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Research paper

The 9-year clinical course of depressive and anxiety disorders: New NESDA findings

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ABSTRACT

Background: In longitudinal research, switching between diagnoses should be considered when examining patients with depression and anxiety. We investigated course trajectories of affective disorders over a nine-year period, comparing a categorical approach using diagnoses to a dimensional approach using symptom severity.
Method: Patients with a current depressive and/or anxiety disorder at baseline ($N = 1701$) were selected from the Netherlands Study of Depression and Anxiety (NESDA). Using psychiatric diagnoses, we described 'consistently recovered,' 'intermittently recovered,' 'intermittently recurrent', and 'consistently chronic' at two-, four-, six-, and nine-year follow-up. Additionally, latent class growth analysis (LCGA) using depressive, anxiety, fear, and worry symptom severity scores was used to identify distinct classes.
Results: Considering the categorical approach, 8.5% were chronic, 32.9% were intermittently recurrent, 37.6% were intermittently recovered, and 21.0% remained consistently recovered from any affective disorder at nine-year follow-up. In the dimensional approach, 66.6% were chronic, 25.9% showed partial recovery, and 7.6% had recovered.
Limitations: 30.6% of patients were lost to follow-up. Diagnoses were rated by the interviewer and questionnaires were completed by the participant.
Conclusions: Using diagnoses alone as discrete categories to describe clinical course fails to fully capture the persistence of affective symptoms that were observed when using a dimensional approach. The enduring, fluctuating presence of subthreshold affective symptoms likely predisposes patients to frequent relapse. The commonness of subthreshold symptoms and their adverse impact on long-term prognoses deserve continuous clinical attention in mental health care as well further research.

1. Introduction

Longitudinal research is essential to validate diagnostic classifications and tailor treatment plans for optimal effectiveness and efficiency for patients with affective disorders (Gillis et al., 1995; Kendell and Jablensky, 2003; Kraepelin, 1921; Lorenzo-Luaces et al., 2017; McGorry et al., 2016; Penninx et al., 2011). In longitudinal research, depressive and anxiety disorders should be investigated synchronously considering that major depressive disorder (MDD) and anxiety disorders often co-occur (Angst et al., 2009; Giandinoto and Edward, 2015; Hayden and Klein, 2001; Howland et al., 2009; Kessler et al., 2005; Kleiboer et al., 2016; Lamers et al., 2011; Moffitt et al., 2007; Rush et al., 2006), and as time passes, one disorder will often switch over to the other ("diagnostic switching") (Gregory et al., 2007; Hovenkamp-Hermelink et al., 2016; Scholten et al., 2016). For example, those recovered from MDD may then meet criteria for generalized anxiety disorder (GAD) and still experience functional impairment and a decreased quality of life (Angst et al., 2009; Maj et al., 2002; Wells et al., 1992). Patients may also switch over to dysthymic disorder, the more chronic but milder form of depression (Klein et al., 2008; Rhebergen et al., 2012).

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The selected observation period may also reveal crucial insights into the course of depressive and anxiety disorders. A shorter window of less than two years has led to relatively positive findings with regard to prognosis (Gilchrist and Gunn, 2007; Hendriks et al., 2013; Richards, 2011; Steinert et al., 2014). For example, previous research has shown that more than half (50 – 70%) of patients recovered within one year from MDD (Richards, 2011; Steinert et al., 2014), and approximately half (43 – 73%) of patients recovered within two years from anxiety disorders (Hendriks et al., 2013). However, when extending the observation window, lower levels of recovery were found, which may be due to diagnostic switching (Caspi et al., 2020; Gregory et al., 2007; Hovenkamp-Hermelink et al., 2016; Plana-Ripoll et al., 2019; Scholten et al., 2016), relapse (Hardeveld et al., 2010; Mueller et al., 1999; Scholten et al., 2013; Verduijn et al., 2017), or continuous subthreshold or subclinical symptoms (Ormel et al., 1993; Wagner et al., 2000).

The course of depressive and anxiety disorders can be and have been described using two clinically-relevant approaches: with psychiatric diagnosis criteria according to the Diagnostic Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) (i.e., categorical approach) or scores on symptom severity scales (i.e., dimensional approach) (Wardenaar et al., 2014). Use of DSM diagnoses allows us to examine participants who (continue to) meet full DSM criteria over time, whether these are comorbid diagnoses or transitions to other diagnoses. Alternatively, symptom severity scores are regularly used throughout the treatment follow-up process to assess change of symptoms over time, such as in routine outcome monitoring (ROM) (e.g., de Beurs et al., 2011). Using symptom severity scores may also help reveal and describe the heterogeneity in (sub)clinical symptom profiles (Brunoni, 2017; Fried and Nesse, 2015a). Considering that depression and anxiety DSM-diagnoses can be viewed as discrete categorical syndromes imposed on a continuum of depressive or anxiety symptoms of varying severity and duration (Kendler and Gardner, 1998; Klein et al., 2006, 2008; Torpey and Klein, 2008), comparing both approaches is relevant. Latent class growth analysis (LCGA) with both depressive and anxiety symptoms would allow us to examine how symptoms change over time as a dimensional approach and to compare the outcome to the categorical approach with DSM diagnoses.

The present study aimed to describe and compare course trajectories of depressive and anxiety disorders over a nine-year period using a categorical approach for DSM-diagnosis trajectories and a dimensional approach for symptom pathways using LCGA. We considered depressive and anxiety comorbidity, switching to other diagnoses over time, and switching to other trajectories over time. We specified how participants intermittently recover and relapse over a nine-year period and how the DSM diagnoses concur with fluctuating symptom scores. For the categorical approach, we hypothesized that those with baseline comorbid depressive and anxiety disorders, compared to those with baseline depression or anxiety disorder, would have higher levels of chronicity at nine-year follow-up (Hendriks et al., 2013; Richards, 2011; Steinert et al., 2014). Likewise, for the dimensional approach, we hypothesized that those with higher baseline symptom levels would coincide with a more chronic course. Finally, we hypothesized that the trajectories according to the categorical approach would correspond highly with the dimensional symptom pathways.

2. Method

2.1. Study sample and procedure

Data were used from the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2021), an ongoing longitudinal cohort study examining the course of depressive and anxiety disorders (for the extensive protocol, see Penninx et al., 2008). At baseline (2004–2007), a total of 2981 participants aged between 18 and 65 years were recruited from community (19.0%), primary care (54.0%), and specialized mental healthcare (27.0%). After baseline, face-to-face follow-up assessments were conducted at two years (87.1%, $n = 2596$), four years (80.6%, $n = 2402$), six years (75.5%, $n = 2256$), and nine years (69.4%, $n = 2069$). The nine-year follow-up was completed in 2016.

For the present study, we selected a total of 1701 participants with MDD, dysthymic disorder, and/or anxiety in the six months prior to baseline (i.e., a current six-month diagnosis) (see below).

2.2. Measures

2.2.1. Categorical course trajectories

To determine the categorical trajectories, we examined the presence of depressive (MDD, dysthymic disorder) and anxiety disorders (panic disorder, social phobia, generalized anxiety disorder (GAD), and agoraphobia) according to the DSM-IV criteria at each assessment. The disorders were assessed in person using the Composite Interview Diagnostic Instrument (CIDI) version 2.1 by trained research personnel (Wittchen, 1994; Wittchen and Nelson, 1996). To extrapolate whether the CIDI diagnoses were consistently present during follow-up periods, we examined the continuous presence of diagnosis-related symptoms reported in the Life Chart Interview (LCI; Lyketsos et al., 1994) for that same follow-up period. More information regarding the instruments can be found in the **Supplementary Material**.

Using the CIDI, participants were first divided into subgroups at baseline: 1) depression only (single or any combination of MDD and/or dysthymic disorder); 2) anxiety only (single or any combination of panic disorder, social phobia, GAD, and agoraphobia); and 3) comorbid depression-anxiety (any combination of both depressive and anxiety disorders). The following "primary" categorical diagnosis trajectories were then described at two-, four-, six-, and nine-year follow-up for the total group and for each of the subgroups by examining whether participants had any CIDI diagnosis at each following assessment after baseline: *'consistently recovered'* (fixed diagnosis-free period at each assessment), *'intermittently recovered'* (variable diagnosis-free period preceded by a diagnosis-present period with or without discontinuous LCI symptoms), *'intermittently recurrent'* (variable diagnosis-present period with discontinuous LCI symptoms), and *'consistently chronic'* (fixed diagnosis-present period at each assessment with continuous LCI symptoms). The trajectories of 'intermittently recovered' and 'intermittently recurrent' allowed us to explore the ebb and flow of diagnoses across the nine-year period. At nine-year follow-up, we defined three "comparison" trajectories, where each percentage was aggregated at each subsequent assessment point: *'recovered'* (diagnosis-free period), *'recurrent'* (diagnosis-present period with discontinuous LCI symptoms), and *'chronic'* (diagnosis-present period with continuous LCI symptoms). This allowed us to compare our results to Verduijn et al. (2017), who examined the six-year follow-up NESDA data. An extended description of the trajectories can also be found in the **Supplementary Material** (see "Description of categorical trajectories"). The specific differences with Verduijn et al. (2017) are also outlined in the **Supplementary Material** (see "Comparison with previous NESDA study").

2.2.2. Dimensional course trajectories

To determine dimensional trajectories, we used depressive and anxiety symptom severity measures. For depressive symptom severity, we used the Inventory of Depressive Symptomatology – Self-Report (IDS-SR; Rush et al., 1996; Trivedi et al., 2004). For anxiety symptom severity, we used the Beck Anxiety Inventory - Self-Report (BAI; Beck et al., 1988; De Ayala et al., 2005; Muntingh et al., 2011; Steer et al., 1993); the Fear Questionnaire (FQ; Marks and Mathews, 1979; Oei et al., 1991); and the Penn State Worry Scale (PSWQ; Meyer et al., 1990; Salarifar and Pouretemad, 2012; Verkuil and Brosschot, 2012). Finally, we examined functional (dis)ability, which was measured using the World Health Organization Disability Assessment Schedule (WHO-DAS-II; Chwastiak and Von Korff, 2003). More information regarding these instruments can be found in the **Supplementary Material**.

2.3. Statistical analyses

Sociodemographic characteristics. We reported baseline characteristics as percentages or as means with standard deviations (*SD*). We inspected baseline symptom severity scores for clinically-relevant threshold levels (IDS > 13; BAI > 7; approximations FQ > 30; PSWQ > 48) (Gillis et al., 1995; Rush et al., 1996).

Categorical approach using diagnoses. For the categorical approach, we described the "primary" DSM-diagnoses trajectories using variable and aggregated percentages and "comparison" DSM-diagnoses trajectories using aggregated percentages. We also examined the trajectories without any missing CIDI data at all follow-up assessments. Moreover, we conducted a contingency table analysis with adjusted residuals (Beasley and Schumacker, 1995; García-Pérez and Núñez-Antón, 2003), to test whether there was an association between baseline diagnostic subgroup (i.e., depression only, anxiety only, and depression-anxiety) and the four course trajectories at nine-year follow-up.

Dimensional approach using symptom severity. For the dimensional approach, we used latent class growth analysis (LCGA), a type of mixture modeling with latent class analysis, to identify subgroups of participants with distinct patterns of change in their longitudinal symptom severity assessments, relative to baseline (using the 'hlme' function of the 'lcmm' package in R version 3.6.1) (Proust-Lima et al., 2017). In LCGA, participants are clustered into classes representing trajectories with similar mean levels and mean-level changes of symptom severity by modeling a latent categorical variable. Unlike conventional growth mixture modeling (GMM), the analysis was conducted with the variance of the latent slope and intercept fixed to zero within class, thus limiting the heterogeneity within the latent classes, allowing us to identify course-trajectory classes that were optimally differentiated from each other (Armour et al., 2012; Asparouhov, 2006; Berlin et al., 2014; Cicchetti and Rogosch, 1999; Curran and Hussong, 2003; deRoon-Cassini et al., 2010; Jung and Wickrama, 2008; Muthén and Muthén, 2000; Nylund et al., 2007). For more information, see "Description and interpretation criteria of the latent class growth analysis" and the checklist for the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS; van de Schoot, 2015) in the **Supplementary Material.**

Comparison of categorical and dimensional approaches. We compared the outcome of both the categorical and dimensional approaches at nine-year follow-up. Hereafter, we examined the overlap across the identified dimensional symptom severity pathways and the "primary" and "comparison" DSM-diagnosis trajectories at nine-year follow-up. For the "comparison," trajectories, where a 3 × 3 contingency table was possible, we tested the level of agreement between the categorical and dimensional approaches with the Kappa statistic as a complete-case analysis, where 0.01–0.20 = none to slight/very poor, 0.21–0.39 = minimal, 0.40–0.59 = weak, 0.60–0.79 = moderate and 0.80–0.90 = strong (Cohen, 1960; de Raadt et al., 2019; McHugh, 2012). We then examined the average functional (dis)ability scores across the identified dimensional symptom severity pathways.

To further compare the symptom severity pathways with the DSM-diagnoses trajectories, we examined the trends of symptom severity per questionnaire across the assessment points based on baseline diagnosis subgroups and functional (dis)ability across the assessment points. We split the IDS-SR, BAI, FQ, PSWQ, and WHO-DAS-II scores into quartiles based on the baseline total score of that particular questionnaire and used mixed model regression analysis to yield marginal mean values at each follow-up assessment per questionnaire. Given that depression and anxiety frequently emerge in younger adulthood (Caspi et al., 2020; Ernst and Angst, 1992; Moffitt et al., 2007), we tested whether there was a potential effect of age and gender on depressive, anxiety, fear and worry severity symptoms. Age was split into quartiles, or four age groups. We then examined these trajectories over the nine-year follow-up.

Statistics programs for the analyses. The descriptive analyses and categorical approach analysis were conducted using IBM SPSS version 25.0. For the dimensional approach, we used R statistical software (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.R-project.org/). The mixed-model analyses were also conducted using R software using the 'lme4' package. Alpha was set at 0.05, except for the chi-square post hoc contrasts, where alpha was set to 0.0042 after a Bonferroni correction.

Table 1
Baseline Socio-Demographic and Clinical Characteristics ($N = 1701$).

Age, years, mean (*SD*)	41.3 (*12.4*)
Sex, female,% (*n*)	67.0 (*1140*)
Education, years, mean (*SD*)	11.8 (*3.3*)
Married or life partner, yes,% (*n*)	65.3 (*1110*)
Single depressive disorder,% (*n*)	19.9 (*339*)
Comorbid depressive disorders,% (*n*)	3.4 (*57*)
Severity of depressive symptoms (IDS-SR), mean (*SD*)	27.6 (*11.6*)
Severity of anxiety symptoms (BAI), mean (*SD*)	12.1 (*8.9*)
Severity of fear symptoms (FQ), mean (*SD*)	21.7 (*16.8*)
Severity of worry symptoms (PSWQ), mean (*SD*)	29.3 (*15.7*)
Severity of functional disability (WHO-DAS-II), mean (*SD*)	31.6 (*16.0*)
Single anxiety disorder,% (*n*)	22.6 (*384*)
Comorbid anxiety disorders (2 to 3),% (*n*)	9.3 (*159*)
Severity of depressive symptoms (IDS-SR), mean (*SD*)	21.9 (*9.8*)
Severity of anxiety symptoms (BAI), mean (*SD*)	14.7 (*9.5*)
Severity of fear symptoms (FQ), mean (*SD*)	31.1 (*18.5*)
Severity of worry symptoms (PSWQ), mean (*SD*)	29.7 (*14.4*)
Severity of functional disability (WHO-DAS-II), mean (*SD*)	25.1 (*15.4*)
Comorbid depression and anxiety,% (*n*)	44.8 (*762*)
Severity of depressive symptoms (IDS-SR), mean (*SD*)	34.2 (*13.1*)
Severity of anxiety symptoms (BAI), mean (*SD*)	20.8 (*11.5*)
Severity of fear symptoms (FQ), mean (*SD*)	38.8 (*21.9*)
Severity of worry symptoms (PSWQ), mean (*SD*)	32.4 (*18.2*)
Severity of functional disability (WHO-DAS-II), mean (*SD*)	41.1 (*17.2*)

Note. Depression only = depressive disorders such as major depressive disorder or dysthymia. Anxiety only = anxiety disorders such as social phobia and generalized anxiety disorder. Comorbid depression and anxiety = MDD, dysthymic disorder and anxiety disorders. *IDS-SR* = Inventory of Depressive Symptomatology – Self-Report; *BAI* = Beck Anxiety Inventory; *FQ* = Fear Questionnaire; PSWQ = Penn State Worry Scale; WHO-DAS-II = World Health Organization Disability Assessment Schedule (standardized).

3. Results

3.1. Baseline sociodemographic information

Table 1 shows the baseline characteristics of the study sample ($N = 1701$). Participants were on average 41.3 years old ($SD = 12.4$), 67.0% were female ($n = 1140$), and 65.3% had a spouse or partner ($n = 1110$). The mean total IDS-SR and BAI scores were 31.5 ($SD = 10.9$) and 18.3 ($SD = 10.6$), respectively, reflecting a moderate level of depressive and anxiety symptom severity at baseline. Nearly half of our participant sample (44.8%) had comorbid depression and anxiety at baseline.

3.2. Categorical approach using depression and anxiety diagnoses

Fig. 1 presents four stacked bar charts showing the proportions of participants at each follow-up assessment who were 'consistently recovered,' 'intermittently recovered,' 'intermittently recurrent,' and 'consistently chronic,' divided by baseline diagnostic status. Over the course of nine years, the prognosis of each group was relatively positive: the percentage of participants who recovered increased, and the percentage of those with consistently chronic diagnoses decreased. Specifically, at nine-year follow-up, across all groups, between 51.9 and 68.6% had recovered from any disorder (when combining both consistent and intermittent recovery) and between 2.9 and 11.8% maintained consistently chronic disorders. Approximately one-third of participants experienced intermittent recurrence across all groups at four-, six- and nine-year follow-up. Looking specifically at nine-year follow-up, baseline diagnostic status was significantly associated with course, χ^2 (6, $N = 966$) = 61.5, $p < .0001$, with a lower proportion of participants with

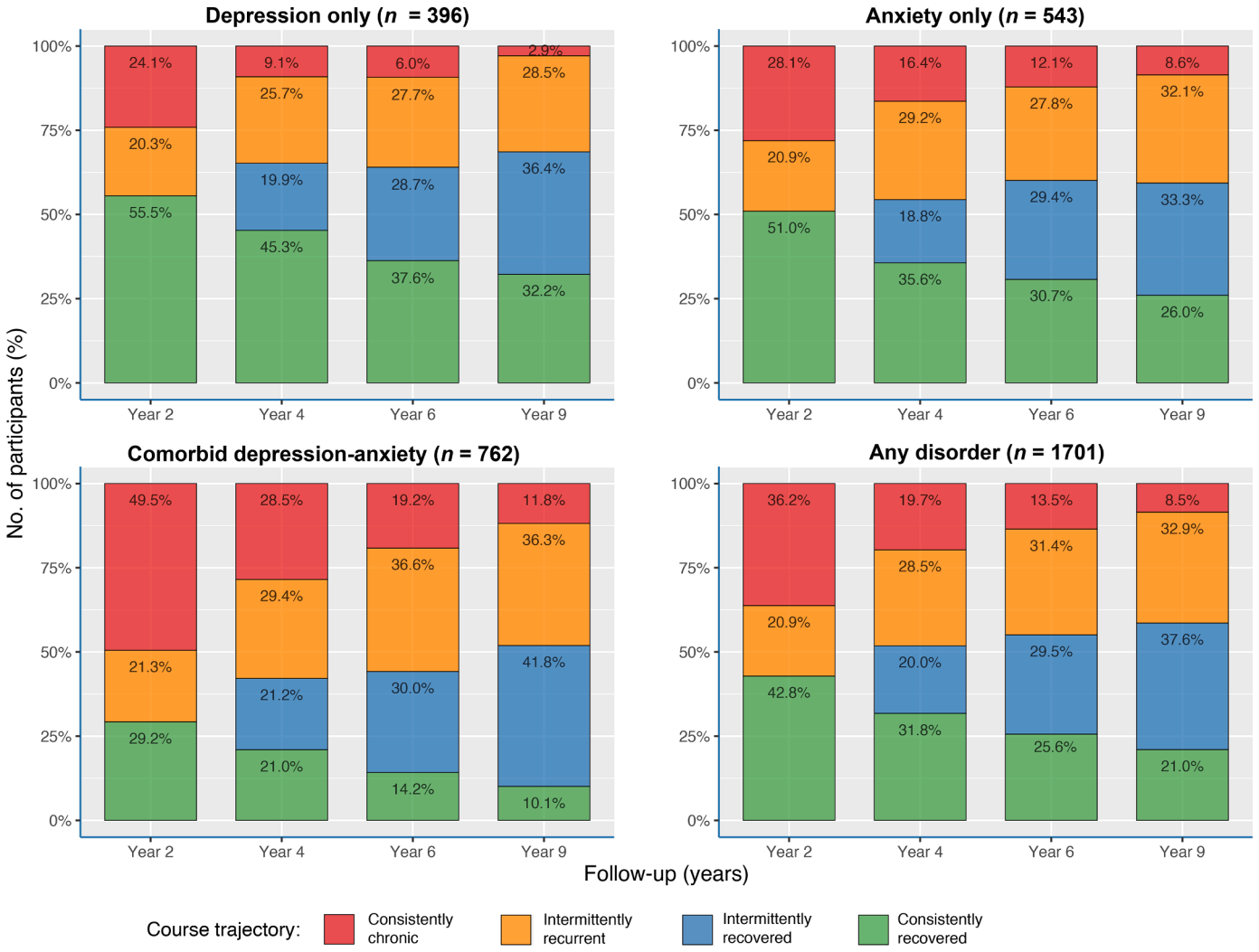

Fig. 1. Categorical trajectories of diagnoses at two-, four-, six-, and nine-year assessments, based on any CIDI affective disorder and LCI data. Depression only = depressive disorders such as major depressive disorder or dysthymia. Anxiety only = anxiety disorders such as social phobia and generalized anxiety disorder.

baseline depression-anxiety comorbidity experiencing consistent recovery than participants with baseline depression ($p < .0001$), and a higher proportion of participants with depression-anxiety comorbidity experiencing consistent chronicity than participants with baseline depression ($p = .0012$). Additionally, when examining recovery more closely at nine-year follow-up, only 10.1% of participants with baseline comorbid depression-anxiety were consistently recovered, 26.0% of the anxiety-only group were consistently recovered, and 32.2% of the depression-only group were consistently recovered. Lastly, for the total group with any disorder, 21.0% were consistently recovered. When using a sample without missing CIDI diagnoses at any follow-up assessment ($N = 956$), we found the same pattern as in the primary categorical trajectories. For comparison with trajectories of Verduijn et al. (2017), see Figure A and "Comparison with previous NESDA study" in the **Supplementary Material**. The main finding of the comparison trajectories is that 78.5% of participants with any disorder experienced recurrence over a nine-year period.

3.3. Dimensional approach using symptom severity

Table 2 shows the fit indices resulting from the log-linear LCGA with one- to six-classes.

Table 2
Fit Indices of One- to Six-Class Latent Class Growth Analysis over a Nine-Year Follow-Up ($N = 1693$).

Classes	Log-Likelihood	AIC	BIC	SA-BIC	Entropy	Percentage of Individuals in Class					
						1	2	3	4	5	6
1	−5735.8	11,477.6	11,493.9	11,484.3	1.00	100	–	–	–	–	–
2	−4827.9	9667.8	9700.5	9681.4	0.71	22.1	77.8	–	–	–	–
3	−4598.8	9215.6	9264.5	9235.9	0.69	7.5	66.6	25.9	–	–	–
4	−4505.9	9035.9	9101.1	9063.0	0.62	4.7	14.1	18.9	62.4	–	–
5	−4452.1	8934.2	9015.7	8968.1	0.65	2.4	7.6	62.3	19.5	8.2	–
6	−4427.9	8891.8	8989.7	8932.5	0.66	1.2	2.4	61.4	7.5	19.8	7.8

Note. AIC = Akaike Information Criterion (Akaike, 1987); BIC = Bayesian Information Criterion (Schwartz, 1978); SA-BIC = sample-size-adjusted BIC (Sclove, 1987); Entropy (Ramaswamy et al., 1993).

Taking all fit indices into account, the three-class model was considered the optimal solution. The AIC and SA-BIC values showed a marked drop between one-, two- and three-class models (see elbow plots in **Fig. B** in **Supplemental Material**), and hereafter, the differences in AIC and SA-BIC values were smaller, suggesting that the addition of more classes did not further improve the model. Also, solutions with four to six classes had very small numbers of participants (<5%) in some classes. Examining the entropy value of the three-class model (0.69) indicated that a moderate to high proportion of participants were correctly classified. The grid search also confirmed a three-class model.

Fig. 2**A** delineates the three latent classes that were identified using pooled standardized mean severity scores of depressive, anxiety, fear,

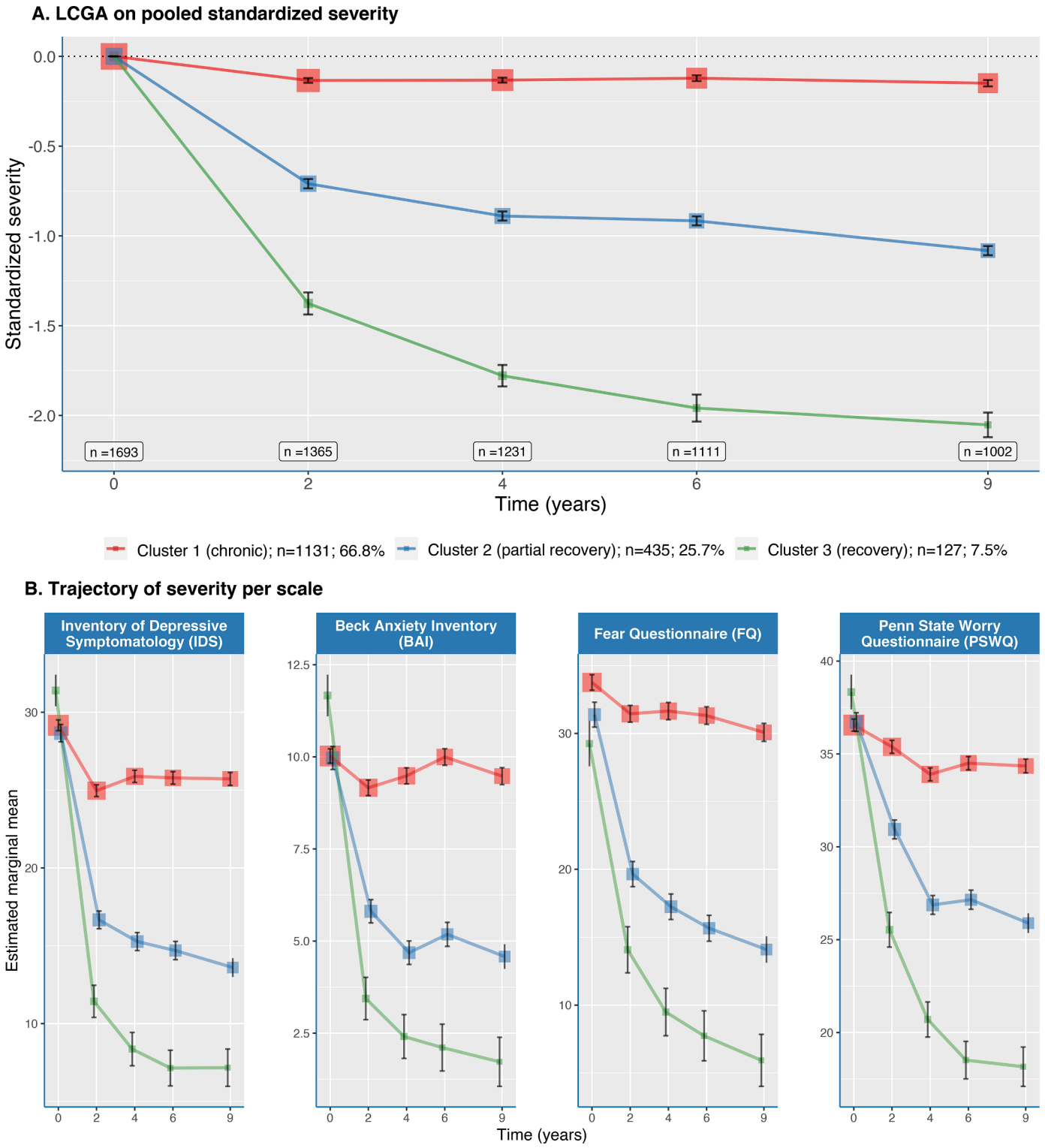

Fig. 2. Three latent class solution of pooled standardized mean severity scores of depressive, anxiety, fear, and worry symptoms (LCGA: latent class growth analysis). Panel A shows the average change in standardized severity over time as compared to baseline severity, and Panel B shows the standardized severity scores per scale over time. Error bars represent standard errors, and the box size is proportional to the number of participants.

and worry symptom questionnaires: class 1: *chronic* (66.8%); class 2: *partial recovery* (25.7%); and class 3: *(sustained) recovery* (7.5%). Class 1 (red) remained stable and severe; whereas symptom levels decreased moderately in class 2 (blue) and markedly in class 3 (green). This was consistent with the latent classes of pooled symptom severity for depression, anxiety, fear, and worry symptom levels, viewing each questionnaire separately (see Fig. 2**B**): the group with the highest symptom levels maintained high symptom levels throughout the nine-year period; the moderate level group showed slow decline and intermittent increases in anxiety and worry; and the lowest symptom level group showed a larger and steady decline. Moreover, inspection of the classes, or symptom pathways, showed that there was a relatively greater change in symptom severity between baseline and the first follow-up, after which the course showed less change between follow-up assessments and began to stabilize, suggesting that the log-linear function best described these symptom pathways. For a comparison with alternative models, see "Alternative models using latent class growth analysis" in the **Supplementary Material**. Recomputing the model without any missing data and comparing these to the abovementioned classes resulted in highly corresponding models: 94.9% similarity for class 1 (chronicity), 89.9% similarity for class 2 (partial recovery), and 100% similarity for class 3 (recovery).

3.4. Comparison of categorical and dimensional approaches

We compared the diagnosis trajectories of the total sample using the categorical approach at nine-year follow-up with the three identified symptom severity pathways of the dimensional approach. The 'intermittently recurrent' trajectory and the 'partially recovered' pathway corresponded relatively well (32.9% versus 25.7%). However, the percentages of the '(consistently) chronic' and '(consistently) recovered' trajectories did not align. In the categorical approach compared to the dimensional approach, chronicity was lower (8.5% versus 66.8%), and (combined) recovery was higher (58.6% versus 7.5%). The 'recovered' dimensional pathway appeared to correspond more to the 'consistently recovered' diagnosis trajectory (10.1%) at nine-year follow-up.

We then compared the primary and comparison DSM-diagnosis trajectories and three identified symptom severity pathways using cross-tabulation at nine-year follow-up (see Table 3).

First, we looked at the four primary DSM-diagnosis trajectories. Participants who were 'consistently recovered,' 'intermittently recovered,' and 'intermittently recurrent' from a DSM diagnosis were spread across all three symptom severity pathways. No clear pattern of correspondence emerged. Second, we looked at the three comparison DSM-diagnosis trajectories with the symptom severity pathways, and the overlap of was low, with very poor agreement, $\kappa = 0.02$. Participants from the categorical 'recovered' trajectory, for example, were also allocated to the 'partially recovered' and 'chronic' dimensional pathways. Regarding functional disability, participants in the 'chronic' symptom severity pathway experienced the highest functional disability, followed by the 'partial recovery', then 'recovered' pathway.

Finally, we tested whether there was a potential effect of age (in quartiles) and gender on depressive, anxiety, fear, and worry severity symptoms (see **Fig. C** in **Supplemental Material**). There were age group and gender differences, with age having a slightly higher effect on severity symptoms. Fig. 3 presents the trends of depressive (A), anxiety (B), fear (C), and worry (D) severity symptoms for subsamples of participants with depression only, anxiety only, or comorbid depression-anxiety, based on baseline severity scores split into quartiles. These were adjusted for the effects of age and gender. However, the adjusted mixed model regression analyses resulted in similar trajectories as the non-adjusted analyses.

Throughout the nine-year period, those with the highest baseline severity levels (red line) on average maintained the highest severity scores, remaining above clinically-relevant threshold levels. In general, all baseline quartiles had trends that ran rather parallel over time and remained stable after an initial drop in severity at two-year follow-up. Furthermore, comparing the three subsamples, those with comorbid depression-anxiety at baseline appeared to have the highest scores across all symptom measures compared to the depression only and anxiety only groups.

Finally, to assess the trends of functional disability, we reviewed the WHO-DAS-II scores at each follow-up assessment over the nine-year period for subgroups of depression only, anxiety only, and comorbid depression-anxiety based on baseline total scores split into quartiles (see Fig. 2**E**). Those with comorbid depression-anxiety appeared to have higher disability than those with depression only or anxiety only.

Table 3
Comparison of the Three Identified Dimensional Symptom Severity Pathways of the Latent Class Growth Analysis (LCGA) with the Primary and Comparison Categorical Diagnosis Trajectories based on Overlap and Disability at Nine-Year Follow-Up.

Categorical diagnoses trajectories[a]	Dimensional symptom severity pathways orLCGA classes		
	Recovered	Partially Recovered	Chronic
Consistently Recovered	33	92	78
% within categorical trajectories	16.3%	45.3%	38.4%
% within LCGA classes	52.4%	29.7%	13.2%
Intermittently Recovered	25	135	203
% within categorical trajectories	6.9%	37.2%	55.9%
% within LCGA classes	39.7%	43.5%	34.2%
Intermittently Recurrent	5	75	238
% within categorical trajectories	1.6%	23.6%	74.8%
% within LCGA classes	7.9%	24.2%	40.1%
Consistently Chronic	0	8	74
% within categorical trajectories	0.0%	9.8%	90.2%
% within LCGA classes	0.0%	2.6%	12.5%
Categorical diagnoses trajectories[b]			
Recovered	**33**	92	78
% within LCGA classes	40.7%	24.3%	9.0%
% within categorical trajectories	16.3%	45.3%	38.4%
Recurrent	48	**278**	715
% within LCGA classes	59.3%	73.5%	82.5%
% within categorical trajectories	4.6%	26.7%	68.7%
Chronic	0	8	**74**
% within LCGA classes	0.0%	2.1%	8.5%
% within categorical trajectories	0.0%	9.8%	90.2%
Disability (WHO-DAS-II), mean (*SD*)	5.3 (7.9)	13.9 (12.6)	28.8 (17.6)

[a] 4 primary trajectories of the categorical approach, $N = 966$.
[b] 3 comparison/aggregated trajectories of the categorical approach, $N = 1326$.
In **bold** = overlap between the comparison/aggregated categorical trajectories and dimensional pathways.
WHO-DAS-II = World Health Organization disability assessment schedule.

4. Discussion

Our findings show that using DSM diagnoses alone fails to fully capture the persistence of depressive and anxiety symptoms over time. The categorical trajectories using diagnoses were not congruent with results of the identified dimensional pathways using symptom severity, further emphasizing the need to better capture clinical course (Batelaan et al., 2014). In other words, diagnostic recovery was not equivalent to symptomatic recovery. When using the categorical approach with any depressive or anxiety diagnosis, approximately 8% were consistently chronic, 33% had intermittently relapsed, 38% had intermittently recovered, and 21% remained consistently recovered at nine-year follow-up, showing a higher estimation of recovery compared to the dimensional approach. However, when we examined participants with baseline comorbid depression and anxiety, only 10.1% remained consistently recovered at nine-year follow-up, which paralleled the 7.5% who were recovered using the dimensional approach.

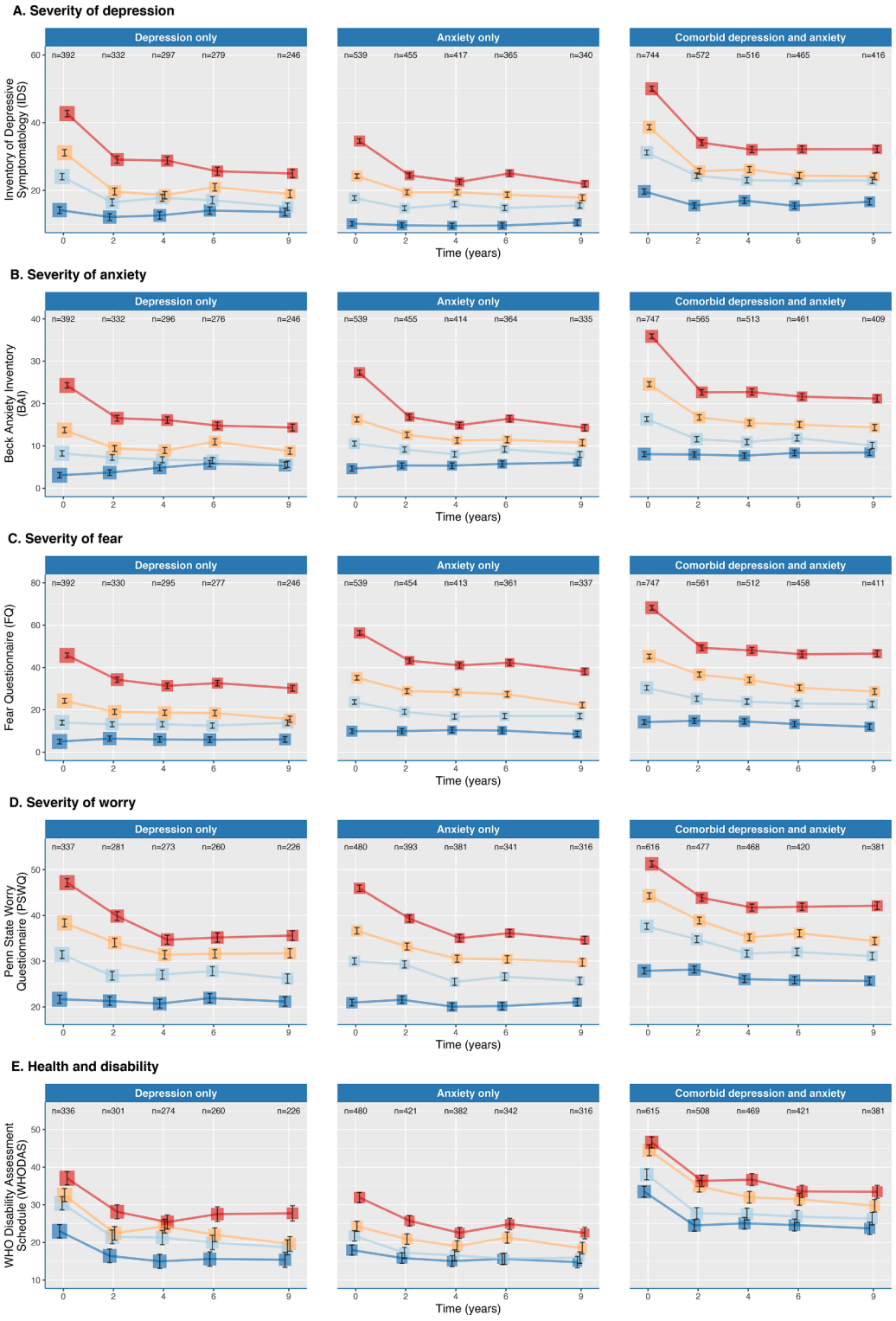

Fig. 3. Trajectories of depressive, anxiety, fear, and worry symptoms, controlled for the effect of age and gender. Error bars represent standard errors, and the box size is proportional to the number of participants.

Additionally, compared to the categorical trajectories of comorbid depression and anxiety, the chronicity of the dimensional symptom severity pathway was much higher (11.8% versus 66.8%). When using aggregated trajectories, we found that 78.5% of participants with any disorder experienced recurrence over a nine-year period. This was much higher than the 25.7% who were partially recovered when using the dimensional approach.

The discrepancy between the trajectories could be explained by the following reasons. First, the discrepancy may be due to the inherent differences of the methods used to assess the dimensional versus the categorical outcomes. Specifically, the dimensional approach used self-report questionnaires to determine the change in symptom severity over time while the categorical approach used a structured interview to establish DSM diagnoses and examine them over time. Although the self-

report questionnaires encompassed the same symptoms as the depression and anxiety syndromes in the structured interview, the questionnaires assessed a shorter duration period of one to two weeks. For the diagnoses, we allowed a longer recency period of six months. The diagnosis, therefore, may not have been present at the moment of assessment and might have been present up to five and a half months ago. Moreover, in the structured interview, the trained interviewer examined the number of symptoms, duration of the symptoms, and the patient's level of functioning. Thus, if a patient had the required number of symptoms yet a higher level of functioning, a DSM diagnosis was not recorded. At the outset, due to the specific diagnostic criteria, using a categorical approach with DSM diagnoses may be less inclusive when compared to the dimensional approach, which may have resulted in higher recovery rates and lower chronicity. Because of the inclusion of the functional disability criterion, we consider DSM diagnoses to be a better indicator of psychological suffering than self-report questionnaires. Second, the discrepancy in results could be due to enduring, fluctuating subthreshold affective symptoms and the higher prevalence of individuals experiencing recurrence of diagnoses. Those with remitted affective diagnoses, for instance, may still suffer from subthreshold disease (e.g., minor depression), or they could have been assessed during a short period in which affective symptoms had slightly receded (Batelaan et al., 2014; Torpey and Klein, 2008). Previous research has shown that, compared to those without symptoms, those with subthreshold symptoms relapsed sooner (Cuijpers and Smit, 2004; Fawcett, 1994; Judd et al., 1998; Karsten et al., 2011) and were found to suffer more chronic episodes and fewer symptom-free weeks (Arnow and Constantino, 2003; Judd and Akiskal, 2000). Other studies have also found a recurrent course with (non)chronic episodes in at least 50% of participants (Bobes et al., 2018; Bruce et al., 2005; Scholten et al., 2016, 2013; Verduijn et al., 2017; Yonkers et al., 2003) and up to 80% (Judd, 1997).

Furthermore, when using the categorical approach, as expected, those with comorbid depressive and anxiety disorders had a relatively poorer long-term course when compared to those with baseline depressive disorders only. This finding is in line with previous research examining anxiety and (comorbid) depressive disorders (Batelaan et al., 2014; Bruce et al., 2005; Rhebergen et al., 2011; ter Meulen et al., 2021). According to Batelaan et al. (2014), however, baseline severity, duration of symptoms, and disability appear to be better indicators of a poor prognosis than DSM-categories.

4.1. Clinical significance of the results

Kraepelinian nosology (Kraepelin, 1921) emphasizes that course, functional outcome, and etiology support a dimensional approach of depression and anxiety. In light of our findings, the question arises whether we should view individuals with comorbidity as having two or more distinct DSM disorders or as having a single dimensional disorder, or symptoms on a continuum, in which myriad etiological factors may result in diverse syndromes that are modified with time and environmental exposures (Angst and Wicki, 1991; Cardno et al., 2002; Hyman, 2010; Kendler et al., 1992; Krueger and Markon, 2006). Previous studies (Fried and Nesse, 2015b; Fried et al., 2014; Lux and Kendler, 2010; van Eeden et al., 2019) have identified risk factors, such as neuroticism and baseline chronicity, that affected individual depressive symptoms to varying degrees, suggesting that depression is not one unified latent construct. On the other hand, abandoning the current DSM criteria would reduce reliability and leave psychiatry without a common language (Kendell and Jablensky, 2003; Patten, 2015). Therefore, until a better dimensional model is proposed, we suggest the integrative use of diagnostic classification, symptom severity, symptom duration, and levels of impairment (Batelaan et al., 2014; Hyman, 2010; Patten, 2015). An example is the Activity, Cognition, and Emotion (ACE) model that groups symptoms commonly present in mood disorders like depression and bipolar disorder according to functional domains (Malhi et al., 2018). Another option is the symptom-based framework which looks at individual symptoms and how they influence each other (Fried, 2015). However, more research is needed to confirm whether a dimensional symptom-oriented tool will lead to more accurate symptom-specific tailored treatment plans and better outcomes. Moreover, clinicians may consider the adoption of longer-term treatment strategies (Vos et al., 2004) that may include relapse prevention strategies and psychiatric rehabilitation (i.e., functional recovery) for those with high levels of subthreshold symptoms and a high risk of recurrence of disorders over nine years. Well-designed interventions studies looking into the types and effectiveness of relapse prevention strategies are warranted.

4.2. Strengths and limitations

This study has some noteworthy strengths. First, NESDA was designed to gain more insight into the long-term clinical course of depression and anxiety in a large cohort study with access to the full range of depression and anxiety disorders from primary and secondary care. Patients were rigorously diagnosed using diagnostic interviews and followed over a nine-year time period with multiple assessment points. Moreover, rather than investigating the course of single MDD or anxiety disorders, we examined variable course categories that allowed comorbidity and diagnostic switching, which may be more ecologically and clinically relevant. To strengthen our conclusions, we used the data-driven LCGA method, to distinguish groups with similar symptom severity trajectories, which handles missing data rather well. The findings were further confirmed by inspecting symptom severity scores, diagnoses, and functional (dis)ability. Additionally, we compared our models to those without missing data, and results were not significantly altered.

With regard to our study limitations and research recommendations, the following may be mentioned. First, the current study used data from NESDA, which concerns DSM-IV criteria rather than the newest DSM-5 criteria. In the DSM-5, there is a duration criterion for social phobia and agoraphobia, which could be useful in excluding patients with only transient fears (Batelaan et al., 2014). Second, NESDA was set up as an observational, naturalistic study, and therefore, the effects of treatment on outcomes could not be examined (e.g., due to confounding by indication effects). While general data were collected regarding medication use, treatment duration, and setting (e.g., primary or secondary care, or psychotropic use), data on the specifics of type, duration, and intensity of psychotherapeutic interventions were not collected. Third, to maximize our sample, we selected participants with a diagnosis in the six months prior to baseline, a period during which some participants may have remitted. Fourth, NESDA did not include participants with obsessive compulsive disorder (OCD), bipolar disorders, or other common mental disorders, which participants may also be experiencing, thereby potentially increasing prevalence rates of chronicity. Fifth, our sample included participants recruited from the community, primary care and specialized mental health care, resulting in a heterogenous cohort (Patten, 2015; Regier et al., 1998). Thus, our results may not be generalizable to each population. Sixth, at each follow-up there was a selective loss of participants, which were those with the highest baseline severity levels. Thus, chronicity may have been underestimated. Seventh, the Life Chart Interview (LCI), which relies on the recall of past memories, was used to establish the continuity of symptoms between assessment points in the categorical approach. Recall error of autobiographical information may have had an impact on the accuracy of the sustained recovered or consistently chronic categorical trajectories (Drasch and Matthes, 2013; Reimer and Matthes, 2007). Although the LCI uses an event history calendar with landmark events, which has been shown to be an effective tool for the reliable retrieval of older memories (Belli, 1998; Belli et al., 2001; Drasch and Matthes, 2013; Vaart and Glasner, 2011), memory is not always reliable, and any results using retrospective recall should be carefully considered (Glasner and

Vaart, 2009; Patten et al., 2010). Eighth, NESDA used the CIDI to diagnose DSM-IV disorders. However, there is an alternative semi-structured clinical interview, namely the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology (SPIKE) (Angst and Dobler-Mikola, 1985; Angst et al., 2009; Angst and Wicki, 1991; Ernst and Angst, 1992), which has a lower threshold than the CIDI to meet diagnostic criteria. The strict criteria of the CIDI may make it less inclusive, potentially leading to an underestimation of chronicity levels in the current study. Ninth, LCGA classes were calculated primarily with log-linear functions and with too few assessments. Therefore, our dimensional approach may not have been able to fully describe the "waxing and waning" of symptom severity. However, examining alternative models with other shape trajectories corresponded highly with the log-linear primary model. Tenth, while we did examine the functional disability in the dimensional approach using mixed-model regression analyses, functional disability was not included in the main LCGA due to bias. Future research using a longitudinal design and a dimensional approach that includes both rater-based versus self-rated symptom scales would be of value and may help improve the prediction of the clinical course.

5. Conclusion

This study showed that, when taking comorbidity, switching between diagnoses, and symptom duration into consideration to examine the long-term course of depression and anxiety, using categorical diagnoses alone to describe clinical course led to a high estimation of recovery, low estimation of chronicity, and appeared to inadequately capture the persistence of affective symptoms. Discrepancies in the clinical course using DSM-categories or symptom severity could be explained by the enduring, fluctuating presence of subthreshold affective symptoms that do not meet diagnosis criteria but still may lead to recurrence of disorders. The commonness of subthreshold symptoms and their adverse impact on long-term prognoses deserve continuous clinical attention in mental health care as well further research.

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Data availability statement

According to European law (GDPR) data containing potentially identifying or sensitive patient information are restricted; our data involving clinical participants are not freely available in a public repository. However, data are – under some specifications - available upon request via the NESDA Data Access Committee (nesda@ggzingeest.nl). See also our website: www.nesda.nl

CRediT authorship contribution statement

Ericka C. Solis: Formal analysis, Writing – original draft. **Albert M. van Hemert:** Writing – review & editing. **Ingrid V.E. Carlier:** Writing – review & editing. **Klaas J. Wardenaar:** Writing – review & editing. **Robert A. Schoevers:** Writing – review & editing. **Aartjan T.F. Beekman:** Writing – review & editing. **Brenda W.J.H. Penninx:** Writing – review & editing. **Erik J. Giltay:** Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.08.108.

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