Comorbidity Patterns of Anxiety and Depressive Disorders in a Large Cohort Study: the Netherlands Study of Depression and Anxiety (NESDA)

Femke Lamers, PhD; Patricia van Oppen, PhD; Hannie C. Comijs, PhD; Johannes H. Smit, PhD; Philip Spinhoven, PhD; Anton J. L. M. van Balkom, MD, PhD; Willem A. Nolen, MD, PhD; Frans G. Zitman, MD, PhD; Aartjan T. F. Beekman, MD, PhD; and Brenda W. J. H. Penninx, PhD

Background: Comorbidity of depressive and anxiety disorders is common and has been shown to be a consistent predictor of chronicity. Comorbidity patterns among specific depressive and anxiety disorders have not been extensively reported. This study examines comorbidity patterns and temporal sequencing of separate depressive and anxiety disorders using data from a large psychiatric cohort.

Method: Baseline data (N = 1,783) of the Netherlands Study of Depression and Anxiety, collected between September 2004 and February 2007, were used. Current and lifetime comorbidity rates for depressive and anxiety disorders (*DSM-IV-TR* criteria) were calculated. Associations of comorbidity with sociodemographic, vulnerability, and clinical characteristics, and temporal sequencing of disorders were examined.

Results: Of those with a depressive disorder, 67% had a current and 75% had a lifetime comorbid anxiety disorder. Of persons with a current anxiety disorder, 63% had a current and 81% had a lifetime depressive disorder. Comorbidity of depressive and anxiety disorders was associated with more childhood trauma (OR = 1.19; 95% CI, 1.06–1.33), higher neuroticism (OR = 1.05; 95% CI, 1.02–1.08), earlier age at onset of first disorder (OR = 1.59; 95% CI, 1.22–2.07), longer duration of depressive and/or anxiety symptoms (OR = 1.01; 95% CI, 1.01–1.01), and higher symptom severity (ORs ranging from 1.01 to 1.03; all *P* values < .05). In 57% of comorbid cases, anxiety preceded depression, and in 18%, depression preceded anxiety. Comorbidity with preceding depression compared to preceding anxiety was associated with a shorter duration of symptoms of depressive and/or anxiety symptoms (OR = 0.99; 95% CI, 0.98–0.99), earlier age at first onset (OR = 0.46; 95% CI, 0.31–0.68), and fewer fear symptoms (OR = 0.98; 95% CI, 0.97–0.99).

Conclusions: Comorbidity rates in anxiety and depressive disorders were very high, indicating that it is advisable to assess both disorders routinely regardless of the primary reason for consultation. This is especially important since comorbid patients showed a specific vulnerability pattern, with more childhood trauma, neuroticism, and higher severity and duration of symptoms.

J Clin Psychiatry 2011;72(3):341–348

Submitted: *April 14, 2010; accepted August 30, 2010.*
Online ahead of print: *January 25, 2011 (doi:10.4088/JCP.10m06176blu).*
Corresponding author: *Femke Lamers, PhD, Department of Psychiatry, VU University Medical Center, AJ Ernststraat 1887, 1081 HL Amsterdam, The Netherlands (f.lamers@vumc.nl).*

In the past decades, comorbidity of psychiatric disorders has been the topic of interest in an increasing number of psychiatric studies. Epidemiologic studies from Europe as well as the United States have shown consistently high comorbidity rates for depressive and anxiety disorders, ranging from 40%–80%.[1–3] Moreover, comorbid disorders, especially comorbidity between depressive and anxiety disorders,[4] have been found to be more severe, carry more disability and higher health care utilization, and have a greater persistence and duration than "pure" disorders.[3,5–12] This evidence shows that comorbidity is a consistent predictor of chronicity.

Because of the large impact of comorbidity on course and prognosis, identifying factors associated with comorbidity is important as a first step in its prevention. Previous studies[13,14] have further indicated that, compared to persons with pure disorders, persons with depression-anxiety comorbidity were less educated, less often employed, less often had a partner, and more often had a positive parental psychiatric history and childhood trauma. Another study[15] found lower education and younger age to be associated with comorbid depression as compared to pure depression. Also, higher neuroticism scores have been observed in comorbid cases compared to pure anxiety and pure depression.[16] However, the effects of multiple sociodemographic factors and vulnerability factors have not often been studied in concert with clinical characteristics. Whether associations of these factors with comorbidity are independent of earlier observed clinical characteristics is, until now, unclear and indicates that a fully comprehensive understanding of contributing factors to comorbidity is not currently available.

It is further known from comorbidity studies that anxiety disorders often precede depressive disorders, although some studies challenge this prevailing notion.[17] Because a reversed pattern—depressive disorders preceding anxiety disorders—may represent a different etiologic pathway, it is also important to evaluate whether characteristics of comorbidity with preceding anxiety are different from comorbidity with preceding depression. An earlier study on this subject revealed that a pattern of depressive disorder preceding anxiety disorder was more likely among higher educated persons and those who had experienced parental divorce.[1]

Most comorbidity studies focus on only 1 or 2 separate diagnoses or aggregate rates for depressive and anxiety disorders instead of reporting rates for separate disorders. Also, comorbidity rates from different studies cannot always be directly compared due to differences in sampling frame or

diagnostic method and recency of disorders, and only few studies have evaluated how comorbidity patterns vary between different subtypes of anxiety and depressive disorders.[18] The Netherlands Study of Depression and Anxiety (NESDA) offers the opportunity to explore comorbidity patterns among a wide range of depressive and anxiety diagnoses to see if some comorbidity combinations are more common than others.

The aim of this study is to evaluate comorbidity patterns between the most common depressive disorders (major depressive disorder [MDD], dysthymia) and the most common anxiety disorders (generalized anxiety disorder [GAD], social phobia, panic disorder with/without agoraphobia, agoraphobia) in the NESDA study. Second, we will evaluate which sociodemographic factors, vulnerability factors (personality, life events, childhood trauma, family history), and clinical characteristics are independently associated with comorbidity. Third, the temporal sequence of anxiety and depressive disorders will be examined and sociodemographics, vulnerability factors and clinical correlates of comorbidity with preceding depression versus comorbidity with preceding anxiety will be examined to evaluate whether differential ordering identifies different comorbidity concepts.

METHOD

Sample

The NESDA is a longitudinal cohort study, consisting of 2,981 persons (aged 18–65 years), including those with anxiety and/or depressive disorders (78%) as well as healthy controls (22%). The study aims to describe the long-term course and consequences of depression and anxiety disorders. Participants were recruited from the community (19%), in primary care (54%), and in specialized mental health settings (27%). Exclusion criteria used were (1) a primary clinical diagnosis of psychotic disorder, obsessive-compulsive disorder, bipolar disorder, or severe addiction disorder and (2) not being fluent in Dutch. Approval of the study protocol was granted by the Ethical Review Boards of all participating centers, and all participants gave written informed consent. A detailed description of the NESDA study design can be found elsewhere.[19] The baseline assessment included a 4-hour interview in which information on a wide range of domains was collected, such as psychopathology, demographic characteristics, and physical and psychosocial functioning, and it further included a medical assessment, computer tasks, and 2 self-administered questionnaires. For the present study, we used the baseline assessment. We included all persons with a current (12-month) diagnosis of depressive and/or anxiety disorder (N = 1,783). The baseline data were collected between September 2004 and February 2007.

Psychopathology

The Composite International Diagnostic Interview (CIDI) lifetime version 2.1[20] was used to establish the presence of depressive disorders (MDD and dysthymia) and anxiety disorders (social phobia, panic disorder, agoraphobia, and GAD) according to *DSM-IV-TR* criteria.[21] The CIDI is a valid and reliable instrument for assessing psychopathology[22] and was conducted by trained clinical research staff. In line with *DSM-IV* definitions,[21] organic exclusion rules were used in defining diagnoses excluding persons whose symptoms could be explained by purely organic causes. As is standard in comorbidity studies,[3,13,18] hierarchy-free diagnoses were made to allow a thorough examination of comorbidity. The NESDA study assessed only the most prevalent anxiety disorders; posttraumatic stress disorder and obsessive-compulsive disorder were not assessed. Therefore, the term *anxiety disorders* used in this article refers to social phobia, panic disorder, agoraphobia, and GAD.

In order to study differences in characteristics between comorbid and "pure" disorders, a categorical variable was constructed classifying persons as having (1) current depression alone and no lifetime anxiety disorder, (2) current anxiety alone and no lifetime depressive disorder, and (3) current comorbid depression and anxiety, based on 12-month diagnoses.

Risk Indicators of Comorbidity

Sociodemographic characteristics under study were gender, age, educational level, ethnicity, and partner status, all assessed during the baseline interview.

Vulnerability factors included positive first-degree family history of depression or anxiety assessed using the family tree method.[23] Childhood trauma was assessed using the structured inventory from the Netherlands Mental Health Survey and Incidence Study (NEMESIS), which constructs an index (range, 0–4) incorporating the occurrence and frequency of 4 types of abuse before age 16 (emotional neglect, psychological abuse, physical abuse, and sexual abuse).[24] A count of negative life events in the past year was constructed based on a list of 12 negative life events,[25] and personality (neuroticism, extraversion, openness, agreeableness, conscientiousness) was measured with the NEO-FFI Personality questionnaire.[26]

Depression and anxiety characteristics included various illness characteristics like recruitment setting (community, primary care, specialized mental health care). Duration of anxiety and/or depressive symptoms was based on the Life Chart assessment[27] in which the presence of depressive and anxiety symptoms was assessed for every month in the preceding 4 years and expressed as the percentage of time with depressive and/or anxiety symptoms during those 4 years. Early age at onset was defined as first onset of anxiety or depressive disorder before age 21 years and derived from the CIDI. In case of comorbidity, the onset of the first disorder was used. Three severity indicators were included. Current severity of depressive symptoms was assessed with the Inventory of Depressive Symptomatology,[28] current severity of anxiety was assessed using the Beck Anxiety Inventory,[29] and the level of avoidance was measured with the Fear Questionnaire.[30]

Temporal Sequencing

For persons with a current comorbid depressive and anxiety disorder, temporal sequencing was based on the lowest age at onset of individual disorders as assessed by the CIDI.

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 1. Percentage of Patients With Current Depressive or Anxiety Disorders With Current (12-Month) and Lifetime Comorbidity of Depressive and Anxiety Disorders

	Current Depressive Disorders			Current Anxiety Disorders				
Diagnosis	MDD, n = 1,231	Dysthymia, n = 325	Any Depression, n = 1,275	Social Phobia, n = 697	Panic Disorder With or Without Agoraphobia, n = 710	Agoraphobia Only, n = 193	GAD, n = 494	Any Anxiety, n = 1,363
Social phobia, %								
Current	35[a]	44	35	NA	46	35	44	NA
Lifetime	41[a]	49	41	NA	52	38	48	NA
Panic disorder with or without agoraphobia, %								
Current	37[a]	41	37	47	NA	0	44	NA
Lifetime	42	44	42	51	NA	0	49	NA
Agoraphobia only, %								
Current	8[a]	11	8	10	0	NA	10	NA
Lifetime	10[a]	13	10	14	0	NA	13	NA
GAD, %								
Current	31[a]	44	30	31	31	26	NA	NA
Lifetime	38[a]	52	38	39	39	38	NA	NA
Any anxiety disorder, %								
Current	67	77	67	66[b]	59[b]	48[b]	68[b]	NC
Lifetime	75	84	75	76[b]	68[b]	58[b]	74[b]	NC
MDD, %								
Current	NA	87	NA	63[c,d]	65[c,d]	51[d,e,f]	76[c,e,f]	61
Lifetime	NA	91	NA	82[c,d]	81[c,d]	75[d,e,f]	86[c,e,f]	79
Dysthymia, %								
Current	23	NA	NA	21[c,d]	19[d]	17[d,e]	29[c,e,f]	18
Lifetime	36	NA	NA	37[c,d,f]	32[d,e]	31[d,e]	43[c,e,f]	33
Any depression, %								
Current	NA	NA	NC	65	66	54	78	63
Lifetime	NA	NA	NC	85	82	78	88	81

[a]Different from comorbidity rate in dysthymia ($P < .05$).
[b]This percentage refers to the comorbidity prevalence of anxiety disorders other than the index anxiety disorder.
[c]Different from comorbidity rate in agoraphobia ($P < .05$).
[d]Different from comorbidity rate in GAD ($P < .05$).
[e]Different from comorbidity rate in social phobia ($P < .05$).
[f]Different from comorbidity rate in panic disorder ($P < .05$).
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder, NA = not applicable, NC = not calculated.

A variable with 3 categories was constructed: (1) anxiety was the primary disorder when the onset of anxiety preceded the onset of a depressive disorder, (2) depression and anxiety had a simultaneous onset when depression and anxiety had the same age at onset, and (3) depression was the primary disorder when the onset of depression preceded the onset of an anxiety disorder.

Statistical Analyses

First, comorbidity rates between separate anxiety and depressive disorders were calculated and binomial tests were used to compare comorbidity rated across index disorders. Characteristics of depression alone, anxiety alone, and comorbid depression and anxiety were examined using descriptive statistics. Then, univariable logistic regression analyses were used to evaluate the associations of sociodemographic factors, vulnerability factors, and depression and anxiety characteristics with comorbidity, using persons with pure anxiety and pure depressive disorders as 1 reference group. The reason for combining persons with pure depression with persons with pure anxiety into 1 reference group was that these 2 groups proved to be highly comparable. Two multivariable models were then constructed, 1 model including all sociodemographic and vulnerability factors and 1 model including all clinical characteristics. To evaluate which characteristics were independent risk indicators for comorbidity, all characteristics with $P < .10$ in the 2 multivariable models were entered into a final multivariable model. Temporal sequencing of comorbid disorders was determined for all subtypes of depressive and anxiety disorder separately, and differences in temporal sequencing between disorders were tested with χ^2 tests, and characteristics of comorbidity with preceding depression were evaluated using multivariate logistic regression analysis using a similar modeling strategy as described in the comorbidity analyses. A significance level of $P < .05$ was used for all analyses except post hoc tests for which $P < .005$ was used.

RESULTS

The study sample (N = 1,783) consisted of 67.4% women, the mean age was 41.3 years (SD = 12.4), and the mean years of education was 11.8 (SD = 3.3).

Comorbidity Patterns

Within the NESDA cohort, 1,275 persons had a 12-month depressive disorder and 1,363 had a 12-month anxiety disorder. Of the persons with a depressive or anxiety disorder (N = 1,783), 40% had only 1 disorder, 30% had 2 depressive or anxiety disorders, and another 30% had ≥ 3 depressive

Table 2. Sociodemographic Characteristics, Vulnerability Factors, and Clinical Characteristics of Participants With Depression Only, Anxiety Only, and Comorbid Depression and Anxiety

Variable	Depression Only (group 1), n = 314[a]	Anxiety Only (group 2), n = 253[b]	Comorbid Depression and Anxiety (group 3), n = 855	*P* Value[c]	Post Hoc Comparisons, *P* < .005
Sociodemographic characteristic					
Women, %	62	65	68	.18	
Age, mean (SD), y	40.2 (12.5)	40.7 (13.4)	40.9 (12.0)	.70	
Educational level, mean (SD), y	12.1 (3.2)	12.1 (3.3)	11.4 (3.3)	< .001	3 < 1, 3 < 2
North European ethnicity, %	93	95	92	.53	
Partner (% yes)	74	67	70	.21	
Vulnerability factor					
Family history anxiety/depression, %	82	77	85	.01	3 > 2
Childhood trauma, median (IQR)	0.0 (2.0)	0.0 (2.0)	1.0 (2.0)	< .001	3 > 1, 3 > 2
Negative life events in last year, %	74	66	74	.04	
Personality, mean (SD)					
Neuroticism	38.7 (6.9)	37.3 (7.5)	43.6 (6.3)	< .001	3 > 1, 3 > 2
Extraversion	35.7 (7.2)	37.3 (6.2)	32.6 (6.7)	< .001	3 < 1, 3 < 2
Openness	38.4 (6.0)	37.8 (5.9)	37.5 (6.2)	.09	
Agreeableness	43.4 (5.3)	43.8 (5.2)	42.2 (5.4)	< .001	3 < 1, 3 < 2
Conscientiousness	40.5 (6.9)	41.6 (6.1)	39.1 (6.5)	< .001	3 < 1, 3 < 2
Clinical characteristic					
Setting, %					
General population	9	7	7	< .001	3 vs 2
Primary care	44	56	38		
Specialized mental health care	48	37	55		
Duration of symptoms, median (IQR), %	19.2 (30.8)	49.1 (82.8)	59.1 (72.7)	< .001	3 > 1, 3 > 2, 1 < 2
Early age at onset, %	36	56	64	< .001	3 > 1, 2 > 1
Severity of depressive symptoms					
IDS score, mean (SD)	27.11 (11.6)	20.8 (9.8)	34.1 (12.0)	< .001	3 > 1, 3 > 2, 1 > 2
Severity of anxiety symptoms					
BAI score, mean (SD)	11.8 (8.8)	14.3 (9.7)	20.6 (11.0)	< .001	3 > 1, 3 > 2, 2 > 1
Fear Questionnaire score, mean (SD)	21.7 (17.1)	29.0 (18.9)	38.6 (21.1)	< .001	3 > 1, 3 > 2, 2 > 1

[a]Without lifetime anxiety disorders.
[b]Without lifetime depression. Also, comorbidity among the 4 anxiety disorders was not taken into account.
[c]Based on analyses of variance for continuous variables and χ^2 statistics for categorical variables.
Abbreviations: BAI = Beck Anxiety Inventory, IDS = Inventory of Depressive Symptomatology, IQR = interquartile range.

or anxiety disorders. Comorbidity rates of depression and anxiety disorders (both current and lifetime) are presented in Table 1. Sixty-seven percent of those with a depressive disorder also had a current anxiety disorder, and 75% had a lifetime anxiety disorder. Social phobia and panic disorder were the most common comorbidities in depressive disorders, 41% and 42%, respectively, but GAD was also often present. Comparison of comorbidity rates in binomial tests showed that rates were significantly different between MDD and dysthymia—especially with social phobia and GAD, which were more often present among persons with dysthymia than among persons with MDD. Sixty-three percent of the persons with an anxiety disorder had a current comorbid depressive disorder and as many as 81% had a lifetime comorbid depressive disorder. Comorbidity with depressive disorders was highest in GAD (eg, 76% had current and 86% had lifetime MDD) and lowest in persons with agoraphobia alone, which was confirmed in binomial tests of comorbidity rates across anxiety disorders. The comorbidity of MDD pattern was very comparable for social phobia and panic disorders.

Correlates of Comorbidity

A next step in the analyses was to evaluate differences in sociodemographic characteristics, vulnerability factors, and clinical characteristics. Table 2 presents the characteristics of 3 groups of psychopathology, namely, depression alone, anxiety alone, and comorbid depression and anxiety. Compared to the depression alone and anxiety alone groups, the comorbid group was characterized by lower education, more childhood trauma, higher neuroticism scores, and lower extraversion, agreeableness, and conscientiousness. Also, with respect to clinical characteristics, the comorbid group showed higher severity scores for depression and anxiety, longer duration of depressive and/or anxiety symptoms, and more often an early onset than the pure disorder groups. Univariable and multivariable logistic regression analyses were performed to identify correlates of comorbidity (Table 3) using depression alone and anxiety alone categories as reference. Of the sociodemographic variables (model 1A), fewer years of education was the only variable significantly associated with comorbidity; however, the effect disappeared when clinical characteristics were included in Model 2. More childhood trauma and higher neuroticism remained significantly associated with comorbidity in the final model, independent of clinical characteristics. Longer duration of depressive and/or anxiety symptoms, early age at onset, and higher symptom severity were also associated with an increased odds of comorbidity.

Temporal Sequencing

Temporal sequencing of anxiety and depressive disorders was studied in persons with comorbid depressive and anxiety disorders (n = 855). For each separate anxiety disorder, we assessed whether the index disorder had an earlier,

Table 3. Correlates of Comorbidity in Participants With a 12-Month Depression and Anxiety Disorder (n = 1,422)[a]

Variable	Univariable Model[b]			Multivariable Model 1[c]			Multivariable Model 2[d]		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
				Model 1A					
Sociodemographic characteristic									
Age	1.00	1.00–1.01	.48	1.00	0.99–1.02	.40	…	…	…
Female gender	1.22	0.98–1.52	.08	1.10	0.84–1.43	.51	…	…	…
Educational level (per year increase)	0.94	0.91–0.97	<.001	0.96	0.92–0.99	.04	1.00	0.96–1.04	.90
Ethnicity (percentage North European)	0.82	0.54–1.26	.37	0.78	0.48–1.27	.32	…	…	…
Partner (percentage yes)	0.99	0.79–1.24	.96	0.88	0.68–1.15	.35	…	…	…
Vulnerability factor									
First-degree relatives with anxiety/depression (percentage yes)	1.42	1.08–1.87	.01	1.33	0.97–1.82	.08	1.21	0.86–1.71	.27
Childhood trauma (total score)	1.42	1.29–1.57	<.001	1.23	1.10–1.37	.001	1.19	1.06–1.33	.003
Negative life events (last-year percentage)	1.20	0.95–1.52	.12	0.94	0.72–1.37	.65	…	…	…
Personality									
Neuroticism	1.13	1.11–1.15	<.001	1.11	1.09–1.14	<.001	1.05	1.02–1.08	<.001
Extraversion	0.92	0.90–0.94	<.001	0.96	0.94–0.98	<.001	0.99	0.97–1.01	.44
Openness	0.98	0.97–1.00	.06	1.00	0.97–1.02	.71	…	…	…
Agreeableness	0.95	0.93–0.97	<.001	0.99	0.97–1.02	.57	…	…	…
Conscientiousness	0.96	0.94–0.97	<.001	1.02	1.00–1.04	.14	…	…	…
				Model 1B					
Clinical characteristic									
Setting, %									
General population	Reference								
Primary care	0.87	0.57–1.32	.50	0.65	0.40–1.05	.08	0.64	0.39–1.05	.08
Specialized mental health care	1.42	0.93–2.14	.10	0.85	0.52–1.38	.51	0.85	0.52–1.39	.51
Duration of symptoms (per percentage increase)	1.02	1.01–1.02	<.001	1.01	1.01–1.02	<.001	1.01	1.01–1.01	<.001
Early age at onset	2.20	1.77–2.74	.018	1.90	1.47–2.44	<.001	1.59	1.22–2.07	.001
Severity of depressive symptoms									
IDS score	1.07	1.06–1.09	<.001	1.04	1.02–1.05	<.001	1.02	1.00–1.03	.04
Severity of anxiety symptoms									
BAI	1.08	1.07–1.09	<.001	1.03	1.01–1.02	.001	1.03	1.01–1.05	.001
Fear Questionnaire	1.04	1.03–1.04	<.001	1.01	1.01–1.02	<.001	1.01	1.00–1.02	.01

[a]Reference category used in analyses was depression or anxiety alone.
[b]Based on univariable logistic regression.
[c]Based on multivariable logistic regression with all sociodemographic and vulnerability variables (model 1A) or all clinical characteristics (model 1B) in model.
[d]Based on multivariable logistic regression all variables entered in model that had a $P < .10$ in model 1A or 1B.
Abbreviations: BAI = Beck Anxiety Inventory, IDS = Inventory of Depressive Symptoms.

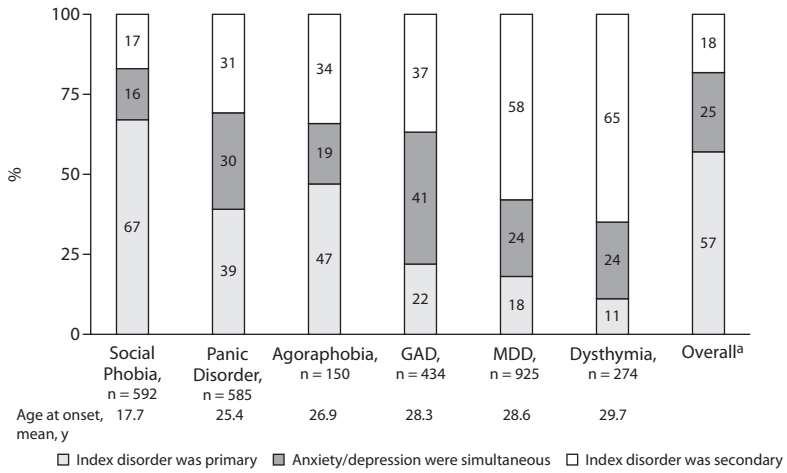
simultaneous, or later onset than the comorbid depressive disorders. Likewise, for MDD and dysthymia, we assessed whether comorbid anxiety disorders occurred before, simultaneously, or after the onset of anxiety disorders. Results of these analyses clearly show that anxiety disorders are more likely to precede depressive disorders (Figure 1). Overall, anxiety disorders preceded depressive disorders in 57% of comorbid cases, simultaneous onset occurred in 25% of the cases, and depressive disorders preceded anxiety disorders in only 18% of cases. Mean age at onset of each disorder was lowest for social phobia and highest for dysthymia (see Figure 1). Social phobia preceded depressive disorders in 67% of the cases. Agoraphobia and panic disorder were also often the primary disorder (47% and 39%, respectively), while the onset of GAD was most often simultaneous with the onset of the depressive disorder (41%). χ^2 Tests showed that the distribution of persons over the 3 categories of temporal sequencing was significantly different between all index disorders (data not shown).

Multivariable logistic regression analyses showed that only a limited number of determinants differentiated between comorbidity with preceding anxiety and comorbidity with preceding depression (Table 4). Comorbid cases with preceding depression had a significantly shorter duration, fewer fear symptoms, and later age at onset compared to cases with preceding anxiety, but no associations with sociodemographic and vulnerability variables were found.

DISCUSSION

Results from our study confirm high current (12-month diagnoses) and lifetime comorbidity rates in anxiety and depressive disorders. Of persons with a depressive disorder, 67% had a current and 75% had a lifetime comorbid anxiety disorder in which rates of comorbid anxiety disorder were higher for those with dysthymia than for those with MDD. Of persons with an anxiety disorder, 63% had a current and as many as 81% had a lifetime comorbid depressive disorder. Rates of comorbid depressive disorder tended to be lowest for persons with agoraphobia only, and highest for GAD. Factors independently associated with comorbidity compared to pure disorders were more childhood trauma, higher neuroticism, earlier onset of first disorder, longer duration of depressive and/or anxiety symptoms, and higher severity of symptoms. Further, in 57% of the comorbid cases, anxiety preceded depressive disorders compared to 18% with depressive disorders

Figure 1. Temporal Sequencing of Depression and Anxiety Comorbidity Patterns Among Patients With Current Disorder Stratified by Index Disorder



[a]Any anxiety used as index disorder.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

preceding anxiety disorders, but comparison of characteristics did not reveal large differences between comorbidity groups based on which disorder appeared first.

Our comorbidity rates are fairly comparable to the rates based on 1-month diagnoses reported by Brown and colleagues.[18] Exceptions are the higher rates of comorbid MDD and comorbid dysthymia in our study and also higher rates of comorbid social phobia in panic disorder and comorbid panic disorder in social phobia. The lifetime rates of comorbid anxiety disorders within lifetime MDD and dysthymia reported in a previous Dutch general population study (NEMESIS)[1] were—with reported rates of 44%–63%—lower than our results. Different sampling frames or recency criteria of disorders may account for some of the differences in results between these studies and ours. In the community-based National Comorbidity Survey and National Comorbidity Survey Replication studies,[7,31] comorbidity rates of current (12-month) anxiety disorders within MDD of 51% and 58%, respectively, were found, which is also lower than the 67% in our study.

As was previously shown by others,[32] setting was not associated with comorbidity, not even in univariable analysis. Higher neuroticism as a risk factor of comorbidity of depressive and anxiety disorders is in line with previous findings.[32,33] High neuroticism is a shared risk factor of anxiety and depressive disorders, which may partly explain the high comorbidity.[34,35] Also, comorbidity of anxiety and depressive disorders is probably largely explained by shared genetic risk factors that also affect neuroticism.[36] In contrast to findings in NEMESIS,[13] none of the sociodemographic variables were associated with comorbidity in our study, but NEMESIS did not include clinical characteristics in their model, which may suggest that the effects of sociodemographic variables are mediated by clinical characteristics. In our study, the effect of education did indeed disappear when clinical characteristics were included in the model. Clinical severity indicators were all associated with comorbidity in our study as was also found by most[5,7,8,10–12] but not all studies.[37] The higher severity of comorbid cases indicates that this group is a relevant group to distinguish in clinical practice.

The comorbidity of GAD with depressive disorders was high (78%–88%), but, since hierarchy rules in the diagnostic interview were ignored (ie, the diagnosis of GAD was made even if GAD occurred exclusively during a mood disorder), the comorbidity rate would likely have been much lower if these hierarchy rules would have been applied as was previously demonstrated.[18] On the other hand, this hierarchy rule is thought by some to obscure true comorbidity rates and results in loss of important clinical information. Studies have shown that persons with GAD occurring during the course of MDD showed levels of functional impairments, negative affect, and psychopathology that were similar to those with actual comorbid GAD and MDD but had higher comorbidity rates and functional impairments than persons with MDD only.[38,39]

Temporal sequencing of depressive and anxiety disorders has been previously evaluated in several studies.[1,17,18,31,40] Our finding that MDD preceded anxiety disorders in 18% of comorbid cases, had a simultaneous onset in 24% of comorbid cases, and occurred after anxiety onset in 58% of comorbid cases is in line with the 8%–15% preceding MDD, 18%–29% simultaneous onset, and 59%–69% of preceding anxiety found in other studies.[1,17,30,37] For dysthymia, the rates of dysthymia preceding anxiety and having a simultaneous onset (11% and 24%) were slightly lower than the rates found by others of 13%–24% and 20%–30%.[1,17] Only Brown and colleagues[18] also evaluated temporal sequencing in separate anxiety disorders. For social phobia and panic, the distributions over categories of anxiety preceding depressive disorders, simultaneous onset, and depressive disorders preceding anxiety found were highly comparable to our distributions. For GAD, Brown and colleagues[18] reported the same percentage of GAD preceding depressive disorders (22%) but found a lower percentage of simultaneous onset (16% versus 41% in our study) and higher percentage of depressive disorder preceding GAD (62% versus 37% in our study). However, this difference is most likely due to the hierarchy rules applied to the GAD diagnosis in the study by Brown et al.[18] Moffit and colleagues[17] found in a New Zealand birth cohort with GAD and MDD that, in comorbid cases, 42% had an earlier onset of anxiety and 26% had a simultaneous onset, while, in 32%, MDD preceded anxiety. The lower percentage of anxiety preceding MDD and higher percentage of anxiety preceding MDD are probably due to data that were collected prospectively in this study, which may yield more reliable estimates because there is no recall bias.

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 4. Correlates of Comorbidity With Preceding Depressive Disorder (versus cormorbidity with preceding anxiety disorders) Among Persons With Comorbid Depression and Anxiety (n = 855)

	Univariable Model[a]			Multivariable Model 1[b]			Multivariable Model 2[c]		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
				Model 1A					
Sociodemographic characteristic									
Age	1.00	0.99–1.02	.78	1.00	0.98–1.02	.95	…	…	…
Female gender	0.86	0.58–1.26	.44	0.82	0.54–1.26	.37	…	…	…
Educational level (per year increase)	1.03	0.98–1.09	.27	1.03	0.97–1.10	.36	…	…	…
Ethnicity (percentage North European)	1.10	0.55–2.23	.77	0.97	0.47–2.01	.93	…	…	…
Partner (percentage yes)	0.90	0.61–1.33	.60	0.97	0.65–1.46	.89	…	…	…
Vulnerability factor									
First-degree relatives with anxiety/ depression (percentage yes)	0.70	0.42–1.15	.16	0.70	0.41–1.18	.18	…	…	…
Childhood trauma (total score)	0.98	0.85–1.14	.79	1.03	0.88–1.21	.74	…	…	…
Negative Life Events (last-year percentage)	0.93	0.61–1.41	.74	0.90	0.58–1.39	.62	…	…	…
Personality									
Neuroticism	0.99	0.96–1.02	.37	1.00	0.96–1.03	.86	…	…	…
Extraversion	1.03	0.99–1.06	.07	1.03	1.00–1.07	.07	0.99	0.96–1.02	.51
Openness	1.01	0.98–1.04	.64	1.00	0.97–1.03	.94	…	…	…
Agreeableness	1.00	0.97–1.04	.95	1.00	0.96–1.04	.89	…	…	…
Conscientiousness	1.00	0.97–1.03	.83	0.99	0.96–1.02	.37	…	…	…
				Model 1B					
Clinical characteristic									
Setting, %									
General population	1.00			1.00			1.00		
Primary care	0.59	0.32–1.10	< .10	0.65	0.34–1.25	.20	0.68	0.36–1.31	.25
Specialized mental health care	0.45	0.25–0.83	.01	0.53	0.28–1.01	.05	0.57	0.30–1.06	.08
Duration of symptoms (per percentage increase)	0.99	0.98–0.99	.001	0.99	0.98–0.99	< .01	0.99	0.98–0.99	< .01
Early age at onset	0.41	0.28–0.61	< .001	0.47	0.32–0.71	< .001	0.46	0.31–0.68	< .001
Severity of depressive symptoms									
IDS score	0.99	0.97–1.01	.18	1.01	0.99–1.04	.23	…	…	…
Severity of anxiety symptoms									
BAI	0.98	0.97–1.00	.07	1.00	0.99–1.04	.88	…	…	…
Fear Questionnaire	0.98	0.97–0.99	< .001	0.98	0.97–0.99	.002	0.98	0.97–0.99	< .01

[a]Based on univariable logistic regression.
[b]Based on multivariable logistic regression with all sociodemographic and vulnerability variables (model 1A) or all clinical characteristics (model 1B) in model.
[c]Based on multivariable logistic regression all variables entered in model that had a $P < .10$ in model 1A or 1B.
Abbreviations: BAI = Beck Anxiety Inventory, IDS = Inventory of Depressive Symptoms.

In addition to studying temporal sequencing, we also evaluated correlates of comorbidity with preceding depression versus comorbidity with preceding anxiety to assess whether these 2 patterns of comorbidity have different characteristics. Only a limited number of associations were found. Comorbidity with preceding depression versus preceding anxiety was associated with a later age at onset of the first disorder, shorter duration of depressive and/or anxiety symptoms, and fewer fear symptoms. In contrast to previous research, no associations were found with sociodemographic variables or childhood trauma.[1] Overall, our findings do not suggest strong conceptual differences between comorbidity with preceding anxiety versus comorbidity with preceding depression, although comorbidity with preceding depression seemed to be a somewhat milder form of comorbidity, with a shorter duration.

Limitations of our study include the cross-sectional character of this study, which does not allow for making causal inferences, and the retrospective data collection of age at onset, which is subject to recall bias. Furthermore, our study included only a selection of the most prevalent anxiety disorders, while obsessive-compulsive disorder and posttraumatic stress disorder were not included. One advantage of this study was the fact that the large number of persons per anxiety and depressive disorder in the NESDA cohort allowed for evaluation of comorbidity patterns in separate anxiety and depressive disorders.

Our study confirmed that comorbidity is the rule rather than the exception. We found that 2 of every 3 persons with a depressive disorder had a current comorbid anxiety disorder and 3 of 4 had a lifetime comorbid anxiety disorder. Among those with an anxiety disorder, approximately 2 of every 3 persons had a current comorbid depressive disorder and as many as 4 of 5 had a lifetime comorbid depressive disorder. Such high comorbidity rates make one wonder whether specialized mental health clinics for depressive disorders and anxiety disorders are appropriate and also suggest that it is important to always assess these disorders routinely in clinical practice no matter what is the primary reason for referral or consultation. This assessment is especially important since comorbid patients showed specific vulnerability patterns, with more childhood trauma and neuroticism as well as higher severity and duration of symptoms, which makes them a clinically relevant group that may require a different or more intensive treatment approach.

Author affiliations: Department of Psychiatry/EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam (Drs Lamers, van Oppen, Comijs, Smit, Balkom, Beekman, and Penninx); Department of Psychiatry, Leiden University Medical Center, Leiden (Drs Spinhoven, Zitman, and Penninx); Institute of Psychology, Leiden University, Leiden (Dr Spinhoven); and Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen (Drs Nolen and Penninx), The Netherlands.
Potential conflicts of interest: During the years 2005–2010, **Dr Nolen** has received grants from the Netherlands Organisation for Health Research and Development, European Union, Stanley Medical Research Institute, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Wyeth; has received honoraria/speaker's fees from AstraZeneca, Pfizer, Servier, and Wyeth; and has served in advisory boards for AstraZeneca, Pfizer, and Servier. All other authors report no financial or other relationship relevant to the subject of this study.
Funding/support: The infrastructure for the Netherlands Study of Depression and Anxiety study (www.nesda.nl) is funded through the Geestkracht program of the Netherlands Organisation for Health Research and Development (Zon-Mw, grant number 10-000-1002) and is supported by participating universities and mental health care organizations: VU University Medical Center, GGZ inGeest, Arkin, Leiden University Medical Center, GGZ Rivierduinen, University Medical Center Groningen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ Healthcare), Netherlands Institute for Health Services Research (NIVEL), and Netherlands Institute of Mental Health and Addiction (Trimbos).

REFERENCES

1. de Graaf R, Bijl RV, Spijker J, et al. Temporal sequencing of lifetime mood disorders in relation to comorbid anxiety and substance use disorders—findings from the Netherlands Mental Health Survey and Incidence Study. *Soc Psychiatry Psychiatr Epidemiol*. 2003;38(1):1–11.
2. Jacobi F, Wittchen HU, Holting C, et al. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). *Psychol Med*. 2004;34(4):597–611.
3. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Arch Gen Psychiatry*. 1994;51(1):8–19.
4. van Balkom AJ, van Boeijen CA, Boeke AJ, et al. Comorbid depression, but not comorbid anxiety disorders, predicts poor outcome in anxiety disorders. *Depress Anxiety*. 2008;25(5):408–415.
5. Andrade L, Eaton WW, Chilcoat H. Lifetime comorbidity of panic attacks and major depression in a population-based study: symptom profiles. *Br J Psychiatry*. 1994;165(3):363–369.
6. Bijl RV, Ravelli A. Current and residual functional disability associated with psychopathology: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Psychol Med*. 2000;30(3):657–668.
7. Kessler RC, Berglund P, Demler O, et al; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095–3105.
8. Roy-Byrne PP, Stang P, Wittchen HU, et al. Lifetime panic-depression comorbidity in the National Comorbidity Survey: association with symptoms, impairment, course and help-seeking. *Br J Psychiatry*. 2000;176(3):229–235.
9. McLaughlin TP, Khandker RK, Kruzikas DT, et al. Overlap of anxiety and depression in a managed care population: prevalence and association with resource utilization. *J Clin Psychiatry*. 2006;67(8):1187–1193.
10. Lecrubier Y, Weiller E. Comorbidities in social phobia. *Int Clin Psychopharmacol*. 1997;12(suppl 6):S17–S21.
11. Merikangas KR, Angst J. Comorbidity and social phobia: evidence from clinical, epidemiologic, and genetic studies. *Eur Arch Psychiatry Clin Neurosci*. 1995;244(6):297–303.
12. Erwin BA, Heimberg RG, Juster H, et al. Comorbid anxiety and mood disorders among persons with social anxiety disorder. *Behav Res Ther*. 2002;40(1):19–35.
13. de Graaf R, Bijl RV, Smit F, et al. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. *Am J Psychiatry*. 2002;159(4):620–629.
14. Hovens JG, Wiersma JE, Giltay EJ, et al. Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs controls. *Acta Psychiatr Scand*. 2010;122(1):66–74.
15. Blazer DG, Kessler RC, McGonagle KA, et al. The prevalence and distribution of major depression in a national community sample: the National Comorbidity Survey. *Am J Psychiatry*. 1994;151(7):979–986.
16. Weinstock LM, Whisman MA. Neuroticism as a common feature of the depressive and anxiety disorders: a test of the revised integrative hierarchical model in a national sample. *J Abnorm Psychol*. 2006;115(1):68–74.
17. Moffitt TE, Harrington H, Caspi A, et al. Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Arch Gen Psychiatry*. 2007;64(6):651–660.
18. Brown TA, Campbell LA, Lehman CL, et al. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *J Abnorm Psychol*. 2001;110(4):585–599.
19. Penninx BW, Beekman AT, Smit JH, et al; NESDA Research Consortium. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int J Methods Psychiatr Res*. 2008;17(3):121–140.
20. World Health Organisation. *Composite International Diagnostic Interview, Core Version 2.1: Interviewer's Manual*. Sidney, Australia: World Health Organisation; 1997.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
22. Wittchen HU. Reliability and validity studies of the WHO—Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res*. 1994;28(1):57–84.
23. Fyer AJ, Weissman MM. Genetic linkage study of panic: clinical methodology and description of pedigrees. *Am J Med Genet* 1999;88(2):173–181.
24. Wiersma JE, Hovens JG, van Oppen P, et al. The importance of childhood trauma and childhood life events for chronicity of depression in adults. *J Clin Psychiatry*. 2009;70(7):983–989.
25. Brugha T, Bebbington P, Tennant C, et al. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol Med*. 1985;15(1):189–194.
26. Costa PT Jr, McCrae RR. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. *J Pers Assess*. 1995;64(1):21–50.
27. Lyketsos CG, Nestadt G, Cwi J, et al. The life-chart method to describe the course of psychopathology. *Int J Methods Psychiatr Res*. 1994;4:143–155.
28. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996;26(3):477–486.
29. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol*. 1988;56(6):893–897.
30. Marks IM, Mathews AM. Brief standard self-rating for phobic patients. *Behav Res Ther*. 1979;17(3):263–267.
31. Kessler RC, Nelson CB, McGonagle KA, et al. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. *Br J Psychiatry Suppl*. 1996;(30):17–30.
32. Spinhoven P, de Rooij M, Heiser W, et al. The role of personality in comorbidity among anxiety and depressive disorders in primary care and specialty care: a cross-sectional analysis. *Gen Hosp Psychiatry*. 2009;31(5):470–477.
33. Kendler KS, Gardner CO, Gatz M, et al. The sources of co-morbidity between major depression and generalized anxiety disorder in a Swedish national twin sample. *Psychol Med*. 2007;37(3):453–462.
34. Bienvenu OJ, Brown C, Samuels JF, et al. Normal personality traits and comorbidity among phobic, panic and major depressive disorders. *Psychiatry Res*. 2001;102(1):73–85.
35. Khan AA, Jacobson KC, Gardner CO, et al. Personality and comorbidity of common psychiatric disorders. *Br J Psychiatry*. 2005;186(3):190–196.
36. Middeldorp CM, Cath DC, Van Dyck R, et al. The co-morbidity of anxiety and depression in the perspective of genetic epidemiology: a review of twin and family studies. *Psychol Med*. 2005;35(5):611–624.
37. Fava M, Rankin MA, Wright EC, et al. Anxiety disorders in major depression. *Compr Psychiatry*. 2000;41(2):97–102.
38. Lawrence AE, Liverant GI, Rosellini AJ, et al. Generalized anxiety disorder within the course of major depressive disorder: examining the utility of the DSM-IV hierarchy rule. *Depress Anxiety*. 2009;26(10):909–916.
39. Zimmerman M, Chelminski I. Generalized anxiety disorder in patients with major depression: is DSM-IV's hierarchy correct? *Am J Psychiatry*. 2003;160(3):504–512.
40. Rohde P, Lewinsohn PM, Seeley JR. Comorbidity of unipolar depression: II. Comorbidity with other mental disorders in adolescents and adults. *J Abnorm Psychol*. 1991;100(2):214–222.