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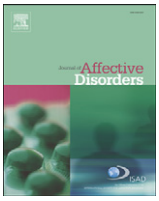

Research report

Clinical relevance of comorbidity in anxiety disorders: A report from the Netherlands Study of Depression and Anxiety (NESDA)

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ABSTRACT

Background: To study the clinical relevance of type of comorbidity and number of comorbid disorders in anxiety disorders. Four groups were compared according to sociodemographic-, vulnerability- and clinical factors: single anxiety disorder, anxiety–anxiety comorbidity, anxiety–depressive comorbidity and "double" comorbidity (i.e. anxiety and depressive comorbidity).
Methods: Data were obtained from the Netherlands Study of Anxiety and Depression (NESDA). A sample of 1004 participants with a current anxiety disorder was evaluated.
Results: As compared with single anxiety, anxiety–anxiety comorbidity was associated with higher severity, greater chronicity and more treatment. Anxiety–anxiety comorbidity was associated with an earlier age of onset and a more chronic course compared with anxiety–depressive comorbidity, while anxiety–depressive comorbidity was associated with more severe symptoms and more impaired functioning than anxiety–anxiety comorbidity. "Double" comorbidity was associated with higher severity, greater chronicity, more treatment and increased disability. Sociodemographic and vulnerability factors were comparable among the four groups.
Limitations
A prospective design would be more appropriate to study the outcome. In this study no distinction was made between whether depression or anxiety disorder preceded the current anxiety disorder.
Conclusions: It is clinical relevant to diagnose and treat comorbidity among anxiety disorders as it is associated with higher severity and more chronicity. Whereas anxiety–anxiety comorbidity has an earlier age of onset and a more chronic course, anxiety–depressive comorbidity leads to more treatment and impaired functioning. "Double" comorbidity leads to even more severity, chronicity and impairment functioning compared with both anxiety–anxiety and anxiety–depressive comorbidity.

1. Introduction

Comorbidity in anxiety disorders represents the rule rather than the exception. Lifetime comorbidity in patients with anxiety disorders occurs in more than 80% (Brown et al., 2001). The prevalence of having a current comorbid axis I disorder is

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estimated at 50%, with anxiety disorders and depressive disorders being the most prevalent comorbid disorders (Brown and Barlow, 1995; Brown et al., 2001).

Comorbidity between anxiety disorders and depressive disorders has been widely investigated. Anxiety–depressive comorbidity has been associated with sociodemographic factors such as female gender, not having a partner, lower socioeconomic status and lower educational level (Alonso et al., 2004; de Graaf et al., 2002; Fichter et al., 2010); with vulnerability factors such as parental psychiatric history, childhood trauma, negative life events and neuroticism (de Graaf et al., 2002); and with clinical factors including younger age of onset (Fichter et al., 2010), illness severity, poorer outcome (Angst and Vollrath, 1991; Merikangas et al., 2003; Rush et al., 2005), higher healthcare utilization (Kessler et al., 1994) and impaired functioning (Fichter et al., 2010; Kessler and Frank, 1997).

Although anxiety–anxiety comorbidity occurs as frequently as anxiety–depressive comorbidity, it has received surprisingly little attention to-date. Fragmentized research suggests that, compared with single anxiety disorders, patients with anxiety–anxiety comorbidity suffer from more severe anxiety symptoms (van Balkom et al., 2008). In addition, anxiety–anxiety comorbidity may be associated with lower levels of extraversion and higher levels of neuroticism (Chambers et al., 2004). Finally, individuals with anxiety–anxiety comorbidity more frequently report a history of childhood abuse (Cougle et al., 2010). However, anxiety–anxiety comorbidity may not be associated with lower levels of functioning compared with single anxiety disorders (Barrera and Norton, 2009; Grant et al., 2005; Norberg et al., 2008).

Given the lack of data regarding anxiety–anxiety comorbidity, further research is needed. It is important to determine whether it is clinically relevant to diagnose type of comorbidity and number of comorbid disorders in anxiety disorders so as to be able to identify patients at a high risk for developing a comorbid disorder and to direct treatment at the disorders present.

1.1. Aims of the study

Using data from the Netherlands Study of Anxiety and Depression (NESDA), the clinical relevance of (i) type of comorbidity and (ii) number of comorbid disorders in a clinical sample suffering from anxiety disorders was studied. Four groups were compared: single anxiety disorder, anxiety–anxiety comorbidity, anxiety–depressive comorbidity and "double" comorbidity (i.e. anxiety and depressive comorbidity). We investigated sociodemographics, vulnerability factors and clinical characteristics to determine whether:

1) anxiety–anxiety comorbidity differs from a single anxiety disorder
2) anxiety–anxiety comorbidity differs from anxiety–depressive comorbidity (type of comorbidity)
3) "double" comorbidity differs from anxiety–anxiety comorbidity and from anxiety–depressive comorbidity (number of comorbid disorders).

2. Methods

2.1. Procedure

Data were obtained from the Netherlands Study of Depression and Anxiety (NESDA). NESDA is a longitudinal cohort study including 2981 adults (18–65 years) with anxiety disorders (panic disorder with or without agoraphobia, social phobia, generalized anxiety disorder (GAD) and agoraphobia without a history of panic disorder) and/or depressive disorders (major depressive disorder, dysthymic disorder) and healthy controls. A detailed description of the NESDA study design can be found elsewhere (Penninx et al., 2008). In short: the NESDA study aims to describe the long-term course and consequences of depressive and anxiety disorders in a sample recruited from the community, primary care settings and specialized mental health care facilities. Specific phobias, post-traumatic stress disorders and obsessive–compulsive disorders were not assessed and were therefore not included in this study. Approval of the study was granted by the Ethical Review Boards of all the participating centers and written informed consent was obtained from all participants. For the present study we used data from the baseline interview, which included a 4-hour interview, a medical assessment, computer tasks and two self-administered questionnaires, all instruments were in Dutch.

2.2. Sample

Of the 2981 participants in the baseline interview, 1363 had had at least one 12-month anxiety disorder. To avoid the confounding of comorbid alcohol dependence, 279 participants with a 12-month diagnosis of alcohol dependence were excluded. Since our research questions regard both type and number of comorbid disorders, we formed four mutually exclusive groups based on those two aspects: participants with a single anxiety disorder, without a depressive disorder (29.4%, n = 295), with two anxiety disorders, without a depressive disorder (10.5%, n = 105), with one anxiety disorder and one depressive disorder (29.1%, n = 292) and with "double" comorbidity (i.e. two anxiety disorders and one or two depressive disorders, 31.1%, n = 312). In addition, 18 patients with three anxiety disorders were excluded, as well as 62 with one anxiety disorder and two depressive disorders. This resulted in a total sample size of 1004.

2.3. Assessment of psychopathology

To diagnose DSM-IV anxiety disorders and depressive disorders in the past 12 months, the Dutch version of the Composite International Diagnostic Interview (CIDI, version 2.1) was used as a baseline assessment. The CIDI is a valid and reliable instrument for axis I diagnoses (World Health Organization, 1997). The CIDI was conducted by trained research staff.

2.4. Correlates of comorbidity

Sociodemographic factors included gender (male/female), age (in years), education (in years) and partner status (present/absent).

Vulnerability factors included a family history of anxiety and depressive disorders, childhood trauma, negative life events and personality traits. A first-degree family history of anxiety and depressive disorders was assessed using the family tree method (Fyer and Weissman, 1999). Childhood trauma was assessed using the second section of the Childhood Trauma Interview previously used in the Netherlands Mental Health Survey and Incidence Study (NEMESIS, de Graaf et al., 2002). Childhood trauma was considered present in cases when participants experienced emotional neglect, psychological abuse or physical abuse on two or more occasions prior to age 16, or sexual abuse on one or more occasions prior to age 16. Negative life events in the past year were measured with the List of Threatening Experiences (Brugha et al., 1985). This list has good reliability and good validity (Brugha and Cragg, 1990). Finally, personality traits were measured with the 60-item NEO-FFI personality questionnaire, which uses 5 dimensions for personality: neuroticism, extraversion, openness, agreeableness and conscientiousness (Costa and MCCrae, 1995). This scale has proven to be reliable and valid (Costa and MCCrae, 1992).

Clinical characteristics included age of onset (in years), chronicity of symptoms (yes/no), severity of depressive, anxiety and avoidance symptoms (assessed as a continuous variable), treatment (yes/no) and disability (assessed as a continuous variable). Age of onset was determined with the CIDI, and the youngest age of onset was used in the case of comorbidity. The chronicity of symptoms was based on the Life Chart Interview (Lyketsos et al., 1994) in which the presence of anxiety and/or depressive symptoms was retrospectively assessed for the preceding 4 years. Symptoms were defined as chronic when they occurred during more than 50% of the months during the preceding 4 years. The Life Chart Interview has shown high validity and reliability (Warshaw et al., 1994). Receiving treatment was defined as having received antidepressant medication and/or psychotherapy. The use of antidepressant medication was determined on the basis of drug container inspection for all drugs used in the month before assessment. Use of antidepressants was considered positive when taken regularly (defined as more than 50% of the time/daily for at least 1 month); these included TCAs, SSRIs and SNRIs. Psychotherapy was defined as more than 5 contacts with a therapist during the past 6 months. A therapist could be a psychologist, psychiatrist, psychotherapist, social worker or social psychiatric nurse working in general health care or in specialized mental health care. The frequency of contacts with a therapist was assessed using the Tic-P (Hakkaart-van Roijen, 2002). This is a validated instrument assessing loss of productivity at work and health care utilization. The severity of anxiety symptoms was assessed with the Beck Anxiety Inventory (BAI, Beck et al., 1988). The BAI is a 21-item self-report list. It is widely used and has proven to be highly valid and reliable (Fydrich et al., 1992). The level of avoidance was measured with the Fear Questionnaire (FQ, Marks and Matthews, 1979), a 15-item self-report list measuring phobic symptoms that has been proven valid in a Dutch population (van Zuuren, 1988). To determine the severity of depressive symptoms the Inventory of Depressive Symptomatology (IDS, Rush et al., 1996) was used. This scale is a 30-item self-report list measuring depressive symptoms that has proven to be valid and reliable (Trivedi et al., 2004). Negative consequences in three domains (cognitive, physical and social disability) were measured with The World Health Organization Disability Assessment Schedule (WHODAS II). This is a 36-item instrument that examines disability in six domains of life during the past 30 days and has proven to be valid and reliable (Chwastiak and Von Kurff, 2003).

2.5. Statistical analyses

All statistical analyses were conducted with the SPSS statistical package version 15.0. As described above, the sample was divided into four mutually exclusive categories: participants with a single anxiety disorder, with anxiety-anxiety comorbidity, with anxiety–depressive comorbidity and with "double" comorbidity. Bivariate multinomial logistic regression analyses were conducted to examine the clinical factors of comorbidity. Dependent on the research question, different groups were taken as the reference group. Subsequently, risk-indicators (sociodemographics and vulnerability factors) were examined. Both bivariate and multivariate multinomial logistic regression analyses were conducted. In the multivariate model, we adjusted for all covariates that were significant in the bivariate analyses.

3. Results

3.1. Characteristics of the sample

The sociodemographics and clinical characteristics of the sample are presented in Table 1. The sample was predominantly female (72.1%). The mean age of onset was 20.9 years (SD: 12.3). Forty-five percent of the sample suffered from chronic symptoms and about half of the sample had received treatment (51.3%).

3.2. Anxiety–anxiety comorbidity

To investigate whether anxiety–anxiety comorbidity is associated with various clinical factors and various risk indicators compared with single anxiety disorders, participants

Table 1
Socio-demographic- and clinical characteristics of the sample (n = 1004).

	%	(n)
Female gender	72.1	(724)
Partner	66.7	(670)
Chronicity	45.3	(455)
Treatment	51.3	(515)
	Mean	**(SD)**
Age (years)	41.0	(12.6)
Education (years)	11.7	(3.2)
Age of onset (years)	20.9	(12.3)
Total IDS score	28.3	(12.6)
Total BAI score	17.7	(10.7)
Total FQ score	34.7	(20.1)
Cognitive disability	31.5	(20.9)
Physical disability	18.7	(21.7)
Social disability	32.8	(20.6)

IDS = Inventory of Depressive Symptomatology, BAI = Beck Anxiety Inventory, FQ = Fear Questionnaire.

with a single anxiety disorder (n = 295) were compared with those with anxiety–anxiety comorbidity (n = 105). The results are presented in Tables 2 and 3.

Participants with anxiety–anxiety comorbidity had an earlier age of onset than those with a single anxiety disorder (19.3 versus 23.0 years; OR: 0.73; 95%CI: 0.58–0.93) and a higher rate of chronicity (53.3% versus 32.2%; OR: 2.41; 95%CI: 1.53–3.79). Participants with anxiety–anxiety comorbidity experienced more severe depressive (OR: 1.52; 95%CI: 1.14–2.03), anxiety (OR: 1.58; 95%CI: 1.20–2.07) and avoidance symptoms (OR: 1.42; 95%CI: 1.10–1.82) than those with a single anxiety disorder. They experienced more social disability compared with participants with a single anxiety disorder (OR: 1.45; 95%CI: 1.16–1.98), but similar rates of cognitive and physical disability. Participants with anxiety–anxiety comorbidity did not receive significantly more treatment (40.0% versus 30.8%; OR: 1.50; 95%CI: 0.94–2.37).

Unadjusted bivariate analyses show that participants with anxiety–anxiety comorbidity more often had a positive family history of anxiety or depressive disorders (63.8% versus 46.4%) compared with participants with a single anxiety disorder. Those with anxiety–anxiety comorbidity had higher neuroticism levels and lower extraversion levels. The groups did not differ critically with respect to age at the baseline interview, childhood trauma, negative life events in the past year and personality traits other than neuroticism and extraversion. (Unadjusted statistics are not shown in the table.)

After adjusting for all covariates that were significant in the bivariate analyses, the higher rate of positive family history (OR: 2.07; 95%CI: 1.30–3.30) and the elevated neuroticism levels (OR: 1.51; 95%CI: 1.16–1.98) remained significant, whereas the lower levels of extraversion were no longer significant (OR: 0.83; 95%CI: 0.64–1.08).

3.3. Type of comorbidity

To investigate whether anxiety–anxiety comorbidity is different from anxiety–depressive comorbidity with regard to all of the aspects mentioned above, participants with anxiety–anxiety comorbidity (n = 105) were compared with participants with anxiety–depressive comorbidity (n = 292).

Participants with anxiety–anxiety comorbidity had an earlier age of onset than those with anxiety–depressive comorbidity (19.3 years versus 22.6 years; OR: 1.33; 95%CI: 1.05–1.68) and a higher rate of chronic anxiety or depressive symptoms (53.3% versus 41.4%; OR: 0.62; CI: 0.40–0.99). The severity of anxiety and avoidance symptoms did not significantly differ between the groups. The depressive symptoms were however more severe among those with anxiety–depressive comorbidity (OR: 2.09; 95%CI: 1.58–2.77). Those with anxiety–depressive comorbidity had received significantly more treatment (55.1% versus 40.0%; OR: 1.84; 95%CI: 1.17–2.90) and they also experienced more cognitive (OR: 1.88; 95%CI: 1.44–2.46), physical (OR: 1.34; 95%CI: 1.02–1.76) and social disability (OR: 1.46; 95%CI: 1.13–1.89).

Like the unadjusted analyses, adjusted analyses show that participants with anxiety–anxiety comorbidity more often had a positive family history for anxiety or depressive disorders (63.8% versus 45.9%; OR: 0.48; 95%CI: 0.30–0.76) and elevated conscientiousness scores (OR: 0.77; 95%CI:

Table 2
Clinical characteristics of anxiety–depressive comorbidity (n = 1004).

Group (total n = 1004)	1 Single anxiety disorder n = 295 (29.4%)	2 Anxiety–anxiety comorbidity n = 105 (10.5%)	3 Anxiety–depressive comorbidity n = 292 (29.1%)	4 Double comorbidity n = 312 (31.1%)	Comparison 1 vs 2 OR (95% CI)	2 vs 3 OR (95% CI)	2 vs 4 OR (95% CI)	3 vs 4 OR (95% CI)
Clinical characteristics								
Age of onset[a] (years, SD)	23.0 (12.8)	19.3 (11.5)	22.6 (12.3)	18.0 (11.3)	**0.73 (0.58–0.93)**	**1.33 (1.05–1.68)**	0.88 (0.67–1.12)	**0.66 (0.59–0.77)**
Chronicity (% with chronic anxiety or depressive symptoms, n)	32.2 (95)	53.3 (56)	41.4 (121)	58.7 (183)	**2.41 (1.53–3.97)**	**0.62 (0.40–0.99)**	1.24 (0.80–1.94)	**2.01 (1.45–2.77)**
Total IDS score[a] (mean, SD)	19.8 (9.0)	23.0 (9.6)	29.5 (10.8)	37.1 (11.8)	**1.52 (1.14–2.03)**	**2.09 (1.58–2.77)**	**4.52 (3.35–6.10)**	**2.16 (1.78–2.63)**
Total BAI score[a] (mean, SD)	12.9 (8.5)	16.0 (9.3)	16.8 (9.8)	23.8 (11.1)	**1.58 (1.20–2.07)**	1.09 (0.85–1.42)	**2.15 (1.66–2.78)**	**1.97 (1.65–2.35)**
Total FQ score[a] (mean, SD)	27.7 (18.3)	33.2 (17.5)	31.4 (18.1)	44.9 (20.4)	**1.42 (1.10–1.82)**	0.90 (0.70–1.15)	**1.80 (1.42–2.29)**	**2.01 (1.68–2.39)**
Treatment (% yes, n)	30.8 (91)	40.0 (42)	55.1 (161)	70.8 (221)	1.50 (0.94–2.37)	**1.84 (1.17–2.90)**	**3.64 (2.30–5.77)**	**1.98 (1.41–2.77)**
Cognitive disability[a] (mean, SD)	21.0 (18.3)	22.5 (17.5)	32.9 (19.1)	43.5 (19.2)	1.11 (0.85–1.46)	**1.88 (1.44–2.46)**	**3.28 (2.50–4.32)**	**1.74 (1.46–2.08)**
Physical disability[a] (mean, SD)	11.6 (16.6)	13.0 (18.4)	17.7 (20.6)	28.7 (24.3)	1.16 (0.86–1.55)	**1.34 (1.02–1.76)**	**2.11 (1.61–2.76)**	**1.58 (1.34–1.86)**
Social disability[a] (mean, SD)	21.5 (16.7)	27.3 (18.6)	33.5 (18.5)	44.9 (19.6)	**1.45 (1.16–1.98)**	**1.46 (1.13–1.89)**	**2.69 (2.07–3.50)**	**1.85 (1.54–2.10)**

IDS = Inventory of Depressive Symptomatology, BAI = Beck Anxiety Inventory, FQ = Fear Questionnaire.
OR; odds ratio, CI; confidence interval. P < 0.05 indicates bold data.
[a] OR per SD increase using multinomial logistic regression analyses.

Table 3
Risk indicators of anxiety–depressive comorbidity (n = 1004).

Group (total n = 1004)	1 Single anxiety disorder n = 295 (29.4%)	2 Anxiety anxiety comorbidity n = 105 (10.5%)	3 Anxiety depressive comorbidity n = 292 (29.1%)	4 Double comorbidity n = 312 (31.1%)	Comparison 1 vs 2 OR (95% CI)	2 vs 3 OR (95% CI)	2 vs 4 OR (95% CI)	3 vs 4 OR (95% CI)
Socio-demographic factors								
Age (years, SD)	42.4 (13.4)	40.0 (11.5)	40.1 (12.5)	40.9 (12.2)	0.99 (0.97–1.00)	1.00 (0.98–1.02)	1.01 (0.99–1.02)	1.00 (0.99–1.02)
Gender (% female, n)	70.8 (209)	71.4 (75)	73.6 (215)	72.1 (225)	1.03 (0.63–1.68)	1.12 (0.68–1.84)	1.03 (0.63–1.69)	0.93 (0.95–1.33)
Education (years, SD)	12.2 (3.3)	12.3 (3.0)	11.8 (3.2)	10.9 (3.2)	1.01 (0.95–1.08)	0.95 (0.89–1.02)	**0.91 (0.84–0.98)**	**0.78 (0.65–0.93)**
Partner (% yes, n)	67.8 (200)	64.8 (68)	67.5 (197)	65.7 (205)	0.87 (0.55–1.40)	1.13 (0.71–1.80)	1.04 (0.66–1.66)	0.92 (0.66–1.30)
Vulnerability factors								
Family history (% yes, n)	46.4 (137)	63.8 (67)	45.90 (134)	52.6 (164)	**2.07 (1.30–3.30)**	**0.48 (0.30–0.76)**	0.74 (0.46–1.20)	1.31 (0.95–1.80)
Childhood trauma (% yes, n)	42.4 (125)	40.0 (42)	51.0 (149)	59.3 (185)	0.91 (0.58–1.43)	1.56 (0.99–2.46)	1.50 (0.93–2.43)	1.09 (0.77–1.53)
Negative life events (number, SD)	0.6 (0.9)	0.5 (0.9)	0.8 (1.0)	0.80 (1.1)	0.91 (0.70–1.17)	1.23 (0.95–1.59)	1.30 (1.00–1.68)	1.05 (0.90–1.22)
Neuroticism[a] (total score, SD)	36.8 (7.3)	40.1 (7.1)	41.5 (6.3)	44.9 (5.9)	**1.51 (1.16–1.98)**	1.26 (0.98–1.60)	**1.86 (1.38–2.49)**	**1.60 (1.30–1.97)**
Extraversion[a] (total score, SD)	37.3 (6.4)	35.4 (6.3)	34.5 (6.3)	31.5 (6.3)	0.83 (0.63–1.08)	0.87 (0.69–1.10)	**0.67 (0.51–0.88)**	**0.70 (0.58–0.85)**
Openness[a] (total score, SD)	31.2 (5.4)	31.5 (5.8)	30.9 (5.1)	30.0 (5.5)	1.10 (0.90–1.34)	0.82 (0.68–1.00)	0.83 (0.67–1.03)	0.97 (0.86–1.11)
Agreeableness[a] (total score, SD)	43.9 (5.0)	44.1 (5.5)	43.0 (4.7)	2.1 (5.7)	1.05 (0.83–1.31)	0.80 (0.63–1.00)	0.85 (0.67–1.09)	0.87 (0.73–1.03)
Conscientiousness[a] (total score, SD)	37.9 (5.4)	37.1 (6.1)	35.7 (5.8)	37.9 (5.4)	0.91 (0.71–1.16)	**0.77 (0.62–0.97)**	1.01 (0.78–1.32)	0.91 (0.77–1.07)

OR; odds ratio, CI; confidence interval.
Mentioned OR are after adjustment for covariates. P < 0.05 indicates bold data.
[a] OR per SD increase using multinomial logistic regression analyses.

0.62–0.97). The other risk-indicators did not differ critically between both types of comorbidity.

3.4. Number of comorbid disorders

To investigate whether "double" comorbidity may be distinguished from anxiety–depressive comorbidity and anxiety–anxiety comorbidity, clinical factors and risk-indicators were compared. Both anxiety–anxiety comorbidity (n = 105) and anxiety–depressive comorbidity (n = 292) were compared with the group with double comorbidity (n = 312). The differences found are presented in Tables 2 and 3.

Compared with anxiety–anxiety comorbidity, "double" comorbidity was associated with more severe depressive (OR: 4.52; 95%CI: 3.35–6.10), anxiety (OR: 2.15; 95%CI: 1.66–2.78) and avoidance symptoms (OR: 1.80; 95%CI: 1.42–2.29). Participants with "double" comorbidity also received more treatment (70.8% versus 40.4%; OR: 3.64; 95%CI: 2.30–5.77) and experienced more disability in all domains compared with anxiety–anxiety comorbidity.

Compared with anxiety–depressive comorbidity, "double" comorbidity was associated with an earlier age of onset (18.0 versus 22.6 years; OR: 0.66; 95%CI: 0.59–0.77) and a higher rate of chronicity (58.7% versus 41.4%; OR: 2.01; 95%CI: 1.45–2.77). Those with "double" comorbidity experienced more severe depressive (OR: 2.16; 95%CI: 1.78–2.63), anxiety (OR: 1.97; 95%CI: 1.65–2.35) and avoidance symptoms (OR: 2.01; 95%CI: 1.68–2.39). They also received more treatment compared with those with anxiety–depressive comorbidity (70.8% versus 55.1%; OR: 1.98; 95%CI: 1.41–2.77) and experienced more disability in all domains.

The unadjusted bivariate models show that, compared with those with anxiety–anxiety comorbidity, participants with "double" comorbidity were less educated (10.9 versus 12.3 years) and were less likely to have a positive family history of anxiety or depressive disorders (52.6% versus 63.8%). They were more likely to have experienced childhood trauma (59.3% versus 40.4%) and negative life events in the past year (0.8 versus 0.5 negative life events). Those with "double" comorbidity had elevated neuroticism and conscientiousness levels and lower extraversion, openness and agreeableness levels. (Unadjusted statistics are not shown in the Table). After adjustment for all significant covariates in the bivariate model, the lower level of education (OR: 0.91; 95%CI: 0.84–0.98), higher neuroticism levels (OR: 1.86; 95%CI: 1.38–2.49) and lower extraversion scores (OR: 0.67; 95%CI: 0.51–0.88) remained significantly different between those with "double" comorbidity and those with anxiety–anxiety comorbidity.

Comparing participants with "double" comorbidity with those with anxiety–depressive comorbidity, unadjusted models show that those with "double" comorbidity were less educated (10.9 versus 11.8 years) and more likely to have experienced childhood trauma (59.3% versus 51.0%). They had elevated neuroticism levels and lower extraversion and openness levels. After adjustment for all significant covariates in the bivariate model, the lower level of education remained significantly different between those with "double" comorbidity and those with anxiety–depressive comorbidity (OR: 0.78; 95%CI: 0.65–0.93), as did the elevated neuroticism

levels (OR: 1.60; 95%CI: 1.30–1.97) and decreased extraversion levels (OR: 0.79; 95%CI: 0.58–0.85).

4. Discussion

4.1. Clinical characteristics of comorbidity

In a well-defined subsample of the NESDA study of 1004 participants with at least one anxiety disorder, the clinical relevance of comorbidity was studied. We may conclude that both the type of comorbidity and the number of comorbid disorders are clinically important to diagnose.

Anxiety–anxiety comorbidity was associated with more severe clinical characteristics compared with a single anxiety disorder. Patients with anxiety–anxiety comorbidity experienced more severe symptoms, more chronic symptoms and more social impairment. It should be noted that in anxiety–anxiety comorbidity, not only anxiety symptoms were more severe, depressive symptoms were also more severe. These findings confirm an earlier finding of an association between anxiety–anxiety comorbidity and severity of symptoms (Cougle et al., 2010). The finding that anxiety–anxiety comorbidity is associated with more social impairment contradicts earlier research that could not find an association between the number of anxiety disorders and the quality of life (Barrera and Norton, 2009; Grant et al., 2005; Norberg et al., 2008).

Anxiety–anxiety comorbidity was associated with critically different clinical factors compared with anxiety–depression comorbidity: The course of anxiety–anxiety comorbidity was worse than the course of anxiety–depressive comorbidity, with an earlier age of onset and more chronicity. Anxiety–depressive comorbidity, however, is associated with more treatment and higher levels of disability. These results suggest that the type of comorbidity is important to diagnose, because it differentiates anxiety–anxiety comorbidity from anxiety–depressive comorbidity: the first type is more chronic, the second type is more invalidating. “Double” comorbidity in anxiety disorders appeared to lead to more severe symptoms, more treatment and more day-to-day impairment compared with anxiety–anxiety comorbidity or anxiety–depressive comorbidity. This indicates that the number of diagnoses present is related to severity, use of health care and negative consequences.

4.2. Sociodemographics and vulnerability factors of comorbidity

After adjusting for covariates, this study found that neuroticism is the most consistent risk-indicator associated with comorbidity in anxiety disorders. Neuroticism was lowest in patients with a single anxiety disorder, higher in patients with anxiety–anxiety comorbidity and anxiety–depressive comorbidity and highest in those with double comorbidity. This finding may not be specific for anxiety disorders but may reflect general vulnerability given that more psychiatric disorders are associated with high neuroticism (Cox et al., 2004; Enns and Cox, 1997; van Os and Jones, 2001). Ormel et al. (2004) argue that the association of neuroticism and psychopathology is tautological, since neuroticism reflects the presence of subthreshold anxiety and depressed feelings over a period of time, which obviously predict the development of an anxiety or depressive disorder.

4.3. Limitations and strengths

Several strengths and limitations should be taken into account. Strengths include the large sample size, the well-implemented design of the NESDA study and the use of the CIDI as a diagnostic instrument safeguarding statistical power and the reliability of results. Limitations include the cross-sectional design. A prospective design would be more appropriate to study the outcome. Another potential limitation of this study is Post Traumatic Stress Disorder, Obsessive–Compulsive Disorder and Specific Phobia were not assessed in the NESDA study. Moreover, the single anxiety disorders that were assessed were collapsed into one group to achieve sufficient statistical power. If these disorders had had different sociodemographics, vulnerability factors or clinical characteristics, analyzing anxiety disorders as one group could have resulted in a bias. Therefore, we have compared the specific anxiety disorders with each other (data not shown). All anxiety disorders appeared to be similar. Based on this, we feel it is justified to examine anxiety disorders as one group. Finally, in this study no distinction was made between whether depression or anxiety disorder preceded the current anxiety disorder, thus hampering establishment of whether or not comorbid depression might be secondary to the anxiety disorder. However, a recent study (Lamers et al., 2011) found no differences in clinical characteristics between comorbidity with preceding depression and comorbidity with preceding anxiety.

5. Conclusion

This study adds to current knowledge on comorbidity in anxiety disorders. Its results clearly showed that it is important to diagnose comorbidity among anxiety disorders as it is associated with higher severity and more chronicity compared with single anxiety disorders. In addition, it is also important to distinguish the type and number of comorbid disorders: Whereas anxiety–anxiety comorbidity has an earlier age of onset and a more chronic course, anxiety–depressive comorbidity leads to more treatment and impaired functioning. Furthermore, “double” comorbidity leads to even more severity, chronicity and impairment compared with both anxiety–anxiety and anxiety–depressive comorbidity. These findings indicate that in clinical practice all comorbid disorders present in patients with an anxiety disorder should be diagnosed. Given the more severe symptomatology, unfavorable course and impaired functioning, patients with an anxiety disorder and comorbid anxiety and depressive symptoms should receive prompt and adequate treatment.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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References

Alonso, J., Angermeyer, M.C., Bernert, S., Bruffaerts, R., Brugha, T.S., Bryson, H., de Girolamo, G., Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J.M., Katz, S.J., Kessler, R.C., Kovess, V., Lépine, J.P., Ormel, J., Polidori, G., Russo, L.J., Vilagut, G., Almansa, J., Arbabzadeh-Bouchez, S., Autonell, J., Bernal, M., Buist-Bouwman, M.A., Codony, M., Domingo-Salvany, A., Ferrer, M., Joo, S.S., Martínez-Alonso, M., Matschinger, H., Mazzi, F., Morgan, Z., Morosini, P., Palacín, C., Romera, B., Taub, N., Vollebergh, W.A., 2004. 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatrica Scandinavica. Supplementum 420, 28–37.

Angst, J., Vollrath, M., 1991. The natural history of anxiety disorders. Acta Psychiatrica Scandinavica 84, 446–452.

Barrera, T.L., Norton, P.J., 2009. Quality of life impairment in generalized anxiety disorder, social phobia and panic disorder. Journal of Anxiety Disorders 23 1086-1080.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. Journal of Consulting and Clinical Psychology 56, 893–897.

Brown, T.A., Barlow, D.H., 1995. Comorbidity among anxiety and mood disorders: implications for treatment and DSM-IV. Journal of Consulting and Clinical Psychology 63, 408–441.

Brown, T.A., Campbell, L.A., Lehman, C.L., Grisham, J.R., Mancill, R.B., 2001. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. Journal of Abnormal Psychology 110, 585–599.

Brugha, T., Cragg, D., 1990. The list of threatening experiences: the reliability and validity of a brief live events questionnaire. Acta Psychiatrica Scandinavica 82, 77–81.

Brugha, T., Bebbington, P., Tennant, C., Hurry, J., 1985. The list of threatening experiences: a subset of 12 life event categories with considerable long-term contextual threat. Psychological Medicine 15, 189–194.

Chambers, J.A., Power, K.G., Durham, R.C., 2004. The relationship between trait vulnerability and anxiety and depressive diagnoses at long-term follow-up of Generalized Anxiety Disorder. Journal of Anxiety Disorders 18, 587–607.

Chwastiak, L.A., Von Kurff, M., 2003. Disability in depression and back pain: evaluation of the World Health Organization Disability Assessment Schedule (WHO DAS II) in a primary care setting. Journal of Clinical Epidemiology 56, 507–514.

Costa, P.T., McCrae, R.R., 1992. Revised NEO. Personality Inventory (NEO-PR-I) and the Five Factor Inventory (NEO-FFI): Professional Manual. Psychological Assessment Resources, Odessa, FL.

Costa, P.T., McCrae, R.R., 1995. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. Journal of Personality Assessment 64, 21–50.

Cougle, J.R., Timpano, K.R., Sachs-Ericsson, N., Keough, M.E., Riccardi, C.J., 2010. Examining the unique relationship between anxiety disorders and childhood physical and sexual abuse in the National Comorbidity Survey-Replication. Psychiatry Research 177, 150–155.

Cox, B.J., MacPherson, P.S., Enns, M.W., McWilliams, L.A., 2004. Neuroticism and self-criticism associated with posttraumatic stress disorder in a nationally representative sample. Behaviour Research and Therapy 42, 105–114.

De Graaf, R., Bijl, R.V., Smit, F., Vollebergh, W.A., Spijker, J., 2002. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. The American Journal of Psychiatry 159, 620–629.

Enns, M.W., Cox, B.J., 1997. Personality dimensions and depression: review and commentary. Canadian Journal of Psychiatry 42, 274–284.

Fichter, M.M., Quadflieg, N., Fischer, U.C., Kohlboeck, G., 2010. Twenty-five-year course and outcome in anxiety and depression in the Upper Bavarian Longitudinal Community Study. Acta Psychiatrica Scandinavica 122, 75–85.

Fydrich, T., Dowdall, D., Chambless, D.L., 1992. Reliability and validity of the Beck Anxiety Inventory. Journal of Anxiety Disorders 6, 55–61.

Fyer, A.J., Weissman, M.M., 1999. Genetic linkage study of panic: clinical methodology and description of pedigrees. American Journal of Medical Genetics 88, 173–181.

Grant, B.F., Hasin, D.S., Stinson, F.S., Dawson, D.A., June Ruan, W., Goldstein, R.B., Smith, S.M., Saha, T.D., Huang, B., 2005. Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Psychological Medicine 35, 1747–1759.

Hakkaart-van Roijen, L., 2002. Trimbos/iMTA questionnaire for costs associated with psychiatric illness (TIC-P). Institute for Medical Technology Assessment, Rotterdam.

Kessler, R.C., Frank, R.G., 1997. The impact of psychiatric disorders on work loss days. Psychological Medicine 27, 861–873.

Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.U., Kendler, K.S., 1994. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Archives of General Psychiatry 51, 8–19.

Lamers, F., Van Oppen, P., Comijs, H.C., Spinhoven, P., Van Balkom, A.J., Nolen, W.A., Zitman, F.G., Beekman, A.T., Penninx, B.W., 2011. Comorbidity patterns of anxiety and depressive disorders in a large cohort study. The Journal of Clinical Psychiatry 72, 341–348.

Lyketsos, C.G., Nestadt, G., Cwi, J., 1994. The life chart interview: a standarized method to describe the course of psychopathology. International Journal of Methods in Psychiatric Research 4, 143–155.

Marks, I.M., Matthews, A.M., 1979. Brief standard self-rating for phobic patients. Behaviour Research and Therapy 17, 263–267.

Merikangas, K.E., Zhang, H., Avenevoli, S., Acharyya, S., Neuenschwander, M., Angst, J., 2003. Longitudinal trajectories of depression and anxiety in a prospective community study. The Zurich cohort study. Archives of General Psychiatry 60, 993–1000.

Norberg, M.M., Diefenbach, G.J., Tolin, D.F., 2008. Quality of life and anxiety and depressive disorder comorbidity. Journal of Anxiety Disorders 22, 1516–1522.

Ormel, J., Rosmalen, J., Farmer, A., 2004. Neuroticism: a non-informative marker of vulnerability to psychopathology. Social Psychiatry and Psychiatric Epidemiology 39, 906–912.

Penninx, B.W., Beekman, A.T., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., De Jong, P.J., Van Marwijk, H.W., Assendelft, W.J., Van Der Meer, K., Verhaak, P., Wensing, M., De Graaf, R., Hoogendijk, W.J., Ormel, J., Van Dyck, R., 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. International Journal of Methods in Psychiatric Research 17, 121–140.

Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychological Medicine 26, 477–486.

Rush, A.J., Zimmerman, M., Wisniewski, S.R., Fava, M., Hollon, S.D., Warden, D., Biggs, M.M., Shores-Wilson, K., Shelton, R.C., Luther, J.F., Thomas, B., Trivedi, M.H., 2005. Comorbid psychiatric disorders in depressed outpatients: demographic and clinical features. Journal of Affective Disorders 87, 43–55.

Trivedi, M.H., Rush, A.J., Ibrahim, H.M., Carmody, T.J., Biggs, M.M., Suppes, T., Crismon, M.L., Shores-Wilson, K., Toprac, M.G., Dennehy, E.B., Witte, B., Kashner, T.M., 2004. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychological Medicine 34, 73–82.

Van Balkom, A.J., Boeijen, C.A., Van Boeke, A.J., Van Oppen, P., Kempe, P.T., Van Dyck, R., 2008. Comorbid depression, but not comorbid anxiety disorders, predicts poor outcome in anxiety disorders. Depression and Anxiety 25, 408–415.

Van Os, J., Jones, P.B., 2001. Neuroticism as a risk factor for schizophrenia. Psychological Medicine 31, 1129–1134.

Van Zuuren, F.J., 1988. The fear questionnaire. Some data on validity, reliability and layout. British Journal of Psychiatry 153, 659–662.

Warshaw, M.G., Keller, M.B., Stout, R.L., 1994. Reliability and validity of the longitudinal interval follow-up evaluation for assessing outcome of anxiety disorders. Journal of Psychiatric Research 28, 531–545.

World Health Organization, 1997. Composite International Diagnostic Interview (CIDI): version 2.1. Geneva, Switzerland.