Chapter 8

The 7-year course of Depression and Anxiety in the general population

ABSTRACT

Objective Insight into the long-term course of depression and anxiety.

Method Data were derived from NEMESIS/NESDA, epidemiologic surveys in the adult population in the Netherlands. 303 Respondents with depressive and/or anxiety CIDI-disorder were interviewed, examining the 7-year course of depression (n=141), anxiety (n=102) and the comorbid state (n=60) and possible prognostic factors. Outcomes were CIDI-diagnostic status after 7 years and percentage of time during 7 years with depressive and/or anxiety symptoms, retrospectively assessed by the Life Chart Interview (LCI).

Results After 7 years, 60.7% of the subjects were free from a 12-month CIDI depression or anxiety diagnosis. The odds for having a CIDI-diagnosis at follow-up were higher for subjects with anxiety and comorbidity compared to subjects with depression. Low physical functioning and high neuroticism predicted the presence of a diagnosis after 7 years.

During 7-years follow-up, 37.3% of the subjects were free from depressive and anxiety symptoms according to the LCI, 51.8% had symptoms <50% of the time, and 10.9% ≥50% of the time. (Comorbid) anxiety resulted in a poorer course. High neuroticism and childhood adversity predicted more follow-up time with symptoms.

Conclusion Course trajectories were more favorable than expected, although comorbidity resulted in poorer course. Neuroticism, physical functioning and childhood adversity predicted an unfavorable course.

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INTRODUCTION

Depressive and anxiety disorders are considered common and pervasive mental disorders (Kessler et al., 2005). Knowledge on course trajectories and predictors of course is of great importance for clinical care as well as in debates on the nosology of mental disorders. Previously, it was consistently demonstrated that comorbidity was associated with poorer course trajectories than either depression or anxiety alone (Angst and Vollrath, 1991; Keller et al., 1992, 2005; Bruce et al., 2005; Fichter et al., 2010; Preisig et al., 2001). Less is known about the course trajectories of pure depression or anxiety disorders. Comparing the results of the Harvard/Brown Anxiety Research program (HARP) (Bruce et al., 2005) with the Collaborative Depression Study (CDS) (Keller et al., 1992), Bruce and colleagues (2005) suggested that anxiety disorders more often have a chronic course than depressive disorders and that comorbidity with an anxiety disorder results in a longer episode and less recovery than pure Major Depressive Disorder. However, both studies focused on respectively depressed or anxious patients and were not able to directly compare the prognosis of pure depression, pure anxiety and a comorbid depression/ anxiety in one study. In addition, clinical samples were included, resulting in an overrepresentation of chronic cases, the so-called Berkson's bias (Berkson, 1946). The few existing long-term naturalistic studies in community settings, with a focus on both depressive and anxiety disorders, have provided inconsistent results on the course of depression and anxiety, as well as on the predictors of course (Fichter et al., 2010; Murphy, 1990; Merikangas et al., 2003; Vollrath and Angst, 1989). In the Stirling County study, depressive disorders had a more chronic course than anxiety disorders (Murphy, 1990), whereas both the Zurich study (Angst and Vollrath, 1991, Vollrath and Angst, 1989) and the Bavarian study (Fichter et al., 2010) found the opposite.

Our aim was to directly compare the 7-year course trajectories of pure depressive disorder, pure anxiety disorder and comorbid depressive and anxiety disorder, and to explore their prognostic factors. We hypothesized a priori that comorbid depressive and anxiety disorders would have a poorer long-term course trajectory than pure anxiety disorders, which in turn would have a poorer long-term course trajectory than pure depressive disorders.

METHODS

Sample and attrition

The current study is based on a general adult population sample that was recruited in the Netherlands Mental Health Survey and Incidence Study (NEMESIS) and naturalistically followed up through the Netherlands Study of Depression and Anxiety (NESDA) (n=303). In NEMESIS, data were gathered in three waves: at baseline in 1996 (T_0), after one year (T_1, 1997) and after 3 years (T_2, 1999). At T_0, 7076 persons participated; 5618 could be re-interviewed at T_1 (79.4%) and 4796 at T_2 (85.4% of T_1) (De Graaf et al., 2000). After adjustment for socio-demographic variables, a 12-month disorder at T_0 only slightly

increased the probability of loss to follow-up between T_0 and T_1 as well as between T_0 and T_2 (OR 1.20 [95% CI 1.04-1.38]; OR 1.29 [95% CI 1.15-1.46]) (De Graaf et al., 2000). Of the initial 7076, 766 persons were selected for later inclusion in NESDA (T_3, 2004). Selection criteria were a CIDI-diagnosis of a Major Depressive Disorder, Dysthymic Disorder, Generalized Anxiety Disorder, Panic Disorder with or without Agoraphobia, Agoraphobia, or Social Phobia during one of the NEMESIS-interviews (12-month diagnosis at T_0 or T_1, or a 24-month diagnosis at T_2). Of these 766, 9 had died, 8 had left the Netherlands, and 87 could not be traced despite several attempts. Of the 662 subjects approached, 359 (54.2%) refused to participate and 303 (45.8%) could be followed up in NESDA (Penninx et al., 2008). Those who were followed up in NESDA did not differ in terms of age (p=.77), gender (p=.79), or type of baseline disorder (anxiety, depression or comorbid disorder, p=.97) from those not participating (Penninx et al., 2008). The methodology of NEMESIS and NESDA has been more fully described elsewhere (Bijl et al., 1998b; Penninx et al., 2008) and has been approved by the Ethical Review Board. Written informed consent was obtained from all participants.

The final sample of 303 was divided according to their index diagnosis, established during one of the three NEMESIS waves, irrespective of lifetime history (henceforth called the baseline diagnosis). We classified three groups: 1) a depressive disorder group (Major Depressive Disorder and/or Dysthymic Disorder, n=141, further called depression), 2) an anxiety disorder group (Generalized Anxiety Disorder, Panic Disorder with or without Agoraphobia, Agoraphobia, and/or Social Phobia, n=102, further called anxiety), and 3) a comorbid group (Depressive Disorder and Anxiety Disorder, n=60). For 173 (57.1%) respondents their baseline disorder was established at T_0 (1996), for 67 (22.1%) respondents at T_1 (1997) and for the remaining 63 (20.8%) at T_2 (1999), resulting in an average follow-up duration of 7.2 years (SD=1.1), with a range of 5-9 years.

Assessment of psychopathology

In NEMESIS, the Composite International Diagnostic Interview (CIDI), version 1.1 (Smeets and Dingemans, 1993), was administered, classifying disorders according to the DSM-III-R. Diagnostic status at follow-up in NESDA was established with the CIDI version 2.1 (WHO, 1998), which classifies diagnoses according to the DSM-IV criteria. Organic exclusion rules were used in defining diagnoses, and hierarchy-free diagnoses were made to allow for research into comorbidity. The CIDI is a structured interview with acceptable reliability and validity (Wittchen, 1994; Wittchen et al., 1991). In our own study, no detailed information on the reliability and validity of the Dutch version of the CIDI is available. However, cross-cultural comparison that also included a Dutch version of the CIDI (Wittchen et al., 1991), confirmed good inter-rater reliability. In addition, previous studies showed that the CIDI generated DSM diagnoses consistent with those obtained in semi-structured clinical reappraisal interviews in community surveys (Haro et al., 2006). More detailed information on the presence of anxiety and depressive symptoms during follow-up was assessed with

the Life Chart Interview (LCI) (Lyketsos et al., 1994). This instrument first explores the occurrence of life events in a particular period to re-fresh memory and then assesses presence and severity of symptoms of depression and anxiety during the successive years. We have LCI information on the years between T_1 and T_2 (NEMESIS, 2 years) and between T_2 (NEMESIS) and T_3 (NESDA) (5 years).

Measures of depression and anxiety over time

The development of depression and anxiety over time was measured in two ways. First, we used the presence of a 12-month CIDI-diagnosis of depression (i.e. Major Depressive Disorder or Dysthymic Disorder and/or anxiety (i.e. Generalized Anxiety Disorder, Panic Disorder with or without Agoraphobia, Agoraphobia, or Social Phobia) at the most distal time point (on average 7 years after baseline) as a dichotomous indicator for persistence or recovery of mental disorders. Although this measure ignores the in-between trajectory and residual symptoms, it is a clinically relevant and significant indicator of the long-term course of depression and anxiety. Second, as a more detailed, cumulative course indicator covering the entire follow-up period, we calculated a continuous indicator for the percentage of time during follow-up that respondents experienced depressive or anxiety symptoms as assessed by the LCI. For 173 subjects the baseline disorder was diagnosed at T_0, allowing a total of 8 years of follow-up. However, for others the baseline disorder occurred at T_1 (n=67) or T_2 (n=63), resulting in a follow-up duration of around 7 and 5 years. For the year between T_0 and T_1 we lack Life Chart information. Therefore, the presence of a CIDI-diagnosis of depression or anxiety at T_1 was used to determine the presence of depressive and/or anxiety symptoms during the initial follow-up year. Recency information was used to estimate the number of months with symptoms. Likewise, CIDI-diagnostic status information was used for the few subjects with lacking Life Chart data at T_2 (n=12). At T_3, Life Chart data were available for all respondents. Based on the summed information of the Life Charts, we calculated the number of months with depressive or anxiety symptoms divided by the number of months of follow-up, resulting in the percentage of time during on average 7-year of follow-up with depressive and/or anxiety symptoms. Since this outcome measure was not normally distributed, percentage of time with any depressive or anxiety symptoms was divided into three groups (0%; 1-50% and >50% of the time symptoms), enabling multinomial regression analyses of prognostic factors.

Prognostic factors

Socio-demographics and other prognostic factors, recorded at the time of the baseline disorder in NEMESIS, were used. Socio-demographics included gender, age (≤ 40 versus >40 years), living with a partner (yes versus no), educational level (lower than or equal versus higher than secondary school). Other prognostic factors included the number of comorbid somatic illnesses, mental functioning, physical functioning, childhood adversity and neuroticism. The number of comorbid somatic illnesses was defined as the number of

somatic illnesses, treated or monitored by a doctor during the last year. This was assessed by means of a 31-item semi-structured list, based on the Health Interview Survey of Statistics Netherlands (Van de Berg and Van de Bos, 1989) and recorded as a count variable. Level of functioning was measured by the mental health summary scale and the physical health summary scale of the Short-Form-36 Health Survey (SF-36) (Aaronson et al., 1998). The mental health summary scale involves 4 subscales consisting of role limitations due to mental health, vitality, social functioning, and mental health. The physical summary scale covers 4 subscales including physical functioning, role limitations due to physical health, bodily pain, and general health. Good reliability and validity of this instrument have been shown elsewhere (Aaronson et al., 1998; McHorney et al., 1993, 1994), and both summary scales have sufficient internal reliability in NEMESIS (Cronbach's α=0.81 and 0.85, respectively). Scoring was performed on a 0-100 scale, with 100 defined as maximum functioning. To facilitate interpretation of the odds ratios, inversed scales are reported in Table 3 and 4, with high scores reflecting low functioning. Childhood adversity was assessed using a structured interview in which respondents were asked to recall whether they had experienced before the age of 16 emotional neglect, psychological abuse, physical abuse on two or more occasions or sexual abuse on one or more occasion. Neuroticism was assessed using the Groningen Neuroticism Questionnaire (Ormel et al., 2001), a 14-item, 3 point scale with sufficient internal reliability in NEMESIS (Cronbach's α=0.80). High scores reflected high levels of neuroticism.

Statistical analyses

The distribution of characteristics of participants across the depression group, anxiety group and comorbid group was compared using two-tailed chi-square statistics for categorical variables and one-way-analysis of variance statistics (ANOVA) for continuous variables. In order to describe the course of the main diagnostic groups, we compared both course outcomes (yes/no presence of CIDI disorders at most distal time point, and the % of time during follow-up with symptoms) across the three baseline groups. In unadjusted and adjusted logistic regression analyses and multinomial regression analyses, we examined whether subjects with anxiety or comorbid disorders had different course trajectories as compared to subjects with depression.

The second aim was to investigate which putative predictors determine a poor course. Therefore, logistic regression and multinomial regression analyses were performed in a stepwise fashion. In the first model, baseline diagnostic status was entered, adjusted for socio-demographics (gender, age, partner status, educational level), and in a second model, diagnostic groups, socio-demographics and other putative predictors were entered. The logistic regression analyses with CIDI-status at distal time point were adjusted for time of follow-up. The multinomial analyses were not adjusted for time of follow-up, since this was already accounted for in the outcome measure: percentage of time with symptoms. All analyses were conducted using SPSS (version 15) (SPSS, 2006).

RESULTS

Characteristics

Baseline socio-demographic and clinical characteristics of the study sample are summarized in Table 1. Mental and physical functioning was lowest for comorbid disorders, followed by depressive disorders. In addition, subjects with comorbid disorders reported more childhood adversity and a higher level of neuroticism than subjects with pure depression or anxiety. Finally, subjects with anxiety or a comorbid disorder had a significantly longer follow-up (respectively 7.6 and 7.4 years) than persons with pure depression (6.9 years). Post-hoc analyses showed that persons included at T_0, T_1 or T_2 did not differ in socio-demographic nor clinical characteristics, except for time of follow-up (data not shown).

Table 1: Baseline characteristics of persons with depression, anxiety, or a comorbid depressive and anxiety disorder.

		Depressive disorder n=141	Anxiety disorder n=102	Comorbid disorder n=60	Statistics		
					X^2/ F	p- overall	p- between groups*
Gender	*% Female*	61.7	69.6	75.0	3.84	0.15	ns
Age (mean ± SD)		38.8 (± 9.0)	37.7 (± 9.7)	38.2 (± 8.8)	0.48	0.62	ns
Partner	*% Yes*	61.7	69.6	55.0	3.66	0.16	ns
Education	*% Yes*	67.4	55.9	56.7	4.00	0.14	ns
No. somatic disorders mean (± SD)		1.0 (± 1.3)	1.0 (± 1.2)	1.2 (± 1.4)	1.07	0.34	ns
Mental functioning mean (± SD)		67.5 (± 21.1)	76.7 (± 14.4)	60.3 (± 22.5)	14.50	<.001	a=<.001 b=.03 c=<.001
Physical functioning mean (± SD)		78.4 (± 18.9)	81.5 (± 15.1)	74.9 (± 20.9)	2.60	0.08	c=.02
Childhood adversity	*% Yes*	53.2	61.8	70.0	5.29	0.07	b=.03
Neuroticism mean (± SD)		64.9 (± 4.9)	65.2 (± 4.7)	68.6 (± 6.2)	11.90	<.001	b=<.001 c=<.001
Follow-up years mean (± SD)		6.9 (± 1.2)	7.6 (± 0.8)	7.4 (± 1.1)	16.72	<.001	a=<.001 b=.004

*a= depressive disorder versus anxiety disorder; b= depressive disorder versus comorbid disorder; c= anxiety disorder versus comorbid disorder. Only significant comparisons are presented.

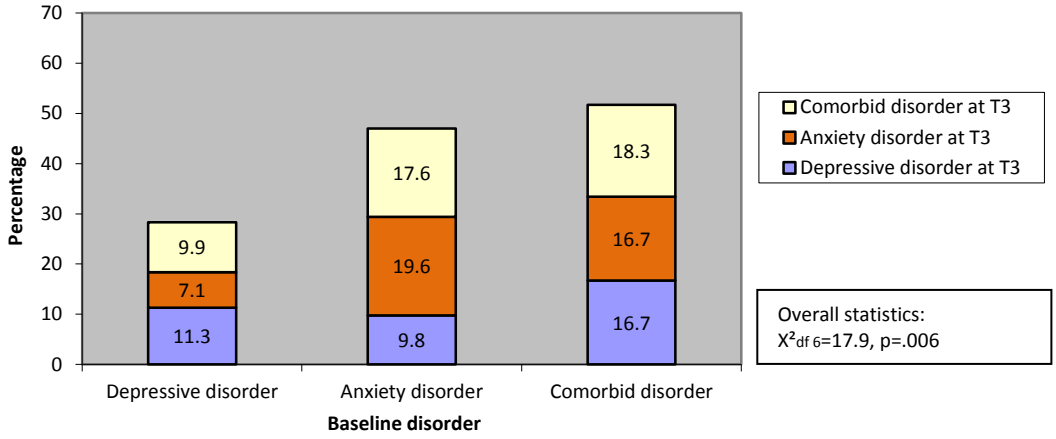
Course

CIDI diagnosis 7 years after baseline – At follow-up, 60.7% of the participants were free from a 12-month CIDI-diagnosis of depression or anxiety. As shown in Figure 1, persons with a depression at baseline were most likely to be free from diagnosis (71.6%), compared to those with anxiety (52.9%) or the comorbid state (48.3%). Persons with a depression and persons with anxiety at baseline had similar percentages of a depressive disorder at follow-

up (respectively 11.3% and 9.8%), which was lower than that of persons with a comorbid disorder (16.7%). Persons with a depression were less likely to have an anxiety disorder at follow-up (7.1%), as compared to persons with anxiety (19.6%), or a comorbid state (16.7%). Similarly, they were less likely to have a comorbid disorder at follow-up (9.9%), as compared to persons with anxiety (17.6%) and the comorbid state (18.3%).

Post-hoc analyses showed that a considerable number of the participants, who were free of a 12-month CIDI-diagnosis at follow-up, had symptoms of depression and/or anxiety at a subthreshold level, defined as fulfilling one of the core criteria of depression or anxiety during last month, while not fulfilling the definition of a depression or anxiety disorder (22.7% of persons with depression, 18.6% of persons with anxiety and 21.7% of persons with a comorbid depressive and anxiety disorder). These numbers did not differ significantly across the groups. Hence, this did not alter the conclusions on differences in course trajectories between depression, anxiety and their comorbid state.

Figure 1. 12-Months prevalence of CIDI diagnoses across baseline disorder groups after a mean follow-up of 7 years (T3).



Differences between groups: depressive disorder versus anxiety disorder p=.004; depressive disorder versus comorbid disorder p=.01; anxiety disorder versus comorbid disorder p=.62

Table 2. Course trajectories in terms of % of follow-up months with symptoms of anxiety or depressive symptoms across baseline disorder groups after a mean follow-up period of 7-years.

Baseline disorder	n	% of follow-up months with any[a] symptoms			Statistics	% of follow-up months with depressive symptoms			statistics	% of follow-up months with anxiety symptoms			statistics
		0%	<50%	≥ 50%		0%	<50%	≥ 50%		0%	<50%	≥ 50%	
Depressive disorder	141	44.7	46.8	8.5	X^2_{df4}=7.9 p=.01 a=.15 b=.05 c=.54	54.6	41.1	4.3	X^2_{df4}=9.0 p=.06 a= .69 b=.04 c=.05	63.8	30.5	5.7	X^2_{df4}=10.6 p=.03 a= .03 b=.03 c=.91
Anxiety disorder	102	32.4	56.9	10.8		51.0	46.1	2.9		46.5	43.6	9.9	
Comorbid disorder[b]	60	28.3	55.0	16.7		38.3	50.0	11.7		43.3	46.7	10.0	
Total	303	37.3	51.8	10.9		50.2	44.6	5.3		54.0	38.1	7.9	

[a] any symptoms i.e. any depressive or anxiety symptoms; [b] comorbid disorder i.e. comorbid depressive and anxiety disorder; a= depressive disorder versus anxiety disorder; b= depressive disorder versus comorbid disorder; c= anxiety disorder versus comorbid disorder

Percentage time of follow-up with symptoms - As shown in Table 2, during the follow-up period around one-third (37.3%) of all participants (n=303) were free of symptoms, 51.8% reported symptoms less than 50% of the time and 10.9% reported symptoms more than 50% of the time during 7-year follow-up. Subjects with a depression at baseline had the best course trajectory: 44.7% were free from symptoms during follow-up (versus 32.4% of persons with anxiety and 28.3% of persons with a comorbid state) and only 8.5% suffered from symptoms for more than 50% of the time (versus 10.8% of persons with anxiety and 16.7% of persons with a comorbid state). When outcome was defined as depressive symptoms during follow-up, overall differences were borderline significant (p=.06). However, although depressed persons did not differ from persons with anxiety at baseline, persons with a comorbid state had significantly more depressive symptoms during follow-up than the two other groups. When outcome was defined as anxiety symptoms during follow-up, depressed persons were most likely to be free from symptoms of anxiety (63.8%) as compared to persons with anxiety (46.5%) and persons with a comorbid state (43.3%). Finally, comparison across categories shows that 49.0% of the persons with pure anxiety had depressive symptoms during follow-up, whereas a substantially lower proportion of 36.2% of the persons with pure depression had anxiety symptoms during follow-up.

Putative prognostic factors

In Table 3, the association between baseline disorder status, socio-demographics and other prognostic factors and having a 12-month CIDI-diagnosis of depression or anxiety at the most distal time-point (T_3) is presented. Logistic regression analyses, adjusted for socio-demographics (gender, age, partner status, level of education, time of follow-up), showed that anxiety at baseline was associated with a 1.85-fold increased odds for having any disorder at follow-up (95% CI 1.04-3.27) and a comorbid state with a 2.34-fold increased odds (95% CI 1.23-4.46), as compared to depression (reference). Full adjustment of the model for putative predictors (somatic illnesses, mental functioning, physical functioning, childhood adversity and neuroticism), resulted in a 2.47-fold increased odds for having any disorder at follow-up for persons with anxiety at baseline (95% CI 1.27-4.53) and persons with a comorbid state with a 1.80-fold increased odds (95% CI 0.87-3.61), as compared to depressed persons (reference). Of the putative predictors, high neuroticism (OR 1.47 [95% CI 1.10-1.98]) and low physical functioning (OR 1.52 [95% CI 1.09-2.13]) predicted poor outcome as defined by CIDI-diagnosis after 7 years.

Table 3. Results from logistic regression analyses associating baseline diagnosis, socio-demographics and putative predictors with having a depressive and/or anxiety disorder at T3, after a mean follow-up period of on average 7 to 9 years.

	Model 1 -adjusted for socio-demographics-	Model 2 -fully adjusted-
	OR (95% CI)	OR (95% CI)
Baseline diagnosis		
Depression	Reference	Reference
Anxiety	1.85 (1.04-3.27)	2.47 (1.27-4.53)
Comorbid disorder	2.34 (1.23-4.46)	1.80 (0.87-3.61)
Sociodemographics		
Female gender	1.34 (0.80-2.25)	1.31 (0.76-2.29)
Age >40 years	1.00 (0.62-1.65)	0.84 (0.48-1.45)
Living with partner	1.09 (0.66-1.81)	1.46 (0.84-2.57)
Higher education	0.85 (0.51-1.40)	1.04 (0.61-1.82)
Mean follow-up time [a]	1.20 (0.96-1.51)	1.13 (0.93-1.58)
Putative predictors		
Somatic illnesses [a]	-	0.98 (0.77-1.25)
Low mental functioning [a]	-	1.27 (0.94-1.69)
Low physical functioning [a]	-	1.52 (1.09-2.13)
Childhood adversity	-	1.17 (0.68-2.01)
Higher neuroticism [a]	-	1.47 (1.10-1.98)

[a] Reported per SD increase; SD mean follow-up time= 1.1; SD somatic illnesses= 1.3; SD mental functioning= 19.2; SD physical functioning= 18.5; SD neuroticism= 5.0. Abbreviations: OR= Odds Ratio; CI= Confidence Interval; SD= Standard Deviation.

Table 4. Results from multinomial regression analyses associating baseline diagnosis, socio-demographics and putative predictors with the risk of having <50% and ≥ 50% of the time depressive and/or anxiety symptoms during follow-up, compared to having no symptoms during follow-up (reference).

	<50% of follow-up with depression or anxiety symptoms		≥ 50% of follow-up with depression or anxiety symptoms	
	Model 1 [b] OR (95% CI)	Model 2 [b] OR (95% CI)	Model 1 [b] OR (95% CI)	Model 2 [b] OR (95% CI)
Baseline diagnosis				
Depression	Reference	Reference	Reference	Reference
Anxiety	1.63 (0.93-2.86)	1.71 (0.93-3.15)	1.58 (0.62-4.03)	1.86 (0.62-5.57)
Comorbid disorder	1.87 (0.94-3.74)	1.29 (0.61-2.73)	2.76 (1.07-7.60)	1.03 (0.31-3.41)
Sociodemographics				
Female gender	1.43 (0.85-2.41)	1.50 (0.86-2.62)	1.80 (0.74-4.39)	1.98 (0.72-5.41)
Age >40 years	0.85 (0.51-1.40)	0.73 (0.42-1.28)	0.89 (0.40-2.00)	0.69 (0.27-1.76)
Living with partner	1.34 (0.80-2.24)	2.12 (1.19-3.78)	1.00 (0.44-2.30)	2.32 (0.90-5.96)
Higher education	1.34 (0.80-2.27)	1.41 (0.80-2.49)	0.67 (0.30-1.53)	1.07 (0.42-2.74)
Putative predictors				
Somatic illnesses [a]	-	0.89 (0.69-1.14)	-	0.97 (0.64-1.45)
Low mental functioning [a]	-	1.27 (0.93-1.72)	-	1.52 (0.91-2.50)
Low physical functioning [a]	-	1.02 (0.72-1.45)	-	1.01 (0.57-1.79)
Childhood adversity	-	1.87 (1.09-3.22)	-	3.41 (1.18-9.82)
Higher neuroticism [a]	-	1.79 (1.28-2.50)	-	3.50 (2.03-6.04)

[a] Reported per SD increase; SD somatic illnesses= 1.3; SD mental functioning= 19.2; SD physical functioning= 18.5; SD neuroticism= 5.0. [b] Model 1: adjusted for socio-demographics. Model 2: adjusted for socio-demographics, as well as other putative predictors.

As presented in Table 4, multinomial regression analyses, adjusted for socio-demographics, showed that a comorbid state was associated with a 2.76-fold significantly increased odds (95% CI 1.07-7.60) for having more than 50% of the time anxiety and/or depressive symptoms during follow-up, as compared to depression (reference). Of the putative predictors, neuroticism (OR 3.50 [95% CI 2.03-6.04]) and childhood adversity (OR 3.41 [95% CI 1.18-9.82]) predicted longer duration of symptoms.

DISCUSSION

Course

Our hypothesis, that comorbid depressive and anxiety disorders would have a poorer long-term course trajectory than pure anxiety disorders, which in turn would have a poorer long-term course trajectory than pure depressive disorders, was largely confirmed. Furthermore, course among the general population seems to be rather favorable: only 10.9% of the participants experienced a chronic course with symptoms during more than half of the time. A percentage of 37.3% was free of symptoms during the entire 7-year follow-up, indicating a rapid and lasting recovery of symptoms after the index episode, and around 60% of the participants was free from a 12-month CIDI-diagnosis at follow-up (T_3).

Our prevalence for favorable outcomes appears to be somewhat higher than in previous studies: Tyrer et al. (2004) found that 36% of 210 out-patients with a neurotic disorder (Dysthymia, Panic Disorder or Generalized Anxiety Disorder) was free from a DSM-diagnosis after 12 years of follow-up. However, their study was based on out-patients and did not include persons with a Major Depressive Disorder, who have better course trajectories than Dysthymic patients. In the Zurich study, a community based study, one quarter of the subjects was free from symptoms after 7 years of follow-up (versus 37.3% in our study), with a slightly higher recovery rate for subjects with depression only (32%), as compared to pure anxiety or comorbid disorder (respectively 23% and 22% free from symptoms) (Angst and Wicki, 1991). In the Zurich study symptoms were assessed by means of the Structured Diagnostic Interview for Psychopathologic and Somatic Syndromes (SPIKE) (Angst and Wicki, 1991), whereas we employed the Life Chart method. Recently, Fichter et al. (2010) also showed rather favorable course trajectories for persons with anxiety and/or depression in the Upper Bavarian Longitudinal Community Study. Recovery rates, after 5 years of follow-up, for pure anxiety and depression were around 70%, for mixed anxiety and depression around 50%. After 25 years of follow-up, around 60% of persons with anxiety, over 70% of persons with depression and around 65% of persons with mixed states had no disorder. Although these numbers are in line with our results, the 5-year course trajectory of anxiety was more favorable than in our study. In the Upper Bavarian Community study the Standardized Psychiatric Interview (SPI) was used. The SPI addresses anxiety on a more general level than CIDI-definitions, including symptoms of Generalized Anxiety Disorder, Phobias and Obsessive-Compulsive Disorder (Fichter et al., 2010), hence persons with subthreshold anxiety disorders might have been included in the study population.

Around 10% of all participants in our study had symptoms more than 50% of the time. Keller et al. (1992) showed that 12% of the subjects with a Major Depressive Disorder still had not recovered by 5 years. This is slightly higher than the 8.5% of persons with a depression at baseline in our study. However, the Collaborative Depression Study of Keller (1992) was based on both in- and out-patients and different methods were applied. Considering anxiety disorders, Bruce et al. (2005) found probabilities for recovery after 12 years of follow-up for Generalized Anxiety Disorder, Panic Disorder with Agoraphobia and Social Phobia of respectively 0.37, 0.48 and 0.58. Overall, the probabilities for a chronic unremitting course trajectory were higher than the 10.8% for persons with anxiety and 16.7% for persons with the comorbid state in our study. Differences may be due to differences in methodology, as well as due to the fact that the Harvard/Brown Anxiety Disorder Research Program was based on out-patients. Furthermore, in order to have an adequate sample size, we were forced to combine various anxiety disorders, including Panic Disorder without Agoraphobia, which has probably a better course trajectory (Bruce et al., 2005).

Next, our results showed that persons with anxiety had higher odds to develop (comorbid) depression than vice versa. In previous studies (Merikangas et al., 2003; Hagnell and Grasbeck, 1990), persons with anxiety states alone tended to develop either depression alone, or a comorbid state during follow-up. In contrast: depression alone and depression comorbid with anxiety had fewer diagnostic conversions towards anxiety (Fichter et al., 2010; Merikangas et al., 2003).

Finally, the poor course trajectories of comorbid depressive and anxiety disorders as compared to pure disorders have been consistently demonstrated (Kessler et al., 1996; Sherbourne and Wells, 1997; Merikangas et al., 1996). However, our study provides a more detailed view on comorbidity: depressed persons with a comorbid anxiety disorder had a higher probability of depression at follow-up than persons with only depression at baseline, whereas persons with a comorbid depressive disorder had an equal probability of anxiety at follow-up, as compared to persons with only anxiety at baseline. As Bruce et al. (2005) suggest, a comorbid anxiety disorder might reduce the likelihood of recovering from a comorbid depressive disorder, whereas a comorbid depression does not alter the course of an anxiety disorder. In a hierarchical perspective, anxiety seems to be of greater importance for course trajectories than depression. This finding might fuel the debates on the suggestion of the DSM-V workgroup to add an anxiety dimension to depression categories.

Predictors of course

Considering the various covariates included in our multivariate models, we found high neuroticism to be significantly associated with unfavorable course outcomes in both multivariate regression analyses. Neuroticism has previously been identified as a prognostic factor for both depression as well as anxiety (Tyrer et al., 2004; Spijker et al., 2001; Kendler et al., 2004; Rhebergen et al., 2009). It was noticed that this finding may reflect underlying vulnerability, partly resulting from genetic makeup and childhood experience (Beard et al., 2008). However, since neuroticism was assessed at the time of the baseline disorder, it may also reflect the severity of the disorder and, likewise, it might be severity that is associated with the observed differences across depression and anxiety groups. On the other hand, mental functioning (SF-36) may reflect severity of the disorder as well, but failed to be associated with course trajectory. This suggests an additional potentially specific effect of neuroticism. Other prognostic factors in our study were childhood adversity and physical functioning. However, significant associations were only found in one of the two regression analyses. In previous studies on both depression and anxiety (Kendler et al., 2004; Beard et al., 2008), childhood adversity was identified as a risk factor for both the occurrence as well as persistence of depression and anxiety. Physical illness was previously demonstrated to have predictive value for episode duration of depressive disorders (Kuehner and Huffziger, 2009; Spijker et al., 2004) and was associated with anxiety disorders (Beekman et al., 1998). Finally, in our study living with a partner was associated with having less than 50% of the

time symptoms of depression and/or anxiety, but there was no association for partner status with a more chronic course (symptoms more than 50% of the time), nor with CIDI-diagnostic status at follow-up. Findings in literature regarding the importance of partner status are inconsistent. Keller (1994) showed that being married was a determinant of persistence of depression, whereas other studies did not find significant associations (Tyrer et al., 2004; Spijker et al., 2004). Other socio-demographics were not associated with course, whereas other studies suggest that the course of depression in old age may be less favorable as compared to the course of depression in younger adults (Licht-Strunk et al., 2009). In addition, female gender and low education were previously identified as strong predictors of the onset of depressive and anxiety disorders (Seedat et al., 2009; Bijl et al., 1998a). The lack of significant association with course trajectories in our study, might indicate that, although they might predict onset, they are probably not as important in determining the prognosis.

Strengths and limitations

Strengths of this study are its prospective design and its long-term follow-up of (on average) seven years. Moreover, depression and anxiety were defined and diagnosed through well established criteria and instruments and an extensive assessment battery was used, which enabled us to perform multivariate analyses on a range of potential risk factors. However, in the course of time, some changes were made in the different versions of the CIDI. Relevant for our study was the modification of the criteria for Panic Disorder in CIDI 2.1, requiring recurrent unexpected Panic Attacks accompanied by a month or more of persistent concern of having attacks or about the implications of an attack, whereas in CIDI 1.1, based on DSM-III-R, either four attacks in 4 weeks, or one attack followed by a month of persistent fear for having another attack, was required (Penninx et al., 2008; Bijl et al., 1998a). These changes resulted in a stricter definition of Panic Disorder at follow-up and might, therefore, result in an underestimation of the long-term persistence of anxiety disorders. Hence, our conclusion that a (comorbid) anxiety disorder resulted in a poorer course trajectory would have been stronger when the same diagnostic criteria would have been used. A strength of the present study is that it was carried out among a large, random sample of adults in the community, thereby avoiding selection bias inherent in clinical studies, the so-called Berkson's bias. This is bias arising from an overrepresentation of comorbid, and hence more severe, cases in treatment settings (Berkson, 1946). However, also in the present study, chronic cases are more likely to occur than acute cases, since we included prevalent cases at T_0. We performed post-hoc analyses that confirmed a slightly poorer course trajectory for the persons included at T_0. Thus, even with a relative overrepresentation of more chronic cases, course was still rather favorable, thereby strengthening our conclusion that course in the general population is more favorable than expected. Next, the limited number of respondents per disorder did not allow us to perform post-hoc analyses for each depressive and anxiety disorder separately. However, both in depressive disorders, as well as in anxiety disorders, various types of disorders wax and wane within the same individual (Wittchen et

al., 2000). These pleiomorphic course trajectories justify the grouping of anxiety disorders and depressive disorders for the current analyses. In addition, we did not include the full range of depressive and anxiety disorders in the selection of the current study. We acknowledge that our findings are not generalizable to other depressive and anxiety disorders, such as minor depression, post-traumatic stress disorder and obsessive compulsive disorder. Finally, we did not include treatment in our models because of evidence of strong selection bias in population-based cohorts. Persons who are more severely ill, have more treatment, but in general have a poorer course trajectory. Thus, differences in course between a treated and untreated group primarily reflect this selection bias rather than treatment effects (Sherbourne et al., 1997).

To conclude, our study clearly demonstrates the relatively poorer course trajectory for persons with (comorbid) anxiety as compared to persons with depression only. Overall, course trajectories were more favorable than expected, with a relatively low number of chronic cases. Finally, we identified some predictors of poor course trajectory. In clinical care, attention should be paid to neuroticism, poor physical functioning and childhood adversity as significant predictors of the poorest course trajectories of depression and/or anxiety.

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