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Review article

Depressive and anxiety disorders in concert–A synthesis of findings on comorbidity in the NESDA study

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ABSTRACT

Background: Comorbidity of depressive and anxiety disorders is common and remains incompletely comprehended. This paper summarizes findings from the Netherlands Study of Depression and Anxiety (NESDA) regarding prevalence, temporal sequence, course and longitudinal patterns; sociodemographic, vulnerability and neurobiological indicators; and functional, somatic and mental health indicators of comorbidity.
Methods: Narrative synthesis of earlier NESDA based papers on comorbidity (n=76).
Results: Comorbidity was the rule in over three-quarter of subjects with depressive and/or anxiety disorders, most often preceded by an anxiety disorder. Higher severity and chronicity characterized a poorer comorbidity course. Over time, transitions between depressive and anxiety disorders were common. Consistent comorbidity risk indicators in subjects with depressive and anxiety disorders were childhood trauma, neuroticism and early age of onset. Psychological vulnerabilities, such as trait avoidance tendencies, were more pronounced in comorbid than in single disorders. In general, there were few differences in biological markers and neuroimaging findings between persons with comorbid versus single disorders. Most functional, somatic, and other mental health indicators, ranging from disability to cardiovascular and psychiatric multimorbidity, were highest in comorbid disorders.
Limitations: The observational design of NESDA limits causal inference. Attrition was higher in comorbid relative to single disorders.
Conclusions: As compared to single disorders, persons with comorbid depressive and anxiety disorders were characterized by more psychosocial risk determinants, more somatic and other psychiatric morbidities, more functional impairments, and poorer outcome. These results justify specific attention for comorbidity of depressive and anxiety disorders, particularly in treatment settings.

1. Introduction

In psychiatry, comorbidity is a common and pervasive phenomenon that generally occurs at a higher rate than expected by coincidence (Plana-Ripoll et al., 2019). Several epidemiological studies worldwide have reported that among those with at least one index psychiatric diagnosis, 46% to 54% have one or more additional lifetime disorder(s) (Andrews et al., 2009; Kessler et al., 1994). The most common psychiatric comorbidity is the co-occurrence of depressive and anxiety disorders (De Graaf et al., 2002; Gorman, 1996; Kroenke et al., 2007) which has a major negative individual and societal impact in terms of course, outcome, and societal cost (Bijl and Ravelli, 2000; Fichter et al., 2010; Gorman, 1996; Kroenke et al., 2007). Not surprisingly, this particular comorbidity has been the subject of many studies in the past decades.

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The high prevalence and the large impact of the comorbidity of depressive and anxiety disorders translated into the key rationale of the design of the Netherlands Study of Depression and Anxiety (NESDA), to study depressive and anxiety disorders in concert (Penninx et al., 2008). Simultaneous research is implicated for many reasons. For health care, important research goals are to better inform patients with a comorbid condition about prognosis, course, and outcome, and to identify possible targets to tailor and improve treatment. This is relevant because it is well established that the mere diagnostic categories do not adequately predict clinical course, nor do they effectively guide and predict treatment response (Beekman et al., 2012).

Another reason for investigating both disorders in concert, is to further advance our understanding of risk factors (Kendler, 2019) and possible etiological pathways to the comorbidity of depressive and anxiety disorders. Little is known about the unique contribution of risk indicators to comorbidity, as most etiological studies did not distinguish comorbid from single depressive and/or anxiety disorders. More insight into shared and unique etiological factors of comorbidity may help to understand how comorbidity evolves and why the impact of comorbidity is so detrimental when compared to the impact of single conditions.

Finally, simultaneous investigation may aid our understanding of whether depressive and anxiety disorders are conceptually different or similar. Overlapping risk indicators of depressive and anxiety disorders have clearly been demonstrated in genetic (Anttila et al., 2018; Wray et al., 2018) and environmental (De Graaf et al., 2002) domains, and it is well established that depressive and anxiety symptoms and syndromes overlap (Gorman, 1996). These findings suggest that the current clinical diagnostic boundaries of depressive or anxiety disorders may not be reflected by distinctive etiological pathways. Also in clinical practice, depressive and anxiety disorders do not adhere to these diagnostic borders. Such etiological and symptomatic overlap could be conceived as a side-effect of the categorical approach instead of the more fitting dimensional approach (Brown and Barlow, 2009; Schoevers et al., 2003). Research into risk indicators and outcome, while delineating comorbidity form single depressive or anxiety disorders, is relevant to further advance this conceptual understanding.

In the past years, various NESDA papers have provided information on the prevalence, etiology, and consequences of comorbid depressive and anxiety disorders, that could contribute to clarify aforementioned clinical and scientific issues. This paper aims to provide a comprehensive overview of NESDA findings on the comorbidity of depressive and anxiety disorders. For this purpose, findings of NESDA will be summarized regarding prevalence, course, temporal patterns, risk indicators and consequences of comorbidity. Findings will subsequently be discussed and translated into implications for clinical practice.

2. Methods

2.1. Search strategy

For the current narrative synthesis (Green et al., 2006) we searched all published empirical papers in the NESDA database (www.nesda.nl) that were based on NESDA data from the first publication in September 2008 (Penninx et al., 2008) to September 2020. We focused on comorbidity defined as the presence of a DSM-IV defined depressive disorder and an anxiety disorder within a certain timeframe (Van den Akker et al., 1996). This diagnosis timeframe varied in NESDA from either lifetime prevalence to a more limited timeframe such as 1-month recency. Inclusion criteria for this narrative synthesis were all empirical studies a) that compared in a case-control design the comorbid depressive and anxiety disorder group and at least one of the two single disorder groups (only depressive or only anxiety disorders) with a control group without depressive and/or anxiety disorders; or that compared in a within-patient design the comorbid group directly to single depressive or anxiety disorder groups; b) on results falling into any of the following three research themes: 1. Prevalence, temporal sequence, course, and longitudinal patterns of comorbidity; 2. sociodemographic, vulnerability, and neurobiological indicators of comorbidity; and 3. functional, somatic, and other mental health indicators of comorbidity.

2.2. Study sample and depressive and/or anxiety diagnosis

NESDA is a longitudinal cohort study, consisting of 2981 persons (aged 18-65 years) at baseline, including controls (22%) and persons with a lifetime diagnosis of anxiety and/or depressive disorders (78%). Participants were recruited from the community (19%), primary care (54%), and specialized mental health settings (27%). This sampling frame was designed to represent the various developmental stages of depressive and anxiety disorders. Baseline data were collected between September 2004 and February 2007 and follow-up assessments took place at baseline, and after 2, 4, 6 and 9 years. Not being fluent in Dutch was a baseline exclusion criterium, as well as the presence of a primary other clinical diagnosis such as severe substance use disorder, obsessive compulsive disorder, posttraumatic stress disorder, or psychotic disorder. A detailed description of the NESDA study design can be found elsewhere (Penninx et al., 2008). In short, assessments consisted of an extensive face-to-face interview by trained interviewers, including paper-and-pencil questionnaires and a diagnostic psychiatric interview with the Composite International Diagnostic Interview (CIDI; version 2.1 (Wittchen, 1994)), which classifies diagnoses hierarchy-free and according to the DSM-IV criteria of the American Psychiatric Association. In NESDA, the assessed diagnoses among depressive disorders were major depressive disorder (MDD) and dysthymia; and among anxiety disorders were generalized anxiety disorder (GAD), agoraphobia, social phobia, and panic disorder. Additionally, specific disorder characteristics such as recency and age of onset were available. NESDA was approved centrally by the Ethical Review Board of the VU University Medical Centre and subsequently by the local review boards of each participating center, and all participants signed written informed consent.

2.3. Outcome measures

The instruments that were used to assess sociodemographic and vulnerability indicators are listed in supplementary table 1 (S1); and the instruments for assessing functional, somatic, and other mental health indicators can be found in supplementary table 2 (S2). Neurobiological indicators in NESDA relevant to this paper covered biological markers from blood or saliva, and neuroimaging data, also listed in S1. Temporal patterns of depressive and/or anxiety disorders in NESDA were described by the presence or absence of a current CIDI diagnosis at follow-up waves. Course variables such as remission, recurrence, or incidence were also derived from the CIDI. Severity of depressive symptoms was assessed by the 30-item Inventory of Depressive Symptomatology (IDS, (Rush et al., 1996)). Severity of anxiety symptoms was measured with the 21-item Beck Anxiety Inventory (BAI, (Beck et al., 1988)) and the 15-item Fear Questionnaire (Marks and Mathews, 1979). In those subjects with depressive or anxiety symptoms on the CIDI, the Life Chart Interview (LCI; Lyketsos et al., 1994) assessed the percent of time spent with these symptoms during the period between assessments, as well as the severity of these symptoms, ranging from minimal to very severe. In NESDA, duration of symptoms was operationalized as the percentage of months between two assessments with depressive or anxiety symptoms of at least mild severity. Based on a combination of the LCI and CIDI, other course indicators were created such as time to remission or to recurrence of an index disorder. Chronicity refers to those without remission on both LCI and CIDI for at least 2 years.

3. Results

3.1. Study selection

Among the total of 76 empirical articles that met inclusion criteria, 13 partially overlapping articles covered prevalence and temporal sequence (n=1), course (n=12), and longitudinal patterns (n=4) of comorbidity. One of these and 33 other articles – listed in S1- described sociodemographic and vulnerability indicators (n=11) and neurobiological indicators (n=23) of comorbidity. Another 30 partially overlapping articles – summarized in S2 - focused on functional (n=7), somatic (n=16) and other mental health (n=8) indicators of comorbidity.

3.2. Prevalence and temporal sequence

Among NESDA respondents with current depressive and/or anxiety disorders at baseline (n=1783), comorbidity of both disorders was the rule rather than the exception (Lamers et al., 2011b). Fig. 1 shows that the large majority of those with a current depressive disorder met criteria for a comorbid current (68%) or lifetime (75%) anxiety disorder, while subjects with a current anxiety disorder frequently had a comorbid current (63%) or lifetime (81%) depressive disorder. Fifty percent of those with depressive and anxiety comorbidity had a total of two disorders, while the other 50% had three or more depressive and/or anxiety disorders. The upper column chart in Fig. 1 shows that in current depressive disorders the most frequent comorbid anxiety disorders were panic disorder and social phobia, while agoraphobia was least frequent. The bottom column chart shows that MDD was more often comorbid than dysthymia among current anxiety disorders. Across the separate depressive disorders, anxiety disorders were not evenly distributed: both current and lifetime anxiety disorders co-occurred more often in dysthymia (77% current anxiety and 84% lifetime) than in MDD (67% and 75%). Likewise, comorbidity rates of depressive disorders varied considerably across the separate anxiety disorders: highest rates of current and lifetime comorbid depression occurred in GAD (78% current depression and 88% lifetime) and lowest but still considerable rates in agoraphobia (54% and 78%).

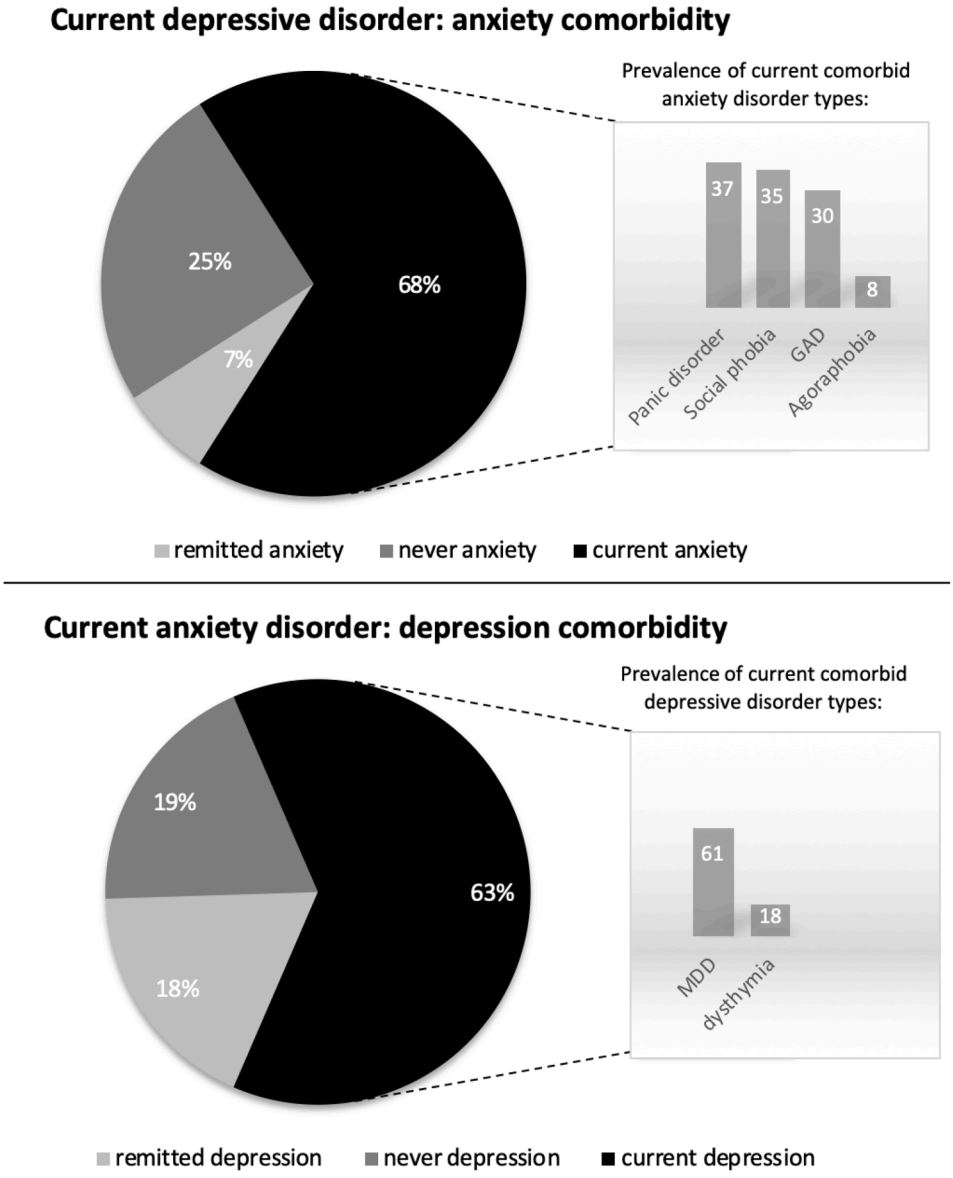

Fig. 1. Comorbidity patterns among those with current (12-month) depressive (upper pie chart; n=1275) and current anxiety (bottom pie chart; n=1363) disorders in NESDA at baseline. The column charts at the right show the type and percentage of anxiety comorbidity in depressive disorders (upper column chart); and of depressive comorbidity in anxiety disorders (bottom column chart; data based on (Lamers et al., 2011b)).

Temporal sequencing showed that the lifetime temporal order of comorbid depressive and anxiety disorders does not occur randomly, but with a clear tendency for anxiety disorders to occur first. Anxiety disorders were more likely to precede depressive disorders (57% of comorbid cases) than the reverse (18%), while in the remaining 25% both conditions had originated simultaneously within the same year (Lamers et al., 2011b). Among the single depressive and anxiety disorders, social phobia most frequently occurred as a primary condition: in 67% of those with social phobia, the condition occurred prior to the onset of a depressive disorder, at a mean age of onset of 17.7 years. Among dysthymia, the onset of dysthymia occurred most frequently (65%, mean age 29.7 years) after to the onset of an anxiety disorder, while the onset of GAD most often (41%, mean age 28.3 years) occurred simultaneously with the onset of a depressive disorder (Lamers et al., 2011b).

3.3. Course

The comorbidity of depressive and anxiety disorders in NESDA coincided with a range of adverse clinical outcomes. Cross-sectionally, those with current comorbidity compared to single depressive or anxiety disorders experienced higher ratings of both depressive and anxiety symptom scores, and had longer symptom duration over the past 4 years (Lamers et al., 2011b; Penninx et al., 2011), independent of sociodemographic and vulnerability risk factors (Lamers et al., 2011b). Subjects with current depressive disorder with versus without comorbid current anxiety disorders had a longer duration of depressive episodes (ten Have et al., 2017) and more chronicity (van Eeden et al., 2019).

Longitudinal course was considerably poorer for comorbid patients compared to those with single disorders, as exemplified by the course indicators in Fig. 2. Fig. 2 shows more chronicity after 2 years, a lower likelihood of having no current diagnosis after 2 years, and more symptomatic time over 2 years in comorbidity (Penninx et al., 2011). In addition, while comorbid patients and the single disorders had rather comparable rates of first remission and recurrence over 2 years, the median time to first remission was longer for comorbid subjects (Penninx et al., 2011). In a subset of n=303 subjects who were initially recruited in another cohort and followed-up through NESDA, those with comorbidity were more likely to have a depressive and/or anxiety diagnosis after 7 years (OR=2.34, 95%CI=1.23–4.46) than those with single depressive disorders (reference group) or those with single anxiety disorders (OR=1.85, 95%CI=1.04–3.27; (Rhebergen et al., 2011)).

Among those with initially remitted depressive and/or anxiety disorders, recurrence over 4 years was more common among remitted comorbid than remitted single disorder groups (Scholten et al., 2016). In those with current MDD, comorbid anxiety disorders also predicted poorer remission and higher severity of MDD after 1 year (Lamers et al., 2011a), and more chronicity after 2 (Gaspersz et al., 2017) and 4 years

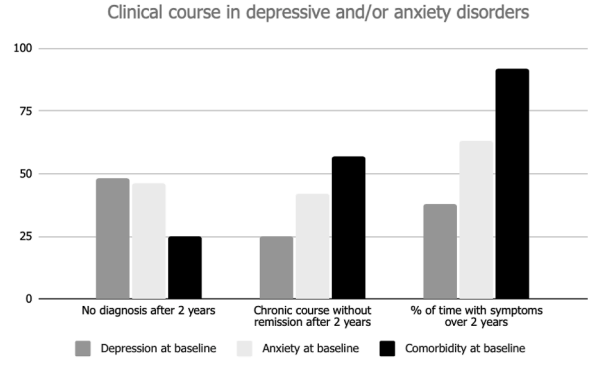

Fig. 2. Clinical course indicators over 2 years in n=1209 subjects with current (1-month recency) single depressive (dark grey; n=267), single anxiety (light grey; n=487) or comorbid disorders (black; n=455) at baseline (data based on (Penninx et al., 2011)).

(Boschloo et al., 2014). Likewise, in those with current anxiety disorders, comorbid depressive disorders predicted more chronicity of anxiety after 2 years (Batelaan et al., 2014), while this comorbidity predicted recurrence over 2 years in those with previously remitted anxiety disorders (Scholten et al., 2013). From the perspective of staging of psychiatric disorders (Fava and Kellner, 1993), NESDA analyses by Bokma et al. (2020) indicated that comorbidity affects the psychiatric outcome in progressed as well as in earlier disease stages. In their heuristic model of staging of anxiety disorders, comorbidity with versus without depressive disorders showed a worse 2-, 4- and 6-year longitudinal course across all clinical stages of anxiety (Bokma et al., 2020).

The adverse course of comorbid disorders raises the question whether all comorbidity is the same, or whether certain clinical features are indicative of differential outcome trajectories. In NESDA, a cross-sectional study by Klein Hofmeijer-Sevink et al. (2012) showed that comorbid subjects with a higher number of depressive and anxiety disorders had more chronicity and more severe depressive and anxiety symptoms. Lamers et al. (2011b) compared comorbid subjects who had experienced depression as the first lifetime disorder to those who had an anxiety disorder as the first lifetime disorder. Comorbidity with first-onset anxiety differed from comorbidity with first-onset depression, by a longer duration of depressive and/or anxiety symptoms, earlier age at first onset, and more fear symptoms (Lamers et al., 2011b). The clinical relevance of these findings seems modest as no differences were present in other course indicators such as symptom severity or age of onset.

3.4. Longitudinal patterns

Comorbidity is not only an important determinant of a poorer clinical course in depressive and anxiety disorders, it also deserves attention *during* the course of specific disorders. A general assumption about depressive or anxiety disorders is that most persons remit while a substantial minority persists (Richards, 2011). However, it is a limited focus to only evaluate the course of the index disorder without considering comorbidity as part of the overall outcome. For example, Penninx et al. (2011) demonstrated that 24% of those with an initial single depressive disorder developed a *de novo* anxiety disorder over the course of 2 years. Of these 24%, 8% transited to anxiety without current depressive disorders while 16% developed current comorbidity of depressive and anxiety disorders. Likewise, 23% of those with an initial single anxiety disorder developed a *de novo* depressive disorder over 2 years, consisting of 7% who transited to current depressive without current anxiety disorders and 16% who developed current comorbidity (Penninx et al., 2011). A similar picture, of either transitions or extension of depressive or anxiety disorders beyond their original diagnostic boundaries occurred after 4 and 6 years of follow-up among those with lifetime depressive and/or anxiety disorders (Hovenkamp-Hermelink et al., 2016; Scholten et al., 2016).

Another approach to gain a more ecologically valid temporal picture of depressive and anxiety disorders was taken in a prospective study into the 2-6 year course of MDD (Verduijn et al., 2017b). Psychiatric outcome was first narrowly defined as the remission versus chronicity/recurrence of MDD, and second more broadly as the remission versus chronicity/recurrence of all related mood disorders, not just including MDD only but also dysthymia, incident bipolar disorders and anxiety disorders. Duration of follow-up was either short (2 years) or long (6 years). With the narrow, short perspective, a majority of 58% of the n=903 MDD patients remitted, and 21% had a chronic episode (consecutive symptoms for at least two years). By contrast, in the long, and broader outcome perspective the remission rate was reduced to 17%, while 55% of the patients experienced chronic episodes. Thus, remission rates were considerably lower and chronicity was common when follow-up was longer and comorbidity was considered as part of the depression course pattern. In conclusion, the conception of an episodic (Posternak et al., 2006) and fairly favorable (Richards, 2011)

course of depressive and anxiety disorders should be attenuated, as depressive and anxiety disorders seem to wax and wane or persist, and switching between the two disorders is common.

3.5. Sociodemographic and vulnerability indicators

In NESDA, sociodemographic and vulnerability risk indicators of comorbidity compared to single disorders were lower educational level, a positive first-degree family history for depressive and/or anxiety disorders, several personality traits (higher neuroticism, lower extraversion, agreeableness and conscientiousness), and earlier age of onset (Lamers et al., 2011b). Gender, age, ethnicity, partner status, and life events were not further discriminating comorbid versus single disorders. To account for the interplay of sociodemographic with vulnerability correlates, these indicators were first investigated together which showed that lower educational level, childhood trauma, higher neuroticism, lower extraversion and earlier age of onset remained as sociodemographic and vulnerability risk indicators of comorbidity. To further consider the interplay of these sociodemographic and vulnerability correlates with clinical characteristics (recruitment setting, age of onset, duration and severity of symptoms), all these indicators were investigated in concert in adjusted analyses. These adjusted analyses showed that childhood trauma, higher neuroticism, and earlier age of onset remained as independent risk indicators of comorbidity within persons with depressive and/or anxiety disorders (Lamers et al., 2011b), and indicated that the earlier association with lower education could be mediated by clinical characteristics.

Several NESDA studies focused on the relationship between childhood trauma and comorbidity. Regardless of the type of childhood trauma, a self-reported history of childhood trauma conferred an increased risk of having current (12-month recency) comorbidity, higher than the risk of having single disorders (Hovens et al., 2010; n=1931). For example, the ORs of depressive and/or anxiety disorders in those with versus without a history of frequent childhood emotional neglect were 9.03 for having comorbidity (95%CI=6.19–13.2), 4.56 (95% CI=2.92–7.13) for single depressive disorders and 2.23 (95% CI=1.34–3.72) for single anxiety disorders (Hovens et al., 2010). Likewise, a childhood trauma history conferred a higher risk of having comorbid as compared to depressive disorders after two years (Hovens et al., 2012). In a sample without depressive or anxiety disorders (n=1167) childhood trauma history conferred a higher risk for developing comorbidity than single depressive disorders after 2 years (Hovens et al., 2015).

Regarding personality traits, the relationship of comorbidity with higher neuroticism (Lamers et al., 2011b) was also found in those with current MDD (van Eeden et al., 2019). Several personality traits and psychological vulnerabilities other than neuroticism were investigated in NESDA. Among subjects with depressive and/or anxiety disorders those with comorbidity showed the poorest levels of dispositional optimism, a personality trait characterized by generalized positive expectations towards the future (Broekhof et al., 2015). Lifetime comorbidity was also most prominently associated with lower happiness and lower emotional wellbeing, followed by the single disorders (Spinhoven et al., 2015), and with higher trait anger and anger attacks (de Bles et al., 2019). Regarding self-esteem, measures of deliberative self-evaluative processes (explicit self-esteem; ESE) can be differentiated from automatically elicited affective self-associations (implicit self-esteem; ISE). Compared to controls, those with current comorbidity had lower ESE than single disorders, while lower ISE was specific to current comorbidity (Van Tuijl et al., 2016). The instability of self-esteem was lowest in comorbid subjects (van Tuijl et al., 2018). Finally, increased trait avoidance tendencies were found across all disorders groups but most pronounced in comorbid subjects (Struijs et al., 2017).

3.6. Neurobiological indicators

Of the neurobiological indicators listed in S1, the main cross-sectional findings are summarized in Table 1. Table 1 shows that many neurobiological indicators differed between persons with depressive and/or anxiety disorders and controls, but that overall these markers did not distinguish subjects with comorbidity from the single disorders. This was true for markers of oxidative stress (Black et al., 2018, 2017), most fatty acid measurements (Thesing et al., 2018), brain-derived neurotrophic factor (BDNF; Molendijk et al., 2012), inflammation (Lamers et al., 2019; Vogelzangs et al., 2016, 2013), serum lipoproteins (Van Reedt Dortland et al., 2010a), fatty acids (Thesing et al., 2018), cellular aging (Verhoeven et al., 2015, 2014) and autonomous nervous system activity (Licht et al., 2012, 2009, 2008). The lack of clear differences in biological markers of comorbid disorders versus single disorders was also confirmed by longitudinal data on inflammation (Lamers et al., 2019), BDNF (Bus et al., 2015) and the hypothalamic-pituitary-adrenal (HPA) axis (Vreeburg et al., 2013). Among the cross-sectional HPA axis findings, evening cortisol and dexamethasone suppression test (DST) levels in saliva were neither distinctive for comorbidity (Vreeburg et al., 2010, 2009), but a higher cortisol awakening response (CAR) was significantly more present in those with comorbidity when examined within persons with MDD (Vreeburg et al., 2009) or anxiety disorders (Vreeburg et al., 2010). Also, those with current comorbidity, not pure depressive or anxiety disorders, had higher cortisol levels in hair compared to controls (Gerritsen et al., 2019). Furthermore, within antidepressant free depressed persons, lower BDNF levels were found in those with comorbid anxiety disorders, which became non-significant after additional adjustment for demographical and some clinical characteristics (Molendijk et al., 2011). Within depressed persons, lower vitamin D levels were found in those with comorbid disorders, which also became non-significant after additional adjustment for lifestyle factors and chronic diseases (Milaneschi et al., 2014).

The neuroimaging data in Table 1 show that altered resting-state functional connectivity (RSFC) of certain cortical regions (the bilateral precuneus and the right precentral gyrus) with a limbic network – not other networks – was found in comorbid depressive and anxiety disorders (Pannekoek et al., 2015). By contrast, cortical volumes of brain regions involved in the HPA-axis and emotion regulation did not distinguish comorbid from single disorders (Van Tol et al., 2010). Likewise, prefrontal hyperactivation during planning was neither exclusively altered in subjects with comorbid disorders (van Tol et al., 2011).

Taken all NESDA sociodemographic and vulnerability findings together, consistent comorbidity risk indicators in subjects with depressive and/or anxiety disorders were childhood trauma, neuroticism, and early age of onset. In addition to neuroticism, most other psychological vulnerabilities showed higher levels in all disorder groups compared to controls, but most prominently in those with comorbid depressive and anxiety disorders. The findings of neurobiological and neuroimaging data did overall not consistently support a (neuro)biological distinction between persons with comorbid and single disorders, as the vast majority of examined (neuro)biological indicators was not significantly associated with comorbidity status within patient groups.

3.7. Functional, somatic and other mental health indicators

In NESDA, the comorbidity of depressive and anxiety disorders concurred with a range of functional, somatic and other mental health indicators, that are summarized in S2 and illustrated by Fig. 3. Fig. 3 depicts exemplary findings from cross-sectional NESDA studies that compared comorbid, single depressive, and single anxiety disorder subjects to those without a disorder in terms of Cohen's d effect sizes (ES). For this purpose, odds ratios (OR) were converted to ES according to Chinn (2000) and beta's were converted to ES by the formula (beta /

Table 1
Cross-sectional associations between neurobiological indicators and single anxiety disorders (AD), single depressive disorders (DD), and comorbid depressive and anxiety disorders (CD). Numbered superscripts refer to the original papers listed in the footnote. Displayed associations were largely unadjusted, eventual adjustment (s) are summarized in S1. Alphabet superscripts denote those associations that changed after additional adjustment(s) and refer to a short footnote explanation (full explanation in S1).

	Comparison against controls without disorder			Comparison within patients	
	Single Anxiety Disorder	Single Depressive Disorder	Comorbid Disorder	Comorbid versus pure AD	Comorbid versus pure DD
Biological:					
Cortisol awakening response[1,2] (saliva)	+[2]	+[1]	+[1,2]	+[2]	+[1]
Cortisol evening[1,2] (saliva)	=[2]	=[1§]	=[1§,2]	=[2]	=[1]
Cortisol DST[1,2] (saliva)	=[2]	=[1]	=[1,2]	=[2]	=[1]
Cortisol (hair)[3]	=	=	+		
Cortisone (hair)[3]	=	=	=		
Cortisol: cortisone ratio (hair)[3]	=	=	=		
Omega-3 polyunsaturated fatty acids[4] (blood)	=	=	-		
Omega-3: fatty acid ratio[4] (blood)	=	+	+		
Omega-6 polyunsaturated fatty acids[4] (blood)	=	=	=		
Omega-6: fatty acid ratio[4] (blood)	=	=	=		
Uric acid[5] (blood)	-	-	-		
F2-isoprostanes[6] (blood)	=	=	=		
8-hydroxy-2′-deoxyguanosine[6] (blood)	-[a]	-[a]	-[a]		
Brain derived neurotrophic factor (BDNF)[7] (blood)	=	=	=		=
BDNF in antidepressant free subjects[8] (blood)		-	-		-[b]
LPS-stimulated inflammation index[9] (blood)	=	=	=		
Interleukin-6[10,11] (blood)	=[10]	+[10]	+[10]	=[11]	
C-reactive protein[10,11] (blood)		=[10]	=[10]	=[11]	
Tumor necrosis factor alpha[11] (blood)				=[11]	
Telomere length[12,13] (blood)				=[13]	=[12]
Serum lipoproteins: LDL, HDL, triglycerides[14] (blood)					=
Vitamin D[15] (blood)					-[c]
Heart rate variability[16,17] (cardiac monitoring)				=[17]	=[16]
Pre-ejection period[18] (cardiac monitoring)	=	=	=		
Imaging:					
RSFC in limbic network[19]	=	=	+		
RSFC in default mode network[19]	=	=	=		
RSFC in salience network[19]	=	=	=		
RSFC in sensory–motor network[19]	=	=	=		
vMRI of rostral-dorsal anterior cingulate gyrus[20]	-	-	-		
vMRI of lateral temporal cortex[20]	-	=	=		
vMRI of inferior frontal cortex[20]	=	-	=		
fMRI activity during planning in prefrontal cortex[21]	=	+	=		

Abbreviations: AD = single anxiety disorders; DD = single depressive disorders; CD = comorbid disorders; DST = dexamethasone suppression test; fMRI = functional magnetic resonance imaging; HDL = high density lipoproteins; LDL = low density lipoproteins; LPS = lipopolysaccharides; RSFC = Resting-state functional connectivity; vMRI = volumetric magnetic resonance imaging.
Symbols: + (significant positive association); - (significant negative association); = (no significant association); § (evening cortisol levels were elevated only in current MDD, and then at 10 PM but not at 11 PM).
References: 1= Vreeburg et al., 2009; 2= Vreeburg et al., 2010; 3= Gerritsen et al., 2019; 4= Thesing et al., 2018; 5= Black et al., 2018; 6= Black et al., 2017; 7= Molendijk et al., 2012; 8= Molendijk et al., 2011; 9= Vogelzangs et al., 2016; 10= Lamers et al., 2019; 11= Vogelzangs et al., 2013; 12= Verhoeven et al., 2014; 13= Verhoeven et al., 2015; 14= Van Reedt Dortland et al., 2010a; 15= Milaneschi et al, 2014; 16= Licht et al., 2008; 17= Licht et al., 2009; 18= Licht et al., 2012; 19= Pannekoek et al., 2015; 20= Van Tol et al., 2010; 21= Van Tol et al., 2011.
Alphabet superscripts:
[a] Insignificant after additional adjustment for antidepressant use.
[b] Univariate association; multivariate analyses including demographical and various clinical characteristics such as smoking and depression severity rendered the association insignificant.
[c] Insignificant after additional adjustment for smoking, alcohol, BMI, physical activity, chronic diseases and creatinine clearance.

($\sqrt{(n)}$*SE)) or (beta/SD (Baguley, 2009)). These converted ES are listed in S2. What stands out from all three spider graphs is that the risks of adverse outcomes were nearly consistently largest in comorbidity compared to the single disorders, as represented by the continuous black lines in the spider graphs. In addition, often a gradient was found, with second largest risks in single depressive disorders (striped lines), followed by single anxiety disorders (dotted lines). The largest ES were found in the domains of functional and other mental health outcomes.

Regarding the functional outcomes (Fig. 3a), various indicators of social functioning were significantly impaired across all disorder groups compared to controls, and most prominently in patients with comorbid disorders (ES up to 1.76 for perceived social disability), followed by depressive and then by anxiety disorders (Saris et al., 2017). Such a gradual pattern also emerged longitudinally for work disability and long-term work absenteeism over the course of 4 years, also after adjustment for various sociodemographic, psychiatric course and work variables (Hendriks et al., 2015). Likewise, within those with MDD, comorbid anxiety disorders predicted disability after 2 years (Gaspersz et al., 2017). In a subsample of n=1249 subjects who were employed for at least 12 hours per week, increased risks for long-term work absenteeism in 1 year were also found in current comorbid (OR=2.35) and current single depressive (OR=3.19) disorders (Kok et al., 2017). Once sick-listed, having comorbidity as well as either of the single disorders was not predictive of sustainable return to work after 2 years (Lammerts

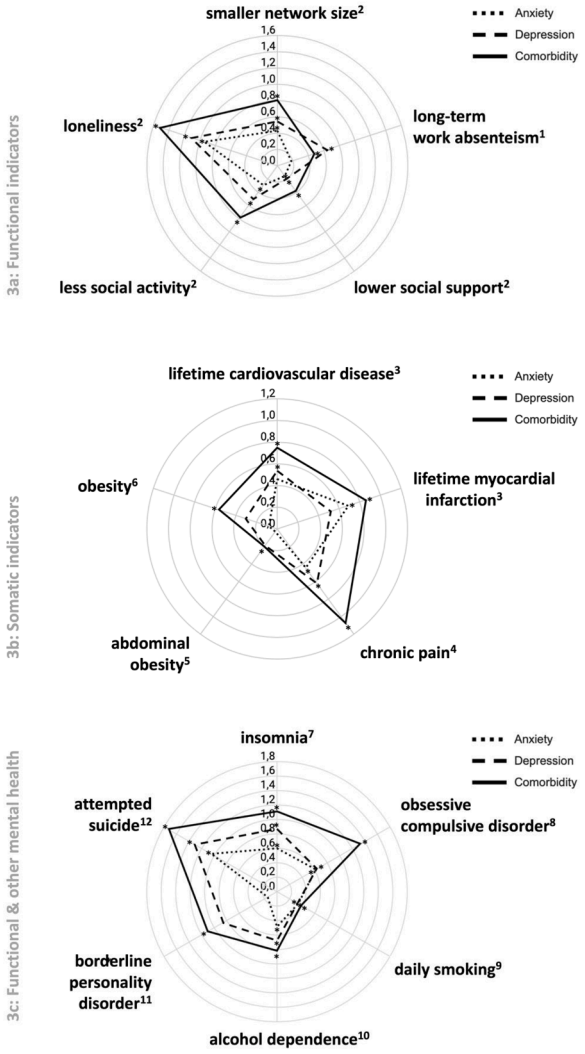

Fig. 3. Spider graphs displaying effect sizes (ES) of several cross-sectional outcome indicators of single anxiety disorders (dotted line), single depressive disorders (striped line) or comorbid depressive and anxiety disorders (continuous line), versus controls as reference group. Corresponding ES and the instruments used to assess the outcomes are displayed in supplementary table 2 (S2). ES with an asterix (*) denote significance.

Outcome categories: 3a. Functional indicators; 3b. Somatic indicators; 3c. Mental health indicators.

References: 1. (Kok et al., 2017); 2. (Saris et al., 2017); 3 (Vogelzangs et al., 2010); 4 (Generaal et al., 2014); 5 (Van Reedt Dortland et al., 2010b); 6 (De Wit et al., 2010); 7 (Prather et al., 2015); 8 (Hofmeijer-Sevink et al., 2018); 9 (de Wit et al., 2015); 10 (Boschloo et al., 2011); 11 (Distel et al., 2016); 12 (Eikelenboom et al., 2012).

et al., 2016). Within employed subjects with current depressive and/or anxiety disorders, comorbidity conferred an almost 3-fold risk of poorer work functioning and impaired work performance (Plaisier et al., 2010). Functional impairments were not confined to those with current comorbidity: in those who remitted from MDD, comorbidity was predictive of residual functional disability over the course of 6 years (Iancu et al., 2020), which rendered insignificant after adjustment for several clinical factors, such as avoidance behavior severity.

Fig. 3b depicts that several somatic indicators were poorest in comorbid disorders, followed by any of the single disorders. As such, the risk of lifetime cardiovascular disease (CVD) was increased in those with comorbidity and in single anxiety disorders, also after adjustment for lifestyle and health factors (Vogelzangs et al., 2010). This applied to all types of CVD, and OR's ranged up to 4.75 for the risk of lifetime myocardial infarction in comorbidity (Vogelzangs et al., 2010). Longitudinally, those with comorbidity as well as single depressive disorders were at increased risk of incident CVD in CVD-free subjects (Seldenrijk et al., 2015). Furthermore, disorder groups and particularly subjects with comorbidity were at increased risk of having chronic pain in various body sites (Generaal et al., 2014; Ligthart et al., 2013), especially migraine, chest pain and neck pain (Ligthart et al., 2013), as well as pain in musculoskeletal, gastrointestinal, and cardiorespiratory locations (De Heer et al., 2014). Conversely, in those with current depressive and/or anxiety disorders, chronic pain predicted having single and particularly comorbid disorders after 2 years (Gerrits et al., 2012).

Somatic indicators that were significantly altered in comorbidity and not in the single disorders were obesity (De Wit et al., 2010; Fig. 3b), abdominal obesity (Van Reedt Dortland et al., 2010b; Fig. 3b), arterial stiffness (Seldenrijk et al., 2011a), and 2-year weight gain (de Wit et al., 2015), independent of lifestyle and health indicators (Seldenrijk et al., 2011a; Van Reedt Dortland et al., 2010b). The relationship between comorbidity and weight gain was further confirmed by longitudinal data, showing that within those with lifetime MDD, comorbid anxiety disorders predicted the likelihood of weight gain over the course of 2 years by 66% (Gibson-Smith et al., 2016). Lower physical activity occurred across all disorder groups and the relationship was strongest with comorbidity compared to the single disorders (De Wit et al., 2010), which was also measured by actigraphy (Difrancesco et al., 2019). Likewise, those with comorbidity showed more sedentary behavior independent of general physical activity level (de Wit et al., 2011). Somatic and lifestyle indicators that were not significantly altered in comorbid and single disorders were diabetes, hypertension, triglycerides (Seldenrijk et al., 2015), carotid atherosclerosis (Seldenrijk et al., 2011b), metabolic syndrome and its components other than abdominal obesity (Van Reedt Dortland et al., 2010a), and daily units of alcohol intake (de Wit et al., 2015; Seldenrijk et al., 2015). In addition, within those with current depressive disorders, no associations were found between anxiety comorbidity and objective measures of physical functioning (hand grip strength and lung function (Van Milligen et al., 2011)).

Spider graph 3c demonstrates that the likelihood of having other mental health problems was highest in those with depressive and anxiety comorbidity compared to the single disorders, but not specific for comorbidity. Mental health problems included multimorbidity of depressive and anxiety comorbidity with obsessive-compulsive disorder (Hofmeijer-Sevink et al., 2018), probable borderline personality disorder (Distel et al., 2016), daily smoking (de Wit et al., 2015), and alcohol dependence (Boschloo et al., 2011). In those with current depressive and/or anxiety disorders, comorbidity conferred a more than 3-fold risk of having multimorbidity with probable ADHD (Bron et al., 2016). Other mental health problems that occurred most prominent – but not exclusively - in comorbidity were insomnia (Prather et al., 2015) and lifetime suicide attempts and suicidal ideation (Eikelenboom et al., 2012). This relationship between comorbidity and suicidality was also longitudinally present: those with current comorbid anxiety and depressive disorders were at highest risk of suicide attempts over the course of 6 years followed by single depressive disorders (Eikelenboom et al., 2019), which rendered insignificant after taking clinical characteristics such as severity, symptom duration and previous attempts into account.

In summary, persons with comorbid depressive and anxiety disorders were characterized by more functional impairments and more other psychiatric and somatic morbidity, compared to persons with single disorders. In addition, functional, somatic and mental health indicators generally did not distinguish comorbidity from the pure disorders.

4. Discussion

We summarized the main findings from NESDA papers that covered the comorbidity of depressive and anxiety disorders. Strengths of

NESDA are the large sample size, longitudinal design, and extensive psychiatric evaluation. In addition, the long follow-up gives a more realistic estimation of psychiatric course compared to shorter time-frames and retrospective designs. Furthermore, the sampling frame of NESDA from the community to specialized mental health care ensures that various treatment settings are represented in NESDA. These advantages of NESDA support the quality of the findings regarding prevalence, etiology, and consequences of comorbidity as presented in this narrative review.

In summary, comorbidity was the rule in over three-quarter of subjects with depressive and/or anxiety disorders in NESDA, most often preceded by an anxiety disorder, particularly social phobia. Consistent comorbidity risk indicators in subjects with depressive and/or anxiety disorders were childhood trauma, neuroticism, and early age of onset. Other psychological vulnerabilities were generally most prominent in those with comorbid disorders as compared to the single disorders. The body of biological markers and neuroimaging findings did not strongly support a (neuro)biological distinction between comorbidity and the single disorders. Those with comorbid depressive and anxiety disorders were characterized by more functional impairments and more other psychiatric and somatic morbidity, as compared to persons with single disorders. Higher severity and chronicity illustrated a poorer comorbidity course, and transitions between depressive and anxiety disorders were common at follow-up. No clear clinical profilers indicative of a differential comorbidity course were found in NESDA.

The comorbidity rates in NESDA were rather comparable to that of another outpatient sample (Brown et al., 2001) and slightly higher than population-based studies (de Graaf et al., 2003; Kessler et al., 2003), which may most likely be explained by the different sampling frames. The finding that anxiety disorders preceded depressive disorders in more than half of comorbidity subjects confirmed previous findings (de Graaf et al., 2003; Moffitt et al., 2007; Schoevers, 2005). Regarding the sociodemographic and vulnerability risk indicators linked to psychiatric disorders in general (Kendler, 2019), consistent comorbidity risk indicators in NESDA were childhood trauma, age of onset, and neuroticism, which is in line with other research (Kendler et al., 2007) and occurred independent of sociodemographic, clinical, and other vulnerability characteristics. Furthermore, NESDA data demonstrated that previously found associations between comorbidity and sociodemographic risk factors (De Graaf et al., 2002) could be mediated by clinical characteristics (Lamers et al., 2011b). Psychological vulnerabilities were generally most protruding in those with comorbid disorders as compared to the single disorders, which was in line with the few studies that specifically examined the association between psychological vulnerabilities and comorbidity (Judd et al., 2013; Kendler et al., 2007). More functional and psychiatric impairments in comorbidity were also found by others (Norberg et al., 2008; Plana-Ripoll et al., 2019). Higher severity and chronicity in comorbid versus single depressive or anxiety disorders was endorsed by most (Kessler et al., 2003; Merikangas and Angst, 1995; Roy-Byrne et al., 2000) but not all (Fava et al., 2000) studies, which may be due to different sampling frames.

In NESDA, various (neuro)biological dysregulations in the presence of depression and/or anxiety disorders were confirmed. Nevertheless, findings did not confirm that such dysregulations are more severe in those with comorbid disorders, so the (neuro)biological signature does not seem to be specific for comorbid patients. First, (neuro)inflammatory alterations are a shared finding across psychiatric disorders (Réus et al., 2015), and the lack of differences in inflammation (Lamers et al., 2019; Vogelzangs et al., 2016, 2013) and BDNF (Molendijk et al., 2012) in comorbid versus pure depressive or anxiety disorders does not endorse a specific role of inflammation in comorbidity. Likewise, shorter telomere length is found across several psychiatric disorders and most consistently in depressive and anxiety disorders (Monroy-Jaramillo et al., 2018) and the absence of telomere length alterations specific to comorbidity in NESDA (Verhoeven et al., 2015, 2014) argues against a specific role of cellular aging in comorbidity. Moreover, cortisol alterations occur across several psychiatric disorders (Zorn et al., 2017) and the overall absence of salivary cortisol differences between comorbidity and pure disorders in NESDA (Vreeburg et al., 2010, 2009) was also found in a study of HPA-axis stress reactivity in MDD (Young et al., 2004). Furthermore, the lack of differences in uric acid between comorbid and pure disorders in NESDA (Black et al., 2018) was endorsed by a study (Maes et al., 2018) that compared MDD with or without GAD. Finally, the absence of differences in serum lipoproteins between comorbid and pure depressive disorders (Van Reedt Dortland et al., 2010a) was not confirmed by the study of Maes et al. (2018) regarding HDL in MDD with versus without GAD, although serum lipids other than HDL were not investigated in their study and analyses were not adjusted for lipid-modifying factors.

While the vast majority of examined (neuro)biological indicators in NESDA showed no clear alterations specific to comorbid disorders, a few exceptions need consideration. First, the higher hair cortisol levels in comorbidity compared to single disorders (Gerritsen et al., 2019) were also associated with higher severity (Gerritsen et al., 2019) and may be indicative of chronic stress (Staufenbiel et al., 2013) in those with comorbidity. Second, the higher CAR in comorbidity (Vreeburg et al., 2010, 2009) may represent higher HPA axis reactivity to stress (Yoon and Joormann, 2012; Young et al., 2004) but should be interpreted against the absence of other salivary cortisol abnormalities in comorbidity (Vreeburg et al., 2010, 2009; Young et al., 2004). Third, lower BDNF (Molendijk et al., 2012) and lower vitamin D (Milaneschi et al., 2014) levels in depressed subjects with versus without comorbidity were no longer significant after additional adjustments for somatic diseases (Milaneschi et al., 2014), symptom severity (Molendijk et al., 2011) and lifestyle factors (Milaneschi et al., 2014; Molendijk et al., 2011), which suggests a probable interplay of neurobiological, psychiatric, somatic and lifestyle indicators. Fourth, resting state alterations in a limbic network – not in other networks - in comorbidity (Pannekoek et al., 2015) need replication and could be related to alterations in emotion regulation (Grecucci et al., 2013).

To further advance the ontological comprehension of comorbidity of depressive and anxiety disorders, some have suggested that comorbidity is just an artefact (Maj, 2005), while others stated that comorbidity of depressive and anxiety disorders is more than a sum of the parts (Kleiman and Riskind, 2012). In NESDA, the association between comorbidity and several vulnerability, functional, and mental health indicators remained when clinical factors such as symptom severity (Hendriks et al., 2015; Lamers et al., 2011b) or disease status (current versus remitted; (Distel et al., 2016; Hofmeijer-Sevink et al., 2018)) were taken into account. Hence, severity and disease status may be part, but not all, of the explanation why almost all outcomes tended to be more adverse and protruded in comorbid as compared to the single disorders. Comorbidity may therefore be regarded as more than a sum of the parts and further comprehension of comorbidity may lie in the conceptual understanding of depressive and anxiety disorders.

Several findings of NESDA have aided this conceptual understanding of depressive and anxiety disorders. First, in addition to the existing evidence of overlapping genetic (Anttila et al., 2018; Wray et al., 2018) and environmental (De Graaf et al., 2002) underpinnings of depressive and anxiety disorders, little distinction was found in neurobiological markers and other vulnerability traits between persons with comorbid versus single disorders in NESDA, which further supports the notion of a shared etiological pathway to both depressive and anxiety disorders. In addition, findings from NESDA confirmed that depressive and anxiety disorders considerably co-occur (Gorman, 1996) and expanded this by showing that transitions over time occur often between depressive and anxiety disorders, and that extension beyond de diagnostic boundaries of the single disorders is common. Such etiological and symptomatic overlap endorses a dimensional approach (Brown and Barlow, 2009) to depressive and anxiety disorders. In such a dimensional view, the waxing and waning of depressive and anxiety disorders over time can be viewed as phenotypic expressions of the same underlying disorder, and

concurrent comorbidity could be regarded from this viewpoint as a profiler indicative of a more severe psychiatric and functional outcome trajectory.

How can these findings about risk indicators be merged in prevailing etiological models for comorbidity? Childhood trauma may affect personality development, leading to adverse personality features and dysfunctional cognitive styles (Hovens et al., 2017). Such adverse personality and cognitive profiles, as well as genetic susceptibility (Anttila et al., 2018; Ferentinos et al., 2015; Verduijn et al., 2017a), facilitate early onset of anxiety and/or depressive symptoms and syndromes. Subthreshold symptoms pave the way to the occurrence of established depressive and/or anxiety disorders (Karsten et al., 2011), and the combination with the psychological vulnerability factors further facilitates comorbid disorders. Once established comorbidity, a detrimental interplay between poorer clinical course at one hand, and functional disability and poorer mental health at the other hand may further aggravate the clinical picture. For instance, social dysfunction was predictive of still having a depressive and/or anxiety disorders at 2 year follow up (Saris et al., 2017), while having a depressive and/or anxiety disorders was predictive of developing multimorbidity with alcohol dependence (Boschloo et al., 2013). The term "illness extension" was recently introduced by Shah et al. (2020) to describe how a mental illness expands beyond the original diagnostic boundaries, including the emergence of co- and multimorbidity. NESDA findings clearly demonstrated that – so defined - illness extension is common in depressive and anxiety disorders. From the perspective of staging, illness extension (Shah et al., 2020) and disease progression (Scott et al., 2013) both imply a gradual increase in severity or complexity, along with increased risk of persistence or recurrence (Shah et al., 2020).

For future research, further investigation into the clinical heterogeneity within comorbid disorders is recommended, in order to find profilers indicative of specific etiological pathways or particular outcome trajectories. In addition, the effectiveness of promising transdiagnostic treatments (Barlow et al., 2017; Garber et al., 2016; Newby et al., 2015) should be further compared against existing evidence-based psychological treatments with particular focus on the effects on comorbidity. Prevention and particularly treatment of anxiety in youth also reduced depression - and vice-versa - (Garber et al., 2016) but long-term studies are sparse (Benjamin et al., 2013), hence longitudinal studies are strongly needed with long post-intervention follow-up into such cross-over effects and particularly into the prevention of lifetime comorbidity. Also, a thorough assessment of depression and anxiety-related symptoms should be an outcome indicator of every clinical trial, regardless of whether the index disorder is depression or anxiety. Furthermore, the presence of a comorbid anxiety disorder is not marked yet as a marker of staging in the current staging models of depressive disorders (Hetrick et al., 2008; Verduijn et al., 2015), while comorbidity was an indicator of poorer course across all stages of anxiety disorders (Bokma et al., 2020). Therefore, comorbidity could be a useful addition as a staging marker across all clinical stages of depressive disorders in future studies, and the concept of illness extension (Shah et al., 2020) could be a valuable addition to such staging research. Another research recommendation is to further explore a dimensional instead of a categorical approach to depressive and anxiety disorders (Conway and Brown, 2018). Finally, as our data supported that depressive and anxiety disorders tend to interplay, novel strategies aimed at this interplay deserve further attention, such as unravelling bridge mental states (Groen et al., 2020) as a possible venue for therapeutic strategies.

Various recommendations for clinical practice need consideration. First, it seems imperative to distinguish comorbid from single conditions in health care. An important criterion to organize and finance health care, is the severity of a disease and the intensity of the treatment needed, which are both prominent in comorbid compared to the single disorders. In addition, it is well possible that common – and lighter – interventions that are effective for single disorders, are less effective in comorbidity. Hence, stepped care might be better reserved for the single disorders, while more vigorous treatment options – for instance cognitive behavioral therapy in conjunction with pharmacotherapy – should be considered in those with comorbid disorders, as proposed in a review by Schoevers et al. (2008). Regardless of treatment setting, vulnerability factors of comorbidity - especially childhood trauma and neuroticism - should be more consequently targeted in treatment settings. Given the high rates and impact of comorbidity, prevention of the onset of depression or anxiety by effective strategies (Garber et al., 2016; Gladstone et al., 2020) should be encouraged analogous to early intervention programmes in psychosis, and first episodes of single depressive or anxiety disorders need to be more adequately recognized (Wang et al., 2007) and subsequently treated, particularly in the presence of risk factors of developing comorbidity. Finally, the high prevalence of comorbidity and common transitions or extension of depressive or anxiety disorders beyond their original diagnostic boundaries, indicate that a thorough assessment of both depressive and anxiety-related symptoms should be part of every assessment of patients with either index disorder.

Several limitations and considerations of this study deserve attention. Due to the observational design of NESDA, causality cannot be inferred and the impact of treatment on course cannot be fully assessed. In addition, we were not able to prospectively analyze the developmental trajectory to comorbidity which requires longitudinal youth cohorts, as depressive and particularly anxiety disorders typically originate in adolescence (Garber et al., 2016; Lamers et al., 2011b). Furthermore, the results may not be fully generalizable to ethnic minorities, non-European subjects, elderly, adolescents, patients in clinical mental health settings, or to those with a primary other clinical diagnosis such as a severe substance use disorder. Another limitation is that some studies had missing data on the relevant outcome measure under study. Subjects excluded for this reason often had higher rates of comorbid depressive and anxiety disorders compared to those included (for example: de Wit et al., 2015; Prather et al., 2015), which may have led to an underestimation of the influence of comorbidity on that particular outcome. Likewise, attrition was associated with comorbidity (Lamers et al., 2012) which may further limit the generalizability of the outcomes. However, this limitation only applies to those papers based on data other than cross-sectional baseline data, and attrition was relatively low in NESDA (Lamers et al., 2012). Some data were retrospectively retrieved, such as age of onset and childhood trauma, which may be subject to recall bias. Finally, it should be noted that the papers in the current review employed DSM-IV classifications while the currently used DSM-5 contains more diagnostic categories and slightly different criteria for depressive and anxiety disorders.

Data availability

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

Author statement

All authors contributed to conceptualization, writing, editing and revision of the manuscript, and all approved the final article. WtM, SD, AB and BP designed the study, and interpreted the data. WtM and SD performed the search strategy and analyses. WtM prepared the figures and tables. BP was involved in funding acquisition and data curation.

Declaration of Competing Interest

All other authors declare that they have no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.02.004.

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