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Hovenkamp-Hermelink, Ans

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Chapter 5

Low stability of diagnostic classifications
of anxiety disorders over time:
A six-year follow-up of the NESDA study

Johanna H.M. Hovenkamp-Hermelink, Harriëtte Riese, Date C. van der Veen, Neeltje M. Batelaan, Brenda W.J.H. Penninx, Robert A. Schoevers

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ABSTRACT

Background: Stability of diagnosis was listed as an important predictive validator for maintaining separate diagnostic classifications in DSM-5. The aim of this study is to examine the longitudinal stability of anxiety disorder diagnoses, and the difference in stability between subjects with a chronic versus a non-chronic course.

Methods: Longitudinal data of 447 subjects with a current pure anxiety disorder diagnosis at baseline from the Netherlands Study of Depression and Anxiety were used. At baseline, 2-, 4-, and 6-year follow-up mental disorders were assessed and numbers (and percentages) of transitions from one anxiety disorder diagnosis to another were determined for each anxiety disorder diagnosis separately and for subjects with a chronic (i.e. one or more anxiety disorder at every follow-up assessment) and a non-chronic course.

Results: Transition percentages were high in all anxiety disorder diagnoses, ranging from 21.1% for social anxiety disorder to 46.3% for panic disorder with agoraphobia at six years of follow-up. Transition numbers were higher in the chronic than in the non-chronic course group ($p = 0.01$).

Limitations: Due to the two-year sample frequency, the number of subjects with a chronic course may have been overestimated as intermittent recovery periods may have been missed.

Conclusions: These data indicate that anxiety disorder diagnoses are not stable over time. The validity of the different anxiety disorder categories is not supported by these longitudinal patterns, which may be interpreted as support for a more pronounced dimensional approach to the classification of anxiety disorders.

INTRODUCTION

Anxiety disorders are common and impose a considerable burden on those affected as well as on their relatives and society [1–5]. A range of anxiety disorders that differ in their specific symptom patterns is distinguished in the subsequent versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), including the latest version, the DSM-5 [6]. The DSM-classification system contains ‘simple reliable rules for categorical assignments required for clinical and research purposes’ [7]. Still, symptoms such as panic attacks and avoidance behaviour as well as impairment are shared between diagnoses and across diagnostic boundaries, leading to high comorbidity between different anxiety disorders [7–10]. For this reason, a dimensional approach of describing mental disorders is receiving increasing attention [11]. As a possible approach, Shear et al. [7] suggested a ‘hybrid categorical-dimensional model’, which would both be clinically useful and provide a better understanding of symptoms that are found across diagnoses. One of the proposals for maintaining separate diagnoses of social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia, generalized anxiety disorder and other anxiety disorders is their presumed stability, which was listed as an important predictive validator in the ‘Guidelines for Making Changes to DSM-5’ [12].

If the different anxiety disorder classifications are not diagnostically stable across time, and would show many transitions from one anxiety disorder to another, this could indicate that they are not really distinct disorders, but should rather be regarded as one entity with different phenotypes or varying presentations over time. This issue of longitudinal stability of diagnosis has been studied a number of times before, but many questions currently remain unresolved. A five-year follow-up population study of 3,021 Germany subjects aged 14–24 years at baseline found a considerable degree of transitions between anxiety and other affective disorders as well as with somatoform and substance use disorders [13]. Remitted cases of baseline social anxiety disorder had an increased risk of developing other anxiety (especially generalized anxiety disorder and panic disorder) and depressive disorders in follow-up. Nay et al. [14] found in a population study of 43,093 subjects aged 18 years and older that social anxiety disorder at baseline predicted the onset of panic disorder with agoraphobia after three-year follow-up, but not the development of panic disorder without agoraphobia. They also reported that a history of panic attacks, generalized anxiety disorder and/or major depression is a predictor of incidence and relapse of panic disorder with or without agoraphobia. To the best of our knowledge no longitudinal studies examining stability of diagnosis of other anxiety disorders have been published to date. Further, it is not known whether diagnostic transitions would occur more often in subjects with remissions and relapses versus subjects in whom the disorder has a chronic course. Transitions from anxiety to depressive disorder diagnoses and the impact

of a comorbid depressive disorder at baseline were not examined. The focus of the current study was to investigate whether transitions from one anxiety disorder diagnosis to another occurred and vice versa, i.e. how do anxiety disorders relate to each other.

The Netherlands Study of Depression and Anxiety (NESDA) has followed up 1101 patients with different anxiety disorders for six years, including diagnostic assessments every two years. Earlier work in NESDA has shown that courses varied for different anxiety disorders [15], while Scholten et al. [16] reported that, in case of recurrence, a new anxiety disorder (i.e., a transition from the baseline disorder to the anxiety disorder at follow-up) occurred in 32.7% of the cases. The earlier NESDA publications were based on two-year follow-up data. Moreover, stability of diagnosis has not been systematically assessed in pure anxiety disorder categories, distinguishing between either a persistent course (chronic course) or a course with remissions and relapses (non-chronic course). Now, data from four waves, spanning 6 years, are available and will be used to address this issue. The aim of the current study is to determine the longitudinal stability of diagnosis of pure social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia and generalized anxiety disorder. Subjects with a course marked by remissions and relapses are more likely to have a change of diagnosis than subjects with a chronic course. Therefore, the second aim of this study is to look at differences in diagnostic stability between subjects with a chronic versus non-chronic course.

METHODS

Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is a national study designed to investigate the course and consequences of depressive and anxiety disorders. Briefly, four assessment waves have been completed to date, and the fifth wave is currently ongoing. The study started with 2981 subjects with a mean age of 41.9 years ($SD = 13.0$, range 18-65 years; 66.4% women), including healthy controls ($n = 652$; 22%) and subjects with a past or current depressive and/or anxiety disorder ($n = 2329$; 78%). To represent various settings and stages of psychopathology, subjects were recruited in the general population ($n = 564$; 19%), in general practices ($n = 1610$; 54%), and in mental health organizations ($n = 807$; 27%). Excluded were subjects with a primary psychotic, obsessive-compulsive, bipolar or severe addiction disorder and those not being fluent in Dutch. The research protocol was accredited by the Ethics Committee of participating universities and written informed consent was obtained from all subjects. The attrition rate was relatively low as participation rates were 87.1%, 80.6% and 75.7% for the 2-, 4-, and 6-year follow-up. More details of the NESDA study and its design have been described before [17]. Of the initial study cohort 1101 subjects had a current anxiety disorder diagnosis. Of those, 693 subjects had a pure anxiety disorder diagnosis, i.e.

a single anxiety disorder without comorbidity of other anxiety disorders. A previous history of an anxiety disorder was not included in the analyses. Because of the many uncertainties regarding the stability of anxiety disorder diagnoses, the focus of this study lies solely on the course of diagnosed anxiety disorders themselves. As transition percentages of subjects with non-pure (multiple) anxiety disorder diagnoses cannot be compared with transition percentages of pure anxiety disorder diagnoses, subjects with multiple anxiety disorder diagnoses were excluded from the study. Furthermore, comorbidity with another diagnosis (e.g., depression) was not taken into account as an exclusion criterion. Only subjects with complete data on all follow-up waves were selected for the current study (N = 447).

Comparisons were made between the baseline characteristics of pure and non-pure (multiple) anxiety disorder diagnoses as well as between subjects who had participated at all assessment waves vs subjects who had not participated at all assessment waves. The comparisons were made on the following relevant variables: age, gender, years of education, severity of symptoms as measured by Beck Anxiety Inventory [18] and Fear Questionnaire [19], baseline comorbid depressive disorder (major depressive disorder, MDD and/or dysthymia), disability measured by World Health Organization Disability Assessment Schedule II (WHODAS II) [20], and the number of chronic diseases at baseline.

Classification of anxiety disorders

At baseline, 2-, 4-, and 6-year follow-up, mental disorders were assessed with the Composite International Diagnostic Interview (CIDI, version 2.1) based on the DSM-IV [21,22]. The CIDI interview is a highly standardized and reliable instrument for assessing mental disorders. The test-retest reliability of the CIDI is high with kappa values ranging of 0.64-0.84 for the different anxiety disorder diagnoses [21] and an interrater kappa value above 0.90 for all anxiety disorder diagnoses [23]. The interviews were conducted by a specially trained clinical research staff. These research assistants lacked knowledge of the baseline diagnoses. Moreover, CIDI data cleaning, checking and scoring was performed by an independent data manager. A diagnosis was considered to be present in case the disorder was diagnosed at the assessment or in the month prior to the assessment. For the current study, data of the following anxiety disorder diagnoses were used: social anxiety disorder, panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia and generalized anxiety disorder.

Definitions

Two overall course types of anxiety disorders were defined: 1) The course of subjects with an anxiety disorder diagnosis was defined as chronic when they were diagnosed with one or more anxiety disorders at every follow-up assessment. 2) The course of an anxiety disorder diagnosis was defined as non-chronic in case remissions with or without subsequent relapses

were found at the follow-up assessments. Remission was defined as the absence of any anxiety disorder diagnosis at one or more follow-up measurements. Relapse was defined as the recurrence of any anxiety disorder diagnosis after a remission.

Two definitions of 'stability of diagnosis' were used: 1) An anxiety disorder was considered diagnostically stable when subjects were again diagnosed with the same pure baseline anxiety disorder at all follow-up assessments where an anxiety disorder was present (with or without any comorbid anxiety disorder diagnosis) or when subjects were in remission; 2) Transition of diagnosis was defined as having one or more new anxiety disorder diagnoses, other than the baseline diagnosis, at any follow-up measurement where an anxiety disorder was diagnosed, while the baseline anxiety disorder was no longer present. If a subject had a transition of diagnosis at any measurement, he or she remained in the 'transition' category in the following measurements. After being included in the transition category, more transitions are possible. For analysis of the stability of diagnosis of the chronic and the non-chronic course groups, subjects with a remission at one of the follow-up waves without a relapse were excluded.

Statistical analyses

Descriptives and statistical analyses were performed in IBM SPSS 20.0 using p -value < 0.05 to indicate statistical significance (SPSS Inc, Chicago, IL, USA). For every subject we identified all anxiety disorder diagnoses at each assessment wave. Total numbers (and percentages) of subjects with a chronic and non-chronic overall course were calculated. Next, total numbers (and percentages) of subjects with a stable anxiety disorder diagnosis and a transition in diagnosis were calculated.

First, chi-square statistics were used to determine the differences in overall course type (numbers of subjects with a chronic course) between the five anxiety disorder diagnoses. Second, stability of anxiety disorders was tested using chi-square statistics by comparing the transition numbers between the baseline pure anxiety disorders at each follow-up wave. Longitudinal changes in transition numbers were assessed for each anxiety disorder separately with Cochran's Q tests. In case of a statistical significance, posthoc McNemar tests were used for pair-wise comparisons between the three (2- and 4-year, 2- and 6-year, and 4- and 6-year) follow-up assessments. We adjusted for multiple testing using the Bonferroni method. The new p -value regarded as significant was $0.05/3 = 0.017$. Third, chi-square statistics were used to test for stability of diagnosis comparing transition numbers of the chronic and the non-chronic course group.

RESULTS

Descriptives

Sociodemographic characteristics of the 447 subjects in the study sample indicated that the sample consisted of more women than men (70.0% women), in their middle ages (mean age = 41.65 years, SD = 12.7, range = 18-65) with a mean number of years of education of 12.3 (SD = 3.17, range = 5-18). Compared with subjects with a pure anxiety disorder diagnosis, subjects with non-pure, multiple anxiety disorder diagnoses were characterized by higher Beck Anxiety Inventory and Fear Questionnaire scores, more comorbid depressive disorder, more disability, and less years of education. This indicates more severity in case of non-pure, multiple anxiety disorder diagnoses. Subjects who discontinued participation were more often man, had less years of education and had higher Beck Anxiety Inventory scores. (For an overview of the baseline characteristics of subjects with pure anxiety disorder diagnoses and subjects with non-pure multiple anxiety disorders as well as of subjects participating and not participating at all assessment waves, see Supplement 1). In Table 1 the presence of anxiety disorder diagnoses is shown for all assessment waves separately. At baseline, social anxiety disorder had the highest and agoraphobia the lowest prevalence. The percentage of subjects with no anxiety disorder diagnosis at 2-, 4-, and 6-year follow-up is between 54 and 82%.

Overall course

Data on the overall course are presented in Table 1. Of the 447 subjects, 195 (43.6%) were in remission after 2 years and stayed in remission for the whole follow-up period. 94 subjects (21.0%) had a remission after 4 or 6 years and 109 (24.4%) subjects had a remission followed by a relapse during the 6-year follow-up (data not shown). A chronic course was found in 49 subjects (11.0%), comprising 4.2% (generalized anxiety disorder) to 16.7% (agoraphobia) of the baseline diagnoses. There were no differences in the overall course (chronic versus non-chronic) between the five anxiety disorder diagnoses ($\chi^2_{(4)} = 8.74, p = 0.07$).

Table 1: Presence of pure anxiety disorder diagnoses at baseline and any anxiety disorder diagnosis at the follow-up assessment waves

baseline diagnosis (N)	2-year follow-up N (%)		4-year follow-up N (%)	
	none	one or more	none	one or more
	SAD (147)	86 (58.8)	61 (41.5)	95 (64.6)
PDA (95)	52 (54.7)	43 (45.3)	60 (63.2)	35 (36.8)
PD (55)	37 (67.3)	18 (32.7)	36 (65.5)	19 (34.5)
AG (54)	36 (66.7)	18 (33.3)	35 (64.8)	19 (35.2)
GAD (96)	67 (69.8)	29 (30.2)	75 (78.1)	21 (21.9)
Total (447)	278 (62.2)	169 (37.8)	301 (67.3)	146 (32.7)

Note: SAD = social anxiety disorder; PDA = panic disorder with agoraphobia; PD = panic disorder without agoraphobia; AG = agoraphobia; GAD = generalized anxiety disorder; % of baseline numbers; one or more = one of the pure anxiety disorders (not necessarily the same as on baseline)

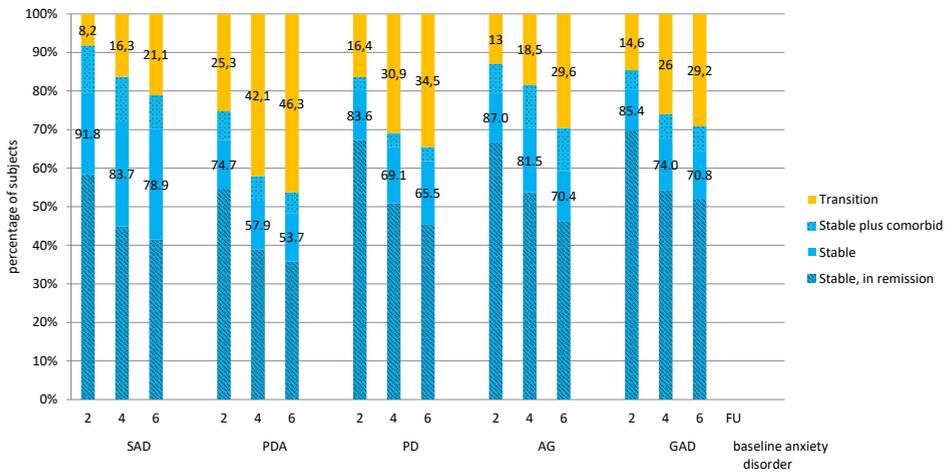


Figure 1: Diagnoses at follow-up of the baseline pure anxiety disorders; percentages of the total number of subjects who participated at all waves (= 100%). Subjects were considered diagnostically stable when diagnosed with the same pure baseline anxiety disorder at follow-up, with or without comorbidity, or when subjects were in remission; subjects were considered to have a transition of diagnosis when diagnosed with one or more new anxiety disorder diagnoses, other than the baseline diagnosis, at follow-up, while the baseline anxiety disorder was no longer present (see method section for more details). Dotted part of the columns = stable anxiety disorder plus comorbidity of one or more other anxiety disorders; striped part of the columns = stable anxiety disorder diagnosis, but subjects were in remission (without relapse during follow-up); SAD = social anxiety disorder; PDA = panic disorder with agoraphobia; PD = panic disorder without agoraphobia; AG = agoraphobia; GAD = generalized anxiety disorder

6-year follow-up		overall course	
N (%)		N (%)	
none	one or more	non-chronic	chronic
104 (70.7)	43 (29.3)	129 (87.8)	18 (12.2)
62 (65.3)	33 (34.7)	81 (85.3)	14 (14.7)
43 (78.2)	12 (21.8)	51 (92.7)	4 (7.3)
36 (66.7)	18 (33.3)	45 (83.3)	9 (16.7)
79 (82.3)	17 (17.7)	92 (95.8)	4 (4.2)
324 (72.5)	123 (27.5)	398 (89.0)	49 (11.0)

or more than one pure anxiety disorder; non-chronic course = remissions with or without subsequent relapses were found at the follow-up assessments; chronic course = one or more anxiety disorders at every follow-up assessment

Stability of diagnosis

In Figure 1 the stability of diagnosis is depicted for each anxiety diagnosis separately. After 6 years social anxiety disorder showed highest percentages of stable diagnosis (78.9%), whereas panic disorder with agoraphobia was least (53.7%). Differences in transition numbers between the five baseline anxiety disorder diagnoses were statistically significant at every follow-up (2 years $X^2_{(4)} = 13.66, p = 0.008$; 4 years $X^2_{(4)} = 22.24, p < 0.001$; 6 years $X^2_{(4)} = 17.73, p = 0.001$). The difference in transition numbers between diagnoses could possibly have been affected by the numbers of subjects with a remission without relapse per diagnostic category. Posthoc analysis of these remission numbers of the separate anxiety disorders was performed with a chi-square test at every follow-up wave. The results yielded no statistically significant difference ($X^2_{(1)} = 6.52, p = 0.16$; $X^2_{(1)} = 6.00, p = 0.20$; $X^2_{(1)} = 5.67, p = 0.23$ at 2-, 4-, and 6-years follow-up respectively). From the longitudinal comparison of transition numbers, it was found that the differences were statistically significant for all five anxiety disorders (social anxiety disorder $Q_2 = 29.16, p < 0.001$; panic disorder with agoraphobia $Q_2 = 33.60, p < 0.001$; panic disorder without agoraphobia $Q_2 = 14.36, p = 0.001$; agoraphobia $Q_2 = 14.00, p = 0.001$; generalized anxiety disorder $Q_2 = 22.93, p < 0.001$). This result indicates that the transition numbers increased significantly over time. Post hoc McNemar tests were used to make pair-wise comparisons of the transition numbers of two assessment waves with the following results: all comparisons differed statistically significant, with an exception for panic disorder with agoraphobia (4-6 years: $p = 0.125$); panic disorder without agoraphobia (4-6 years: $p = 0.250$); agoraphobia (2-4 years: $p = 0.250$), and generalized anxiety disorder (4-6 years: $p = 0.625$). To validate our findings a posthoc robustness check was conducted by rerunning the Cochran's Q test and subsequently McNemar tests while including subjects who had maximal missing data on one of the assessment waves ($N = 533$). The findings were very similar, leading to the same conclusion.

Looking at the type of transitions, it became clear that all kinds of transitions occurred during the six-year follow-up period (see Supplement 2 for details on types and numbers of transitions). Some subjects had different anxiety disorder diagnoses at every point of follow-up; others had transitions from one anxiety disorder to multiple other anxiety disorder diagnoses. There were also transitions from the baseline anxiety disorder diagnosis to another and back to the baseline diagnosis as well as transitions in combination with remission in the intervening period.

Stability of diagnoses according to overall course type

A chronic course or a course with remissions and relapses was found at 158 subjects. Of the 49 subjects with a chronic course 36 (73.5%) had a transition. Of the 109 subjects with remissions and relapses 57 had a transition (52.3%). The number of transitions was higher in those with a chronic course compared to those with a non-chronic course ($X^2_{(1)} = 6.26, p = 0.01$). The robustness of this result was validated with a posthoc test, by which the analysis was performed on a sample where subjects with one remission at one of the follow-up waves were included in the chronic group. This new chronic group ($N = 137$) had 85 transitions (62.0%), while the remaining non-chronic group ($N = 52$) had 24 transitions (46.2%). The difference was statistically significant ($X^2_{(1)} = 3.90; p = 0.048$).

DISCUSSION

The aim of the current study was to determine the longitudinal stability of the diagnoses of social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia, and generalized anxiety disorder. In case anxiety disorder diagnoses are stable, we expected high stability percentages. In this study we found percentages clearly below 70% or just at the level of 70%. Our findings indicate that pure anxiety disorder diagnoses are not stable over time. Transitions of diagnosis are common, and the number of transitions is increasing over time. The type of transitions appeared to be quite random. This low stability of diagnoses found is in line with the few previous studies we were able to identify [13,14,16] and extends on these findings by using a more rigorous longitudinal design with two-yearly follow-up assessments. A chronic course, defined as having an anxiety disorder diagnosis at every follow-up assessment, was found in a minority of the subjects (11%). This finding is in line with the study of [24], who reported 10.8% chronicity, but it does not support several other studies, which mentioned that anxiety disorders are in majority characterized by a chronic course. This difference could be due to a different definition of chronicity (a waxing and waning course was in many studies equivalent to a chronic course) or due to a different sample selection. Unlike in the current study comorbidity, associated with more chronicity [15,25–27] was not always excluded.

The results of this study showed that subjects with our rigorous definition of a chronic course had even considerably more transitions than subjects with a non-chronic course. This suggests that the symptoms can change over time, without temporary remission, which may result in developing another diagnostic classification even during the same episode.

To our knowledge, this is the first study reporting on the stability of diagnoses of pure anxiety disorders across a period of six years. This long follow-up period, together with the large sample size with repeated CIDI diagnoses, are definite strengths of this study. However, some limitations should be mentioned as well. First, the definition of chronicity used in this study for the category of subjects with an anxiety disorder at all waves does not rule out the possibility that subjects could have had a remission followed by a relapse in the interval between two assessment waves. For that reason, the number of chronic subjects may actually be somewhat lower than we now presented. Second, our strict definition of chronicity means that subjects with a chronic course have four anxiety disorder diagnoses at four time points (at baseline, and at 2-, 4-, and 6-year follow-up), whereas subjects with a non-chronic course have such a diagnosis at less time points (they have at least one remission). Consequently, the probability of finding a transition is higher in the chronic group than in the non-chronic group. To check the robustness of the stability analysis in these two groups, the analysis was repeated while subjects with one remission during follow-up were categorized as member of the chronic group. This analysis showed again that transitions were more common in the chronic group than in the non-chronic group. Third, subjects with a comorbid depression at baseline were not excluded from the study. Comorbid depression could possibly have affected transition percentages. However, the primary interest of this study was how anxiety disorder diagnoses relate to each other. Fourth, as information of the impact of any treatment subjects received is unavailable in NESDA, any possible effects of treatment on transition percentages could not be studied. Fifth, the CIDI is an established diagnostic tool, yet some diagnostic misclassifications cannot be ruled out when considering the not perfect reliability of the instrument. This may have resulted in a slightly overestimation of transition percentages. Research findings should be considered in light of this statistical mechanism. Finally, to answer our research question only subjects with a pure anxiety disorder diagnosis were selected in our study. With this selection subjects with non-pure, multiple anxiety disorder diagnoses who were more severely affected were not included. Furthermore, as in NESDA not all anxiety disorder diagnoses mentioned in the DSM were included, the conclusions of this study should be considered as resulting from a clinically not representative group of anxiety disorder subjects.

Kendler et al. [12] had stability of diagnoses denoted as an important prerequisite for making distinctions between the different anxiety disorder diagnoses in DSM-5. If stability of diagnoses is apparent, this would support the current categorical classification of anxiety disorders. On the basis of our findings of low stability of anxiety disorder diagnoses we

have to conclude that this prerequisite is not met. The categorical classification is mainly based on clinical manifestations which are now shown to vary across time within and between patients who had different pure anxiety disorders at baseline. Furthermore, comorbidity among anxiety disorders is high [28,29] and there is increasing knowledge about the aetiology of anxiety disorders, showing that different anxiety disorder diagnoses also share common underlying pathophysiology. Genetic and environmental risk factors may be shared [30] and neuroimaging studies have shown that common underlying neural networks are involved in different anxiety disorders [31], although differences were also found. In line with this, it was recommended that symptoms shared by the different diagnostic disorders should be recognized and that the classification system should be complemented with dimensional aspects such as severity, duration, disability and subthreshold features [7,32,33]. There is growing interest in the dimensional nature of anxiety disorders [34,35] and Norton [36] even proposed to define only one clinically relevant single anxiety disorder diagnosis with diagnostic criteria on a 9-point severity scale. Findings from the current study in which frequent transitions from one anxiety disorder diagnosis to another were found, suggest that making a distinction between different anxiety disorder diagnoses does not reflect the anxiety disorder classification adequately and may be taken as support for the idea of a single anxiety disorder diagnosis, in which dimensional aspects are incorporated. More research should be done to validate the idea of one comprehensive group of anxiety disorders.

An argument against the suggestion of a single anxiety disorder diagnosis could be that we found significant differences in transition percentages between the different anxiety disorders. High transition rates were found for panic disorder with and without agoraphobia, based on DSM-IV criteria [37] and DSM-5 no longer makes this distinction [6,38,39]. Furthermore, Batelaan et al. [32] indicated that the course of anxiety disorders is better predicted by variables as severity, duration and functioning than by DSM-IV diagnoses. This is more consistent with our suggestion of one single anxiety disorder diagnosis than with the separate diagnoses of the DSM.

In summary, this study has shown that the anxiety disorder classification in DSM-IV has little stability over time. Transitions from one anxiety disorder diagnosis to another frequently occur, and transitions seem random. A suggestion was made to add dimensional aspects to the categorical classification as used in DSM-5 and subsequently lump the examined anxiety disorders into one comprehensive group. The low stability of diagnosis of social anxiety disorder, panic disorder with and without agoraphobia, agoraphobia and generalized anxiety disorder may have important implications in clinical practice. Practitioners should be aware that symptoms are likely to change over time and be prepared to change their treatment focus in order to provide optimal care.

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SUPPLEMENTARY MATERIALS

Supplement 1. Baseline characteristics of subjects with a pure anxiety disorder diagnosis vs multiple anxiety disorder diagnoses and subjects participating at all waves vs not participating at all waves

Baseline characteristics

N

Age in years, mean (SD)

Gender, % female

Education in years, mean (SD)

Beck Anxiety Inventory, mean (SD)

Fear Questionnaire, mean (SD)

Baseline comorbid depressive disorder (MDD and/or dysthymia) (%)

Disability (WHODAS-II, standardized total score, mean (SD)

Number of chronic diseases, mean (SD)

Baseline characteristics

N

Age in years, mean (SD)

Gender, % female

Education in years, mean (SD)

Beck Anxiety Inventory, mean (SD)

Fear Questionnaire, mean (SD)

Baseline comorbid depressive disorder (MDD and/or dysthymia) (%)

Disability (WHODAS-II, standardized total score, mean (SD)

Number of chronic diseases, mean (SD)

* based on chi-square statistics for categorical variables and on t-test for continuous variables

Pure anxiety disorders	Multiple anxiety disorders	P*
693	408	
41.99 (12.63)	42.57(11.53)	.58
671	67.4	.92
11.9 (3.25)	11.0 (3.18)	< .001
16.74 (9.90) (n=683)	24.15 (11.07) (n=403)	< .001
31.61 (19.24)	45.91 (21.06)	<.001
304 (43.9)	260 (63.7)	< .001
26.75 (16.26) (n=448)	36.02 (16.35) (n=202)	< .001
1.00 (1.11)	1.08 (1.11)	.27
Subjects participating at all waves	Subjects not participating at all waves	P*
447	246	
42.65 (12.71)	42.59 (12.50)	.35
70.0	61.8	.03
12.33 (3.17)	11.13 (3.27)	< .001
15.87 (9.06)	18.36 (11.14)	.003
31.26 (17.98)	32.24 (21.37)	.52
186 (41.6)	118 (48.0)	.107
26.71 (16.21)	26.82 (16.40)	.94
1.01 (1.11)	1.00 (1.10)	.88

Supplement 2: Transitions in follow-up

Baseline diagnosis (N)	Follow-up	Subjects with transitions	Transition type (N)		
			SAD	PDA	PD
Social Anxiety Disorder (147)	2 yr	12	-		3
	4 yr	24	-		6
	6 yr	31	-		9
Panic disorder with Agoraphobia (95)	2 yr	24	5	-	3
	4 yr	40	7	-	7
	6 yr	44	7	-	7
Panic disorder without Agoraphobia (55)	2 yr	9	3	1	-
	4 yr	17	7	1	-
	6 yr	19	7	1	-
Agoraphobia (54)	2 yr	7	1	1	2
	4 yr	10	2	2	2
	6 yr	16	3	5	3
Generalized Anxiety Disorder (96)	2 yr	14	8		3
	4 yr	25	12	1	7
	6 yr	28	14	1	8

Note: The numbers of transitions of 2-, 4-, and 6-year follow-up are cumulative. SAD = social anxiety disorder; PDA = panic disorder with agoraphobia; PD = panic disorder without agoraphobia; AG = agoraphobia; GAD = generalized anxiety disorder

Transition type (N)											
AG	GAD	SAD +	SAD +	SAD +	SAD +	PDA +	PD +	AG +	SAD +	SAD +	
		PDA	PD	AG	GAD	GAD	GAD	GAD	PD +	AG +	
									GAD	GAD	
3	5								1		
8	8								2		
9	10						1	2			
10	1		1	1	1			1		1	
15	5		1	2	1			1		1	
17	5		1	2	1			1	1	1	1
1	3					1					
2	6					1					
2	7					1	1				
-						1		1		1	
-		1				1		1		1	
-	1	1				1		1		1	
2	-		1								
4	-		1								
4	-		1								

