated in the LCGA as a continuous variable. The LCGAs were conducted using M-plus version 5 (Muthén and Muthén, 2007).

To determine which model best fitted the data, we combined the smallest Bayesian Information Criterion (BIC), the Lo-Mendell-Rubin likelihood ratio test (LMR), entropy and proportions of the classes, with interpretability and clinical relevance of the latent trajectory classes. Of the traditionally used Information Criterions, like Aikaike's (AIC) and Bayesian Information Criterion (BIC), the BIC performs best (Nylund et al. 2007). The accuracy of the Aikaike's Information Criterion (AIC) decreases as the sample size increases, since there is no adjustment for sample size (Nylund et al. 2007). Lower BIC values indicate better model fit. The Lo-Mendell-Rubin test (LMR) provides a p-value, which 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, as well as the proportions of individuals in each class. In order to identify clinically relevant classes, we only considered models with classes greater than five percent.

After the identification of the classes, persons were assigned to their most likely class based on model probabilities. Then, we briefly 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 chi-square statistics for categorical variables, one-way-analysis of variance statistics (ANOVA) 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 were examined (model 1). Next, 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). Finally, the association between other characteristics and class membership was examined. All comparisons were conducted using SPSS (version 15) (SPSS, 2006).

RESULTS

In Table 1 the maximum likelihood values, the Bayesian Information Criteria (BIC), the Entropy, the Lo-Mendell-Rubin (LMR) likelihood ratio tests and the proportion of individuals in each class of each Latent Class Growth 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 didn't yield adequate estimates either. 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 6-class model onwards. Hence, the 5-class linear model provided the best fit for the observed data.

Table 1. Parameters of fit of Latent Class Growth Analyses.

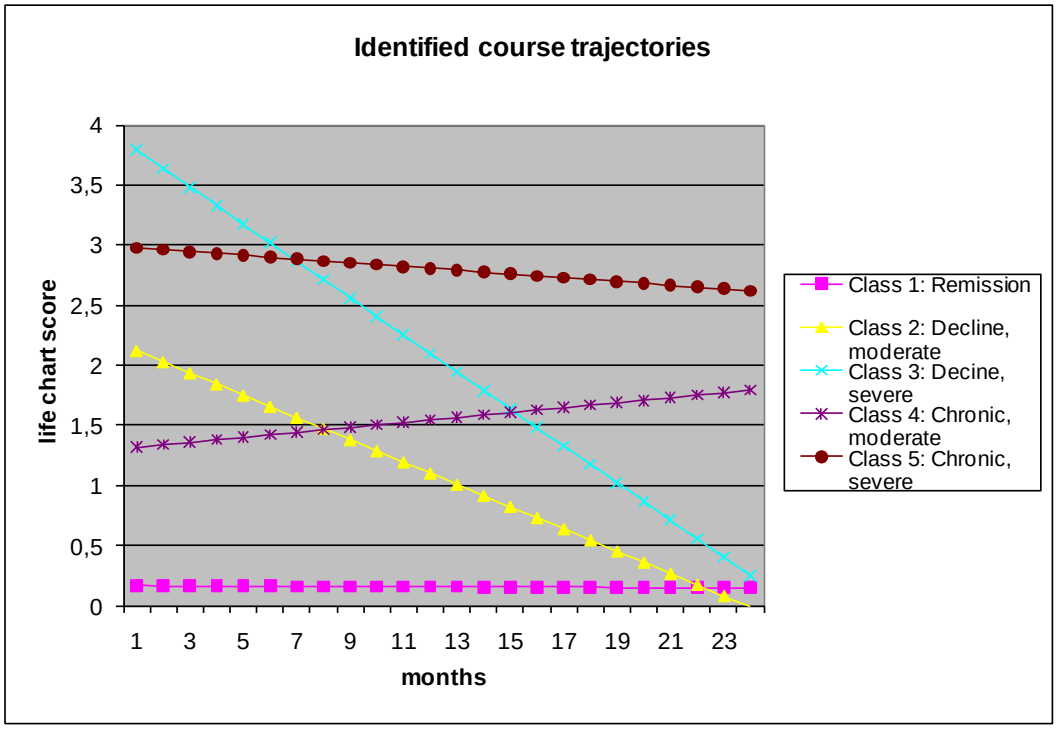
Class	Maximum Likelihood	BIC[1]	ENT[2]	Lo-Mendell-Rubin		Proportion of individuals in class					
				2LL*	p	1	2	3	4	5	6
1											
2	-27123.643	54441.25	0.96	7895.32	<.001	0.58	0.42	-	-	-	-
3	-25956.525	52127.08	0.96	2334.24	.04	0.16	0.50	0.34	-	-	-
4	-25267.652	50769.40	0.96	1377.75	.03	0.10	0.49	0.15	0.26	-	-
5	-24752.198	49758.55	0.97	1030.90	.01	0.44	0.24	0.10	0.15	0.07	
6	-24438.526	49151.27	0.97	627.344	.42	0.23	0.09	0.43	0.09	0.05	0.12

[1]BIC= Bayesian Information Criterion; 2LL= 2 log likelihood; [2]ENT= Entropy

Figure 1 shows the course trajectories of the five identified latent classes. 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, burden of depressive symptoms at baseline was higher compared to the first class. The third class (prevalence 9.8%) showed a gradual decline of symptom, 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.

Figure 1. Identified course trajectories, derived from Latent Class Growth Analysis.



To facilitate interpretation, class numbering corresponds to increasing severity and/or duration of depressive symptoms.

Validation of the course trajectories

We tested the validity of the 5-class model by examining the distribution of severity measures (IDS-score, level of functioning) and measures of change (decline IDS-score, improvement of functioning, CIDI-diagnosis of depression after two years) across the identified course trajectory classes (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 (class 2 and 4, class 3 and 5) do not differ on baseline severity measures, but differ on measures of change. This was confirmed. In addition, we expected no differences between chronic course trajectories (class 4 and 5) on measures of change (decline IDS-score, improvement in functioning), whereas difference in severity measures are expected. This was also confirmed. The course trajectory over two 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 two years were more similar to class 4 (chronic, moderate) (no significant differences, except baseline severity measures) than to 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 Major Depressive Disorder, Dysthymic Disorder, and Double Depression across the identified trajectory classes. 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 Double Depression gradually rose. In addition, the fourth class (chronic, moderate) had within the class the highest relative percentage of persons with Dysthymic Disorder (9.1%) and the fifth class (chronic, severe) had a relatively high percentage of persons with Double Depression (44.4%). However, when DSM-categories represent clinically relevant course types, persons with MDD should mainly be allocated to the most favourable course trajectory, whereas persons with Dysthymia en Double Depression 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, Major Depressive Disorder was most prevalent among the rapidly improving, mild class (class 1, 50%). However, almost two third (61.7%) of the persons with Dysthymic Disorder at baseline was allocated to the best course trajectory classes (38.2% class 1; 23.5% class 2). Similarly, over half of the persons with Double Depression 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.

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

Class description	Class 1 Remission, mild severity	Class 2 Decline, moderate severity	Class 3 Decline, Severe	Class 4 Chronic, moderate severity	Class 5 Chronic, severe	Overall statistics
	n=356 (44.3%)	n=194 (24.1%)	n=79 (9.8%)	n=121 (15.0%)	n=54 (6.7%)	X^2 (df)/ F (df) p-value
IDS at baseline, mean (±SD)	30.3 (10.8)	35.6 (10.4)	38.6 (10.5)	35.7 (11.5)	41.1 (9.9)	21.9 (4) <.001
IDS at 2-year follow-up, mean (±SD)	18.1 (9.8)	25.3 (12.1)	28.8 (13.4)	28.0 (13.0)	33.4 (11.6)	40.5 (4) <.001
Percentage decline of 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) <.001
Functioning (high scores= low functioning) at baseline, mean (±SD)	67.7 (17.7)	75.4 (17.5)	80.0 (19.5)	73.9 (17.5)	81.3 (15.2)	15.0 (4) <.001
Functioning (high scores= low functioning) after 2-year follow-up, mean (±SD)	25.2 (18.1)	34.7 (21.3)	41.1 (21.3)	37.9 (21.9)	51.4 (23.1)	29.9 (4) <.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) <.001
Current CIDI-diagnosis of depression after 2-year follow-up	24.5%	60.3%	62.0%	73.6%	100%	185.8 (4) <.001

Significant differences across classes (p<.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-baseline, IDS-2yrs, (functioning baseline p=.06), functioning-2 years, improvement functioning; Class 2 versus 4: Decline IDS, CIDI-disorder after two years, (IDS-2 yrs p=.06); Class 2 versus 5: All parameters significantly different; Class 3 versus 4: (IDS-baseline p=.07), functioning-baseline; Class 3 versus 5: IDS-2 yrs, functioning-2 yrs, improvement functioning, CIDI-disorder after two years; Class 4 versus 5: All parameters significantly different, except change-IDS

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

Class description	Class 1 Remission, mild severity	Class 2 Decline, moderate severity	Class 3 Decline, severe	Class 4 Chronic, moderate severity	Class 5 Chronic, severe	Overall statistics
	n=356 (44.3%)	n=194 (24.1%)	n=79 (9.8%)	n=121 (15.0%)	n=54 (6.7%)	X^2 (df)/F (df) p-value
Baseline DSM-diagnosis						
Depressive disorders per class						
- Major Depressive Disorder	80.6	69.1	67.1	58.7	51.9	
- Dysthymic Disorder	3.7	4.1	0	9.1	3.7	46.0 (8) <.001
- Double Depression	15.8	26.8	32.9	32.2	44.4	
Depressive disorders across classes						
Major Depressive Disorder (% of MDD at baseline, n=573)	50.0	23.4	9.3	12.4	4.9	35.4 (4) <.001
Dysthymic disorder (% of Dysthymia at baseline, n=34)	38.2	23.5	0	32.4	5.9	10.9 (4) .03
Double Depression (% of DD at baseline, n=197)	28.4	26.4	13.2	19.8	12.2	33.7 (4) <.001
Severity/ duration						
IDS at baseline, mean (±SD)	30.3 (10.8)	35.6 (10.4)	38.6 (10.5)	35.7 (11.5)	41.1 (9.9)	21.9 (4) <.001
Depressed months prior to baseline, mean (±SD)	18.0 (15.6)	21.6 (16.7)	26.4 (17.9)	28.0 (18.8)	28.0 (16.8)	12.2 (4) <.001
Other characteristics						
Age, mean (±SD)	40.7 (12.5)	42.8 (12.5)	41.2 (11.8)	44.4 (10.9)	43.5 (11.6)	2.8 (4) .03
Gender (% female)	69.3	63.4	67.1	59.5	57.4	6.2 (4) .18
Education, mean (±SD)	11.7 (3.2)	11.5 (3.3)	11.2 (3.1)	11.3 (3.5)	11.9 (3.8)	0.7 (4) .59
Comorbid anxiety disorder (any disorder) (% yes)	61.1	66.0	67.1	63.6	74.1	4.3 (4) .37
Age of onset of depression, mean (±SD)	27.8 (12.2)	28.1 (13.1)	27.6 (13.8)	28.1 (12.7)	22.4 (11.6)	2.4 (4) .05
Childhood trauma, mean (±SD)	1.1 (1.1)	1.3 (1.2)	1.4 (1.3)	1.4 (1.3)	1.4 (1.3)	2.6 (4) .04
No. somatic illnesses, mean (±SD)	0.6 (0.9)	0.7 (0.9)	0.8 (1.0)	1.0 (1.2)	0.8 (0.8)	3.1 (4) .01
Neuroticism, mean (±SD)	41.5 (6.8)	43.3 (6.4)	44.5 (5.7)	43.6 (6.3)	44.3 (4.9)	6.6 (4) <.001
Extraversion, mean (±SD)	34.2 (6.6)	31.8 (6.1)	31.4 (7.2)	31.9 (5.8)	30.5 (7.0)	8.8 (4) <.001
Family history of depression (% yes)	85.1	84.0	87.3	79.3	94.4	7.2 (4) .13

Significant differences across classes (p<.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, Dysthymia, 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: (Dysthymia p=.07), IDS-baseline, months depressed; Class 2 versus 4: MDD, (Dysthymia p=.07), months depressed, somatic illnesses; Class 2 versus 5: MDD, DD, IDS-baseline, months depressed, family with depression; Class 3 versus 4: Dysthymia, age; Class 3 versus 5:Age of onset; Class 4 versus 5:IDS-baseline, age of onset, family with depression. Abbreviations: MDD= Major Depressive Disorder, DD= Double 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) (reference).

Reference= class 1 Remission, mild severity	Class 2 Decline, moderate severity	Class 3 Decline, Severe	Class 4 Chronic, moderate severity	Class 5 Chronic, severe
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Model 1: Baseline DSM-diagnosis				
-Major Depression	Reference	Reference	Reference	Reference
-Dysthymic Disorder	1.31 (0.53-3.24)	NA	**3.41 (1.47-7.93)**	1.570.34-7.32)
-Double Depression	**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)**
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				
-Major Depression	Reference	Reference	Reference	Reference
-Dysthymic disorder	1.35 (0.54-3.41)	NA	**2.80 (1.16-6.76)**	1.58 (0.33-7.70)
-Double Depression	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)**
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)
Comorbid 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)

[a] Reported per SD increase: IDS-score at baseline SD= 11; months depressed SD= 17; age SD= 12; education SD= 3; childhood adversity SD= 1; somatic illnesses SD= 1; neuroticism SD= 7; extraversion SD=7. NA= Not applicable (no Dysthymics in class 3). Bold is significant association (p<.05)

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 can be seen in Table 4, the association between Double Depression and class membership showed an increase in ORs across the classes. Dysthymic Disorder 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% CI 1.56-2.65]; class 5: OR 2.56 [95% CI 1.86-3.52]). Number of months was associated with class 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 in order to test whether DSM-categories would have additional predictive value over duration and severity measures only, in predicting class membership (model 3). Whereas IDS-score continued to predict class membership, Double Depression was only associated with class 5 (chronic, severe). Dysthymic Disorder 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 class 1 and 3 and had a significantly higher number of somatic illnesses, compared to class 1 and 2. In addition, the fifth class (chronic, severe) had a lower age of onset, compared to class 1, 3 and 4, and a higher number of family members with depression, compared to class 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]). Likewise, 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]), however not reaching significance. In a post-hoc analysis comparing both chronic classes, a family history of depression was significantly associated with class 5 (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 Netherlands Study of Depression and Anxiety (NESDA) and to compare these with DSM-categories of MDD, Dysthymia and Double Depression. 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 is taken into account.

Over 40 percent of the respondents had a rapid remission of the depressive symptoms (class 1) and significantly differed on a broad range of characteristics from the other classes, whereas 20 percent of the respondents had a chronic course trajectory (class 4 and 5) that was associated with specific putative predictors of course. Spijker et al. (2002) have found similar percentages of chronic course trajectories of depressed persons in a large 3-year follow-up population based study, however, they did not employ data-driven techniques, such as LCGA. In a recent review, 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, like 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 Figure 1, a worsening class is lacking in our model. Since we limited our model to clinically relevant classes, representing at least five percent of the respondents, this class was not identified. In a higher-class model we indeed identified a small worsening class of less than five percent (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, a considerable number of Dysthymic Disorder (61.7%) and Double Depression (54.8%) was allocated to the two most favorable classes (class 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 this study, we found that 50.0% of persons with Dysthymic Disorder at baseline were free from any diagnosis after one year, rising to 70.8% after three years. Likewise, 46.4% of persons with Double Depression were free from any depressive diagnosis after one year, rising to 69.1% after three years. These results indicate that the current diagnostic categories do not accurately distinguish or predict clinically relevant course trajectories. Although Dysthymic Disorder and Double Depression 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 Dysthymia in the persistent depressed class. All persons in this class had a lifetime diagnosis of MDD and half (50.0%) had a lifetime diagnosis of Dysthymic Disorder. They concluded that this class seems to represent chronic or Double Depression. We found a similar number of persons with Dysthymic Disorder in our chronic, severe class: Dysthymic Disorder was present in 48.1% of the respondents. However, although percentages of Dysthymic Disorder and Double Depression within classes were as expected, the division of baseline disorders across classes differed from expectations. The majority of persons with Dysthymic Disorder or Double Depression at baseline were allocated to the milder classes. Since Olino et al. (2010) recruited high school students with a history of psychopathology and controls without psychopathology, they did not investigate whether persons with Dysthymic Disorder were allocated as expected to the chronic classes or not. In addition, Olino et al. (2010) 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 Dysthymic Disorder 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, Dysthymic Disorder or Double Depression. 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 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. Dysthymic Disorder only predicted class 4 membership (chronic, moderate) and Double Depression 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 Dysthymic Disorder and Double Depression additionally predicted chronic course trajectories (class 1 reference), this suggest 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 (Vuorilehto et al., 2009; Ormel et al., 2004; Spijker et al., 2002). An earlier (albeit non-

longitudinal) Latent Class Analysis-study in the general population also identified a differentiation in subclasses based on severity (Sullivan et al., 1998). In this context, Klein and colleagues (2006) and McCullough et al. (2000, 2003) 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 (2003) to characterize depressive disorders on cross-cutting categories or dimensions, based on chronicity and severity of the index disorder. Continuous measurements, like 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). Interestingly, 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 comorbidity (Angst et al., 2009) and an earlier age of onset of depression were previously associated with chronic depressions, compared to non-chronic depressions (Angst et al., 2009; Mondimore et al., 2006). Whereas most studies to date did not employ data-driven techniques, Olino et al. (2010) also employed 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. Since Olino and colleagues (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, a considerable number of 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 as well as 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. Likewise, Angst et al. (2009) could not demonstrate significant differences between a family history of depression between chronic and non-chronic depressions. 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. It discriminated 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 (McCullough et al., 2003; Yang and Dunner, 2001). Klein (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 et al. (Judd and 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 remitted and symptom free. This pleiomorphic course cannot completely be described 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 time frame 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, 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. However, in our model, mean posterior probabilities ranged from 0.96-0.97 across classes, indicating that assigning individuals to their class was done with precision. Finally, Life Chart Interviews

retrospectively assess depressive symptoms and perceived burden, which is prone to recall bias.

To conclude, MDD, Dysthymic Disorder and Double Depression 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. Life Chart Interview-information may be helpful for clinical practice, as 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.

REFERENCES

Angst J, Gamma A, Rossler W, Ajdacic V, Klein D. Long-term depression versus episodic major depression: results from the prospective Zurich study of a community sample. Journal of Affective Disorder 2009; 115: 112-121.

Angst J, Wicki W. The Zurich Study. XI. Is dysthymia a separate form of depression? Results of the Zurich Cohort Study. European Archives of Psychiatry and Clinical Neuroscience 1991; 240: 349-354.

Bijl R, Van Zessen G, Ravelli A, De Rijk C, Langendoen Y.The Netherlands Mental Health Survey and Incidence Study (NEMESIS): objectives and design. Social Psychiatry and Psychiatric Epidemiology 1998; 33: 581-586.

Campbell SB, Morgan-Lopez AA, Cox MJ, McLoyd VC. A latent class analysis of maternal depressivesymptoms over 12 years and offspring adjustment in adolescence. Journal of Abnormal Psychology 2009; 118: 479-493.

Chwastiak LA, Von Korff M. Disability in depression and back pain: evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. Journal of Clinical Epidemiology 2003; 56: 507-514.

Colman I, Ploubidis GB, Wadsworth MEJ, Jones PB, Croudace TJ. A longitudinal typology of symptoms of depression and anxiety over the life course. Biological Psychiatry 2007; 62: 1265-1271.

Costa PT, McCrae RR. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. Journal of Personality Assessment 1995; 64: 21-50.

Fyer AJ, Weissman MM. Genetic linkage study of panic: clinical methodology and description of pedigrees. American Journal of Medical Genetics 1999; 88: 173-181.

Hayden EP, Klein DN. Outcome of dysthymic disorder at 5-year follow-up: the effect of familial psychopathology, early adversity, personality, comorbidity, and chronic stress. American Journal of Psychiatry 2001; 158: 1864-1870.

Judd LL, Akiskal HS. Delineating the longitudinal structure of depressive illness: beyond clinical subtypes and duration thresholds. Pharmacopsychiatry 2000; 33: 3-7.

Judd LL, Schettler PJ, Akiskal HS. The prevalence, clinical relevance, and public health significance of subthreshold depressions. Psychiatric Clinics of North America 2002; 25: 685-698.

Jung T, Wickrama K. An introduction to LCGA and GMM. Social and Personality Psychology Compass 2008; 2: 302-317.

Kendler KS, Fiske A, Gardner CO, Gatz M. Delineation of two genetic pathways to major depression. Biological Psychiatry 2009; 65: 808-811.

Klein DN, Schatzberg AF, McCullough JP, Keller MB, Dowling F, Goodman D, Howland RH, Markowitz JC, Smith C, Miceli R, Harrison WM. Early- versus late-onset dythymic disorder: comparison in out-patients with superimposed major depressive episodes. Journal of Affective Disorders 1999; 52: 187-196.

Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. American Journal of Psychiatry 2006; 163: 872-880.

Lamers F, Hoogendoorn A, Smit J, van Dyck R, Zitman FG, Nolen WA, Penninx BW. Sociodemographic and psychiatric determinants of attrition in the Netherlands Study of Depression and Anxiety (NESDA). Comprehensive Psychiatry 2012; 53: 63-70.

Li LW. From caregiving to bereavement: trajectories of depressive symptoms among wife and daughter caregivers. Journal of Gerontology 2005; 60: 154-168.

Lyketsos C, Nestadt G. The life-chart method to describe the course of psychopathology. International Journal of Methods in Psychiatric Research 1994; 4: 143-155.

Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, Meyer JM, Toomey R, Faraone SV, Merla-Ramos M, Tsuang MT. A registry-based twin study of depression in men. Archives of General Psychiatry 1998; 55: 468-472.

McCullough JP, Klein DN, Keller MB, Holzer CE, Davis SM, Kornstein SG, Howland RH, Thase ME, Harrison WM. Comparison of DSM-III-R chronic major depression and major depression superimposed on dysthymia (double depression): validity of the distinction. Journal of Abnormal Psychology 2000; 109: 419-427.

McCullough JP, Klein DN, Borian FE, Howland RH, Riso LP, Keller MB, Banks PL. Group comparisons of DSM-IV subtypes of chronic depression: validity of the distinctions, part 2. Journal of Abnormal Psychology 2003; 112: 614-622.

Mondimore FM, Zandi PP, Mackinnon DF, McInnis MG, Miller EB, Crowe RP, Scheftner WA, Marta DH, Weissman MM, Levinson DF, Murphy-Ebenez KP, Depaulo JR, Potash JB. Familial aggregation of illness chronicity in recurrent, early-onset major depression pedigrees. American Journal of Psychiatry 2006; 163: 1554-1560.

Muthén LK, Muthén BO. Mplus User's Guide. Fifth Edition. 2007. Muthén and Muthén, Los Angelas, CA.

Nandi A, Beard JR, Galea S. Epidemiologic heterogeneity of common mood and anxiety disorders over the lifecourse in the general population: a systematic review. BMC Psychiatry 2009; 9: 31.

Nylund KL, Asparouhov T, Muthen BO. Deciding on the number of classes in Latent Class Analysis and Growth Mixture Modeling: a Monte Carlo Simulation Study. Structural Equation Modeling 2007; 14: 535-569.

Olino TM, Klein DN, Lewinsohn PM, Rohde P, Seeley JR. Latent trajectory classes of depressive and anxiety disorders from adolescence to adulthood: descroption of classes and associations with risk factors. Comprehensive Psychiatry 2010; 51: 224-235.

Ormel J, Oldehinkel AJ, Nolen WA, Vollebergh W. Psychosocial disability before, during, and after a major depressive episode: a 3-wave population-based study of state, scar, and trait effects. Archives of General Psychiatry 2004; 61: 387-392.

Penninx BW, Beekman AT, Smit JH, Zitman FG, Nolen WA, Spinhoven P, Cuijpers P, De Jong PJ, Van Marwijk HW, Assendelft WJ, Van der Meer K., Verhaak P, Wensing M, De Graaf R, Hoogendijk WJ, Ormel J, Van Dyck R. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. International Journal of Methods in Psychiatric Research 2008; 17: 121-140.

Rhebergen D, Beekman AT, De Graaf R, Nolen WA, Spijker J, Hoogendijk WJ, Penninx BW. The three-year naturalistic course of major depressive disorder, dysthymic disorder and double depression. Journal of Affective Disorders 2009; 115: 450-459.

Rhebergen D, Batelaan NM, De Graaf R, Nolen WA, Spijker J, Beekman ATF, Penninx BWJH.The 7-year course of depression and anxiety in the general population. Acta Psychiatrica Scandinavica 2011; 123: 297-306.

Robison EJ, Shankman SA, McFarland BR. Independent associations between personality traits and clinical characteristics of depression. Journal of Nervous and Mental Disorders 2009; 197: 476-483.

Rush AJ, Giles DE, Schlesser MA, Fulton CL, Weissenburger J, Burns C. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Research 1986; 18: 65-87.

Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychological Medicine 1996; 26: 477-486.

Shankman SA, Klein DN. Dimensional diagnosis of depression: adding the dimension of course to severity, and comparison to the DSM. Comprehensive Psychiatry 2002; 43: 420-426.

Skipstein A, Janson H, Stoolmiller M, Mathiesen KS. Trajectories of maternal symptons of anxiety and depression. A 13-year longitudinal study of a population-based sample. BMC Public Health 2010; 10: 589.

Spijker J, De Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Duration of major depressive episodes in the general population: results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). British Journal of Psychiatry 2002; 181: 208-213.

SPSS. SPSS for Windows: version 15.0. 2006. Chicago, SPSS.

Stoolmiller M, Kim HK, Capaldi DM. The course of depressive symptoms in men from early adolescence to young adulthood: identifying latent trajectories and early predictor. Journal of abnormal psychology 2005; 114: 331-345.

Sullivan PF, Kessler RC, Kendler KS. Latent class analysis of lifetime depressive symptoms in the national comorbidity survey. American Journal of Psychiatry 1998; 155: 1398-1406.

Taylor DH, Ezell M, Kuchibhatla M, Ostbye T, Clipp EC. Identifying trajectories of depressive symptoms for women caring for their husbands with dementia. Journal of the American Geriatrics Society 2008; 16: 322-327.

Vuorilehto MS, Melartin TK, Isometsa ET. Course and outcome of depressive disorders in primary care: a prospective 18-month study. Psychological Medicine 2009; 39: 1697-1707.

Wiersma JE, Hovens JG, Van Oppen P, Giltay EJ, Van Schaik DJ, Beekman AT, Penninx BW. The importance of childhood trauma and childhood life events for chronicity of depression in adults. Journal of Clinical Psychiatry 2009; 70: 983-989.

Wiersma JE, Van Oppen P, Van Schaik DJF, Van der Does AJW, Beekman ATF, Penninx BWJH. Psychological characteristics of chronic depression: a longitudinal cohort study. Journal of Clinical Psychiatry 2011; 72: 288-294.

Wittchen HU. Reliability and validity studies of the WHO-Composite International Diagnostic Interview (CIDI): a critical review. Journal of Psychiatric Research 1994; 28: 57-84.

Wittchen HU, Zhao S, Abelson JM, Abelson JL, Kessler RC. Reliability and procedural validity of UM-CIDI DSM-III-R phobic disorders. Psychological Medicine 1996; 26: 1169-1177.

World Health Organization. Composite International Diagnostic Interview (CIDI), version 2.1. 1998. Geneva, WHO.

Yang T, Dunner DL. Differential subtyping of depression. Depression and Anxiety 2001; 13: 11-17.