Two-Year Course Trajectories of Anxiety Disorders: Do *DSM* Classifications Matter?

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ABSTRACT

Objective: Anxiety disorders have been shown to differ in their course, but it is unknown whether *DSM*-categories represent clinically relevant course trajectories. We aim to identify anxiety course trajectories using a data-driven method and to examine whether these course trajectories correspond to *DSM*-categories or whether other clinical indicators better differentiate them.

Method: 907 patients with panic disorder with agoraphobia, panic disorder without agoraphobia , agoraphobia, social phobia, or generalized anxiety disorder according to *DSM-IV* criteria were derived from a prospective cohort study (Netherlands Study of Depression and Anxiety). Baseline data were collected between September 2004 and February 2007; follow-up data, between October 2006 and March 2009. Latent class growth analysis was conducted, based on symptoms of anxiety and avoidance assessed with the Life Chart Interview covering a 2-year time period. Identified course trajectories were compared with *DSM-IV* diagnoses and a wider set of predictors.

Results: We identified a class with minimal symptoms over time (41.7%), a moderately severe chronic class (42.8%), and a severe chronic class (15.4%). Panic disorder with agoraphobia (OR = 2.14; 95% CI, 1.48–3.09) and social phobia (OR = 1.97; 95% CI, 1.46–2.68) predicted moderately severe chronicity; panic disorder with agoraphobia (OR = 2.70; 95% CI, 1.66–4.40), social phobia (OR = 2.46; 95% CI, 1.62–3.74), and generalized anxiety disorder (OR = 1.86; 95% CI, 1.23–2.82) predicted a severe chronic course. However, baseline severity, duration of anxiety, and disability better predicted severe chronic course trajectories than *DSM*-categories. Additionally, partner status, age at onset, childhood trauma, and comorbid depressive disorder predicted chronic courses.

Conclusions: Course of anxiety was pleomorphic with over 40% having a favorable course, thereby questioning the common notion of chronicity of anxiety disorders. Severity, duration of anxiety, and disability were able to better identify severe chronic course trajectories as compared with *DSM-IV* categories. These findings facilitate the identification of chronic course trajectories of anxiety disorders in clinical care and support current debates on staging and profiling of mental disorders.

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Longitudinal observations are important to validate clinical entities. Generally, anxiety disorders are regarded as "chronic" or as "waxing and waning" disorders. Direct comparisons across anxiety disorders have shown different course trajectories across anxiety disorders.[1–3] For example, panic disorder without agoraphobia has a more favorable course as compared to panic disorder with agoraphobia.[1,2,4] In the Harvard/Brown Anxiety Disorders Research Program study, persons with panic disorder with agoraphobia or social phobia spent the most time in an illness episode,[1] and also in the Netherlands Study of Depression and Anxiety, a chronic course without remission was most often found in panic disorder with agoraphobia and social phobia.[2] Generalized anxiety disorder seems to take an intermediate position, with (slightly) less time spent in an illness episode[1] and less often a chronic course as compared to both social phobia and panic disorder with agoraphobia.[2] Considering these distinct course trajectories, it has been concluded that the *DSM-IV* categories of anxiety disorders are useful in predicting outcome.[2,5]

Taking *DSM*-categories as a starting point to investigate course trajectories, however, fails to account for heterogeneity in clinical presentation. By contrast, data-driven techniques like latent class growth analysis (LCGA) cluster persons based on their endorsed symptom pattern over time, free from any a priori assumptions. This approach may thus result in a more empirically based classification. Hence, the question is whether *DSM* categories would be the best way to predict course, or, in other words, given that longitudinal data are important to validate *DSM*-categories, we wonder whether course trajectories— identified by data-driven methods—would support the predictive value of *DSM* categories. To date, only few studies employed this approach to assess course trajectories of anxiety,[6–11] with the latter 2 studies[10,11] examining symptoms of anxiety and depression combined. Since these studies investigated different age groups and, moreover, investigated course trajectories in the general population (including persons without symptoms at baseline), information on course trajectories in adult patient populations is largely lacking. In addition, only Olino et al[10] compared *DSM*-categories with empirically derived course trajectories. Because they included adolescents from the general population, it remains difficult to extrapolate conclusions to adults with anxiety disorders.

Using a large cohort of patients with anxiety disorders participating in the Netherlands Study of Depression and Anxiety (NESDA), we identify 2-year course trajectories of anxiety disorders using LCGA. We compare the predictive value of *DSM-IV* categories on course trajectories with the predictive value of measures of severity and duration of anxiety and level of functioning. These dimensions have been frequently found to predict an unfavorable course of anxiety.[2,4,12] Finally,

we examine putative predictors of course trajectories, including sociodemographics, vulnerability factors, and comorbidities.

- Course was favorable in 41.7% and chronic in the rest of outpatients with anxiety disorders. The relatively high percentage of favorable course trajectories questions the common notion that anxiety is chronic and emphasizes the need to better predict course trajectories in daily clinical care.
- *DSM* classifications do not adequately predict severe chronic course trajectories. Indicators of severity, duration of anxiety, and disability better identify those at risk for severe chronic course trajectories and can be easily assessed during clinical care.

Clinical Points

METHOD

Study Sample

The Netherlands Study of Depression and Anxiety is a multisite naturalistic cohort study of adults (N = 2,981; 18–65 years), including those with a lifetime and/or current anxiety and/or depressive disorder (n = 2,329; 78%) and healthy controls (persons without depressive or anxiety disorders; n = 652; 22%). To include various developmental stages of disorders and different levels of severity, participants were recruited from the general population (n = 564; 19%), general practices (n = 1,610; 54%), and mental health organizations (n = 807; 27%). The methodology of NESDA is more fully described elsewhere (see Penninx et al[13]). For response rates across the recruitment settings, see Penninx et al[13] and Van Der Veen et al.[14] In general, nonresponse was slightly higher in young males, whereas selective nonresponse due to psychopathology was absent.[13,14] The study protocol was approved by the Ethical Review Board of all participating institutes, and written informed consent was obtained from all respondents. For the current study, we selected all respondents from the NESDA baseline assessment with a 6-month diagnosis of panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia, social phobia, or generalized anxiety disorder, who confirmed symptoms in the month prior to baseline on the Composite International Diagnostic Interview (CIDI) (n = 1,103; data collection between September 2004 and February 2007). Of these, 907 (82.2%) were reassessed after 2 years (data collection between October 2006 and March 2009). Nonresponse was adversely associated with years of education (OR = 0.82; 95% CI, 0.71–0.95), and marginally associated with generalized anxiety disorder (OR = 1.37; 95% CI, 1.00–1.87) and younger age (OR = 0.87; 95% CI, 0.73–1.02). Nonresponse was not associated with gender, partner status, other anxiety disorders, or the presence of multiple anxiety disorders. Of the final sample of 907 respondents, 66.6% were female, the mean age was 42.1 years (SD 12.2), the mean years of education was 11.7 years (SD 3.3), and 65.2% had a partner. With regard to baseline psychiatric status, 54.4% had social phobia, 33.6% panic disorder with agoraphobia, 16.9% panic disorder without agoraphobia, 15.7% agoraphobia, and 36.8% generalized anxiety disorder.

Measurements

Anxiety disorders. Panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia, social phobia, and generalized anxiety disorder were established using the CIDI version 2.1,[15] according to *DSM-IV* criteria.[16] Specific phobia, obsessive-compulsive disorder, and posttraumatic stress disorder were not the primary foci for the NESDA study, and subjects requesting treatment for these specific disorders were not initially recruited in NESDA. The CIDI is a structured interview with acceptable reliability and validity.[17,18] It was administered by specially trained research staff.

Anxiety symptoms. The LCGA was based on the presence of symptoms of anxiety and avoidance derived from a Life Chart Interview (LCI),[19] assessed by a trained interviewer at the 2-year follow-up assessment. Because self-generated, personal, and affectively laden landmarks are the best anchors to refresh memory (see references[20–22]), the occurrence of life events over the 2-year period between baseline and follow-up was explored first. Then the presence of symptoms of anxiety and avoidance was assessed during each month of this period, and, if present, the burden associated with the symptoms was rated on a 4-point scale. As a result, scores per month ranged from 0 (no symptom) to 4 (symptom present, severe burden). We used the highest score of either anxiety or avoidance as a combined score of anxiety and/or avoidance for each successive month. Similar instruments, such as the Life History Calendar of Freedman et al[23] and the Longitudinal Interval Follow-Up Evaluation (LIFE),[24,25] show a good test-retest reliability for periods of months (LIFE) to 5 years (Life History Calendar), suggesting that recall of symptoms is accurate for the time span used in the present study.

External validators. To assess the validity of the course trajectories identified by LCGA, we examined the distribution of various validators across the identified classes both at baseline and at 2-year follow-up. Severity of anxiety was measured using the 21-item Beck Anxiety Inventory (BAI), a frequently used self-report measure of anxiety,[26,27] which is reliable and valid.[26,28] Avoidance was measured with the 15-item Fear Questionnaire (FQ),[29] which has been found to be reliable and valid.[30,31] Functioning was measured by the World Health Organization Disability Assessment Schedule II (WHODAS).[32] The WHODAS queries difficulties in various domains of life (cognition, mobility, self-care, interpersonal interactions, and participation in society) during the last 30 days. We computed total scores with high scores indicating lower functioning. Finally, we examined the presence and number of 6-month anxiety diagnoses.

Putative predictors. We also examined the predictive value of sociodemographics, vulnerability factors, and comorbid disorders, all assessed at baseline. Sociodemographics included age, gender, partner status (yes vs no), and level of education (number of years of education). Vulnerability factors included age at onset, childhood trauma, and the presence of

Table 1. Parameters of Fit of Latent Class Growth Analysis Based on Highest Scores of Anxiety or Avoidance Symptoms During 2-Year Follow-Up (N = 907)[a]

Classes	Maximum Likelihood	BIC	ssaBIC	BLRT	Entropy	Lo-Mendell-Rubin 2LL	Lo-Mendell-Rubin *P*	Proportion of Individuals in Class 1	2	3	4	5	6
2	−30,161.7	60,521.0	60,428.9	<.001	0.98	12,648.3	<.001	0.43	0.57				
3	**−28,022.0**	**56,262.0**	**56,160.4**	**<.001**	**0.97**	**4,279.4**	**.02**	**0.42**	**0.43**	**0.15**			
4	−27,008.3	54,255.0	54,143.9	<.001	0.97	2,027.4	.14	0.12	0.26	0.36	0.27		
5	−26,283.1	52,825.0	52,704.2	<.001	0.97	1,450.6	.08	0.34	0.22	0.11	0.13	0.19	
6	−25,901.9	52,083.0	51,952.8	<.001	0.97	762.3	.09	0.34	0.08	0.17	0.19	0.11	0.12

[a]Boldface indicates the model that best fits the data.
Abbreviations: BIC = Bayesian Information Criterion, BLRT = bootstrapped likelihood ratio test, ssaBIC = sample-size–adjusted BIC, 2LL = 2 log likelihood.

a family member with an anxiety and/or depressive disorder. Age at onset of anxiety disorder was assessed with the CIDI, using the earliest age at onset for those with multiple anxiety disorders. Childhood trauma was assessed using a structured interview from the Netherlands Mental Health Survey and Incidence Study (NEMESIS),[33] 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 trauma index was computed (range, 0–4). The presence of an anxiety or depressive disorder in first-degree family members was assessed using the family tree method.[34] Comorbid disorders included comorbid depressive disorder and chronic somatic illnesses. Comorbid depressive disorder included a 6-month major depressive disorder and/or dysthymia, assessed with the CIDI.[15] The presence of somatic illnesses was assessed by counting the number of somatic diseases for which one receives medical treatment.

Statistical Analyses

Our first aim was to identify course trajectories of anxiety disorders. LCGAs were performed. LCGA is used to identify different classes of persons showing a comparable course of symptoms.[35] It starts with 1 class, suggesting 1 type of course fitting for all persons. Then successively more classes are added to determine the best-fitting model. Since LCGAs are susceptible to converging on local, rather than global solutions,[35] 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.[36] The LCI score was treated in the LCGA as a continuous variable. The LCGAs were conducted using M-plus version 5.[37] To determine which model best fitted the data, we combined maximum likelihood, Bayesian information criterion (BIC), sample-size–adjusted BIC (ssaBIC), bootstrapped likelihood ratio test (BLRT), entropy, Lo-Mendell-Rubin likelihood ratio test (LMR), and proportions of the classes, with clinical relevance of the latent trajectory classes. 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 external validators (measures of severity, number of anxiety disorders, and functioning) across classes. To do so, 2-tailed χ^2 statistics were used for categorical variables and 1-way analysis of variance statistics (ANOVA) for continuous variables. Additional pairwise comparisons were performed to test for differences between pairs of classes.

Our second aim was to compare the identified course trajectories with *DSM-IV* categories of anxiety disorders, including panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia, social phobia, and generalized anxiety disorder, and next, to compare the predictive value of *DSM*-categories with the predictive value of measures of severity and duration of anxiety and level of functioning. The prevalence of anxiety disorders across classes was examined. To examine the distribution of putative risk factors across classes, 2-tailed χ^2 statistics were used for categorical variables and ANOVA for continuous variables. Additional pairwise comparisons were performed to test for differences between pairs of classes.

To examine putative predictors of class membership, the association between predictors and class membership was further examined using multinomial, multivariate, logistic regression analyses. As an overall measure of discriminative ability of the multivariate models to predict chronic course trajectories (versus favorable course trajectory), the concordance statistic (c-statistic) was calculated per class.[38] In model 1, the association between *DSM-IV* categories of anxiety disorders and class membership was examined; in model 2, the association between measures of severity, duration, and functioning and class membership was assessed. Next, to examine whether *DSM-IV* categories have predictive value over and above measures of severity, duration, and functioning, both models were combined (model 3). Our third aim was to explore characteristics, including sociodemographics, vulnerability factors, and comorbidities, that influence the anxiety course trajectories and are therefore useful for clinical practice (model 4).

RESULTS

Course Trajectories and the Validation of These Trajectories

In Table 1, the parameters of fit of each LCGA model are presented. The standard linear model provided a good representation of the various course trajectories. Both cubic and quadratic models appeared to be non-fitting (data

Figure 1. Identified Course Trajectories of Anxiety Disorders (N = 907)

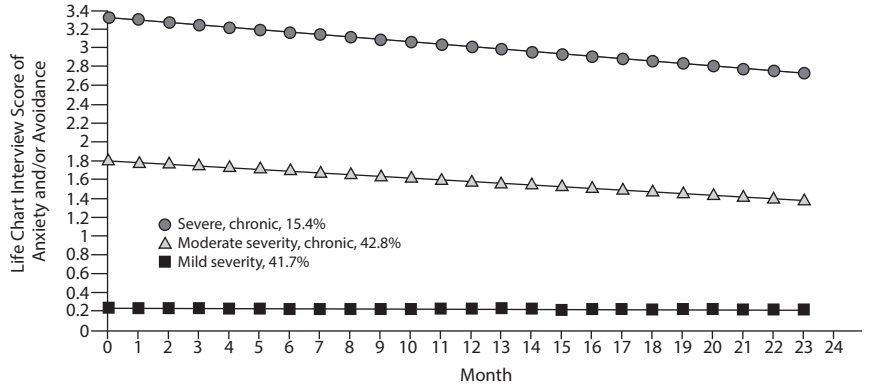

Table 2. Distribution of Putative Validators Across the Three Identified Course Trajectories of Anxiety and Avoidance Symptomatology (N = 907)

Class Description	Class 1 Mild Severity, n = 378 (41.7%)	Class 2 Moderate Severity, Chronic, n = 390 (42.8%)	Class 3 Severe, Chronic, n = 139 (15.4%)	Overall Statistics and Statistics Between Classes χ^2 or F ($df = 2$)	P Value
Baseline measurements					
BAI, mean (SD)	16.8 (9.4)	19.0 (10.5)	25.0 (12.0)	32.3	<.001[a,b,c]
FQ, mean (SD)	31.1 (18.9)	38.5 (18.4)	48.2 (21.6)	42.8	<.001[a,b,c]
No. of 6-mo CIDI diagnosis of anxiety, mean (SD)	1.4 (0.6)	1.6 (0.7)	1.8 (0.8)	17.0	<.001
Functioning (high scores = low functioning), mean (SD)	34.8 (20.5)	40.3 (21.0)	53.9 (21.7)	42.8	<.001[a,b,c]
Two-year follow-up measurements					
BAI, mean (SD)	10.5 (7.7)	14.1 (9.0)	20.4 (11.0)	65.4	<.001[a,b,c]
FQ, mean (SD)	22.5 (16.4)	32.4 (19.0)	43.3 (21.0)	72.3	<.001[a,b,c]
6-mo CIDI diagnosis of anxiety (%)	27.8	65.1	87.8	187.0	<.001[a,b,c]
No. of 6-mo CIDI diagnosis of anxiety, mean (SD)	0.3 (0.6)	0.9 (0.8)	1.6 (0.9)	151.1	<.001[a,b,c]
Functioning (high scores = low functioning), mean (SD)	23.8 (18.5)	31.5 (20.3)	46.6 (22.8)	66.6	<.001[a,b,c]

[a]Class 1 versus class 2 significant at $P < .05$.
[b]Class 2 versus class 3 significant at $P < .05$.
[c]Class 1 versus class 3 significant at $P < .05$.
Abbreviations: BAI = Beck Anxiety Inventory, FQ = Fear Questionnaire.

not shown). Although the BIC, ssaBIC, and BLRT values continued to diminish in the linear model, the LMR test failed to reach significance from the 4-class model onward. Based on the LMR test and interpretability and prevalence of the course trajectories, we chose the 3-class linear model as providing the best fit for the observed data. The means of the intercept and slope are 0,225 for the intercept and −0,001 for the slope of class 1; 1,1801 for the intercept and −0,019 for the slope of class 2; and 3,320 for the intercept and −0,026 for the slope of class 3.

Figure 1 shows the course trajectories of the 3 identified latent classes. The first class, consisting of 41.7% of our sample, was characterized by minimal burden of anxiety and avoidance at baseline and during follow-up (class 1). The second class (prevalence 42.8%, class 2) and third class (prevalence 15.4%, class 3) both had a chronic course trajectory with a slight decline of symptoms over time. These classes differed with regard to severity both at baseline and during follow-up, with class 3 representing higher level of severity.

We tested the validity of the 3-class model by examining the distribution of severity measures and level of functioning at baseline and at 2-year follow-up (Table 2). As expected, severity measures at baseline significantly increased across the classes representing increasing levels of severity. During follow-up, all severity measures diminished, reflecting a decline of anxiety in all classes. However, differences in severity across classes remained. Finally, chronic course trajectories were reflected in high percentages of 6-month CIDI anxiety diagnoses at follow-up both in class 3 and to a lesser extent in class 2. Thus, our LCGA-identified model was confirmed by all external validators.

Comparison of Course Trajectories With Anxiety Variables

Our second aim was to compare the identified course trajectories with the diagnostic baseline categories of anxiety disorders to examine whether *DSM* diagnoses do identify subsequent different course trajectories (Table 3). Whereas

Table 3. Distribution of Putative Risk Factors Across the Three Identified Course Trajectories of Anxiety and Avoidance Symptomatology (N = 907)

Class Description	Class 1 Mild Severity, n = 378 (41.7%)	Class 2 Moderate Severity, Chronic, n = 390 (42.8%)	Class 3 Severe, Chronic, n = 139 (15.4%)	Overall Statistics χ^2 or F (df = 2)	Overall Statistics P Value
Anxiety disorders					
Panic disorder with agoraphobia (%)	24.9	38.7	43.2	23.2	< .001[a,c]
Panic disorder without agoraphobia (%)	19.0	16.2	12.9	2.9	.2
Agoraphobia (%)	18.8	13.3	13.7	4.8	.09[a]
Social phobia (%)	45.0	60.0	64.0	23.7	< .001[a,c]
Generalized anxiety disorder (%)	35.4	35.1	45.3	5.1	.08[b,c]
Measures of severity					
BAI at baseline, mean (SD)	16.8 (9.4)	19.0 (10.5)	25.0 (12.0)	32.3	< .001[a,b,c]
FQ at baseline, mean (SD)	31.1 (18.9)	38.5 (18.4)	48.2 (21.6)	42.8	< .001[a,b,c]
Measures of duration					
No. of mo with anxiety in 5 y prior to baseline, mean (SD)	22.0 (19.2)	28.0 (19.8)	35.4 (19.5)	25.9	< .001[a,b,c]
No. of mo with avoidance in 5 y prior to baseline, mean (SD)	14.6 (21.3)	21.6 (23.2)	27.5 (24.0)	19.2	< .001[a,b,c]
Measures of functioning					
Functioning at baseline (high scores = low functioning), mean (SD)	34.8 (20.5)	40.3 (21.0)	53.9 (21.7)	42.8	< .001[a,b,c]
Sociodemographics					
Age, mean (SD)	42.6 (12.4)	41.5 (12.1)	42.5 (11.6)	0.85	.43
Gender (% female)	65.1	69.7	61.9	3.5	.17
Partner status (% partner)	71.6	61.5	60.4	8.6	.01[a,c]
Education, mean (SD)	11.8 (3.3)	11.7 (3.1)	11.2 (3.6)	1.91	.15
Vulnerability factors					
Age at onset of anxiety, mean (SD)	23.1 (13.7)	19.1 (12.1)	18.9 (12.8)	10.5	< .001[a,c]
Childhood trauma, mean (SD)	1.0 (1.2)	1.2 (1.2)	1.4 (1.3)	5.3	.01[a,c]
Family history of anxiety or depression (% yes)	88.4	90.8	90.6	1.4	.51
Comorbid disorders					
Comorbid 6-mo mood disorder (% yes)	53.7	54.9	71.2	13.9	.001[b,c]
No. of somatic illnesses, mean (SD)	0.7 (0.9)	0.7 (0.9)	0.8 (0.9)	0.80	.45

[a]Class 1 versus class 2 significant at $P < .05$.
[b]Class 2 versus class 3 significant at $P < .05$.
[c]Class 1 versus class 3 significant at $P < .05$.
Abbreviations: BAI = Beck Anxiety Inventory, FQ = Fear Questionnaire.

class 1 showed a preponderance of pure agoraphobia, the 2 more chronic classes showed significantly higher percentages of panic disorder with agoraphobia and social phobia. Differences between the 2 chronic classes were limited to a significantly higher percentage of generalized anxiety disorder in class 3 only.

Multinomial multivariate logistic regression analyses further tested the association between *DSM-IV* categories of anxiety disorders and course trajectories. First, the association between *DSM-IV* categories and class membership was examined (reference class 1) (Table 4). Panic disorder with agoraphobia and social phobia were associated both with chronic course trajectories with odds ratios ranging between 1.97 and 2.70 and with slightly higher odds ratios for class 3 membership. Additionally, generalized anxiety disorder was associated with class 3. Second, the predictive value of measures of severity and duration of anxiety and functioning was assessed. Model 2 shows that these measures predicted chronic course trajectories, in particular class 3 membership. Next, to examine whether *DSM-IV* categories have predictive value over and above measures of duration, severity, and levels of functioning, both previous models were combined in model 3. Whereas for the moderately severe chronic class, anxiety diagnoses (panic disorder with agoraphobia, social phobia) as well as severity (avoidance) and duration (anxiety) predicted class membership, membership of the severe chronic class was solely predicted by measures of severity (avoidance), duration (anxiety, avoidance), and functioning. Thus, anxiety diagnoses no longer significantly predicted the severe chronic course trajectory.

For prediction of class 2 membership (compared to class 1), the discriminative ability of models 1, 2, and 3 was similar (c-statistics are 0.63, 0.64, and 0.67, respectively). For prediction of class 3 membership, model 2, including measures of severity, duration, and functioning, had higher discriminative ability (c-statistic = 0.80) than the model including anxiety diagnoses (c-statistic = 0.66) (model 1), and an equal discriminative ability compared to model 3 (c-statistic = 0.81). The c-statistic of ≥ 0.80 of models 2 and 3 indicates excellent discriminative ability of these models.[38]

We also explicitly tested predictors of class 3 (severe chronic course) versus class 2 (moderately severe chronic course). In model 1, only generalized anxiety disorder predicted a severe chronic course (OR = 1.57; 95% CI, 1.05–2.33). In model 2, duration of anxiety (OR = 1.30; 95% CI, 1.04–1.62) and level of functioning (OR = 1.53; 95% CI, 1.17–1.99) predicted a severe chronic course. In model 3, combining *DSM*-diagnoses of anxiety disorders and general measures of severity,

Table 4. Results From Multivariate, Multinomial, Logistic Regression Analyses Associating Anxiety Variables With the Identified Course Trajectories Compared to the Most Favorable Course Trajectory (Class 1 = reference)[a]

Class 1 (reference) Mild Severity	Class 2 Moderate Severity, Chronic, n = 390 (42.8%) OR (95% CI)	Class 3 Severe, Chronic, n = 139 (15.4%) OR (95% CI)
Model 1: Anxiety disorders		
Panic disorder with agoraphobia	**2.14 (1.48–3.09)**	**2.70 (1.66–4.40)**
Panic disorder without agoraphobia	1.23 (0.80–1.89)	1.15 (0.61–2.17)
Agoraphobia	1.06 (0.67–1.67)	1.29 (0.68–2.43)
Social phobia	**1.97 (1.46–2.68)**	**2.46 (1.62–3.74)**
Generalized anxiety disorder	1.18 (0.86–1.61)	**1.86 (1.23–2.82)**
C-statistics	0.63	0.66
Model 2: Severity and duration measures and level of functioning		
Total score BAI[b]	1.04 (0.86–1.26)	**1.30 (1.00–1.68)**
Total score FQ[b]	**1.33 (1.10–1.60)**	**1.48 (1.14–1.91)**
No. of mo with anxiety symptoms prior to baseline[b]	**1.24 (1.06–1.45)**	**1.61 (1.28–2.02)**
No. of mo with avoidance symptoms prior to baseline[b]	**1.19 (1.01–1.40)**	1.24 (0.99–1.56)
Functioning (high scores = low functioning)[b]	1.10 (0.90–1.33)	**1.66 (1.26–2.18)**
C-statistics	0.64	0.80
Model 3: Anxiety disorders, adjusted for severity and duration measures and level of functioning		
Panic disorder with agoraphobia	**1.58 (1.03–2.42)**	1.08 (0.59–1.96)
Panic disorder without agoraphobia	1.16 (0.74–1.82)	0.83 (0.42–1.64)
Agoraphobia	0.80 (0.49–1.31)	0.62 (0.30–1.26)
Social phobia	**1.58 (1.14–2.18)**	1.38 (0.87–2.19)
Generalized anxiety disorder	1.00 (0.71–1.40)	1.09 (0.69–1.73)
Total score BAI[b]	0.96 (0.78–1.19)	1.27 (0.97–1.67)
Total score FQ[b]	**1.23 (1.01–1.50)**	**1.41 (1.08–1.84)**
No. of mo with anxiety symptoms prior to baseline[b]	**1.23 (1.04–1.44)**	**1.57 (1.25–1.97)**
No. of mo with avoidance symptoms prior to baseline[b]	1.17 (0.98–1.39)	**1.28 (1.00–1.63)**
Functioning (high scores = low functioning)[b]	1.14 (0.92–1.41)	**1.67 (1.26–2.23)**
C-statistics	0.67	0.81
Model 4: Putative predictors		
Higher age[b]	1.00 (0.85–1.18)	1.05 (0.84–1.31)
Female	1.14 (0.83–1.56)	0.77 (0.50–1.17)
Partner status	**0.69 (0.50–0.93)**	**0.66 (0.43–1.00)**
Higher education[b]	0.95 (0.83–1.09)	0.86 (0.72–1.04)
Age at onset[b]	**0.75 (0.64–0.88)**	**0.72 (0.58–0.90)**
Childhood trauma[b]	1.07 (0.95–1.22)	**1.18 (1.00–1.39)**
Family history of anxiety or depression	0.90 (0.56–1.44)	0.92 (0.47–1.80)
Depressive disorder at baseline	1.01 (0.76–1.36)	**1.96 (1.27–3.02)**
No. of somatic illnesses[b]	1.06 (0.90–1.26)	1.11 (0.99–1.39)
C-statistics	0.62	0.67

[a]Bold indicates significant association ($P < .05$).
[b]Reported per SD increase: BAI at baseline, SD = 11; FQ at baseline, SD = 20; level of functioning at baseline, SD = 22l; months anxiety prior to baseline, SD = 20; months avoidance prior to baseline, SD = 23; age, SD = 12; education, SD = 3; childhood trauma, SD = 1; somatic illnesses, SD = 1.
Abbreviations: BAI = Beck Anxiety Inventory, c-statistics = concordance-statistics, FQ = Fear Questionnaire.

duration, and functioning, generalized anxiety disorder no longer predicted a severe chronic course (OR = 1.12; 95% CI, 0.73–1.73), but duration of anxiety (OR = 1.28; 95% CI, 1.02–1.60) and level of functioning (OR = 1.48; 95% CI, 1.12–1.94) did. As in the comparisons with the favorable course trajectory, c-statistics were higher in model 2 (0.70) than model 1 (0.57), and adding *DSM*-diagnoses to general measures of severity, duration, and functioning (model 3) did not further improve the predictive value of the model (c-statistic of model 3 = 0.70).

Characteristics of the Course Trajectories and Their Predictive Value on Course Trajectories

The third aim of the present study was to explore the characteristics of each identified course trajectory and to examine putative predictors of class membership, hence course trajectories. Class 1 was characterized by a significantly higher number of persons with a partner, a higher age at onset of anxiety disorders, and a lower number of childhood traumas, as compared to both chronic classes. Class 3 was characterized by a higher comorbidity of 6-month depressive disorders at baseline, compared to the 2 other classes. Other differences among the classes were less profound (Table 3).

Predictors of class membership are shown in Table 4 (model 4). Partner status and age at onset were inversely associated with both chronic course trajectories. Childhood adversities and comorbid depressive disorders were associated with class 3 only. The c-statistic of these baseline predictors together was 0.62 (class 2) and 0.67 (class 3), indicating reasonable discriminative ability.

DISCUSSION

This study identified clinically relevant course trajectories of anxiety in a large cohort of anxious adults participating in NESDA, using a data-driven method, and compared these trajectories with *DSM-IV* categories of panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia, social phobia, and generalized anxiety disorder. Three findings are of particular importance for daily clinical care.

First, we found that course of anxiety is pleomorphic. This finding emphasizes the need to better predict course trajectories in clinical care. Two classes represented chronic course trajectories (moderate severity, 42.8%; high severity, 15.4%). Thus, in line with previous research,[1,3] a chronic course was present in the majority of cases. However, a course trajectory with minimal burden of anxiety over time was found in 41.7% of the cases. This finding questions the common notion of the chronicity of anxiety disorders. Previously, we reported similar proportions of respondents with anxiety disorders who had no symptoms over time in a population-based study with a 7-year follow-up.[39] In accordance with previous research,[40,41] severity declined over time in all classes.

Second, indicators of severity and duration of anxiety and functional disability better identify chronic course trajectories as compared with *DSM* categories. *DSM*-categories did have some predictive value. For example, panic disorder with agoraphobia, social phobia, and generalized anxiety disorder predicted chronicity and panic disorder without agoraphobia did not, which is in line with previous findings.[1,2] Our results additionally illustrated that generalized anxiety disorder is particularly associated with severe chronic course. Moreover, our results clearly showed the impact of additional agoraphobia on course of panic disorder, which is also in line with previous research.[1,2,42–44] However, c-statistics of our models convincingly pointed at the superiority of measures of severity, duration, and functioning in predicting chronic, severe course trajectories above *DSM*-categories. Given that the general measures of severity, duration, and functioning can be easily assessed by clinicians, this finding is of importance in daily clinical care. As the presence of multiple anxiety disorders might impact course,[1] we added a variable "number of baseline anxiety disorders" as a predictor to model 2 (including general measures of severity, duration, and functioning). Number of anxiety disorders appeared to not be a significant predictor for the 2 chronic classes (as compared with class 1) (for moderate severity class: OR = 1.13; 95% CI, 0.82–1.56; for severe chronic class: OR = 1.26; 95% CI, 0.99–1.60). By adding this variable to the model, the predictive ability of the model did not improve (for moderate severity, chronic class c-statistic = 0.65 [vs 0.64 without the variable]; for severe chronic class c-statistic remained 0.80). This further supports our conclusion of the importance of general measures of severity, duration, and functioning over *DSM* classifications.

Third, several additional correlates of chronicity could be identified. The absence of a partner predicted chronic course trajectories. Previous research on the impact of partner status is sparse and not unidirectional.[39,41,45–47] Results of our study suggest that age at onset impacts chronicity, with persons with an earlier onset being more likely to have a chronic course trajectory. Also, Penninx et al[3] reported the impact of early age at onset on chronicity, albeit using different methods. By contrast, Ramsawh et al[40] found that age at onset impacted the recurrence rates of panic disorder with agoraphobia only. Previously, early age at onset has been associated with increased severity, comorbidity, and suicide attempts.[48–50] Our findings further demonstrate the relevance of early age at onset for clinical practice by showing its impact on course trajectories. Age at onset might thus be regarded a marker for unfavorable outcome. Childhood trauma and depressive disorders at baseline specifically predicted severe symptoms over time. Although the unfavorable impact of both predictors has been reported previously,[1,3,39,51–56] our results add to earlier studies by using a data-driven method.

Strength and Limitations

This study is one of the largest to date to longitudinally investigate the existence of anxiety course types in a large cohort using data-driven methods. Most studies examined course trajectories in the general population, including persons without symptoms at baseline. By focusing on subjects with anxiety disorders at baseline, our results can be used in clinical care to identify patients at risk for chronicity. Except for Olino et al,[10] previous studies did not compare course trajectories with *DSM* categories. By comparing the predictive value of *DSM* classifications with the predictive value of measures of severity, duration, and functioning, the superiority of the latter measures could be shown. 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. This implicates that the waxing and waning of anxiety symptoms over time may have been summarized into chronic course trajectories. It also implicates that, within a specific course trajectory, other predictors may be at work, such as specific *DSM* diagnoses. In addition, because LCGA does not allow within-class variation, LCGA might "produce" extra classes when variation in severity is present, thereby falsely suggesting that there are different course trajectories. To verify whether our course trajectories represent severity classes or different course trajectories, we conducted growth mixture modeling (GMM), because, in this method, within-class variation is allowed. In GMM, also the 3-class model fitted best. The trajectories in LCGA and GMM were quite similar, as were the prevalences of the 3 classes found. This further supports the existence of 3 different course trajectories that do not only reflect severity classes. In addition, we examined 2-year course trajectories, which may be relatively short. Finally, the current study is conducted using *DSM-IV* criteria, as longitudinal studies using *DSM-5* criteria are not available yet. In *DSM-5*, a duration criteria is added to the diagnostic

criteria of social phobia and agoraphobia, thereby excluding patients with transient fears.[57] A study using *DSM-5* criteria is thus likely to show an even more chronic course as compared to our study.

To conclude, in line with current debates on clinical staging models,[58] the present study showed that dimension-based, predictive algorithms should incorporate duration and severity dimensions and level of functioning in association with correlates of chronicity. These predictive algorithms may guide the use of appropriate stage-specific, evidence-based treatment.[59]

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