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Anxiety in late-life depression

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ANXIETY IN LATE-LIFE DEPRESSION

Date C. van der Veen

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**rijksuniversiteit
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ANXIETY IN LATE-LIFE DEPRESSION

Proefschrift

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Groningen
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CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Disease burden of late-life depression

Among older persons, the prevalence of depressive disorder is high¹. Pooled prevalence rates of major depressive disorder in the community ranges between 1.8% for community-dwelling persons aged 55 years and over² and 7.2% for persons aged 75 years and over³. The difference in prevalence between both meta-analyses is not only age, but also a different sampling structure with including nursing home residents and/or cognitively impaired persons not being excluded in the latter meta-analysis. The disease burden of late-life depression is high, as it is associated with several negative consequences including a higher incidence and worse course of chronic somatic diseases, functional decline with marked disability, decreased quality of life, and even mortality^{1,4-6}.

According to the diagnostic criteria, several subtypes of depression can be distinguished. In de DSM-IV-TR, anxiety is not included as a core component of such a specific subtype⁷. This contrasts with clinical practice, in which professionals have recognized the extreme suffering of anxious-depressed patients and the negative prognostic impact of anxiety in depression. A high level of anxiety symptoms and/or comorbid anxiety disorders is within late-life depression associated with a reduced quality of life^{8,9}, higher levels of suicidal ideation and a history of suicide attempts^{10,11}, and greater chronicity and severity^{12,13}. Nearly half of the patients suffering from a depression also suffer from an anxiety disorder¹⁴, which is rarely integrated in an overall treatment plan. These observations have stimulated the DSM-5 task force for mood disorders to explore the possibility of diagnostic criteria for anxious depression¹⁵⁻¹⁷.

Anxious depression – two cases

In the literature, depressive disorder with anxious distress and depressive disorder with a comorbid anxiety disorders are used interchangeably¹⁸, suggesting that both refer to the same diagnostic entities. The following cases show that this can be challenged.

Case A

Frank (1937) is an 83-year-old widower. He was a shy, young boy and grew up during the Second World War. For Frank this was complicated because his parents affiliated with the National Socialist Movement during the German occupation. This came with certain privileges, but for Frank this meant he had to endure bullying and fights with peers. He withdrew himself from social activities as much as possible. After the war he went to university and became an accountant. He met a lively, social woman, they married and raised three kids. His wife always stimulated him to join her visiting friends and family, but Frank remembers this always triggered his fear of being exposed. He avoided personal conversations and anxiously endured the social activities. When after his pension his wife died Frank became depressed. His feelings of worthlessness and his negative self-esteem led to a persistent pattern of anxious and depressive avoidance.

The question I address in my thesis is: Is Frank solely suffering from a major depression or is his late-life depression complicated by a long-standing social anxiety disorder?

Case B

Jane (1949) is a seventy-one-year-old lady. After the death of her spouse, she became severely depressed and was admitted to a psychiatric hospital. Psychiatric examination revealed a depressed mood and a high level of anxiety symptoms, particularly palpitations, trembling, and hyperventilation. Although she had no psychiatric history, her daughter described Jane as a nervous, panicky person in general. After non-response to several first line antidepressants (SSRI and SNRI) as well as a tricyclic antidepressant, she recovered well on a mono-amine oxidase inhibitor. After being discharged from the hospital, her outpatient care is arduous. Then, when her daughter receives worrisome news concerning her own health and, for a period of time, is less available to her mother, Jane's symptoms exacerbate. She is readmitted and symptoms subside relatively soon. Patients like Jane are commonly known and the question I will address in my thesis is; could Jane be suffering from anxious depression? Was Jane suffering from a recurrent depressive episode? Are dependent personality traits the cause of this exacerbation and is the outpatient care therefore insufficient?

Anxious depression

In this thesis, anxious depression is defined as a depressive disorder with a high anxiety level and/or a comorbid anxiety disorder, as most studies thus use both definitions interchangeably. Nonetheless, both may describe different clinical states.

With respect to comorbid anxiety disorders in late-life depression, the existence of an anxiety disorder is often missed or ignored in clinical practice^{19–21}. For example, excessive worrying due to generalized anxiety disorders may be easily regarded as rumination in depression, agoraphobic avoidance as anhedonia, and finally, classic panic attacks as a symptom of depression severity²¹. Indeed, the prevalence of comorbid anxiety disorders in late-life depression is markedly higher in prospective studies using specifically trained clinicians in the diagnosis of anxiety disorders²² compared with a retrospective analysis of depressed elderly inpatients of the same research group^{23,24}. Moreover, comorbidity tend to increase with higher severity levels of both depression and anxiety²⁵. Finally, as anxiety disorders have an onset before the age of 21 years²⁶, persisting anxiety symptoms become part of the self-narrative of an older patient and are therefore often falsely attributed to the personality factors by both patient and clinician.

With regard to a depressive disorder with anxious distress, patients are generally not receptive for psychotherapeutic interventions, whereas initial increases of anxiety symptoms when starting serotonergic antidepressants complicates pharmacological treatment^{27,28}. The high level of distress of these patients often triggers family members as well as professionals to restrict or take over the autonomy of the patient.

Treatment guidelines exist for mood and anxiety disorders, separately^{29,30} and the addenda Older Adults^{31,32}. Irrespective of the anxiety level, even in case of a comorbid anxiety disorders, according to the hierarchical rules of the DSM-IV, it is considered best-practice to treat the (severe) depressive disorder first³³, assuming anxious distress will ameliorate, but this often leaves a comorbid anxiety disorder untreated. However, when comorbidity complicates the psychiatric state, a case conceptualization can be helpful to identify primary treatment targets for medication or e.g. Cognitive Behavioural Therapy (CBT)³⁴. Case conceptualization brings together all the information gathered during assessment and is combined with the existing theoretical and scientific knowledge. This leads to working hypotheses, which explains how a patient's presenting problems have developed and are being maintained³⁵. Epidemiological studies provide nomothetic knowledge of possible determinants (e.g., personality traits or the impact of life-events) that form a starting point from where the clinician explores idiographic characteristics to personalize the case conceptualization in clinical practice.

OBJECTIVES AND OUTLINE OF THIS THESIS

This thesis was set up to explore the potential diagnostic pitfalls of anxious depression. For this purpose, we used the data gathered within Netherlands Study of Depression in Older persons (NESDO) and the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness (NCISH), as will be described in the appendix. More specifically, we formulated the following research objectives for each part of this thesis:

- I. To examine the level of agreement between late-life depression with a comorbid anxiety disorder and late-life depression with anxious distress (chapter 2).
- II. To explore determinants of anxiety disorders in late life depression:
 - a. What are the determinants of specific comorbid anxiety disorders in late-life depression (chapter 3)?
 - b. What are the determinants of complete remission, defined as being without a depressive as well as an anxiety disorder (Chapter 6)?
 - c. What are the characteristics of depressed older patients with and without comorbid anxiety disorders who died by suicide (Chapter 4)?
- III. To examine personality features (neuroticism, mastery, worrying and cognitive control) as determinants of anxious distress in late life depression:
 - a. Are recent life-events associated with higher anxiety levels in late-life depression and is this conditional upon the level of certain personality traits (Chapter 5 & 6).
 - b. Predict worry and cognitive control the course trajectories of anxiety in older adults with late-life depression (chapter 7)?
- IV. Can diagnostic complexities of descriptive classification be overcome by an idiographic diagnostic approach (Chapter 8)?

Part I - Anxious depression in later life: one or two disorders?

As described, there is no consensus on the diagnostic criteria for anxious depression. To prevent further clinical confusion and inconsistencies in the literature, Ionescu and colleagues suggested a distinction between a depression with high levels of anxious arousal (dimensional approach) and a depression with a comorbid anxiety disorder (syndromal approach)¹⁸. Although these differences are acknowledged, research findings are easily lumped together assuming substantial overlap. Nonetheless, up until now, no studies have examined the level of agreement between two different definitions of anxious depression commonly used in literature. Therefore, we will compare the level of agreement between MDD with high levels of anxiety symptoms and MDD with comorbid anxiety disorders according to the DSM-IV-TR in **chapter 2**. This will be examined in the Netherlands Study of Depression in Older persons (NESDO).

Part II – Late-life depression with comorbid anxiety disorders

Reported prevalence rates of pure anxiety disorders are low in later life, and many studies on anxiety disorders lump different anxiety disorder together³⁶. Therefore, we will first study determinants of any comorbid anxiety disorder in a rather explorative way. In **chapter 3**, we examined personality characteristics as well as early and recent life-events as possible determinants of comorbid anxiety disorders in late-life depression, taking previously examined determinants of higher levels of psychological, social, and somatic distress into account. Since suicide has been specifically associated with anxiety in late life depression³⁷, we examined the behavioural, clinical and care characteristics of depressed older patients with and without anxiety disorders who died by suicide in **chapter 4**. This will be examined in the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness (NCISH).

When lumping anxiety disorder together, differential effects between individual anxiety disorder can be masked. Therefore, in **chapter 3**, we also explore whether determinants of comorbidity differ between individual anxiety disorders. This will be examined in the Netherlands Study of Depression in Older persons (NESDO).

Part III – Late-life depression with anxious distress

In part III we examine determinants of anxious distress (cross-sectionally and over time) hypothesis driven. Since the actual anxiety level of persons can be assumed to be the results of both nature (anxiety sensitive) and nurture (life events)^{38,39}. Therefore, we hypothesise that the severity of anxiety distress is determined by specific personality traits in interaction with life-events. This hypothesis will be examined using cross-sectional data in **chapter 5** and using longitudinal data in **chapter 6**. In particular, we hypothesized that recent life-events are more strongly associated with anxiety symptoms in the presence of high levels of neuroticism as well as a low sense of mastery, whereas other personality characteristics were examined in a more explorative way.

In **chapter 7**, we will examine the predictive value of worry as a maladaptive cognitive emotion regulation strategy, and resources necessary for successful emotion regulation

(i.e., cognitive control and resting heart rate variability (HRV)) for the course of anxiety symptoms in depressed older adults. Moreover, it examines whether these emotion regulation variables moderate the impact of negative life events on severity of anxiety symptoms. In these three studies the data from the Netherlands Study of Depression in Older persons (NESDO) will be used.

Part IV - Symptom dynamics in late-life anxious depression

The primary aim of this proof-of-principle case-study is to explore the feasibility and added value of *Ecological Momentary Assessment (EMA)* and the evaluation of a personalized symptom network in an older patient suffering from treatment resistant depressive and anxious symptoms. This patient was referred to our university hospital for tertiary treatment of an affective disorder, which was previously diagnosed as either a depressive disorder with a comorbid panic disorder as well as a depressive disorder with anxious distress. In **chapter 8**, we will describe the data that were assessed during real-life and the personalized symptom network based on these data focussed on getting more insight into her symptom dynamics and identifying promising treatment targets.

Finally, we will summarise the results of this thesis in **chapter 9**, where after the findings will critically reviewed and recommendations for further research and clinical practice are given.

*Footnote refer to the corresponding chapters in the thesis

Figure 1 | Outline of this thesis

APPENDIX**Netherlands Study on Depression in Older persons (NESDO)**

Five studies, as described in chapter 2, 3, 5, 6, and 7, are based on data from the NESDO study⁴⁰. From 2007 until 2010, the NESDO consortium has recruited 510 depressed and non-depressed older persons (≥ 60 years) at 5 locations throughout the Netherlands. Depressed persons were recruited from both mental health care institutes and general practices in order to include persons with late-life depression in various developmental and severity stages. Non-depressed persons were recruited from general practices. The baseline assessment included written questionnaires, interviews, a medical examination, cognitive tests and collection of blood and saliva samples. Information was gathered about mental health outcomes and demographic, psychosocial, biological, cognitive and genetic determinants. The baseline NESDO sample consists of 378 depressed (according to DSM-IV criteria) and 132 non-depressed persons aged 60 through 93 years. Follow up assessments were 6-monthly written questionnaires and face-to-face interviews after 2 and 6 years.

National Confidential Inquiry into Suicide and Homicide by People with Mental Illness (NCISH)

The study described in chapter 4 was based on the data from NCISH⁴¹. The NCISH was established in 1992 and has been based at the University of Manchester since 1996. Its aims are to collect detailed clinical data on people who commit suicide or homicide in England and Wales and who have been in contact with mental health services and to recommend changes to clinical practice and policy that will reduce the risk of suicide and homicide by psychiatric patients. For each case the psychiatrist was sent a questionnaire and asked to complete it after discussion with other members of the mental health team. The questionnaire consisted of sections covering demographic details, clinical history, details of suicide, details of care in people who had been inpatients, details of care in people who had been in the community, final contact with services, events leading to suicide, respondents' views on prevention, and additional (qualitative) information.

REFERENCES

- 1 Fiske, A., Wetherell, J. L. & Gatz, M. Depression in older adults. *Annu. Rev. Clin. Psychol.* 5, 363–389 (2009).
- 2 Beekman, A. T. F., Copeland, J. R. M. & Prince, M. J. Review of community prevalence of depression in later life. *British Journal of Psychiatry* vol. 174 307–311 (1999).
- 3 Luppá, M. et al. Age- and gender-specific prevalence of depression in latest-life - Systematic review and meta-analysis. *Journal of Affective Disorders* vol. 136 212–221 (2012).
- 4 Schoevers, R. A. et al. Depression and excess mortality: Evidence for a dose response relation in community living elderly. *Int. J. Geriatr. Psychiatry* 24, 169–176 (2009).
- 5 Cuijpers, P. et al. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am. J. Psychiatry* 171, 453–462 (2014).
- 6 Miloyan, B. & Fried, E. A reassessment of the relationship between depression and all-cause mortality in 3,604,005 participants from 293 studies. *World Psychiatry* vol. 16 219–220 (2017).
- 7 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed., text rev.). (2000).
- 8 Fichter, M. M., Quadflieg, N., Fischer, U. C. & Kohlboeck, G. Twenty-five-year course and outcome in anxiety and depression in the upper bavarian longitudinal community study. *Acta Psychiatr. Scand.* 122, 75–85 (2010).
- 9 Lin, C. H., Wang, F. C., Lin, S. C., Chen, C. C. & Huang, C. J. A comparison of inpatients with anxious depression to those with nonanxious depression. *Psychiatry Res.* 220, 855–860 (2014).
- 10 Fava, M. et al. What clinical and symptom features and comorbid disorders characterize outpatients with anxious major depressive disorder: A replication and extension. *Can. J. Psychiatry* 51, 823–835 (2006).
- 11 Seo, H. J. et al. Distinctive clinical characteristics and suicidal tendencies of patients with anxious depression. *J. Nerv. Ment. Dis.* 199, 42–48 (2011).
- 12 Rhebergen, D. et al. The 7-year course of depression and anxiety in the general population. *Acta Psychiatr. Scand.* 123, 297–306 (2011).
- 13 Lenze, E. J., Mulsant, B. H., Shear, M. K., Houck, P. & Reynolds, C. F. Anxiety symptoms in elderly patients with depression: What is the best approach to treatment? *Drugs and Aging* vol. 19 753–760 (2002).
- 14 Beekman, A. T. F. et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am. J. Psychiatry* 157, 89–95 (2000).
- 15 First, M. B. DSM-5 proposals for mood disorders: A cost-benefit analysis. *Curr. Opin. Psychiatry* 24, 1–9 (2011).
- 16 Clarke, D. E. et al. DSM-5 field trials in the United States and Canada, part I: Study design, sampling strategy, implementation, and analytic approaches. *Am. J. Psychiatry* 170, 43–58 (2013).
- 17 Regier, D. A. et al. DSM-5 field trials in the United States and Canada, part II: Test-retest reliability of selected categorical diagnoses. *Am. J. Psychiatry* 170, 59–70 (2013).
- 18 Ionescu, D. F., Niciu, M. J., Henter, I. D. & Zarate, C. A. Defining anxious depression: A review of the literature. *CNS Spectrums* vol. 18 252–260 (2013).
- 19 Bryant, C., Jackson, H. & Ames, D. The prevalence of anxiety in older adults: Methodological issues and a review of the literature. *Journal of Affective Disorders* vol. 109 233–250 (2008).
- 20 Flint, A. J. Generalised anxiety disorder in elderly patients: Epidemiology, diagnosis and treatment options. *Drugs and Aging* vol. 22 101–114 (2005).

- 21 Mohlman, J. et al. Improving recognition of late life anxiety disorders in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: Observations and recommendations of the Advisory Committee to the Lifespan Disorders Work Group. *International Journal of Geriatric Psychiatry* vol. 27 549–556 (2012).
- 22 Lenze, E. J. et al. Comorbid anxiety disorders in depressed elderly patients. *Am. J. Psychiatry* 157, 722–728 (2000).
- 23 Mulsant, B. H., Reynolds, C. F., Shear, M. K., Sweet, R. A. & Miller, M. Comorbid anxiety disorders in late-life depression. *Anxiety* 2, 242–247 (1996).
- 24 Lenze, E. J. et al. Comorbidity of depression and anxiety disorders in later life. *Depression and Anxiety* vol. 14 86–93 (2001).
- 25 Schoevers, R. A., Beekman, A. T. F., Deeg, D. J. H., Jonker, C. & Van Tilburg, W. Comorbidity and risk-patterns of depression, generalised anxiety disorder and mixed anxiety-depression in later life: Results from the AMSTEL study. *Int. J. Geriatr. Psychiatry* 18, 994– 1001 (2003).
- 26 Kessler, R. C. et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry* vol. 62 593– 602 (2005).
- 27 Cipriani, A. et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 373, 746–758 (2009).
- 28 Raju, R., Corrigan, F. M., Davidson, A. J. W. & Johnso, D. Assessing and managing mild to moderate emotion dysregulation. *Advances in Psychiatric Treatment* vol. 18 82–93 (2012).
- 29 Spijker, J. et al. Multidisciplinaire richtlijn Depressie (Derde revisie): Richtlijn voor de diagnostiek, behandeling en begeleiding van volwassen patiënten met een depressieve stoornis. (2013).
- 30 van Balkom, A. J. L. M. et al. Multidisciplinaire richtlijn angststoornissen (Derde revisie): Richtlijn voor de diagnostiek, behandeling en begeleiding van volwassen patiënten met een angststoornis. (2013).
- 31 Trimbos-instituut. ADDENDUM Ouderen bij de MDR Depressie (1.0). <https://www.trimbos.nl/docs/b0822cf7-b915-44a2-9a55-db6ea341267a.pdf> (2008).
- 32 Trimbos-instituut. ADDENDUM Ouderen bij de MDR Angststoornissen (1.0). <https://assets-sites.trimbos.nl/docs/283be54e-a957-4f5d-ac51-f50e3137aeb9.pdf> (2008).
- 33 Schoevers, R. A., Van, H. L., Koppelmans, V., Kool, S. & Dekker, J. J. Managing the patient with co-morbid depression and an anxiety disorder. *Drugs* vol. 68 1621–1634 (2008).
- 34 Tarrier, N. (Ed.). Case formulation in cognitive behaviour therapy: The treatment of challenging and complex cases. *Case formulation in cognitive behaviour therapy: The treatment of challenging and complex cases*. Routledge/Taylor & Francis Group (2006).
- 35 Persons, J. B. Who Needs a Case Formulation and Why: Clinicians Use the Case Formulation to Guide Decision-Making. *Pragmatic Case Stud. Psychother.* 9, 12–12 (2013).
- 36 Schuurmans, J. et al. The outcome of anxiety disorders in older people at 6-year follow-up: Results from the Longitudinal Aging Study Amsterdam. *Acta Psychiatr. Scand.* 111, 420– 428 (2005).
- 37 Allgulander, C. & Lavori, P. W. Causes of death among 936 elderly patients with ‘pure’ anxiety neurosis in Stockholm County, Sweden, and in patients with depressive neurosis or both diagnoses. *Compr. Psychiatry* 34, 299–302 (1993).
- 38 Kendler, K. S., Kuhn, J. & Prescott, C. A. The Interrelationship of Neuroticism, Sex, and Stressful Life Events in the Prediction of Episodes of Major Depression. *Am. J. Psychiatry* 161, 631–636 (2004).

- 39 Spinhoven, P. et al. Positive and negative life events and personality traits in predicting course of depression and anxiety. *Acta Psychiatr. Scand.* 124, 462–473 (2011).
- 40 Comijs, H. & Dekker, J. The Netherlands Study of Depression in Older persons (NESDO). *Int. Psychogeriatrics* 23, S70–S71 (2011).
- 41 Appleby, L. et al. Safety First: Report of the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness. Report for the Department of Health, Department of Health. (2001).

CHAPTER 2

DEFINING ANXIOUS DEPRESSION IN LATER LIFE: A SCARING HETEROGENEITY IN RESULTS

Based on:

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ABSTRACT

Background

Anxiety in depression is challenging as it results in more functional impairment and a worse prognosis. No consensus exists on the definition of anxious depression.

Methods

In 359 older patients with major depressive disorder, we examined the agreement between anxious depression based on different combinations of comorbid anxiety disorders and anxious depression based on high level of anxiety symptoms measured by self-report questionnaires.

Results

Agreement between the definitions of anxious depression was poor, as indicated by kappa statistics ranging between 0.06 and 0.23.

Conclusions

Accepted criteria for anxious depression classify completely different patients as being anxious depressed. This may explain inconsistent results of previous studies on anxious depression. Moreover, progress in this research field is hampered, as studies using different definitions cannot be pooled in meta-analyses.

INTRODUCTION

Almost half of the depressed patients suffer from significant anxiety symptoms, whereas anxiety is no formal criteria of major depressive disorder (MDD)¹⁻⁴. In clinical practice anxious depression is challenging, as high anxiety levels in depression are associated with more impairment and a worse prognosis^{5,6}. Unfortunately, no consensus exists on the diagnostic criteria for anxious depression. Anxious depression has been defined as either MDD with high levels of anxiety symptoms based on symptom severity scales (dimensional approach) or as MDD with concurrent anxiety diagnosis (syndromal approach)^{7,8}. Although these differences are acknowledged, research findings are easily lumped together assuming substantial overlap^{7,8}. To our knowledge, this is the first study comparing the level of agreement between MDD with high levels of anxiety symptoms (dimensional approach) and MDD with comorbid anxiety disorders according to the DSM-IV-TR (syndromal approach).

METHODS

Comorbid anxiety was measured in 359 patients aged 60 years and above (range 60-90 years) suffering from a past 6-month MDD who participated in the Netherlands Study of Depression in Older people (NESDO)⁹. The study protocol of NESDO has been approved centrally by the Ethical Review Board of the VUMC and all persons give informed consent after oral and written information. All assessment instruments and the diagnostic interview used in NESDO have been chosen for their reliability among older people⁹. Furthermore, interviewers have been extensively trained and interviews have been audiotaped for quality assessments⁹.

Psychiatric disorders in the past 6 months were assessed with the Composites International Diagnostic Interview (CIDI) version 2.1 according to DSM-IV-R criteria (American Psychiatric Association, 2001)¹⁰. In addition to assessing MDD, we assessed social phobia (SP), generalized anxiety disorder (GAD), panic disorder (PD) with and without agoraphobia (AGO) and finally AGO. Rules concerning the hierarchical diagnostic structure of the DSM, where GAD cannot be diagnosed in the presence of MDD were not followed to make meaningful comparison possible. We did not assess specific phobia, as these disorders generally have very specific symptoms less relevant to depressive disorder, whereas panic attacks, worrying (or rumination), fear of rejection by others, are typical symptoms of depression as well as anxiety disorders. Moreover, specific phobias result in specific avoidance behaviour and are, especially in later life, unreliably recognised and diagnosed¹¹.

Severity of anxiety symptoms was measured using the Beck Anxiety Inventory (BAI)¹² and a revised version of the Worry Scale for Older Adults¹³. The BAI is a 21 item, self-report questionnaire primarily addressing somatic anxiety symptoms (range 0 – 63). A sum score of 0-9 indicates no anxiety, 10-18 mild to moderate anxiety, 19-29 moderate to severe anxiety, and 30-63, severe anxiety^{14,15}. A cut-off score of 19 is indicative of clinically relevant levels of anxiety, but other cut-off scores have also been suggested¹⁶⁻¹⁸. The Worry Scale was applied, as worry is part of the suggested symptoms in DSM-5 to use as an anxious specifier for major depression (difficulty concentration because of worry, fear that something awful may happen). Among 95 Dutch persons aged 65 years and over, the Worry Scale for Older Adults (WS)¹³ was shortened from 88 to 15 items that have to be rated on 5-point Likert scale (range 0 – 60). Based on factor loadings,

skewness in mean scores on each item, 15 items were selected for the shortened version yielding a Cronbach's alpha of 0.85¹⁹. Test-retest reliability of this shortened version was .90. No cut-off score for clinically relevant levels of worrying is available. In the present study, the correlation between the BAI and the shortened WS is .48 ($p < .001$).

The agreement between different definitions of anxious depression was examined using the Kappa statistic in order to correct for agreement by chance. A kappa of < 0.20 indicates poor agreement, 0.20-0.40 fair agreement, 0.40-0.60 moderate agreement, 0.60-0.80 good agreement, and 0.80-1.00 very good agreement²⁰. The syndromal approach will be based on comorbid anxiety disorders and defined as depression with GAD, depression with social phobia, depression with panic disorder with or without agoraphobia, depression with agoraphobia, and finally depression with any anxiety disorder. The dimensional approach will be based on scoring above a certain cut-off score on the BAI or WS. The cut-off point that results in the highest level of agreement will be reported.

RESULTS

The 359 patients (66% women) had an average age of 70.6 years (standard deviation (SD): 7.4). The mean mini mental state examination (MMSE) indicated good global cognitive functioning by a mean score of 27.7 points (SD: 2.0). The mean number of chronic diseases was 2.1 (SD: 1.5).

The 6-month prevalence of at least one anxiety disorder was 39.3% (141/359); comorbid social phobia occurred in 18.1%, panic disorder with and without agoraphobia in 15.0%, agoraphobia in 10.0% and generalized anxiety disorder in 9.7%. Out of the 141, a total of 41 were diagnosed with two comorbid anxiety disorders and 4 with three comorbid anxiety disorders. Furthermore, 41.9% (139/332) of the depressed patients suffered from clinically relevant anxiety symptoms, using the commonly applied cut-off of 19 on the BAI.

Table 1 shows the level of agreement between the different definitions of anxious depression based on the cut-off score of the BAI or WS that yielded the highest level of agreement of that particular comparison. Repeating the analyses in the subsample of patients with a past-month diagnosis of major depressive disorder and past-month comorbid anxiety disorders, did not substantially improve the level of agreement. As prevalence-rates of depression and anxiety are sex-specific, we also checked whether findings were different depending on gender. These post-hoc analyses did not show sex-differences.

Table 1. | Level of agreement by kappa-statistic (applied cut-off) between different criteria for anxious depression

Six-month diagnoses					
	Any AD	GAD	SP	PD+/-AGO	AGO
BAI	.23 (0.13 - .34) **	.06 (-.06 - .18)	.19 (.07 - .31) **	.19 (.05 - .33)**	.11 (.03 - .19)*
○ Cut-off#	17/18	29/30	25/26	40/41	19/20
WS	.17 (.06 - .22)*	.10 (-.02 - .24)	.07 (-.04 - .22)	.11 (.01 - .19)*	.12 (.03 - .19)*
○ Cut-off#	7/8	11/12	8/9	6/7	7/8
One-month diagnoses					
	Any AD	GAD	SP	PD+/-AGO	AGO
BAI	.18 (.08 - .28)**	.14 (.02 - .26)*	.22 (.09 - .35)**	.12 (-.04 - .28)*	.18 (-.02 - .39)*
○ Cut-off#	12/13	29/30	25/26	41/42	39/40
WS	.14 (.04 - .20)*	.11 (.00 - .23)*	.08 (.01 - .13)*	.07 (.01 - .14)*	.16 (-.03 - .35)*
○ Cut-off#	2/3	9/10	2/3	3/4	21/22

Abbreviations

AD, anxiety disorder; GAD, generalized anxiety disorder; SP, social phobia; PD, panic disorder; AGO, agoraphobia; BAI, Beck Anxiety Inventory; WS, revised Worry Scale.

Statistics

All statistics are based on the kappa-statistic, including the 95% confidence interval in parentheses, based on 332 (df: 331) valid cases for the 6-month diagnoses and 253 (df: 252) valid cases for the 1-month diagnoses.

* $p < .05$

** $p < .001$

The highest value given by the cut-off indicates anxious depression based on this score or higher has the highest level of agreement with the specific comorbid anxiety disorder according to the DSM-IV.

CONCLUSIONS

Our results confirm previously reported high levels of comorbid anxiety in late-life depression, with similar figures based on the syndromal definition (any anxiety diagnosis, 39%) and the dimensional measures (41% scored above predefined cut-off of the BAI). Nonetheless, agreement between the different definitions was very poor. As we explored for each categorical definition of anxious depression the optimal cut-off score on the BAI and WS, we even maximized the diagnostic accuracy in our sample²¹. In reality, results will be even worse. Depressed older persons who report a high level of worrying are thus a completely different group than those with a comorbid GAD of which worrying is a core symptom. Similarly, persons who report high levels of (somatic) anxiety symptoms are a different group than patients suffering from comorbid panic disorder with or without agoraphobia.

A possible explanation might be that depressed individuals reporting high levels of anxiety symptoms represent a clinically distinct depressive subtype (one disorder), whereas those individuals who meet criteria for major depression and an anxiety disorder may indeed suffer from two disorders. If true, our data point to a specific subtype of depression. This explanation fits with the DSM-5 criteria, proposing an anxious distress specifier to the diagnosis of MDD (DSM-5)²². This dimensional definition of anxious depression is defined as DSM- or ICD-diagnosed MDD plus at least two anxiety symptoms (feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, fear that something awful may happen or feeling that the individual might lose control of him- or herself) (DSM-5), but are also covered by BAI and the WS as used in our study.

Our study shows the importance to use a similar anxious distress specifier across studies. As Ionescu and colleagues⁸ state: 'Decreasing heterogeneity within research is a key enrichment strategy that will lead to better identification of neurobiologically salient subgroups, provide important insights into the neurobiology of anxious depression, and eventually lead to the development of novel targets for its treatment.' For example, Andreescu and colleagues showed that in later life, anxious depression defined as depression with high level of anxiety symptoms reported on the Brief Symptom Inventory has a significantly different fMRI activation pattern compared to pure late-life depression^{23,24}.

Accepted criteria for anxious depression classify completely different patients as being anxious depressed. This may explain inconsistent results of previous studies on anxious depression. As the best specifier for anxious symptoms remains unknown, we recommend using different definitions of anxious depression in studies on anxious depression to reduce the heterogeneity we have shown as well as the inconsistencies between studies. By comparing findings of different studies based on the same instruments, e.g., in meta-analytic procedures, more meaningful differences between patients with specific operationalization of anxious depression and non-anxious depression can be studied. This has important scientific as well as clinical benefits.

REFERENCES

- 1 Mulsant, B. H., Reynolds, C. F., Shear, M. K., Sweet, R. A. & Miller, M. Comorbid anxiety disorders in late-life depression. *Anxiety* 2, 242–247 (1996).
- 2 Beekman, A. T. F. et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am. J. Psychiatry* 157, 89–95 (2000).
- 3 Schoevers, R. A., Beekman, A. T. F., Deeg, D. J. H., Jonker, C. & Van Tilburg, W. Comorbidity and risk-patterns of depression, generalised anxiety disorder and mixed anxiety-depression in later life: Results from the AMSTEL study. *Int. J. Geriatr. Psychiatry* 18, 994–1001 (2003).
- 4 Fava, M. et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol. Med.* 34, 1299–1308 (2004).
- 5 Schoevers, R. A. Depression and Generalized Anxiety Disorder: Co-Occurrence and Longitudinal Patterns in Elderly Patients. *Am. J. Geriatr. Psychiatry* 13, 31–39 (2005).
- 6 Lenze, E. J. Comorbidity of depression and anxiety in the elderly. *Current Psychiatry Reports* vol. 5 62–67 (2003).
- 7 Baumeister, H. & Parker, G. A second thought on subtyping major depression. *Psychotherapy and Psychosomatics* vol. 79 388–389 (2010).
- 8 Ionescu, D. F., Niciu, M. J., Mathews, D. C., Richards, E. M. & Zarate, C. A. Neurobiology of anxious depression: A review. *Depression and Anxiety* vol. 30 374–385 (2013).
- 9 Comijs, H. & Dekker, J. The Netherlands Study of Depression in Older persons (NESDO). *Int. Psychogeriatrics* 23, S70–S71 (2011).
- 10 Wittchen, H. U. et al. Cross-cultural feasibility, reliability and sources of variance of the composite international diagnostic interview (CIDI). *Br. J. Psychiatry* 159, 645–653 (1991).
- 11 Mohlman, J. et al. Improving recognition of late life anxiety disorders in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: Observations and recommendations of the Advisory Committee to the Lifespan Disorders Work Group. *International Journal of Geriatric Psychiatry* vol. 27 549–556 (2012).
- 12 Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. An inventory for measuring clinical anxiety: Psychometric properties. *J. Consult. Clin. Psychol.* 56, 893–897 (1988).
- 13 Wisocki, P. A., Handen, B. & Morse, C. K. The Worry Scale as a measure of anxiety among homebound and community active elderly. *Behav. Ther.* 9, 91–95 (1986).
- 14 Beck, A. T. & Steer, R. A. Manual for the Beck Anxiety Inventory. San Antonio, TX, Psychological Corporation (1990).
- 15 Rush, A. J., First, M. B. & Burns, B. Handbook of psychiatric measures, 2nd ed. Washington, DC, American Psychiatric Publishing (2008).
- 16 Stein, M. B. et al. Development of a brief diagnostic screen for panic disorder in primary care. *Psychosom. Med.* 61, 359–364 (1999).
- 17 Leyfer, O. T., Ruberg, J. L. & Woodruff-Borden, J. Examination of the utility of the Beck Anxiety Inventory and its factors as a screener for anxiety disorders. *J. Anxiety Disord.* 20, 444–458 (2006).
- 18 Karsten, J., Nolen, W. A., Penninx, B. W. J. H. & Hartman, C. A. Subthreshold anxiety better defined by symptom self-report than by diagnostic interview. *J. Affect. Disord.* 129, 236–243 (2011).
- 19 Raabe, S., Weijers, A., Emmelkamp, P. M. G. & De Beurs, E. Internal report. Vakgroep Klinische Psychologie and Vrije Universiteit Amsterdam, Vakgroep Psychiatrie.
- 20 Altman, D. G. Practical Statistics for Medical Research. London, Chapman and Hall (1991).
- 21 Dawes, R. M., Faust, D. & Meehl, P. E. Clinical versus actuarial judgment. *Science*. 243, 1668–1674 (1989).

- 22 Regier, D. A. et al. DSM-5 field trials in the United States and Canada, part II: Test-retest reliability of selected categorical diagnoses. *Am. J. Psychiatry* 170, 59–70 (2013).
- 23 Andreescu, C. et al. fMRI activation in late-life anxious depression: A potential biomarker. *Int. J. Geriatr. Psychiatry* 24, 820–828 (2009).
- 24 Andreescu, C. et al. The default mode network in late-life anxious depression. *Am. J. Geriatr. Psychiatry* 19, 980–983 (2011).

CHAPTER 3

COMORBID ANXIETY DISORDERS IN LATE-LIFE DEPRESSION: RESULTS OF A COHORT STUDY

Based on:

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ABSTRACT

Background

Comorbid anxiety disorders are common in late-life depression and negatively impact treatment outcome. This study aimed to examine personality characteristics as well as early and recent life events as possible determinants of comorbid anxiety disorders in late-life depression, taking previously examined determinants into account.

Methods

Using the Composite International Diagnostic Interview (CIDI 2.0), we established comorbid anxiety disorders (social phobia, panic disorder, generalized anxiety disorder, and agoraphobia) in 350 patients (aged ≥ 60 years) suffering from a major depressive disorder according to DSM-IV-TR criteria within the past 6 months. Adjusted for age, sex and level of education, we first examined previously identified determinants of anxious depression: depression severity, suicidality, partner status, loneliness, chronic diseases and gait speed in multiple logistic regression models. Subsequently, associations were explored with the big five personality characteristics as well as early and recent life-events. First, multiple logistic regression analyses were conducted with the presence of any anxiety disorder (yes/no) as dependent variable, where after analyses were repeated for each anxiety disorder separately.

Results

In our sample, the prevalence rate of comorbid anxiety disorders in late-life depression was 38.6%. Determinants of comorbid anxiety disorders were a lower age, female sex, less education, higher depression severity, early traumatization, neuroticism, extraversion and conscientiousness. Nonetheless, determinants differed across the specific anxiety disorders and lumping all anxiety disorder together masked some determinants (education, personality).

Conclusions

Our findings stress the need to examine determinants of comorbid anxiety disorder for specific anxiety disorders separately, enabling the development of targeted interventions within subgroups of depressed patients.

INTRODUCTION

Comorbid anxiety disorders significantly add to the burden of depression in terms of impact on quality of life, physical disability, increased health care utilization and even mortality¹. Moreover, comorbid anxiety disorders negatively impact on treatment outcome of depression²⁻⁴. Knowledge of determinants of comorbid anxiety disorders in depression may guide development of more specific interventions. Nonetheless, the literature on “anxiety in depression” is difficult to interpret as studies on depressed patients with a high level of anxiety symptoms and depressed patients with concurrent anxiety disorders are often grouped together. Recently, we have shown that, in a sample of patients with depression, comorbid anxious distress or as comorbid anxiety disorders, identify completely different patients, where for example depressed older persons who report high levels of (somatic) anxiety symptoms are a different group than patients suffering from comorbid panic disorder⁵. Determinants of anxious distress and of comorbid anxiety disorders should therefore be examined separately. Although a number of studies examined risk factors for anxiety and depression⁶, to our knowledge, only four studies have explored determinants of comorbid anxiety disorders in late-life depression⁷⁻¹⁰. These studies found that comorbid anxiety disorders are associated with both, a higher level of psychological and somatic distress^{8,10}, a higher frequency of completed suicide¹¹ and suicidal ideation^{8,9}, as well as poorer social functioning⁸. Nonetheless, these determinants were not consistently found in each of the studies. Furthermore, personality characteristics as well as early and recent life-events are common risk factors for late-life anxiety and depressive disorders, but have not been studied as determinants of comorbid anxiety disorders in late-life depression⁶. Besides, these characteristics are important moderators for treatment outcome in old age psychiatry^{12,13}. Results from randomized controlled trials suggest that especially cluster C personality disorder negatively impact on antidepressant treatment outcome¹⁴, whereas epidemiological studies point to neuroticism as a predisposing and perpetuating factor in late-life depression¹⁵. Therefore, we hypothesise an association between personality characteristics and comorbid anxiety disorders in late-life depression.

The aim of this study was to examine personality characteristics as well as early and recent life events as possible determinants of comorbid anxiety disorders in late-life depression, taking previously examined determinants of higher levels of psychological, social and somatic distress into account. Since pure anxiety disorders are rare in later life¹⁶⁻¹⁸ and many treatment studies on late-life anxiety lump different anxiety disorder together, we first explored determinants of ‘any concurrent anxiety disorder’, where after we explored further differentiation between the different concurrent anxiety disorders.

METHODS

Study design and participants

This cross-sectional study is based on baseline data from the Netherlands Study of Depression in Older persons (NESDO), is a multi-site naturalistic cohort study that includes 378 depressed and 132 non-depressed subjects aged 60 through 93 years¹⁹. Persons with a clinical diagnosis of dementia or who were suspect for dementia, or a Mini Mental State Examination-score (MMSE)²⁰ under 18 (out of 30 points), and insufficient command of the Dutch language were excluded.

Psychiatric diagnoses were assessed with the Compositing International Diagnostic Interview (CIDI –version 2.1) according to DSM-IV-R criteria²¹.

For the present paper we firstly selected those patients who met the criteria for a major depressive episode within the past 6 months (n=359, 95%), therefore we excluded 19 patients who met the criteria for a minor depression of dysthymia only. Patients were classified as positive for a comorbid anxiety disorder if there was an anxiety disorder in the past 6 months, including social phobia (SP), generalized anxiety disorder (GAD), panic disorder (PD) with and without agoraphobia (AGO) and finally AGO. Rules concerning the hierarchical diagnostic structure of the DSM, where GAD cannot be diagnosed in the presence of MDD were not followed to make meaningful comparison possible. To avoid contamination of depressed patients with a recently remitted anxiety disorder, we excluded a further 9 patients who had an anxiety disorder in the past 12-months, but not anymore in the past 6 months.

Possible determinants of comorbid anxiety disorders

We characterized our population by age, gender and level of education (total educated years) as demographic characteristics. All other determinants were assessed with questionnaires (or tests) that have proven adequate psychometric properties among Dutch older persons. *Psychological functioning* – The severity of depressive symptoms was assessed with the 28-item self-report version of the Inventory of Depressive Symptomatology (IDS-SR)²². Thoughts of death or suicide during the past month were derived from CIDI questions. Participants were divided in three groups: 1) no thoughts of death or suicide; 2) thoughts of death but no thoughts of suicide; 3) thoughts, plans or attempts of suicide.

Physical health - The presence of chronic diseases was assessed by means of a self-report questionnaire applied by interviewer. First, screening questions were asked and in case of a positive answer, more detailed predefined questions are asked. Based on a validated algorithm, the presence of cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, COPD, arthritis, cancer, or any other chronic disease was assessed²³. Compared to general practitioner information, the accuracy of self-reports of these diseases was shown to be adequate and independent of cognitive impairment²³. Gait speed, a proxy for physical frailty²⁴, and best implemented using a short distance²⁵, was assessed by a six meters walk test²⁶.

Social functioning

Social functioning was indexed by having a stable relationship (yes/no) as well as the level of loneliness with the 11-item Loneliness and Affiliation scale²⁷.

Early life-events (childhood trauma)

Childhood trauma, including emotional neglect as well as psychological, physical and sexual abuse before the age of 16, was assessed using a structured inventory previously used in the Mental Health Survey and Incidence Study²⁸ and the Netherlands Study of Depression and Anxiety²⁹. A childhood abuse index was constructed ranging from 0 to 8, with higher scores indicating a higher frequency of childhood abuse³⁰.

Recent life-events

The occurrence of recent stressful life events was assessed using the List of Threatening Experiences (LTE)³¹. These events reflect the presence of life stressors during the past year, such as serious illness and injury, death of close friend or relative, unemployment, major financial loss, and loss of important relationships. The LTE has good test–retest reliability, high agreement between participant and informant ratings, and good agreement with interview-based ratings³². We dichotomized the number of life-events in the past year as none versus one or more life-events.

Personality

We assessed the big-five personality domains, i.e. neuroticism, extraversion, conscientiousness, agreeableness and openness to experience, with the 60-item NEO-Five Factor Inventory (NEO-FFI)³³. The psychometric properties of the Dutch version of the NEO-FFI are generally good³⁴. The internal consistencies of all domains range from acceptable to good, and are comparable to those of the American version. In addition, mastery was assessed with a Short Mastery Scale³⁵.

Analyses

Differences between depressed participants with or without a comorbid anxiety disorder were analysed by independent t-tests or chi-square statistics.

Multivariate logistic regression analyses were performed to assess the association between previously identified determinants of comorbid anxiety disorders. Age, sex and level of education were entered in each regression model with the presence (yes/no) of any comorbid anxiety disorder as the dependent variable. Subsequently, indicators of psychological functioning (depression severity, presence of suicidal ideation or intention), physical functioning (number of chronic somatic disease and gait speed) and social functioning (partner status, loneliness) were added using a forward stepwise procedure. In order to explore specific results for the different anxiety disorders, all analyses were repeated with the specific anxiety disorder as the dependent variable. In these analyses, depressed patients with a comorbid anxiety disorder other than the dependent variable were excluded.

Subsequently, recent life-events, early traumatisation, the big five personality characteristics, and level of mastery were added in separate models. These models will be adjusted for the determinants found to be significantly associated with comorbid anxiety disorders in any of the previous models described above. In these models, we also examined whether the presence of recent life-events interacted with the severity of childhood traumatisation or any of the personality traits, as theoretically, characterological vulnerable people may be more stress-responsive and thereby having a higher chance on a comorbid anxiety disorder.

RESULTS

The mean (standard deviation) age of the 350 patients was 70.7 (7.4) years old; 230 (65.7%) were female. See table 1 for further characteristics of the study population, stratified by the presence of any comorbid anxiety disorder.

Table 1 | Characteristics of study population stratified by presence of any comorbid anxiety disorder

		Comorbid anxiety disorder		
Determinants		No (n=215)	Yes (n=135)	Statistics
<i>Socio-demographic</i>				
• Age (years)	mean (SD)	71.9 (7.7)	68.8 (6.5)	t=3.9, df=348, p<.001
• Female sex	n (%)	132 (61.4)	98 (72.6)	X ² =4.6, df=1, p=.032
• Education (years)	mean (SD)	10.7 (3.4)	10.0 (3.3)	t=1.7, df=348, p=.093
<i>Psychological functioning:</i>				
• Depression severity (IDS-SR)	mean (SD)	28.4 (12.5)	33.3 (13.5)	t=-3.4, df=343, p=.001
• Suicidality (CIDI questions):				X ² =8.6, df=2, p=.014
○ Thoughts of death	n (%)	45 (20.9)	25 (18.5)	
○ Thoughts of suicide	n (%)	14 (6.5)	22 (16.3)	
<i>Social functioning:</i>				
• Stable relationship (yes)	n (%)	107 (49.8)	75 (55.6)	X ² =0.3, df=1, p=.291
• Loneliness scale	mean (SD)	6.7 (3.4)	6.6 (3.5)	t=0.1, df=323, p=.935
<i>Physical health:</i>				
• Number of chronic diseases	mean (SD)	2.1 (1.4)	2.1 (1.6)	t=1.3, df=347, p=.925
• Gait speed (seconds)*	mean (SD)	7.9 (1.5)	6.8 (1.5)	T<0.1, df=342, p=.606
<i>Life-events</i>				
• Presence of recent life-events	n (%)	61 (28.5)	42 (31.3)	X ² =0.3, df=1, p=.572
• Childhood Trauma Index	mean (SD)	0.9 (1.1)	1.3 (1.4)	t=-3.2, df=345, p=.001
<i>Personality:</i>				
• Neuroticism	mean (SD)	38.0 (7.2)	40.4 (6.4)	t=-3.1, df=323, p=.002
• Extraversion	mean (SD)	34.3 (6.0)	32.9 (7.1)	t=1.8, df=322, p=.066
• Openness	mean (SD)	29.7 (5.8)	28.6 (4.6)	t=1.8, df=320, p=.079
• Agreeableness	mean (SD)	43.9 (5.3)	44.4 (5.0)	t=-0.9, df=321, p=.392
• Conscientiousness	mean (SD)	36.9 (5.6)	36.1 (5.7)	t=1.3, df=322, p=.189
• Mastery	mean (SD)	15.0 (3.0)	15.6 (3.3)	t=-1.7, df=317, p=.089

* Analyses based on log-transformed values, which are back transformed for interpretation

A total of 135 (38.6%) patients suffered from any comorbid anxiety disorder. The most frequent comorbid anxiety disorder was social phobia (n=62, 17.7%), followed by panic disorder with and without agoraphobia (n=52, 14.9%), agoraphobia (n=36, 10.3%) and finally generalised anxiety disorder (n=33, 9.4%). Figures of the individual anxiety disorder do not add up to 38.6%, as 40 patients had 2 anxiety disorders and 4 patients had 3 anxiety disorders.

As shown in table 2, having a comorbid anxiety disorder was associated with a lower age and being female. Nonetheless, the determinants differed across the individual anxiety disorders. Of the determinants indicative of poor psychological and social functioning and physical health, only the severity of depressive symptoms reached significance in two of the models, i.e. as determinant of any comorbid anxiety disorder and as determinant of comorbid panic disorder.

Table 2 | Determinants of comorbid anxiety disorders in multivariate logistic regression analysis

Determinants	Any anxiety disorder	Social phobia	Panic disorder	Agoraphobia	GAD
<i>Socio-demographic:</i>					
• Age	0.94 [0.90-0.97]	0.95 [0.91-0.99]	0.95 [0.90-1.00]	n.s.	0.93 [0.88-0.99]
• Female sex	1.80 [1.09-2.97]	n.s.	2.92 [1.33-6.42]	n.s.	n.s.
• Education	n.s.	n.s.	n.s.	0.87 [0.78-0.98]	n.s.
<i>Psychological, social functioning & physical health*:</i>					
• Depression severity	1.02 [1.01-1.04]	n.s.	1.04 [1.02-1.07]	n.s.	n.s.

* Since suicidality, partner status, loneliness, number of somatic diseases, and gait speed did not reach significance in any of the models, these variables are not presented in the table.

Subsequently, we examined in separate logistic regression models (all adjusted for age, sex, level of education and severity of depression) whether recent and early life-events as well as each personality trait was associated with any comorbid anxiety disorder as well as with each comorbid anxiety disorder separately (see table 3). Recent life-events were not associated with any anxiety disorder. Early traumatisation was solely associated with panic disorder. Personality traits were not associated with comorbid anxiety disorders in general, but neuroticism, extraversion and conscientiousness were associated with social phobia, specifically. The presence of recent life-events did neither interact with early traumatisation, nor with any of the personality traits.

Table 3 | Life-events, early traumatisation and personality*

Determinants	Any anxiety disorder	Social phobia	Panic disorder	Agoraphobia	GAD
Traumatisation:					
• Recent life-events	n.s.	n.s.	n.s.	n.s.	n.s.
• Early traumatisation	1.22 [1.00-1.49]	n.s.	1.35 [1.05-1.73]	n.s.	n.s.
Personality:					
• Neuroticism	n.s.	1.06 [1.00-1.11]	n.s.	n.s.	n.s.
• Extraversion	n.s.	0.94 [0.90-0.99]	n.s.	n.s.	n.s.
• Openness	n.s.	n.s.	n.s.	n.s.	n.s.
• Agreeableness	n.s.	n.s.	n.s.	n.s.	n.s.
• Conscientiousness	n.s.	0.93 [0.88-0.98]	n.s.	n.s.	n.s.
• Mastery	n.s.	n.s.	n.s.	n.s.	n.s.

* Adjusted for age, sex, level of education and severity of depressive symptoms (see table 2).

DISCUSSION

In line with previous studies, we found that 38.6% of depressed older patients had a comorbid anxiety disorder^{8,10,36,37}. Important determinants of comorbid anxiety disorders include age, sex, depressive symptom severity and early traumatization. Nonetheless, determinants differ across the individual comorbid anxiety disorders and some determinants are even masked by lumping all anxiety disorders together, like level of education and the personality traits neuroticism, extraversion and conscientiousness. These findings point to the importance of acknowledging the individual comorbid anxiety disorders.

Prevalence

Previously reported prevalence rates of comorbid anxiety disorders in late-life depression ranges from 23% to 47.5%^{8,10,36,37}, which may be explained by several methodological differences. First of all, the heterogeneity in the type of anxiety disorders included is a relevant matter. Some studies have included post-traumatic stress disorder⁸ or obsessive-compulsive disorder^{36,37}, which are not classified as anxiety disorders anymore in the DSM-5, whereas also studies differ on the inclusion (or not) of specific phobia and generalized anxiety disorder^{8,36,37}. Nonetheless, the distribution of individual anxiety disorders as reported in previous studies is comparable to ours, with the highest prevalence rates for comorbid SP, followed by PD with or without AGO, AGO solely and finally GAD⁸. Widely discrepant prevalence rates of GAD can be explained by the minimal duration of these symptoms of 1 month, based on DSM-III criteria³⁷ versus 6 months when applying DSM-IV criteria^{8,10,36}. Secondly, studies use different diagnostic assessment instruments (e.g. the Compositio International Diagnostic Interview (CIDI)¹⁰, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)⁸, the Mini International Neuropsychiatric Interview (MINI)³⁶, or the Diagnostic Interview Schedule (DIS)³⁷ and have applied different time-windows (1-, 6- or 12-month diagnoses)^{10,36,37}.

Determinants

The impact of age was a generic effect across individual anxiety disorders; with younger patients having a higher likelihood of suffering from comorbid anxiety disorders. This is in line with findings of the National Comorbidity Survey-Replication showing a general decline of comorbid mood-anxiety disorders with age (55 years and older)³⁸ as well as with a general decrease in anxiety disorders in older compared to younger patients¹⁷. These findings stress the need to examine determinants of comorbid anxiety by age groups.

Although female sex, severity of depressive illness and early traumatisation were determinants of having any comorbid anxiety disorder, having a comorbid panic disorder primarily drove these effects. In adult samples, females have 2 - 2.5 times the risk of developing a panic disorder³⁹ and are more likely to develop more severe and chronic forms of panic disorder⁴⁰. Furthermore, females have a higher risk of being traumatised in early life⁴¹. Early traumatisation (childhood adversity) predisposes to developing a major depressive disorder as well as panic disorder^{42,43}, and in case of these disorders, early traumatisation is associated with a higher severity⁴⁴.

Besides these general issues that may explain our finding, there might be a diagnostic issue. In DSM-5, the depressive disorder specifier “with anxious distress” focuses on somatic anxiety symptoms. The anxious distress specifier is assumed to identify a more severe form of depression and can be assumed to have considerable overlap with the major depressive disorder with comorbid panic disorder, since somatic anxiety symptoms are the core symptoms of panic disorder. Therefore, we may not be looking at ‘pure’ comorbidity, but merely a heterogeneous group where some have a comorbid panic disorder and some have an anxious depression as a specific subtype of depression⁵.

None of the personality traits was associated with ‘any comorbid anxiety disorder’. When examined for the individual anxiety disorder separately, social phobia appeared to be associated with a higher level of neuroticism, lower level of extraversion and a lower level of conscientiousness. Avoidant personality disorder can be seen as a more severe and chronic form of social phobia^{45,46}. Interestingly, avoidant personality disorder is also associated with a higher level of neuroticism as well as with a lower level of extraversion⁴⁷. Low levels of extraversion typically are most marked in depression and social phobia⁴⁸. Our findings follow the same trend but leave the significantly lower score on conscientiousness unexplained.

In addition to the determinants we found, the absence of some determinants may also be relevant. First of all, recent life-events were neither associated with a comorbid anxiety disorder, nor interacted with any of the personality traits in explaining the presence of a comorbid anxiety disorder. Previously, life-events were found to be associated with anxiety symptoms in late-life depression, but this accounted for only 3% of variance when corrected for depression severity⁴⁹. Secondly, we did not find an independent effect of suicidality with comorbid anxiety disorder, which has been frequently reported in the literature on anxious depression in younger patients^{50,51}. This effect in younger and middle-aged adults have been assumed to be driven by having a

comorbid panic disorder^{11,52,53}. In old age, Bartels and colleagues also found that comorbid anxiety disorders were a significant correlate of suicidal and death ideation after controlling for depressive symptom severity⁹. We also found that having a comorbid anxiety disorder was associated with more thoughts of suicide. When corrected for depression severity, however, this association lost significance, conform earlier findings of Lenze and colleagues, who only found this association with GAD⁸.

Finally, comorbid generalised anxiety disorder as well as agoraphobia were hardly associated with specific determinants. Although speculative, it might be that in later life it is much more difficult to distinguish between worrying in generalised anxiety disorder and rumination in depression as well as depressive avoidance due to a lack of motivation and anxious avoidance due to anticipatory anxiety⁵⁴.

Methodological considerations

The strengths of our study are the large number of older persons suffering depression and high quality of data collection. Moreover, depressed persons were recruited from both mental health care institutes and general practices in order to include persons with late-life depression in various developmental and severity stages⁵⁵. Nonetheless, some limitations should also be acknowledged for proper interpretation. Firstly, the cross-sectional study design precludes causal interpretations of the findings. Secondly, we measured personality traits and depression at the same time. Although personality traits are stable, the presence of depression is known to amplify the personality profile of people prone to depression⁵⁶. After recovery of depression, however, the overall shape of the profile does not change⁵⁶. Furthermore, the relationship between change in personality and change in depressive symptoms is at most moderate⁵⁶⁻⁵⁹.

Implications/interpretation/conclusion

Since high anxiety levels in late-life depression have frequently been associated with negative treatment outcome, determinants of increased anxiety levels are of importance for guiding treatment development and refinement. Except one study, all outcome studies on late-life anxious depression, however, are based on (different) anxiety specifiers. An initial meta-analysis including trials published up to August 2006 did not find any impact on treatment outcome of increased anxiety symptoms in late-life depression⁶⁰. More recent studies, however, all point to negative effects of pre-treatment anxiety levels on treatment outcome in terms of a delayed or reduced response as well as a higher chance of relapse^{4,61-64}. The only two studies examining the impact of comorbid anxiety disorders in late-life depression showed a delayed response^{65,66}. These differential findings stress the need to include formal anxiety disorders as well as (different) anxiety specifiers when examining treatment outcome in late-life anxious depression.

REFERENCES

- 1 Schoevers, R. A., Van, H. L., Koppelmans, V., Kool, S. & Dekker, J. J. Managing the patient with co-morbid depression and an anxiety disorder. *Drugs* vol. 68 1621–1634 (2008).
- 2 Roca, M. et al. Clinical differences between early and late remission in depressive patients. *J. Affect. Disord.* 134, 235–241 (2011).
- 3 Greenlee, A. et al. Anxiety impairs depression remission in partial responders during extended treatment in late-life. *Depress. Anxiety* 27, 451–456 (2010).
- 4 Andreescu, C. et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: Controlled study. *Br. J. Psychiatry* 190, 344–349 (2007).
- 5 Van Der Veen, D. C., Comijs, H. C., Van Zelst, W. H., Schoevers, R. A. & Oude Voshaar, R. C. Defining anxious depression in later life: A scaring heterogeneity in results. *Am. J. Geriatr. Psychiatry* 22, 1375–1378 (2014).
- 6 Vink, D., Aartsen, M. J. & Schoevers, R. A. Risk factors for anxiety and depression in the elderly: a review. *J. Affect. Disord.* 106, 29–44 (2008).
- 7 Allgulander, C. & Lavori, P. W. Causes of death among 936 elderly patients with ‘pure’ anxiety neurosis in Stockholm County, Sweden, and in patients with depressive neurosis or both diagnoses. *Compr. Psychiatry* 34, 299–302 (1993).
- 8 Lenze, E. J. et al. Comorbid anxiety disorders in depressed elderly patients. *Am. J. Psychiatry* 157, 722–728 (2000).
- 9 Bartels, S. J. et al. Suicidal and death ideation in older primary care patients with depression, anxiety, and at-risk alcohol use. *Am. J. Geriatr. Psychiatry* 10, 417–427 (2002).
- 10 Cairney, J., Corna, L. M., Veldhuizen, S., Herrmann, N. & Streiner, D. L. Comorbid depression and anxiety in later life: Patterns of association, subjective well-being, and impairment. *Am. J. Geriatr. Psychiatry* 16, 201–208 (2008).
- 11 Allgulander, C. & Lavori, P. W. Causes of death among 936 elderly patients with ‘pure’ anxiety neurosis in Stockholm County, Sweden, and in patients with depressive neurosis or both diagnoses. *Compr. Psychiatry* 34, 299–302 (1993).
- 12 Veerbeek, M. A., Oude Voshaar, R. C. & Pot, A. M. Effectiveness and predictors of outcome in routine outpatient mental health care for older adults. *Int. Psychogeriatrics* 26, 1565–1574 (2014).
- 13 Newton-Howes, G., Tyrer, P. & Johnson, T. Personality disorder and the outcome of depression: Meta-analysis of published studies. *British Journal of Psychiatry* vol. 188 13–20 (2006).
- 14 Morse, J. Q. Impact of Cluster C Personality Disorders on Outcomes of Acute and Maintenance Treatment in Late-Life Depression. *Am. J. Geriatr. Psychiatry* 13, 808–814 (2005).
- 15 Steunenberg, B., Braam, A. W., Beekman, A. T. F., Deeg, D. J. H. & Kerkhof, A. J. F. M. Evidence for an association of the big five personality factors with recurrence of depressive symptoms in later life. *Int. J. Geriatr. Psychiatry* 24, 1470–1477 (2009).
- 16 Flint, A. J. Generalised anxiety disorder in elderly patients: Epidemiology, diagnosis and treatment options. *Drugs and Aging* vol. 22 101–114 (2005).
- 17 Kessler, R. C. et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Archives of General Psychiatry* vol. 62 593–602 (2005).
- 18 Lenze, E. J. et al. Generalized anxiety disorder in late life: Lifetime course and comorbidity with major depressive disorder. *Am. J. Geriatr. Psychiatry* 13, 77–80 (2005).
- 19 Comijs, H. & Dekker, J. The Netherlands Study of Depression in Older persons (NESDO). *Int. Psychogeriatrics* 23, S70–S71 (2011).
- 20 Folstein, M. F., Folstein, S. E. & McHugh, P. R. ‘Mini-mental state’. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198 (1975).

- 21 Wittchen, H. U. et al. Cross-cultural feasibility, reliability and sources of variance of the composite international diagnostic interview (CIDI). *Br. J. Psychiatry* 159, 645–653 (1991).
- 22 Rush, A. J., Gullion, C. M., Basco, M. R., Jarrett, R. B. & Trivedi, M. H. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol. Med.* 26, 477–486 (1996).
- 23 Kriegsman, D. M. W., Penninx, B. W. J. H., Van Eijk, J. T. M., Boeke, A. J. P. & Deeg, D. J. H. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J. Clin. Epidemiol.* 49, 1407–1417 (1996).
- 24 Peel, N. M., Kuys, S. S. & Klein, K. Gait speed as a measure in geriatric assessment in clinical settings: A systematic review. *Journals of Gerontology - Series A Biological Sciences and Medical Sciences* vol. 68 39–46 (2013).
- 25 Abellan Van Kan, G. et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) task force. *J. Nutr. Heal. Aging* 13, 881–889 (2009).
- 26 Cesari, M. et al. Prognostic value of usual gait speed in well-functioning older people - Results from the health, aging and body composition study. *J. Am. Geriatr. Soc.* 53, 1675– 1680 (2005).
- 27 de Jong-Gierveld, J. & Kamphuis, F. The Development of a Rasch-Type Loneliness Scale. *Appl. Psychol. Meas.* 9, 289–299 (1985).
- 28 De Graaf, R., Bijl, R. V., Ten Have, M., Beekman, A. T. F. & Vollebergh, W. A. M. Pathways to comorbidity: The transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *J. Affect. Disord.* 82, 461– 467 (2004).
- 29 Penninx, B. W. J. H. et al. The Netherlands Study of Depression and Anxiety (NESDA): Rationale, objectives and methods. *Int. J. Methods Psychiatr. Res.* 17, 121–140 (2008).
- 30 Comijs, H. C. et al. Childhood abuse in late-life depression. *J. Affect. Disord.* 147, 241–246 (2013).
- 31 Brugha, T., Bebbington, P., Tennant, C. & Hurry, J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol. Med.* 15, 189–194 (1985).
- 32 Brugha, T. S. & Cragg, D. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatr. Scand.* 82, 77–81 (1990).
- 33 Costa, P. T. Jr & McCrae, R. R. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. *J. Pers. Assess.* 64, 21–50 (1995).
- 34 Hoekstra, H. A., Ormel, J. & de Fruyt, F. NEO-PI-R (NEO Personality Inventory) Big Five. Swets Test Publishers. (2003).
- 35 Pearlin, L. I. & Schooler, C. The structure of coping. *J. Health Soc. Behav.* 19, 2–21 (1978).
- 36 Ritchie, K. et al. Prevalence of DSM-IV psychiatric disorder in the French elderly population. *Br. J. Psychiatry* 184, 147–152 (2004).
- 37 Beekman, A. T. F. et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am. J. Psychiatry* 157, 89–95 (2000).
- 38 Byers, A. L., Yaffe, K., Covinsky, K. E., Friedman, M. B. & Bruce, M. L. High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 67, 489–496 (2010).
- 39 Sheikh, J. I., Leskin, G. A. & Klein, D. F. Gender differences in panic disorder: Findings from the national comorbidity survey. *American Journal of Psychiatry* vol. 159 55–58 (2002).
- 40 Yonkers, K. A., Bruce, S. E., Dyck, I. R. & Keller, M. B. Chronicity, relapse, and illness - Course of panic disorder, social phobia, and generalized anxiety disorder: Findings in men and women from 8 years of follow-up. *Depress. Anxiety* 17, 173–179 (2003).

- 41 Dong, M., Anda, R. F., Dube, S. R., Giles, W. H. & Felitti, V. J. The relationship of exposure to childhood sexual abuse to other forms of abuse, neglect, and household dysfunction during childhood. *Child Abus. Negl.* 27, 625–639 (2003).
- 42 Young, E. A., Abelson, J. L., Curtis, G. C. & Nesse, R. M. Childhood adversity and vulnerability to mood and disorders. *Depress. Anxiety* 5, 66–72 (1997).
- 43 Goodwin, R. D., Fergusson, D. M. & Horwood, L. J. Childhood abuse and familial violence and the risk of panic attacks and panic disorder in young adulthood. *Psychol. Med.* 35, 881–890 (2005).
- 44 Kim, S. W. et al. Impact of childhood adversity on the course and suicidality of depressive disorders: The crescend study. *Depress. Anxiety* 30, 965–974 (2013).
- 45 Lampe, L. & Sunderland, M. Social phobia and avoidant personality disorder: Similar but different? *J. Pers. Disord.* 29, 115–130 (2015).
- 46 Chambless, D. L., Fydrich, T. & Rodebaugh, T. L. Generalized social phobia and avoidant personality disorder: Meaningful distinction or useless duplication? *Depress. Anxiety* 25, 8–19 (2008).
- 47 Samuel, D. B. & Widiger, T. A. A meta-analytic review of the relationships between the five-factor model and DSM-IV-TR personality disorders: A facet level analysis. *Clinical Psychology Review* vol. 28 1326–1342 (2008).
- 48 Saulsman, L. M. & Page, A. C. The five-factor model and personality disorder empirical literature: A meta-analytic review. *Clin. Psychol. Rev.* 23, 1055–1085 (2004).
- 49 Flint, A. J. & Rifat, S. L. Relationship between clinical variables and symptomatic anxiety in late-life depression. *Am. J. Geriatr. Psychiatry* 10, 292–296 (2002).
- 50 Sareen, J. et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: A population-based longitudinal study of adults. *Arch. Gen. Psychiatry* 62, 1249–1257 (2005).
- 51 Goes, F. S. et al. Co-morbid anxiety disorders in bipolar disorder and major depression: Familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. *Psychol. Med.* 42, 1449–1459 (2012).
- 52 Johnson, J., Weissman, M. M. & Klerman, G. L. Panic Disorder, Comorbidity, and Suicide Attempts. *Arch. Gen. Psychiatry* 47, 805–808 (1990).
- 53 Andrade, L., Eaton, W. W. & Chilcoat, H. Lifetime comorbidity of panic attacks and major depression in a population-based study. *Symptom profiles. Br. J. Psychiatry* 165, 363–369 (1994).
- 54 Mohlman, J. et al. Improving recognition of late life anxiety disorders in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: Observations and recommendations of the Advisory Committee to the Lifespan Disorders Work Group. *International Journal of Geriatric Psychiatry* vol. 27 549–556 (2012).
- 55 Comijs, H. C. et al. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Res. Notes* 4, 524 (2011).
- 56 Costa, P. T. Jr, Bagby, R. M., Herbst, J. H. & McCrae, R. R. Personality self-reports are concurrently reliable and valid during acute depressive episodes. *J. Affect. Disord.* 89, 45–55 (2005).
- 57 Santor, D. A., Bagby, R. M. & Joffe, R. T. Evaluating stability and change in personality and depression. *Journal of Personality and Social Psychology* vol. 73 1354–1362 (1997).
- 58 Ormel, J., Oldehinkel, A. J. & Vollebergh, W. Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Arch. Gen. Psychiatry* 61, 990–996 (2004).
- 59 Spinhoven, P., Penelo, E., de Rooij, M., Penninx, B. W. & Ormel, J. Reciprocal effects of stable and temporary components of neuroticism and affective disorders: results of a longitudinal cohort study. *Psychol. Med.* 44, 337–348 (2014).
- 60 Nelson, J. C., Delucchi, K. & Schneider, L. S. Anxiety does not predict response to antidepressant treatment in late life depression: Results of a meta-analysis. *Int. J. Geriatr. Psychiatry* 24, 539–544 (2009).

- 61 Greenlee, A. et al. Anxiety impairs depression remission in partial responders during extended treatment in late-life. *Depress. Anxiety* 27, 451–456 (2010).
- 62 Saghaei, R. et al. Predicting 6-week treatment response to escitalopram pharmacotherapy in late-life major depressive disorder. *Int. J. Geriatr. Psychiatry* 22, 1141–1146 (2007).
- 63 Dew, M. A. et al. Temporal profiles of the course of depression during treatment: Predictors of pathways toward recovery in the elderly. *Arch. Gen. Psychiatry* 54, 1016– 1024 (1997).
- 64 Flint, A. J. & Rifat, S. L. The effect of treatment on the two-year course of late-life depression. *Br. J. Psychiatry* 170, 268–272 (1997).
- 65 Mulsant, B. H., Reynolds, C. F., Shear, M. K., Sweet, R. A. & Miller, M. Comorbid anxiety disorders in late-life depression. *Anxiety* 2, 242–247 (1996).
- 66 Hegel, M. T. Impact of Comorbid Panic and Posttraumatic Stress Disorder on Outcomes of Collaborative Care for Late-Life Depression in Primary Care. *Am. J. Geriatr. Psychiatry* 13, 48–58 (2005).

CHAPTER 4

SUICIDE IN LATE-LIFE DEPRESSION WITH AND WITHOUT COMORBID ANXIETY DISORDERS

Based on:

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ABSTRACT**Background**

Comorbid anxiety in depression increases the risk of suicidal ideation and behavior, although data on death by suicide are scarce. We compared characteristics of depressed older patients with and without anxiety disorders who died by suicide.

Methods

From a 16-year clinical survey of all suicides in the United Kingdom (n=25,128) we identified 1,909 cases aged ≥ 60 years with a primary diagnosis of depression and no comorbidity other than anxiety disorders. Clinical characteristics of cases with (n=333, 17.4%) and without (n=1,576) comorbid anxiety disorders were compared by logistic regression adjusted for demographic differences.

Results

Compared to cases without comorbid anxiety disorders, cases with comorbid anxiety disorders were more likely to have a duration of illness over one year ($OR_{1-5 \text{ year}} = 1.4$ [95% CI: 1.0–1.9], $p=.061$; $OR_{\geq 5 \text{ years}} = 1.4$ [95% CI: 1.6–2.8], $p<.001$), were more frequently prescribed psychotropic drugs other than antidepressants, lithium and antipsychotics ($OR=2.1$ [95% CI: 1.6–2.7], $p<.001$), and were more distressed during their last contact with services ($OR=1.3$ [95% CI: 1.0–1.7], $p=.037$). In contrast, clinicians estimated the immediate as well as long-term suicidal risk lower in those with comorbid anxiety disorders ($OR=0.6$ [95% CI: 0.3–0.9], $p=.011$ and $OR=0.7$ [95% CI: 0.6–1.0], $p=.028$, respectively).

Conclusions

Among depressed suicide cases, a comorbid anxiety disorder was identified in one out of six cases and associated with a higher prevalence of several suicide risk factors. This is important, as the detection of anxiety disorders comorbid to depression seems rather low and even when recognized clinicians rated such individuals as at low suicide risk.

INTRODUCTION

Suicide is the 10th leading cause of death worldwide¹. Elderly suicides add significantly to the number of suicides with a three-fold rise in suicide rates in those aged 75 years and over compared to those aged 15-24 years². About 90% of all suicides are preceded by axis I psychiatric disorders, in later life most often a depressive disorder^{3,4}. Anxiety disorders are often comorbid to depressive illness in later life and may add to the suicidal risk⁵⁻⁷.

The prevalence of comorbid anxiety disorders in late-life depression has been estimated between 35% and 52%^{5,8-11}, with declining prevalence with increasing age¹². Concurrent anxiety disorders add greatly to the burden of depression, reflected in more psychological distress¹³, poorer social functioning^{5,13}, poorer physical functioning¹³, greater memory decline over time¹⁴ and a higher level of suicidality⁵⁻⁷. Studies on the association between suicidality and comorbid depression and anxiety traditionally focus on suicidal ideation and/or attempted suicide as completed suicide is rare, even in high-risk groups. Several studies have indeed identified a higher level of suicidal ideation or higher frequency of suicide attempts in the presence of anxiety, either defined as an increased anxiety level^{15,16} or as a concurrent anxiety disorder^{5,6}. Nonetheless, results are equivocal and negative results have also been reported¹³. The WHO World Mental Health survey showed that psychiatric disorders predicted the onset of suicidal ideation and/or suicide attempts¹⁷. The same surveys, however, also showed that the vast majority of psychiatric disorders did not predict the progression from suicidal ideation to attempts, but the few disorders that did were characterized by poor impulse control or high anxiety levels¹⁷.

To our knowledge, only one study reported on the association between depression-anxiety comorbidity and suicide in later life⁷. Based on a psychiatric case register of inpatients in Stockholm County over the period 1969 – 1986, the authors showed that both anxiety neurosis and depressive neurosis were independently associated with suicide in patients aged 70 years and above. The suicide rate was disproportionally higher in case of comorbid depressive and anxious neurosis⁷. Detailed characteristics of the study population, however, were not available.

The ongoing National Confidential Inquiry into Suicide and Homicide by People with Mental Illness collects detailed data on all cases of suicide in the United Kingdom from as early as April 1996^{18,19}. These data offer the unique opportunity to examine the characteristics of depressed older patients with and without comorbid anxiety disorders who died by suicide, which was the primary aim of the present study. We hypothesised to find 1) high prevalence rates of comorbid anxiety among depressed older patients who died by suicide, and 2) more pronounced suicidal risk indicators in those with comorbid anxiety disorder compared to depressed cases without comorbid anxiety disorder who died by suicide.

MATERIALS AND METHODS

The study was carried out as part of the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness¹⁸, a complete national clinical sample of all people that had been in contact with mental health services in the 12 months prior to their death by suicide. The Inquiry has research ethics approval (South Manchester Research Ethics Committee ERP/96/2771) and approval under Section 60 of the Health and Social Care Act to process patient-identifiable data without consent. The data collection on suicides involved three stages: 1) collection of a comprehensive national sample, irrespective of mental health history; 2) identification of people in the sample who had been in contact with mental health services in the 12 months before death; and 3) collection of clinical data about these individuals. Data collection has been described in detail elsewhere^{20,21}, and is summarized below.

Comprehensive national sample

Information on all deaths in England and Wales receiving a suicide or an open verdict at coroner's inquest was obtained from the Office for National Statistics (ONS). The cases presented here consist of those deaths which occurred between January 1, 1997 and December 31, 2012. In the first 3 years of the study, this information was cross checked against equivalent data from the health authorities in England and Wales; inconsistencies were rare. Open verdicts, recorded as deaths from undetermined external cause, are often reached in cases of suicide in the UK and are conventionally included in research on suicide and in official suicide statistics²². In this study, open verdicts were included unless it was clear that suicide was not considered at inquest – for example, in deaths from an unexplained medical cause.

Identification of mental health service contact and collection of clinical data

Identifying details on each individual who had died by suicide were submitted to the main hospital and community NHS trusts who provided mental health services to people living in the deceased's district of residence. When NHS records showed that contact had occurred in the 12 months before the suicide, the person became an "Inquiry case". For each inquiry case, the consultant psychiatrist was sent a questionnaire and asked to complete it based on their knowledge of the patient, psychiatry case-notes, and in discussion with other members of the mental health team. The questionnaire consisted of sections covering social/demographic characteristics, clinical history, details of the suicide, aspects of care, details of final contact with mental health services and clinicians' views on suicide prevention. Clinicians were also asked for the ICD-10 primary diagnosis and also any ICD-10 secondary diagnoses (or previous versions) for which the patient was in contact with mental health services²³. The social and clinical items reflected many of the most frequently reported risk factors for suicide. The majority of items were factual but some (for example, adherence to treatment) were based on the judgments of clinicians.

Case-ascertainment

Patients aged 60 years or over at the time of suicide with a primary diagnosis of a depressive disorder based on ICD-10 criteria (or previous version) by the responding clinician were selected for the present study. The age cut-off of 60 years was chosen based on previous studies on late-life depression^{24,25}.

Since depressive disorder frequently clusters with other psychiatric disorders, comorbidity other than anxiety disorders might be responsible for increased suicide rates in anxious depression. To preclude contamination by other psychiatric disorders, we a priori decided to exclude all patients with comorbid psychiatric disorders other than an anxiety disorder for the present study. Selected cases were subsequently classified as depression with and without a comorbid anxiety disorder.

In order to show the potential impact of our selection criteria, the prevalence of comorbid anxiety disorders in our study population was also compared to those in younger (<60 years) cases (applying the same selection criteria) as well as in all older cases without any restriction on psychiatric comorbidity.

Statistical analysis

All data are presented as absolute numbers and percentages within groups. If an item of information was not known for a case, the case was removed from the analysis of that item; the denominator in all estimates is therefore the number of valid cases for the item.

First, depressed cases with and without comorbid anxiety disorders who died by suicide were compared with respect to demographic characteristics using t-tests for continuous variables and chi-square tests for categorical variables.

As the study was mainly explorative, group differences with respect to the clinical, behavioural and care characteristics are presented as odds ratios (OR) with 95% confidence intervals (CI) based on logistic regression adjusted for all demographic characteristics significant at $p < .10$.

All analyses were conducted in SPSS version 20.0. As correcting for multiple comparisons may increase the risk of type II error, we have chosen to present all individual p-values²⁶.

RESULTS

Sample characteristics

Over the 16-year study period, the Inquiry received notifications of 94,922 deaths by suicide, including 67,747 (71%) cases in which the coroner's verdict was suicide and 27,175 (29%) open verdicts or deaths from undetermined cause. Of these, 25,740 (27%) were confirmed to have been in contact with mental health services in the year prior to death. Completed questionnaires were received on 25,128 cases, a response rate of 98%. Of the 25,128 persons who died by suicide in the United Kingdom between January 1st 1997 and December 31st 2012, a total of 8,534 (34.0%) had a primary diagnosis of depressive illness.

Table 1 presents the prevalence of comorbid anxiety disorders stratified for age at 60 years and presented with and without psychiatric comorbidity other than anxiety disorders. A total of 333 (17.4%) of our population of interest (n=1,909) had a comorbid anxiety disorder. Of these 1,909 cases, the mean (standard deviation) age at time of death was 69.8 (7.9) years, 1059/1909 (55.5%) were men, and only 52/1909 (2.7%) were of non-white ethnic origin.

Table 1. | Number (n) of suicide cases by age (split at 60 years) and comorbid anxiety disorder

	Age group		
Variable	Young (<60 years)	Old (≥60 years)	χ ² statistics
<i>Comorbidity other than anxiety</i>			
Pure depression, <i>n</i> (%)	5086 (84.6)	2091 (82.9)	<i>p</i> =.059
Comorbid anxiety disorder, <i>n</i> (%)	927 (15.4)	430 (17.1)	
<i>No comorbidity other than anxiety:</i>			
No comorbid anxiety disorder, <i>n</i> (%)	2848 (82.4)	1576 (82.6)	<i>p</i> =.873
Comorbid anxiety disorder, <i>n</i> (%)	609 (17.6)	333 (17.4)	

Table 2. | Socio-demographic characteristics in depressed older (≥60 years) suicide cases with and without comorbid anxiety disorder

Variable	Comorbid anxiety disorder (n=333)	Pure depression (n=1576)	χ^2 statistics
Age (years), mean (SD)	69.5 (7.5)	70.4 (8.0)	$p=.074$
Male sex, n (%)	154 (46.2)	905 (57.4)	$p<.001$
Marital/civil status:			
Divorced, n (%)	42 (12.7)	217 (13.9)	$p=.223$
Married/co-habiting, n (%)	181 (54.7)	760 (48.8)	
Single, n (%)	28 (8.5)	131 (8.4)	$p=.529$
Widowed, n (%)	80 (24.2)	450 (28.9)	
Living in the community (house or flat), n (%)	309 (94.2)	1478 (95.5)	$p=.021$
Living alone, n (%)	211 (63.7)	890 (56.8)	

Table 2 shows that cases with comorbid anxiety disorders were more often female, more often lived alone, and were younger compared to depressed cases without comorbidity, although the latter did not reach statistical significance. Further analyses on the comparison of clinical and care characteristics will therefore be corrected for age, sex and living arrangements.

Method of suicide

The commonest method of suicide among depressed patients with comorbid anxiety disorders ($n=333$) was hanging (119, 35.8%), followed by self-poisoning (80, 24.1%), drowning (44, 13.3%), and jumping from a height or in front of a moving vehicle (41, 12.3%). All other methods were used by less than 10% of the sample: suffocation (16, 4.8%), cutting or stabbing (10, 3.0%), CO-poisoning (7, 2.1%), burning (5, 1.5%), or other methods (10, 3.0%). The most common drugs used in self-poisoning were paracetamol (acetaminophen) either in pure form or combined with opiates (20/72, 27.8%) and antidepressants (18/72, 25.0%), followed by miscellaneous drugs and poisons which could not be categorized meaningfully. Neither the method of suicide nor the substances used in case of self-poisoning differed between patients with anxious and non-anxious depression.

Clinical characteristics

Table 3 presents the clinical and behavioural characteristics. Adjusted for age, sex, and living arrangements, cases with comorbid anxiety disorders had a significantly longer duration of illness compared to those without. Furthermore, at their last contact with a mental health professional before dying by suicide, depressed patients with comorbid anxiety disorders more often suffered from emotional distress, whereas they less often suffered from a deterioration of their physical health or from psychotic symptoms compared to depressed patients without anxiety.

With respect to the frequency of any adverse life-event in the three months before they died by suicide, the two groups did not differ. Nonetheless, with respect to the individual life-events, we found that cases with comorbid anxiety were less likely to have experienced bereavement or physical health problems compared to cases without comorbid anxiety.

Treatment was similar between both groups, excepted for psychotropic drug use other than antidepressants, lithium or antipsychotics, which were prescribed more often in cases of comorbid anxiety.

Finally, both the immediate risk as well as the long-term risk was significantly less often considered at a moderate or high level compared to this risk in purely depressed older patients.

Table 3. | Clinical characteristics of depressed older (≥ 60 years) suicide cases with and without comorbid anxiety disorder

Variable, n (%)	Comorbid anxiety disorder (n=333)	Pure depression (n=1576)	Statistics
	N (%)	N (%)	OR [95% CI], p-value
<i>Psychiatric history</i>			
Duration of depressive illness:			
Less than 12 months	83 (25.1)	580 (37.3)	Reference group
1-5 years	88 (26.6)	451 (29.0)	1.37 [0.99 – 1.90], p=.061
More than 5 years	160 (48.3)	522 (33.6)	2.09 [1.56 – 2.81], p<.001
History of self-harm	176 (53.0)	874 (56.1)	0.85 [0.67 – 1.08], p=.175
History of violence	9 (2.8)	36 (2.3)	1.35 [0.64 – 2.87], p=.435
History of alcohol misuse	28 (8.6)	133 (8.6)	1.14 [1.10 – 1.83], p=.562
History of drug misuse	3 (0.9)	21 (1.4)	0.73 [0.22 – 2.50], p=.620
<i>Somatic history</i>			
Major physical illness *	69 (34.2)	324 (37.7)	0.92 [0.66 – 1.28], p=.623
<i>Life event (in 3 months before suicide)</i>			
Any life-event, n (%)	109 (35.0)	548 (37.3)	0.91 [0.70 – 1.18], p=.476
Interpersonal problems	20 (6.4)	119 (8.1)	0.78 [0.48 – 1.28], p=.320
Bereavement	8 (2.6)	98 (6.7)	0.39 [0.19 – 0.82], p=.013
Health problems in patient	25 (8.0)	174 (11.9)	0.65 [0.41 – 1.02], p=.059
Material (financial/housing) problems	30 (9.6)	117 (8.0)	1.31 [0.86 – 2.01], p=.214
Legal of crime related problems	3 (1.0)	16 (1.1)	0.92 [0.27 – 3.21], p=.898
Other problems	37 (11.9)	125 (8.5)	1.34 [0.90 – 1.99], p=.147
<i>Psychiatric symptoms noted at last contact</i>			
Emotional distress	121 (37.6)	461 (30.1)	1.31 [1.02 – 1.69], p=.037
Deterioration of physical health	35 (10.9)	239 (15.6)	0.67 [1.05 – 1.75], p=.041
Delusions or hallucinations	5 (1.6)	62 (4.0)	0.35 [0.14 – 0.88], p=.025
Hostility	4 (1.2)	35 (2.3)	0.54 [0.19 – 1.53], p=.242
Recent self-harm	25 (7.7)	120 (7.8)	0.97 [0.62 – 1.53], p=.896
Hopelessness	53 (16.8)	234 (15.4)	1.06 [0.76 – 1.47], p=.740
Suicidal ideas	28 (8.9)	162 (10.7)	0.78 [0.51 – 1.20], p=.256
<i>Treatment received in the year prior to death</i>			
Antidepressants:			
SSRI or SNRI	197 (67.5)	899 (66.2)	1.06 [0.81 – 1.39], p=.677
Tricyclic antidepressants	50 (17.4)	199 (14.8)	1.17 [0.83 – 1.65], p=.365
Other antidepressants	50 (22.7)	250 (26.1)	0.82 [0.58 – 1.16], p=.265
All antipsychotics combined	96 (33.2)	443 (32.9)	0.94 [0.71 – 1.23], p=.636
Lithium	29 (10.0)	120 (8.9)	1.13 [0.73 – 1.74], p=.578
Other psychotropic drug use	151 (52.4)	451 (33.6)	2.11 [1.63 – 2.74], p<.001
Psychological treatment	60 (20.3)	232 (17.2)	1.17 [0.85 – 1.61], p=.350
<i>Estimated suicide risk at last contact</i>			
Moderate/high immediate suicide risk:	23 (7.4)	177 (11.8)	0.55 [0.34 – 0.87], p=.011
Moderate/high long term suicide risk:	89 (31.2)	508 (38.2)	0.73 [0.56 – 0.97], p=.028

* Only available for patients who died by suicide after 2005

DISCUSSION

In contrast to our hypothesis, postulating high depression-anxiety comorbidity rates in depressed older patients who had died by suicide, we found that only 17% of cases suffered from a comorbid anxiety disorder. This low prevalence rate of comorbid anxiety disorders is far below reported depression-anxiety comorbidity rates in population-based and clinical samples^{5,9–12,27}. Although underdiagnosis of comorbid anxiety disorders will dilute potential differences between depressed cases with and without comorbid anxiety disorders, our study still shows a more severe psychopathological profile of those cases with comorbid anxiety disorders. Cases with comorbid anxiety disorders had a longer duration of illness, more emotional distress during their last contact with the mental health team and were prescribed more psychotropic drugs (other than antidepressants, lithium or antipsychotics). In contrast with these findings, the short- and long-term suicide risk of depressed patients with comorbid anxiety disorders was considered significantly less by their treating clinicians compared to those without. This suggests that the presence of comorbid anxiety disorders did not trigger clinicians to recognise suicide risk. Since those with depression only were more likely to have experienced recent life events, such as those related to poor physical health or bereavement, this might suggest that clinicians' risk assessments are focussing on immediate or recent risk factors rather than long-term vulnerabilities. Prediction of suicide, however, is still one of the most difficult tasks in mental health care. The accuracy of instruments developed to predict suicide is usually disappointing^{28,29}, which limits their use for supporting clinicians in performing a thorough assessment. However, in a recent study risk stratification based on data of electronic medical records of 7,399 patients with heightened suicide risk was significantly more accurate than clinical assessment aided with an 18-point clinical scale in predicting suicide over the next six months³⁰.

The low prevalence rate of comorbid anxiety disorder merits further discussion. This finding cannot be explained by an age-effect or by our strict inclusion criteria excluding cases with comorbidity other than anxiety disorders (see table 1). Detection bias may be an explanation for the difference with epidemiological and clinical studies. Firstly, responsible clinicians may not diagnose anxiety disorders appropriately in case of late-life depression, leaving many comorbid anxiety disorders unrecognized. For example, a prospective study on the prevalence of comorbid anxiety disorders in late-life depression showed markedly higher comorbidity rates⁵ compared to a retrospective analysis of depressed older inpatients of the same research group³¹. The discrepancy was explained by training effects of clinicians in recognizing and diagnosing late-life anxiety disorders among depressed patients for the prospective study³². For example, excessive worrying due to generalized anxiety disorders may be easily regarded as rumination in depression, agoraphobic avoidance as anhedonia, and finally classic panic attacks as a symptom of depression severity³³. The diagnostic difficulties of assessing anxiety disorders in depressed patients do not seem to be age-specific, since we found similar rates of comorbid anxiety disorders in our younger age group. Secondly, epidemiological studies on comorbidity usually neglect the hierarchical rules of the Diagnostic and Statistical Manual of Mental Disorders (DSM)¹¹, which results in slightly higher comorbidity rates when compared to diagnostic interviews in routine clinical care. If we assume detection bias and comorbidity indeed adds to the suicidal risk, one might thus expect that our findings are conservative.

The main strengths of our study are the large sample size and the detailed information about patients who died by suicide, achieved due to a very high response rate and nearly complete data collection. Nonetheless, the findings of this study need to be interpreted in the context of certain methodological issues. Firstly, data collection relies on clinical reports and respondents are not blind to outcome. While most information is factual and previous studies have shown good reliability and validity of Inquiry questionnaire data³⁴, the diagnosis of depressive disorder and comorbid anxiety disorders are based on clinical judgment. Nevertheless, the procedure of completing the questionnaire after a patients' suicide by the responsible clinician and supported by team members can be considered a longitudinal, expert, all data (LEAD) procedure³⁵. A LEAD procedure is often used as a gold standard for validating diagnostic psychiatric instruments^{36,37}. Furthermore, it is unlikely that a systematic bias would have occurred due to knowledge of comorbidity with an anxiety disorder of the suicide victim by the respondent.

Secondly, this study is a survey of the clinical circumstances preceding suicide, and we are unable to make causal inferences. A control group of depressed patients with comorbid anxiety disorders who had not died by suicide would have been relevant for identification of suicide risk factors specifically valid for this particular patient group.

Finally, we specifically examined anxiety disorders comorbid to depressive illness. We explicitly avoided the term "anxious depression", as definitions of anxious depression differ substantially between studies. Recently, we showed very poor agreement between anxious depression defined as depressive disorder with comorbid anxiety disorders and anxious depression defined as depressive disorder with a high level of anxiety symptoms³⁸. Therefore, our results cannot be generalized to depressive illness with severe anxiety symptoms in the absence of comorbid anxiety disorders. It might be that depression accompanied by high anxiety symptoms based on an anxiety severity scale (often indicative of high arousal levels), is more specifically associated with suicidality. This seems plausible since suicidality is generally highly associated with depression severity³⁹. Nonetheless, this explanation does not rule out that individual anxiety disorders, like panic disorder³⁹ or post-traumatic stress disorders^{40,41} are also associated with increased suicidality levels, as in our study, all anxiety disorders were combined into one category.

CONCLUSION

Our data show two important discrepancies. First, comorbid anxiety disorders seem to go largely undetected in routine clinical care. Secondly and even more important, if comorbid anxiety disorders are recognized, the risk of suicide is generally estimated to be lower than cases with "pure" depression, despite many reports in the literature pointing to an increased suicidal risk and (in our study), indication of more suicide risk factors among those with comorbid anxiety disorders. Acknowledging the role of comorbid anxiety in late-life depression deserves more attention in both clinical practice as well as research settings. Future studies should not only examine the impact of the individual anxiety disorders, but also the potentially differential impact of high anxiety levels and comorbid anxiety disorders.

REFERENCES

- 1 Hawton, K. & van Heeringen, K. Suicide. *The Lancet* vol. 373 1372–1381 (2009).
- 2 World Health Organization. 2005. At www.who.int/mental_health/prevention/suicide. Accessed 2.2.2007.
- 3 Conwell, Y. et al. Relationships of age and axis I diagnoses in victims of completed suicide: A psychological autopsy study. *Am. J. Psychiatry* 153, 1001–1008 (1996).
- 4 Chiu, H. F. K. et al. Elderly suicide in Hong Kong - A case-controlled psychological autopsy study. *Acta Psychiatr. Scand.* 109, 299–305 (2004).
- 5 Lenze, E. J. et al. Comorbid anxiety disorders in depressed elderly patients. *Am. J. Psychiatry* 157, 722–728 (2000).
- 6 Bartels, S. J. et al. Suicidal and death ideation in older primary care patients with depression, anxiety, and at-risk alcohol use. *Am. J. Geriatr. Psychiatry* 10, 417–427 (2002).
- 7 Allgulander, C. & Lavori, P. W. Causes of death among 936 elderly patients with 'pure' anxiety neurosis in Stockholm County, Sweden, and in patients with depressive neurosis or both diagnoses. *Compr. Psychiatry* 34, 299–302 (1993).
- 8 Beekman, A. T. F. et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am. J. Psychiatry* 157, 89–95 (2000).
- 9 Ritchie, K. et al. Prevalence of DSM-IV psychiatric disorder in the French elderly population. *Br. J. Psychiatry* 184, 147–152 (2004).
- 10 King-Kallimanis, B., Gum, A. M. & Kohn, R. Comorbidity of depressive and anxiety disorders for older Americans in the national comorbidity survey-replication. *Am. J. Geriatr. Psychiatry* 17, 782–792 (2009).
- 11 Van Der Veen, D. C. et al. Comorbid anxiety disorders in late-life depression: Results of a cohort study. *Int. Psychogeriatrics* 27(7), 1157–1165 (2015).
- 12 Byers, A. L. et al. High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 67, 489–496 (2010).
- 13 Cairney, J. et al. Comorbid depression and anxiety in later life: Patterns of association, subjective well-being, and impairment. *Am. J. Geriatr. Psychiatry* 16, 201–208 (2008).
- 14 DeLuca, A. K. et al. Comorbid anxiety disorder in late life depression: Association with memory decline over four years. *Int. J. Geriatr. Psychiatry* 20, 848–854 (2005).
- 15 Jeste, N. D., Hays, J. C. & Steffens, D. C. Clinical correlates of anxious depression among elderly patients with depression. *J. Affect. Disord.* 90, 37–41 (2006).
- 16 Fleehtart, S. et al. Prevalence and correlates of suicide ideation in patients with COPD: A mixed methods study. *Int. J. COPD* 9, 1321–1329 (2014).
- 17 Nock, M. K. et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: Findings from the WHO World Mental Health Surveys. *PLoS Med.* 6, (2009).
- 18 Appleby, L. et al. Safety First: Report of the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness. (2001).
- 19 Windfuhr, K. & Kapur, N. Suicide and mental illness: A clinical review of 15 years findings from the UK National Confidential Inquiry into Suicide. *Br. Med. Bull.* 100, 101–121 (2011).
- 20 Hunt, I. M. et al. Suicide within 12 months of mental health service contact in different age and diagnostic groups: National clinical survey. *Br J Psychiatry* vol. 188 135–142 (2006).
- 21 Meehan, J. et al. Suicide in mental health in-patients and within 3 months of discharge: National clinical survey. *Br J Psychiatry* vol. 188 129–134 (2006).
- 22 Lindsley, K. R., Schapira, K. & Kelly, T. P. Open verdict v. suicide - Importance to research. *Br. J. Psychiatry* 178, 465–468 (2001).

- 23 World Health Organisation. The ICD-10: The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. WHO. (1992).
- 24 Oude Voshaar, R. C. et al. Suicide in later life: A comparison between cases with early- onset and late-onset depression. *J. Affect. Disord.* 132, 185–191 (2011).
- 25 Fiske, A., Wetherell, J. L. & Gatz, M. Depression in older adults. *Annu. Rev. Clin. Psychol.* 5, 363–389 (2009).
- 26 Rothman, K. J. No adjustments are needed for multiple comparisons. *Epidemiology* 1, 43– 46 (1990).
- 27 Beekman, A. T. F. et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am. J. Psychiatry* 157, 89–95 (2000).
- 28 Haney, E. M. et al. Suicide Risk Factors and Risk Assessment Tools: A Systematic Review. Department of Veterans Affairs (US), Washington (DC) (2012).
- 29 O'Connor, E., Gaynes, B. N., Burda, B. U., Soh, C. & Whitlock, E. P. Screening for and treatment of suicide risk relevant to primary care: a systematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* 158, 741–54 (2013).
- 30 Tran, T. et al. Risk stratification using data from electronic medical records better predicts suicide risks than clinician assessments. *BMC Psychiatry* 14, (2014).
- 31 Mulsant, B. H., Reynolds, C. F., Shear, M. K., Sweet, R. A. & Miller, M. Comorbid anxiety disorders in late-life depression. *Anxiety* 2, 242–247 (1996).
- 32 Lenze, E. J. et al. Comorbidity of depression and anxiety disorders in later life. *Depression and Anxiety* vol. 14 86–93 (2001).
- 33 Mohlman, J. et al. Improving recognition of late life anxiety disorders in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition: Observations and recommendations of the Advisory Committee to the Lifespan Disorders Work Group. *International Journal of Geriatric Psychiatry* vol. 27 549–556 (2012).
- 34 Appleby, L. et al. Suicide within 12 months of contact with mental health services: national clinical survey. *BMJ* 318, 1235–1239 (1999).
- 35 Spitzer, R. L. Psychiatric diagnosis: Are clinicians still necessary? *Compr. Psychiatry* 24, 399–411 (1983).
- 36 Quintana, M. I. et al. Validity and limitations of the Brazilian version of the Composite International Diagnostic Interview (CIDI 2.1). *Rev. Bras. Psiquiatr.* 29, 18–22 (2007).
- 37 Gerdner, A., Kestenber, J. & Edvinsson, M. Validity of the Swedish SCID and ADDIS diagnostic interviews for substance use disorders: Sensitivity and specificity compared with a LEAD golden standard. *Nord. J. Psychiatry* 69, 48–56 (2015).
- 38 Van Der Veen, D. C. et al. Defining anxious depression in later life: A scaring heterogeneity in results. *Am. J. Geriatr. Psychiatry* 22, 1375–1378 (2014).
- 39 Bogers, I. C. et al. Determinants of thoughts of death or suicide in depressed older persons. *Int. Psychogeriatrics* 25, 1775–1782 (2013).
- 40 Sareen, J. et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: A population-based longitudinal study of adults. *Arch. Gen. Psychiatry* 62, 1249–1257 (2005).
- 41 Nepon, J., Belik, S. L., Bolton, J. & Sareen, J. The relationship between anxiety disorders and suicide attempts: Findings from the national epidemiologic survey on alcohol and related conditions. *Depress. Anxiety* 27, 791–798 (2010).

CHAPTER 5

THE IMPORTANCE OF PERSONALITY AND LIFE-EVENTS IN ANXIOUS DEPRESSION: FROM TRAIT TO STATE ANXIETY

Based on:

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ABSTRACT

Background

Anxious depression is associated with severe impairment and bad prognoses. Contextual factors as well as traits may play a role in anxiety levels in late-life depression. We hypothesize that recent life-events are associated with more anxiety and that this is conditional upon the level of neuroticism and mastery.

Method s

In 333 patients (> 60 years) suffering from a major depressive disorder who participated in the Netherlands Study of Depression in Older people (NESDO), we assessed anxiety with the Beck Anxiety Inventory, personality traits with the NEO-FFI and the Pearlin and Schooler mastery scale, and recent life-events with the Brugha questionnaire. Multiple linear regression analyses were applied with anxiety severity as dependent variable and life-events and personality traits as independent variables, adjusted for confounders.

Results

147 patients (44.1%) had recently experienced one or more life-events. The presence of a life-event is not associated with a higher level of anxiety ($p=.161$) or with depression severity ($p=.440$). However, certain personality traits interacted with life-events in explaining anxiety level. Stratified analyses showed that life-events were associated with higher anxiety levels in case of high levels of neuroticism and openness, low levels of conscientiousness or mastery.

Conclusions

In the face of a life-event, maladaptive personality traits and dysfunctional coping may play a central role in increased anxiety levels in late-life depression. Examination of the personality profile of depressed older persons might be more relevant during a depressed state than previously thought and may stress the importance of improving existing or learning new coping strategies.

INTRODUCTION

Anxious depression has been defined as a major depressive disorder (MDD) with high levels of anxiety symptoms based on symptom severity scales^{1,2}. Albeit high anxiety levels in depression and comorbid anxiety disorders are often lumped together when studying anxious depression, we previously showed that among depressed older patients, comorbid anxious distress or comorbid anxiety disorders, identify completely different patients³. In the present study, we will focus high anxiety symptoms in line with the DSM-V specifier for anxious distress⁴. High anxiety levels in depression refer to a common subtype of depression⁵ that is associated with more impairment, suicidality, and treatment resistance, both in younger and older adults⁶⁻⁸.

Personality traits and life-events have been extensively studied in depressive disorder, while the specific association with the anxiety specifier in depression is scarce. Among adult samples, depression and anxiety disorders are consistently associated with high levels of neuroticism^{9,10}, low levels of conscientiousness¹¹, and a lower sense of mastery¹². Although personality traits and mastery have been less studied in older population, results seem comparable to those found in younger age groups. Late-life depression is associated with higher levels of neuroticism^{13,14}, and lower levels of extraversion^{15,16}, conscientiousness^{17,18} and openness¹⁸.

Interestingly, in an older adult sample, a low sense of mastery was the only common risk factor for pure depression, pure anxiety disorders and their comorbidity¹⁹.

Life-events have consistently been identified as determinants for the onset and course of depressive disorder in both adult and older samples^{14,20-22}. Dealing successfully with life-events, in terms of not developing enduring depressive or anxiety symptoms, is largely dependent on one's personality traits and sense of mastery. From this perspective neuroticism can be defined as the degree of emotional stability, one's tendency to experience negative emotions and cope (poorly) with life-events. Individuals with high levels of neuroticism tend to perceive even moderate events as stressful and their neuropsychological responses (e.g. their attentional and memory bias, hyper-responsiveness behaviorally and of amygdala activation) are stronger than those of individuals with lower levels of neuroticism²³. In other words, in the face of life-events trait anxiety ergo neuroticism could develop into state anxiety. In adult samples the impact of recent life-events on both the course of depressive symptoms as well as anxiety symptoms is conditional upon the level of neuroticism, with more impact in case of a high neuroticism level^{24,25}. Nonetheless, among infantry troops, individuals with high neuroticism were not more reactive to adverse events in terms of the development of post-traumatic stress symptomatology²⁶.

Sense of mastery (or locus of control) involves "the extent to which one regards one's life chances as being under one's own control in contrast to being fatalistically ruled"²⁷. A higher level of mastery is generally considered as a resilience factor for daily stressors²⁸. Whether the impact of life-events on anxiety levels in depression is also conditional on the level of mastery has not been explored yet.

This proof-of-concept study examines the association between recent life-events and the level of anxiety in depressed older patients specifically looking at whether this association is conditional upon the personality profile of the patient. We hypothesize that recent life-events are associated

with the severity of anxiety in late-life depression. We further hypothesize that recent life-events are more strongly associated with anxiety symptoms in the presence of high levels of neuroticism as well as a low sense of mastery, whereas other personality characteristics are expected to have no conclusive moderating effects.

METHODS

Study design and participants

This cross-sectional study is based on baseline data from the Netherlands Study of Depression in Older persons (NESDO), is a multi-site naturalistic cohort study that includes 378 depressed (including major and minor depressive disorders and dysthymia) and 132 non-depressed subjects aged 60 through 93 years²⁹. Persons with a clinical diagnosis of dementia or who were suspect for dementia, a primary diagnoses of psychotic or bipolar disorder, a Mini Mental State Examination-score (MMSE)³⁰ under 18 (out of 30 points), and insufficient command of the Dutch language were excluded.

Psychiatric diagnoses were assessed with the Compositied International Diagnostic Interview (CIDI)³¹ according to DSM-IV-R criteria. The severity of anxiety symptoms was measured using the Beck Anxiety Inventory (BAI)³², a 21 item, self-report questionnaire primarily addressing somatic anxiety symptoms.

For the present paper we first selected those patients who met the criteria for a major depressive episode within the past 6 months ($n=359$, 95%), therefore we excluded 19 patients who met the criteria for a minor depression of dysthymia only. We also excluded 26 patients who had missing data with respect to recent life-events, neuroticism and mastery, leaving a final study sample of 333 patients.

Recent life-events

The occurrence of recent stressful life-events was assessed using the Brugha questionnaire³³. These events reflect the presence of life stressors during the past year, such as serious illness and injury, death of a close friend or relative, unemployment, major financial loss, and loss of important relationships. The Brugha questionnaire has good test-retest reliability, high agreement between participant and informant ratings, and good agreement with interview-based ratings³⁴. Since we hypothesized that the occurrence of a recent life-event is associated with the severity of anxiety in late-life depression we dichotomized the number of life-events in the past year as none versus one or more life-events. Eventually we also explored associations with recent life-events as a continuous independent variable and checked for a cumulative effect when more than one life-event occurred in the past year.

Personality

The big five personality domains, i.e. neuroticism, extraversion, openness to experience, agreeableness and conscientiousness, were assessed with the 60-item NEO-Five Factor Inventory (NEO-FFI)³⁵. The psychometric properties of the Dutch version of the NEO-FFI are generally good³⁶. The internal consistencies of all domains range from acceptable to good, and are comparable to those of the American version.

Since neuroticism partly overlaps with concepts of anxiety as well as depression, we also tested the association with specific facets of neuroticism according to the empirically derived model. This model describes the facets Negative Affect (pertaining to anxiety and depression) and Self-reproach (self-conscious negative emotions, e.g. shame and guilt). The psychometric properties of the model fit well³⁷.

In addition, sense of mastery (or locus of control) was assessed with a the 5-item Dutch version of the Pearlin and Schooler Mastery Scale. A higher score on the Mastery Scale indicates a low sense of mastery²⁷.

Covariates

In all the analyses sex (male-female), age (years) and level of education (number of years) were added as the basic covariates.

Since depression partly overlaps with anxiety and may confound, but also obscure results, we will repeat all analyses with correction for depression severity (sensitivity analyses). The severity of depressive symptoms was assessed with the 28-item self-report version of the Inventory of Depressive Symptomatology (IDS-SR)³⁸.

Analyses

Differences between depressed participants with or without the presence of one or more life-events in the last year were analyzed by independent t-tests or chi-square statistics.

First a linear regression analysis was applied to examine the possible association between anxiety (BAI sum score) as the dependent variable and life-event(s) as the independent variable.

Subsequent, we tested in multiple linear regression models whether the presence of a recent life-event (yes/no) interacted with the personality domains under study (neuroticism total score and facets, extraversion, openness, agreeableness, conscientiousness and mastery) in its potential association with anxiety as the dependent variable. In these analyses, the personality trait under study and the presence of a life-event were included as independent variables, in addition to the interaction term between both variables. When the interaction terms with a certain personality trait were significant ($p < .10$) analyses were repeated, stratified by the presence of a recent life-event.

Finally, we tested in multiple linear regression models whether the presence of a recent life-event (dichotomized and continuously) interacted with the dichotomized personality traits (median split: high/low) in its potential association with anxiety as the dependent variable.

All analyses were adjusted for socio-demographic variables (age, sex and level of education) and depression severity (IDS-SR sum score). A p -value $< .05$ was considered statistically significant; whereas, as noted above $p < .10$ was considered significant for interaction terms³⁹. The analyses were conducted in SPSS 22 for Mac (IBM, Armonk, NY, USA).

RESULTS

Patient characteristics

The mean (standard deviation) age of these 333 patients was 70.6 (sd = 7.3) years old; 220 (66.1%) were female. A total of 147 patients (44.1%) had experienced one or more life-event in the past year. Table 1 presents all characteristics of the study population stratified by the presence of any recent life-event(s).

Associations between life-event(s), personality and anxiety symptoms.

Linear regression with anxiety as the dependent variable showed that the presence of a recent life-event was not associated with the severity of anxiety after correction for age, sex, level of education and depression severity ($\beta = 0.06$, $t_{[330]} = 1.38$, $p = .169$).

Subsequently, we tested in multiple linear regression models whether the presence of a recent life-event (yes/no) interacted with the personality domains under study in its potential association with anxiety as the dependent variable. We found a significant interaction between recent life-events and neuroticism ($\beta = 0.63$, $t_{[329]} = 2.26$, $p = .024$), with its facet self-reproach ($\beta = 0.41$, $t_{[330]} = 1.79$, $p = .074$), openness ($\beta = 0.51$, $t_{[326]} = 1.79$, $p = .074$), conscientiousness ($\beta = -0.66$, $t_{[328]} = -1.98$, $p = .049$) and mastery ($\beta = 0.48$, $t_{[323]} = 1.87$, $p = .062$). Meaning that when a life-event occurred in the past year, higher neuroticism, more self-reproach and openness, less conscientiousness and a lower sense of mastery were associated with more anxiety. When no life-event had occurred this effect was not found. No significant interaction was found with the neuroticism facet negative affect ($\beta = 0.33$, $t_{[317]} = 1.20$, $p = .233$), extraversion ($\beta = -0.30$, $t_{[328]} = -1.04$, $p = .298$) and agreeableness ($\beta = 0.11$, $t_{[327]} = 0.27$, $p = .787$).

Table 1. | Patient characteristics for those with and without any life-event(s) in past year Presence of life-events in last year

	Presence of life-events in last year		
Characteristics	No (n=186)	Yes (n=147)	Statistics
Demographics:			
• Mean (SD) age (years)	71.1 (7.2)	69.9 (7.4)	t=1.5, df=331, p=.137
• Female sex, n (%)	118 (63.4)	102 (69.4)	X ² =1.3, df=1, p=.255
• Mean (SD) level of education (years)	10.2 (3.4)	10.5 (3.5)	t=-0.70, df=331, p=.484
Life-events:			
• Median (IQR) number of life-events	-	1 (58)	Not applicable
Psychopathology:			
• Mean (SD) anxiety level (BAI)	16.8 (11.2)	18.6 (12.0)	t=-1.4, df=331, p=.160
• Mean (SD) depression severity (IDS)	29.8 (12.7)	30.9 (13.4)	t=-0.8, df=329, p=.440
Personality:			
Mean (SD) neuroticism	39.1 (7.3)	39.1 (6.6)	t=0.01, df=330, p=.996
Mean (SD) extraversion	33.3 (6.2)	34.1 (7.0)	t=-1.1, df=329, p=.268
Mean (SD) openness	29.1 (5.2)	29.4 (5.6)	t=-0.6, df=327, p=.583
Mean (SD) agreeableness	43.8 (5.0)	44.4 (5.4)	t=-1.1, df=328, p=.288
Mean (SD) conscientiousness	36.3 (5.8)	36.8 (5.4)	t=-0.8, df=329, p=.404
Mean (SD) mastery	15.2 (3.3)	15.3 (3.0)	t=-0.3, df=324, p=.777

Abbreviations: SD, standard deviation; IQR, interquartile range.

Table 2 shows the results, with respect to neuroticism, the facet subscale self-approach, openness, conscientiousness, and mastery, stratified by the presence of a recent life-event. Higher levels of neuroticism and its facet self-reproach and a lower sense of mastery are associated with more anxiety in both groups. A higher level of openness is associated with more anxiety in the no life-event group, while a higher level of conscientiousness is associated with more anxiety in the any life-event group.

Table 2. | Associations of personality domains and level of anxiety (dependent variable) by linear regression^a, stratified by presence of life-event(s) in case of significant interaction with the personality trait under study

Personality characteristics	Stratified sample by presence of life-event(s) ^b					
	No life-event (n=183)			Any life-event (n=145)		
	B (SE)	beta	p	B (SE)	beta	p
<i>BIG-5 personality traits</i>						
• Neuroticism	0.41 (0.13)	.27	.001	0.65 (0.13)	.36	<.001
○ Self-reproach	0.51 (0.17)	.24	.003	0.76 (0.17)	.31	<.001
• Openness	-0.27 (0.15)	-.13	.069	-0.01 (0.16)	-.01	.964
• Conscientiousness	-0.04 (0.13)	-.02	.775	-0.34 (0.15)	-.15	.026
<i>Sense of mastery</i>						
• Pearlin Mastery Scale	0.75 (0.26)	.22	.005	1.11 (0.29)	.28	<.001

^a Adjusted for age, sex, level of education (years) and severity of depression (IDS-SR sum score).

^b Stratified analyses by presence of life-event(s) only reported in case of a significant interaction term between life-event (no/any) and the personality trait.

Table 3 shows the results of multiple linear regression models with the presence of a recent life-event (yes/no) and their interaction with the dichotomized personality traits (median split: high/low) and with anxiety as the dependent variable. In the group that experienced a recent life-event, belonging to the high neuroticism group was associated with more anxiety. The same results were found for the low self-reproach group and the low conscientiousness group.

Finally, we repeated these analyses with life-events as a continuous variable in the interaction with these dichotomized personality traits and with anxiety as the dependent variable. Belonging to the high neuroticism group is associated with more anxiety. The results are also shown in table 3.

For facilitating the interpretation of the interaction terms, figure 1 shows the graphs of the analyses where both recent life-events and the personality traits are dichotomized. These figures show the differential relationship between life-events and anxiety in for example low and high neurotic patients.

Table 3. | Associations of the dichotomized personality traits and level of anxiety (dependent variable) by linear regression with the presence of life-event(s) continuously and stratified in case of significant interaction with the personality trait under study

	Stratified sample by BIG-5 personality traits (high / low) ^b					
	B (SE)	beta	p	B (SE)	beta	p
Live-events (yes/no)	Neuroticism					
	low (n=173)			high (n=156)		
	-0.86 (1.32)	-.05	.517	4.52 (1.62)	.19	.006
	-0.72 (0.64)	-.08	.261	2.00 (0.86)	.16	.021
Live-events (continuously)	Self-reproach (facet of neuroticism)					
	low (n=177)			high (n=152)		
	3.15 (1.60)	.14	.051	1.40 (0.81)	.12	.089
	0.49 (1.34)	.03	.713	-0.39 (0.67)	-.04	.557
Live-events (yes/no)	Openness					
	low (n=176)			high (n=153)		
	0.15 (1.46)	.01	.919	2.87 (1.51)	.14	.060
	0.26 (0.84)	.02	.756	0.22 (0.68)	.02	.746
Live-events (continuously)	Conscientiousness					
	low (n=181)			high (n=148)		
	3.66 (1.46)	.15	.013	-0.85 (1.47)	-.04	.564
	0.66 (0.72)	.06	.359	-0.41 (0.78)	-.04	.601
Live-events (yes/no)	Sense of mastery					
	low (n=121)			high (n=208)		
	0.50 (1.26)	.02	.694	2.95 (1.82)	.13	.108
	-0.16 (0.69)	-.01	.820	0.59 (0.82)	.06	.475

^a Adjusted for age, sex, level of education (years) and severity of depression (IDS-SR sum score)

^b Those personality traits that showed significant interaction with life-event

Figure 1. | Graphs of the analyses where both recent life-events and personality traits are dichotomized. Bars with 95% C.I. based on standard error of the mean (SEM)

DISCUSSION

Main findings

This study shows that in late life the presence of anxious depression is related to recent life-events, but only in subjects with either high levels of neuroticism, low levels of openness to experience and conscientiousness or a poor sense of mastery. This is the first study showing this association between recent life-events, personality characteristics and anxiety levels in depression.

Comparison with the literature:

Considerable research has shown the association between depression (severity) and personality characteristics⁴⁰. In many of these studies, the anxiety dimension is not specifically taken into account when looking at depression severity. Our study suggests that it is especially this anxiety dimension in depression that is associated with personality. This is in line with the results of a systematic comparison of risk profiles for late life depression and late life anxiety disorders, showing that personality characteristics such as neuroticism and mastery are risk factors for both types of disorders⁴¹. With respect to neuroticism, a post-hoc analyses on the different facets showed that the impact of life-events on anxiety levels seems to be determined by the facet self-reproach (especially when the operationalization of self-reproach is applied in which theoretical items related to negative affect are removed). Self-reproach can be conceived as a vulnerability factor that, in the face of a life-event, increases anxiety. Studies focusing on personality relation transaction show that people who are high in self-reproach tend to withdraw from others^{42,43}, thereby reducing important coping abilities⁴⁴. Furthermore, research has repeatedly established that neuroticism is associated with a greater risk of exposure to life-events as well as a poor ability to cope with them effectively, or to regulate the negative emotional states induced by these life-events^{45,46}.

Additionally, there is evidence that cumulative stress exposure through life-events leads to a 'wear and tear' of the stress system. This has more impact on vulnerable people with high levels of trait neuroticism, thereby increasing their depressive symptomatology, which also includes the anxiety dimension in depression⁴⁷. Yoon and colleagues showed that the use of maladaptive forms of emotion regulation, but not reappraisal, fully mediated the association between neuroticism and the severity of depressive symptoms⁴⁸. The same results were found in relation to anxiety disorders⁴⁹. With regard to these coping and emotion regulation strategies, several studies have shown that (the absence of) social support is associated with anxiety^{14,41}.

Results also show that a high level of openness to experience was negatively associated with anxiety when no life-event had occurred in the preceding year. Openness is described by 'novelty-seeking, intellectual curiosity, a vivid imagination, awareness of inner emotional states, and deep appreciation for the arts'⁵⁰. High openness seems to be a protective factor when dealing with daily hassles. This effect however was no longer significant after having been confronted with a life-event. In contrast to the other personality domains, the conclusions based on different studies concerning openness in relation to health are contradictory. Eldesouky reviews these results and advocates the use of facet models concerning the domain openness to experiences⁵¹. As we have applied the NEO-FFI, the condensed version of the NEO-PI, limited further exploration of our finding.

Finally, we found that a high level of conscientiousness is associated with a lower level of anxiety in the face of a life-event. High conscientiousness, a trait that describes self-discipline, achievement orientation, and orderliness is associated with an increased appraisal of coping abilities, as well as higher levels of control in the context of stressors⁵². Moreover, conscientious individuals tend to find stressful situations less demanding than less conscientious individuals. Similarly, in stressful contexts, higher levels of conscientiousness are associated with using more adaptive coping strategies, such as instrumental problem solving and effective cognitive restructuring⁵³.

Methodological considerations

The strengths of our study are the large number of older persons suffering from depression and high quality of data collection. Depressed persons were recruited from both mental healthcare institutes and general practices in order to include persons with late-life depression in various developmental and severity stages²⁹.

Although personality traits are considered stable over years and we assessed life-events retrospectively over the past year, one can assume a longitudinal association of personality traits interacting with life-events on the development of current level of anxiety. Nonetheless, our study design is still cross-sectional design in nature, limiting causal interpretations. For example, it might be that patients with high neuroticism are more prone for experience negative life-events, thereby resulting in reverse causality. The measurement of personality traits may be partly biased due to a depressed state. Although, personality traits are stable, the presence of depression is known to amplify the personality profile of people prone to depression. After recovery of depression, however, the overall shape of the profile does not change⁵⁴. Nonetheless, the relationship between change in personality and change in depressive symptoms is at most moderate⁵⁵⁻⁵⁷. Furthermore, life-events may simply mark periods of improvement or deterioration in anxiety. With respect to the measurement of life-events, we should also acknowledge that negative life-events may trigger an anxious/depressive episode typically within maximal 3 months⁵⁸. This indicates that our time-frame of 12 months as applied by the Brugha questionnaire is a subsequent limitation. Moreover, the subjective stressfulness or other characteristics of the life-event were not assessed. Nonetheless, since subjective stressfulness partly depends on the personality profile, taken this into account may also led to overcorrection in the analyses.

CONCLUSION

Anxiety symptoms greatly add to the burden of depression. Vulnerable patients, such as older adults with high levels of neuroticism and a low sense of mastery, are more prone to experience negative effects of the exposure to life-events. In the face of these life-events, they have a greater risk of developing anxious depression, which is a more severe form of depression in terms of disability and clinical prognosis. Clinical experience, supported by an accumulating amount of studies, shows that the treatment and care for these patients is challenging, as high anxiety levels in depression are associated with more impairment and a worse prognosis⁵⁹. Although exceeding the result of this study, these findings suggest that proper identification of the vulnerability that derives from the personality of the patient may be of clinical use. Guided by an exploration of

the personal coping strategies, interventions may be chosen that help the patient to develop new ways of dealing with life-events. Likewise, focusing on the patient's social network can strengthen resilience. Finally, in patients with prior depressive episodes, it is important to create a clear relapse prevention plan to detect early (subclinical) symptomatology including proactive strategies to prevent a cascade of symptoms that results in the recurrence of the anxious depressive state. Given that the number of older adults with dysfunctional personality traits—and the corresponding demand for care—will only increase in the future, clear indication criteria for specific therapies and the use of more appropriate behavioral counseling are needed.

REFERENCES

- 1 Baumeister, H. & Parker, G. A second thought on subtyping major depression. *Psychother Psychosom* vol. 79 388–389 (2010).
- 2 Ionescu, D. F., Niciu, M. J., Henter, I. D. & Zarate, C. A. Defining anxious depression: A review of the literature. *CNS Spectrums* vol. 18 252–260 (2013).
- 3 Van Der Veen, D. C., Comijs, H. C., Van Zelst, W. H., Schoevers, R. A. & Oude Voshaar, R. C. Defining anxious depression in later life: A scaring heterogeneity in results. *Am. J. Geriatr. Psychiatry* 22, 1375–1378 (2014).
- 4 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). (American Psychiatric Association, 2013).
- 5 Fava, M. et al. Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. *Psychol. Med.* 34, 1299–1308 (2004).
- 6 Farabaugh, A. et al. Cognitive therapy for anxious depression in STAR*D: what have we learned? *J. Affect. Disord.* 142, 213–218 (2012).
- 7 Fava, M. et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. *Am. J. Psychiatry* 165, 342–351 (2008).
- 8 Lenze, E. J., Mulsant, B. H., Shear, M. K., Houck, P. & Reynolds, C. F. Anxiety symptoms in elderly patients with depression: What is the best approach to treatment? *Drugs Aging* vol. 19 753–760 (2002).
- 9 Gale, C. R. et al. Factors associated with symptoms of anxiety and depression in five cohorts of community-based older people: the HALCyon (Healthy Ageing across the Life Course) Programme. *Psychol. Med.* 41, 2057–2073 (2011).
- 10 Lahey, B. B. Public health significance of neuroticism. *Am. Psychol.* 64, 241–256 (2009).
- 11 Kotov, R., Gamez, W., Schmidt, F. & Watson, D. Linking ‘big’ personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychol. Bull.* 136, 768–821 (2010).
- 12 Benassi, V. A., Sweeney, P. D. & Dufour, C. L. Is there a relation between locus of control orientation and depression? *J. Abnorm. Psychol.* 97, 357–367 (1988).
- 13 Steunenberg, B., Braam, A. W., Beekman, A. T. F., Deeg, D. J. H. & Kerkhof, A. J. F. M. Evidence for an association of the big five personality factors with recurrence of depressive symptoms in later life. *Int. J. Geriatr. Psychiatry* 24, 1470–1477 (2009).
- 14 Vink, D. et al. Onset of anxiety and depression in the aging population: comparison of risk factors in a 9-year prospective study. *Am. J. Geriatr. Psychiatry* 17, 642–652 (2009).
- 15 Weber, K. et al. Volumetric MRI changes, cognition and personality traits in old age depression. *J. Affect. Disord.* 124, 275–282 (2010).
- 16 Weber, K., Giannakopoulos, P. & Canuto, A. Exploring the impact of personality dimensions in late-life depression: from group comparisons to individual trajectories. *Curr. Opin. Psychiatry* 24, 478–483 (2011).
- 17 Hayward, R. D., Taylor, W. D., Smoski, M. J., Steffens, D. C. & Payne, M. E. Association of five-factor model personality domains and facets with presence, onset, and treatment outcomes of major depression in older adults. *Am. J. Geriatr. Psychiatry* 21, 88–96 (2013).
- 18 Weber, K. et al. Personality traits are associated with acute major depression across the age spectrum. *Aging Ment. Health* 16, 472–480 (2012).
- 19 Beekman, A. T. F. et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am. J. Psychiatry* 157, 89–95 (2000).
- 20 Kraaij, V., Arensman, E. & Spinhoven, P. Negative life events and depression in elderly persons: a meta-analysis. *The Journals Gerontol. B, Psychol. Sci. Soc.* 57, P87-94 (2002).
- 21 Moreno-Peral, P. et al. Risk factors for the onset of panic and generalised anxiety disorders in the general adult population: a systematic review of cohort studies. *J. Affect. Disord.* 168, 337–348 (2014).

- 22 Paykel, E. S. Life events and affective disorders. *Acta Psychiatr. Scand.* (418), 61–66 (2003).
- 23 Sandi, C. & Richter-Levin, G. From high anxiety trait to depression: a neurocognitive hypothesis. *Trends Neurosci.* 32, 312–320 (2009).
- 24 Kendler, K. S., Kuhn, J. & Prescott, C. A. The Interrelationship of Neuroticism, Sex, and Stressful Life Events in the Prediction of Episodes of Major Depression. *Am. J. Psychiatry* 161, 631–636 (2004).
- 25 Spinhoven, P. et al. Positive and negative life events and personality traits in predicting course of depression and anxiety. *Acta Psychiatr. Scand.* 124, 462–473 (2011).
- 26 Engelhard, I. M., van den Hout, M. A. & Lommen, M. J. J. Individuals high in neuroticism are not more reactive to adverse events. *Pers. Individ. Dif.* 47, 697–700 (2009).
- 27 Pearlin, L. I. & Schooler, C. The structure of coping. *J. Health Soc. Behav.* 19, 2–21 (1978).
- 28 Neupert, S. D., Almeida, D. M. & Charles, S. T. Age differences in reactivity to daily stressors: The role of personal control. *Journals Gerontol. - Ser. B Psychol. Sci. Soc. Sci.* 62, (2007).
- 29 Comijs, H. & Dekker, J. The Netherlands Study of Depression in Older persons (NESDO). *Int. Psychogeriatrics* 23, 570–571 (2011).
- 30 Folstein, M. F., Folstein, S. E. & McHugh, P. R. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198 (1975).
- 31 Wittchen, H. U. et al. Cross-cultural feasibility, reliability and sources of variance of the composite international diagnostic interview (CIDI). *Br. J. Psychiatry* 159, 645–653 (1991).
- 32 Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. An inventory for measuring clinical anxiety: Psychometric properties. *J. Consult. Clin. Psychol.* 56, 893–897 (1988).
- 33 Brugha, T., Bebbington, P., Tennant, C. & Hurry, J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol. Med.* 15, 189–194 (1985).
- 34 Brugha, T. S. & Cragg, D. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatr. Scand.* 82, 77–81 (1990).
- 35 Costa, P. T. Jr & McCrae, R. R. Domains and Facets: Hierarchical Personality Assessment Using the Revised NEO Personality Inventory. *J. Pers. Assess.* 64, 21–50 (1995).
- 36 Hoekstra, H. A., Ormel, J. & de Fruyt, F. NEO-PI-R (NEO Personality Inventory) Big Five. Swets Test Publishers. (2003).
- 37 Chapman, B. P. Bandwidth and fidelity on the NEO-Five Factor Inventory: replicability and reliability of Saucier's (1998) item cluster subcomponents. *J. Pers. Assess.* 88, 220–234 (2007).
- 38 Rush, A. J., Gullion, C. M., Basco, M. R., Jarrett, R. B. & Trivedi, M. H. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol. Med.* 26, 477–486 (1996).
- 39 Aiken, L. S. & West, S. G. Multiple regression: Testing and interpreting interactions. Sage Publications, Inc (1991).
- 40 Hakulinen, C. et al. Personality and Depressive Symptoms: Individual Participant Meta-Analysis of 10 Cohort Studies. *Depress. Anxiety* 32, 461–470 (2015).
- 41 Vink, D., Aartsen, M. J. & Schoevers, R. A. Risk factors for anxiety and depression in the elderly: a review. *J. Affect. Disord.* 106, 29–44 (2008).
- 42 Bolger, N. & Zuckerman, A. A framework for studying personality in the stress process. *J. Pers. Soc. Psychol.* 69, 890–902 (1995).
- 43 Park, L. E. & Maner, J. K. Does self-threat promote social connection? The role of self-esteem and contingencies of self-worth. *J. Pers. Soc. Psychol.* 96, 203–217 (2009).
- 44 Roohafza, H. R. et al. What's the role of perceived social support and coping styles in depression and anxiety? *J. Res. Med. Sci.* 19, 944–949 (2014).
- 45 Bolger, N. Coping as a personality process: a prospective study. *J. Pers. Soc. Psychol.* 59, 525–537 (1990).

- 46 Watson, D. & Hubbard, B. Adaptational style and dispositional structure: Coping in the context of the Five-Factor model. *J. Pers.* 64, 737–774 (1996).
- 47 Vinkers, C. H. et al. Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. *Depress. Anxiety* 31, 737–745 (2014).
- 48 Yoon, K. L., Maltby, J. & Joormann, J. A pathway from neuroticism to depression: examining the role of emotion regulation. *Anxiety, Stress, Coping* 26, 558–572 (2013).
- 49 Amstadter, A. Emotion regulation and anxiety disorders. *J. Anxiety Disord.* 22, 211–221 (2008).
- 50 John, O. P. & Gross, J. J. Healthy and unhealthy emotion regulation: Personality processes, individual differences, and life span development. *Journal of Personality* vol. 72 1301–1334 (2004).
- 51 Eldesouky, L. Openness to Experience and Health: A Review of the Literature. *The Yale Undergraduate Review of Undergraduate Research in Psychology* (2012).
- 52 Penley, J. A. & Tomaka, J. Associations among the Big Five, emotional responses, and coping with acute stress. *Pers. Individ. Dif.* 32, 1215 (2002).
- 53 Connor-Smith, J. K. & Flachsbart, C. Relations between personality and coping: a meta-analysis. *J. Pers. Soc. Psychol.* 93, 1080–1107 (2007).
- 54 Santor, D. A., Bagby, R. M. & Joffe, R. T. Evaluating stability and change in personality and depression. *J. Pers. Soc. Psychol.* 73, 1354–1362 (1997).
- 55 Costa, P. T. Jr, Bagby, R. M., Herbst, J. H. & McCrae, R. R. Personality self-reports are concurrently reliable and valid during acute depressive episodes. *J. Affect. Disord.* 89, 45–55 (2005).
- 56 Ormel, J., Oldehinkel, A. J. & Vollebergh, W. Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Arch. Gen. Psychiatry* 61, 990–996 (2004).
- 57 Spinhoven, P., Penelo, E., de Rooij, M., Penninx, B. W. & Ormel, J. Reciprocal effects of stable and temporary components of neuroticism and affective disorders: results of a longitudinal cohort study. *Psychol. Med.* 44, 337–348 (2014).
- 58 Faravelli, C., Catena, M., Scarpato, A. & Ricca, V. Epidemiology of life events: life events and psychiatric disorders in the Sesto Fiorentino study. *Psychother. Psychosom.* 76, 361–368 (2007).
- 59 Ionescu, D. F., Niciu, M. J., Mathews, D. C., Richards, E. M. & Zarate, C. A. Neurobiology of anxious depression: A review. *Depression and Anxiety* vol. 30 374–385 (2013).

CHAPTER 6

ANXIETY IN LATE-LIFE DEPRESSION: DETERMINANTS OF THE COURSE OF ANXIETY AND COMPLETE REMISSION

Based on:

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ABSTRACT**Background**

Studies on the course of depression often ignore comorbid anxiety disorders or anxiety symptoms. We explored predictors of complete remission (no depression nor anxiety diagnoses at follow-up) and of the course of comorbid anxiety symptoms. We additionally tested the hypothesis that the course of anxiety disorders and symptoms in depressed patients is explained by negative life-events in the presence of high neuroticism or a low sense of mastery.

Methods

An observational study of 270 patients (≥ 60 years) diagnosed with major depressive disorder and two- year follow-up data, who participated in the Netherlands Study of Depression in Older persons (NESDO). Socio- demographic, somatic, psychiatric, and treatment variables were first explored as possible predictors. A multiple logistic regression analysis was used to examine their predictive value concerning complete remission. Subsequently, negative life-events, personality and their interaction were tested as potential predictors. Linear Mixed Models were used to assess whether the personality traits modified the effect of early and recent life-events, and time and their interactions on the course of the anxiety symptoms.

Results

A total of 135/270 patients achieved complete remission. Depressed patients with a comorbid anxiety disorder at baseline less often achieved complete remission: 38/103 (37.0%) versus 97/167 (58.1%). The severity of depressive and anxiety symptomatology, the presence of a comorbid anxiety disorder, and a poorer physical health at baseline predicted non-remission. In line with our hypothesis, a less favorable course of self-reported anxiety symptoms was associated with more recent negative life-events, but only among patients with a high level of neuroticism or a low level of mastery.

Conclusions

Comorbid anxiety in depression as a negative impact on complete remission at two-year follow-up. The course of anxiety severity seems dependent on the interaction of personality traits and life-events.

INTRODUCTION

Comorbid anxiety in depression is common¹ and several studies demonstrated the negative effect of comorbid anxiety on depression treatment outcome². Two issues emerge when reviewing the literature, i.e. the definition of a remission of the depressive disorder and the measurement of anxiety in depression. Regarding remission, studies traditionally focus on the diagnosis of interest, namely depression, while for patients a meaningful remission means a complete remission of both depression and anxiety diagnoses. Furthermore, most studies include participants based on formal DSM diagnoses but evaluate remission based on symptom severity scales. Regarding the measurement of comorbid anxiety, we previously showed that depressed patients with a comorbid anxiety disorder are a different group of patients compared to depressed patients with a high level of anxiety symptoms with minimal overlap between both groups³⁻⁵.

To our knowledge, predictors of complete remission in depressed older adults, also taking into account remission of comorbid anxiety disorders, are still unknown. In contrast, predictors of depressive and anxiety symptom trajectories, separate from another, have been relatively well-studied. For the depressive symptoms, these predictors include a greater medical disease burden, presence of specific depressive symptoms (anhedonia and neurovegetative), smoking, low self-esteem, and interpersonal difficulties^{6,7}. Few studies have traced the course of anxiety symptoms and its determinants in community-dwelling older adults. A more unfavorable course of anxiety symptoms after 6 years has been associated with female gender and higher levels of neuroticism at baseline^{8,9}. Only one study has focused on the course of anxiety symptoms in depressed older adults. Higher levels of worry and lower levels of cognitive control predicted persistent and severe levels of anxiety symptoms¹⁰.

Increasing health limitations and events involving death and illness of spouses, children, and peers are major sources of stress that come with aging. Exposure to these negative life-events (NLE) has a moderate but significant relation with late-life depression^{11,12}. The association with late-life anxiety is less well studied and results are more ambiguous^{8,13,14}. It has long been theorized that personality dimensions may serve as vulnerability factors¹⁵ and moderators¹⁶ in the development and maintenance of affective symptoms by influencing the way in which persons perceive, react to, or cope with significant life events. Studies in adult samples, however, have shown conflicting results^{17,18}.

One could hypothesize that personality traits account for the considerable differences in course of comorbid anxiety in the presence of stress. Vasunilashorn argues the importance of distinguishing between perceptions of stress and exposure to stressors when studying the links between stress and health among older adults¹⁹. The destabilizing appraisal of stress and the dysfunctional coping with NLE are closely related to personality traits such as neuroticism, which increases a person's vulnerability to experience negative emotions²⁰, and *sense of mastery*^{21,22}.

Given the paucity of data available on complete remission of late life depression, defined as being without depressive as well as anxiety disorder, our first objective was to examine its predictors at baseline in a sample of patients with comorbid disorders. To test the robustness of the results analyses are repeated with complete remission defined as no diagnoses at follow-up

and scores below predefined cut-off points on depression and anxiety severity scales. Our second objective was to examine the course of anxiety symptoms over time. Additionally, we tested the hypothesis that the course of anxiety disorders and symptoms is largely explained by negative life-events during the two-year follow-up period (in contrast to the course of depressive symptoms) and especially in the presence of high neuroticism or a low sense of mastery at baseline.

METHODS

Participants

Data were used from the Netherlands Study of Depression in Older persons (NESDO). NESDO is a multi-site naturalistic and prospective cohort study including 378 depressed and 132 non-depressed older adults aged 60 through 93 years. The population and methods of the NESDO study have been described in detail elsewhere²³. The study protocol of NESDO has been approved centrally by the ethical review board of the VUMC and all persons gave informed consent after oral and written information. Depressed participants were included when they fulfilled the DSM-IV-TR criteria for major depression (N=359; 95.0%) of whom 270 (75.2%) completed the two-year follow-up assessments²⁴. Patients who completed the two-year follow-up did not differ from non-completers with respect to any of the variables of interest that are described below.

Measurements

Psychiatric diagnoses

The current (6-month) major depressive and anxiety disorders (panic disorder with or without agoraphobia, agoraphobia, social phobia, and generalized anxiety disorder) were diagnosed according to DSM-IV-TR criteria at baseline and at 2-year follow-up with the Composite International Diagnostic Interview (CIDI; WHO version 2.1). The CIDI is a structured clinical interview that is designed for use in research and has a high validity for depressive and anxiety disorders²⁵.

Symptom severity

The severity of anxiety symptoms during the 2-year follow-up period was assessed with the Beck Anxiety Inventory (BAI), a 21 item, self-report questionnaire primarily addressing somatic anxiety symptoms²⁶. The BAI was administered at baseline and repeated at 6-, 12-, 18-, and 24-months follow-up. A score ≥ 19 was considered as clinically relevant anxiety.

The severity of the depressive symptoms was assessed with the 30-item self-report version of the Inventory of Depressive Symptomatology (IDS-SR)²⁷ and were administered at the same measurement points as the BAI.

Early and recent negative life events

Early negative life events or childhood trauma, including emotional neglect as well as psychological, physical, and sexual abuse before the age of 16, was assessed at baseline using a structured inventory previously used in the Mental Health Survey and Incidence Study²⁸ and the Netherlands Study of Depression and Anxiety²⁹. A childhood abuse index was constructed by recoding the frequency scores in (0) never, (1) once, sometimes and (2) regularly, often or very often. These scores were summed up, resulting in a childhood abuse index that ranges from 0 to

8, with higher scores indicating a higher frequency of childhood abuse³⁰.

The occurrence of recent negative life-events (NLE), such as the loss of a friend or family member or experiencing serious illness, was assessed using the Brugha questionnaire³¹. These events reflect the presence of life stressors during the last six months before the 6-, 12-, 18-, and 24-months follow-up. For the analyses we used a sum score of the total reported negative life-events (NLEburden), since cumulative stress exposure through life-events may lead to a 'wear and tear' of the stress system^{32,33}.

Personality

The big five personality domains, i.e. neuroticism, extraversion, openness to experience, agreeableness and conscientiousness, were assessed at baseline with the 60-item NEO-Five Factor Inventory (NEO-FFI)³⁴.

Sense of mastery (or locus of control) was assessed at baseline with a the 5-item Dutch version of the Pearlin and Schooler Mastery Scale. A higher score on the Mastery Scale indicates a low sense of mastery³⁵.

Complete remission vs non-remission

Complete remission was defined as not meeting the DSM-IV-TR criteria of either a major depressive, dysthymic disorder, or an anxiety disorder in the six months prior to the two-year follow-up. Non-remission was defined as still meeting the criteria of a current (6 month) major depressive or a dysthymic disorder and/or any anxiety disorder, including a panic disorder with or without agoraphobia, agoraphobia, social phobia, and generalized anxiety disorder at two-year follow-up.

Since a remission of a depressive and anxiety disorder does not necessarily imply that the absence of residual depressive and/or anxiety symptoms, we performed a sensitivity analysis defining complete remission as not only having none if the diagnoses at two-year follow-up, but also scoring below predefined cut-off scores on depression and anxiety severity scales at two-year follow-up. For the IDS-SR this meant a score < 18^{27,36} and for the BAI a score < 19²⁶.

Covariates at baseline

Socio-demographic characteristics including age, sex and years of education were assessed with standard questions. Clinical variables included age of onset of the depression; the severity of the depressive symptoms (IDS-SR); the presence of a comorbid anxiety disorder (yes/no); the number of chronic diseases, assessed with a self-report questionnaire asking whether they currently or previously had any of the following chronic diseases or disease events: cardiac disease (including myocardial infarction), peripheral atherosclerosis, stroke, diabetes mellitus, COPD (asthma, chronic bronchitis or pulmonary emphysema), arthritis (rheumatoid arthritis or osteoarthritis), cancer, or any other chronic disease; the use of any anti-depressive medication (yes/no); and the frequent use (>4/week) of benzodiazepines (yes/no), both self-reported and checked by inspection of the medication participants had to bring in.

Statistical analyses

Chi-square and t-tests were used to test for baseline differences between the non-remitted and completely remitted groups.

Next, a multiple logistic regression analysis with complete remission (yes/no psychiatric diagnoses at two-year follow-up) as the dependent variable, was used to explore the predictive value of all covariates at baseline including socio-demographic, psychopathology, somatic and treatment characteristics. To explore the robustness of the results we repeated the analyses using the stricter definition of complete remission (no diagnoses and low symptom severity levels at two-year follow-up).

Subsequently, personality traits at baseline, life-events (childhood trauma at baseline and negative life-events during two-year follow-up) and their interaction were tested as potential predictors for complete remission (no psychiatric diagnoses at two-year follow-up), adjusted for all the above-mentioned covariates at baseline. For interaction terms, stratified analyses were performed when $p < 0.10$ ³⁷. Dummy variables were then created through median-split for the personality traits (high/low).

We applied Linear Mixed Models (LMM) examining the anxiety symptom severity scores over time. This approach allows for correlated observations over time and handles missing values on different measurements efficiently using maximum likelihood, with data being considered missing at random, conditional on covariates^{38,39}. First, we fitted a standard model with intercept and a linear effect of time. Next, we added a quadratic slope to explore the best fit with the course of the anxiety symptom severity during two-year follow-up. To determine which model best fitted the data we used the log-likelihood statistics. In the final models we allowed a random intercept and a random slope for the independent variable time. Both were allowed to vary across the subjects, following a normal distribution. The covariance structure was estimated as heterogeneous first-order autoregressive structure. Using LMM, we assessed whether personality traits at baseline modified the effect of childhood trauma at baseline and recent life-events during two year-follow-up, and time and their interactions on the course of anxiety symptoms during two-year follow-up. Again, stratified analyses with dummy variables for the personality traits (high/low) at baseline and NLE (high/low) during two-year follow up were performed when an interaction showed a $p < 0.10$.

Multicollinearity was tested by evaluating the Variance Inflation Factor (VIF) and the highest value was found for anxiety (1.84) still far below the cut-off of 2.5 indicative of potentially relevant multicollinearity⁴⁰.

Data were analyzed using Statistical Package of the Social Sciences (SPSS), version 22.0 (IBM SPSS, Chicago, IL).

RESULTS

Descriptives

Patients who completed the two-year follow-up ($N = 270$) had a mean age at baseline of 70.4 years ($SD = 7.4$) at baseline, and 178 (66.0%) were women. The mean years of education was 10.5 ($SD = 3.4$). The mean depression severity at baseline was 30.0 ($SD = 12.9$), which can be categorized as a moderate depression. Among the subgroup of depressed persons, 38.1% (103 of 270) had one

or more comorbid anxiety disorders at baseline, with 18.9% fulfilling diagnostic criteria for Social Phobia, 13.0% for Panic disorder with or without Agoraphobia, 8.9% for Agoraphobia, and 9.6% for Generalized Anxiety Disorder. Furthermore, 39.0% (99 of 254) of the depressed patients had clinically relevant anxiety symptoms at baseline. The participants had a mean number of chronic diseases of 2.1 (SD = 1.5) at baseline. In total, 191 (70.7%) used antidepressant medication at baseline, and 107 (39.6%) used benzodiazepines more than 4 times a week at baseline. Of the 270 participants, 267 provided information about the occurrence of childhood trauma of which 143 (53.6%) reported any childhood trauma. A total of 207 patients provided information about life-events during two-year follow-up. Among those 188 participants (90.8%) experienced one or more negative life events during these two years ($M=4.46$, $SD=3.58$, range = 1-19).

Complete remission vs non-remission

Figure 1 presents detailed results of (non-)remission at two-year follow-up. In the 'pure' depression group 19 participants (11.4%) develop a (comorbid) anxiety disorder during follow-up.

Figure 1. | Diagnostic status at two-year follow-up in older adults with depressive disorder with or without comorbid anxiety disorder at baseline

Table 1 presents the baseline characteristics of the 270 patients, stratified by remission status at two-year follow-up. Of these 270 patients, 103 (38.1%) had a comorbid anxiety disorder at baseline. Depressed patients with a comorbid anxiety disorder at baseline significantly ($X^2=11.4$, $df=1$, $p<.001$) less often had a complete remission at follow-up; 38/103 (37.0%) versus 97/167 (58.1%).

Table 1. | *Determinants of complete remission (neither a depressive nor an anxiety disorder at FU)*

			Outcome at Follow-up			
Determinants			Complete remission (n=135)	Not remitted (n=135)	$X^2_{(df)}/t_{(df)}$	p Value
<i>Socio-demographic</i>						
•	Age (years) ^a	mean (SD)	70.3 (7.1)	70.6 (7.7)	-0.4 ₍₂₆₈₎	0.699
•	Female sex ^b	n (%)	87 (64.4)	91 (67.4)	0.3 ₍₁₎	0.608
•	Education (years) ^a	mean (SD)	10.9 (3.2)	10.2 (3.6)	1.7 ₍₂₆₈₎	0.094
<i>Psychopathology:</i>						
•	Age onset depression ^a	mean (SD)	49.9 (19.7)	45.3 (20.4)	1.9 ₍₂₅₈₎	0.065
•	Comorbid anxiety disorder	n (%)	38 (28.1)	65 (48.1)	11.4 ₍₁₎	0.001
•	Depression severity (IDS-SR) ^a	mean (SD)	25.7 (11.5)	34.2 (12.9)	-5.7 ₍₂₆₅₎	<0.001
•	Anxiety severity (BAI) ^a	mean (SD)	13.4 (9.2)	20.9 (11.4)	-5.8 ₍₂₅₂₎	<0.001
<i>Somatic morbidity:</i>						
•	Number of chronic diseases ^a	mean (SD)	1.7 (1.2)	2.5 (1.7)	-4.4 ₍₂₆₇₎	<0.001
<i>Pharmacological treatment:</i>						
•	Use of any antidepressant	n (%)	97 (72.9)	94 (69.6)	0.4 ₍₁₎	0.550
•	Frequent use of benzodiazepine	n (%)	47 (34.1)	61 (45.2)	3.5 ₍₁₎	0.062
<i>Life-events</i>						
•	NLEburden during FU ^a	mean (SD)	3.8 (3.4)	5.0 (3.7)	-2.5 ₍₂₀₅₎	0.015
•	Childhood Trauma Index ^a	mean (SD)	0.8 (1.1)	1.2 (1.2)	-2.4 ₍₂₆₅₎	0.017
<i>Personality:</i>						
•	Neuroticism ^a	mean (SD)	36.9 (6.0)	41.0 (6.5)	-5.3 ₍₂₅₂₎	<0.001
•	Masterv ^a	mean (SD)	14.4 (2.9)	16.0 (3.2)	-4.0 ₍₂₄₈₎	<0.001

Notes: Bolded p-values indicate $p < 0.05$. BAI: Beck Anxiety Inventory; IDS-SR: Inventory of Depressive Symptomatology self-report version; NLE-burden: reported negative life-events during 2-year follow-up.

^a Independent-samples t tests.

^b χ^2 tests.

The possible determinants for complete remission were explored and shown in Table 1.

In multiple logistic regression analyses including all socio-demographic, psychopathology, somatic and treatment characteristics at baseline, only the severity of depressive symptoms at baseline (OR=1.03 [95% CI: 1.00 – 1.06], $X^2=4.9$, $df=1$, $p=.027$), severity of anxiety symptoms at baseline (OR=1.04 [95% CI: 1.01 – 1.07], $X^2=5.1$, $df=1$, $p=.024$), any anxiety disorder at baseline (OR=2.25 [95% CI: 1.22 – 4.18], $X^2=6.7$, $df=1$, $p=.010$), and the number of chronic diseases at baseline (OR=1.24 [95% CI: 1.01 – 1.54], $X^2=4.1$, $df=1$, $p=.042$) predicted non-remission.

When we performed the sensitivity analyses defining complete remission as not only having none if the diagnoses at two-year follow-up, but also scoring below predefined cut-off scores on depression and anxiety severity scales at two-year follow-up, 196/270 (72,6%) patients were classified as non-remitted. Results of the multiple logistic regression analyses remained the same, with only age of depression onset at baseline showing an additional association with remission. Participants in the more strictly defined complete remission group had a later age of onset of their depression (data not shown).

Adding the variables of interest (life-events and personality) to the model adjusted for covariates, only neuroticism at baseline significantly predicted complete remission (no depressive or anxiety diagnoses at two-year follow-up) (OR=1.06 [95% CI: 1.00 – 1.13], $X^2=4.2$, $df=1$, $p=.040$), but not mastery at baseline, NLEburden during the follow-up period, or childhood trauma at baseline. The only significant interaction was found between baseline measurements of the level of mastery and childhood trauma (OR=1.11 [95% CI: 1.01 – 1.22], $X^2=4.4$, $df=1$, $p=.036$).

Analyses stratified for the presence of childhood trauma revealed the association between complete remission and higher baseline score on the mastery scale (indicative of lower sense of mastery) is more positive among those with a childhood trauma history (1.17 [95% CI: 0.98 – 1.40], $X^2=3.1$, $df=1$, $p=.078$) compared to those without (OR=0.93 [95% CI: 0.79 – 1.09], $X^2=0.8$, $df=1$, $p=.366$).

Predicting course of anxiety

Among the 267 patients with BAI data at during follow-up, 72 (26.7%) suffered from clinically relevant anxiety symptoms (BAI score > 19) at the end of this period.

A linear model with an additional quadratic slope factor provided the best representation of the course of the anxiety symptoms (X^2 change=12.5, df change=1, $p<.01$). The results of the multiple linear mixed models analyses that yield significant interaction effects between the personality traits at baseline and NLE (recent during the two-year follow up and childhood trauma at baseline) on course of anxiety symptoms over time are shown in Table 2. No significant interaction was found with the personality traits of interest and childhood trauma at baseline (Neuroticism*Childhood trauma*time: $b=-0.03$; $t=-0.64$; $df=1021.8$; $p=.525$; Childhood trauma*mastery*time: $b=0.04$; $t=-0.49$; $df=1017.8$; $p=.625$).

Table 2. | Results of linear mixed models of interaction effect of personality (neuroticism and mastery) and negative life-event burden on course of anxiety

Predictor	Course of anxiety		
	Coefficient (95% CI)	<i>t, df</i>	<i>p-value</i>
<i>Neuroticism</i>			
Neuroticism*time	-0.25 (-0.44 to -0.06)	-2.62, 778.1	0.009
Neuroticism *time ²	0.05 (0.009 to 0.10)	2.33, 649.1	0.020
<i>Negative life-events burden</i>			
NLE*time	-0.83 (-2.05 to 0.40)	-1.32, 762.1	0.188
NLE*time ²	0.17 (-0.14 to 0.48)	1.05, 701.0	0.293
Neuroticism*NLE*time	0.03 (-0.004 to 0.06)	1.69, 757.0	0.091
Neuroticism*NLE*time ²	-0.01 (-0.01 to 0.002)	-1.37, 704.3	0.172
<i>Sense of Mastery</i>			
Mastery*time	-0.53 (-0.91 to -0.14)	-2.70, 769.9	0.007
Mastery *time ²	0.11 (0.02 to 0.21)	2.33, 638.1	0.020
<i>Negative life-events burden</i>			
NLE*time	-0.70 (-1.65 to 0.25)	-1.44, 753.2	0.150
NLE*time ²	0.13 (-0.11 to 0.37)	1.09, 690.1	0.276
Mastery*NLE*time	0.06 (-0.004 to 0.12)	1.95, 744.0	0.051
Mastery*NLE*time ²	-0.01 (-0.03 to 0.003)	-1.51, 695.8	0.130

Note: Bolded p-values indicate $p < .10$; adjusted for gender, age, education (in years), number of chronic diseases, presence of an anxiety disorder at baseline, age of onset depressive disorder, depression severity, use of any antidepressant, frequent use of benzodiazepines.

To further graphically explore the course of anxiety symptoms, stratified analyses of the significant interactions between the personality traits and NLEburden are shown in Figure 2 and 3. Figure 2 shows that patients in the high neuroticism group who suffer high NLEburden during two-year follow-up had a higher level of anxiety symptoms during follow-up which after a small initial improvement over the first 6 months revert to the initial level at two-year follow-up. This course contrasted with, patients with low neuroticism (irrespective of the NLEburden) and patients with high neuroticism and low NLEburden in which we found that the overall anxiety level was lower and gradually improved over the two-year follow-up. The same trend can be seen in the low mastery group that suffers high NLEburden during two-year follow-up (Figure 3).

Finally, we checked whether these interactions are unique to the course of anxiety by repeating the analyses for the course of depression. No significant interactions were found for the personality traits neuroticism and sense of mastery at baseline and negative life-events during two-year follow-up, and neuroticism at baseline and reported childhood trauma. A significant interaction effect was found for childhood trauma and sense of mastery at baseline in predicting the course of depression severity ($b=0.20$; $t=-2.04$; $df=1039.6$; $p=.041$).

Figure 2. | Stratified analyses: high and low neuroticism and high and low NLEburden

Figure 3. | Stratified analyses: high and low mastery and high and low NLEburden

DISCUSSION

Main findings

Among 270 older patients suffering from a major depressive disorder at baseline, a total of 135 patients (50.0%) achieved complete remission. The severity of depressive and anxiety symptomatology, the presence of a comorbid anxiety disorder, and poorer physical health at baseline independently predicted non-remission. Also, having a higher level of neuroticism at baseline was associated with non-remission. The impact of mastery at baseline on complete remission differed significantly between patients with and without childhood trauma. The association between a low sense of mastery and childhood trauma was more positive among those with a trauma history than without.

In line with our hypothesis, a less favorable course of self-reported anxiety symptoms was associated with a higher NLEburden during the two-year follow up, but only among patients with a high level of neuroticism or a low level of mastery at baseline.

Complete remission

Two-year remission rates in studies of older persons vary between 48.0% and 83.7% for depressive disorders and between 45.6% and 81.3% for anxiety disorders^{41,42}. Despite the high level of comorbidity between depressive and anxiety disorders in later life, no studies have yet examined complete remission defined as the absence of both a depressive and anxiety disorder. This may be due to the fact that most studies have a clear study objective concerning a single diagnosis (e.g. the depressive disorder). This causes a hiatus in the knowledge for clinical practice for comorbidity rates are known to be high and treatment should target both depressive and anxiety symptoms to achieve lasting remission. rely on symptom severity scales once formal diagnoses have been established, thereby lessening the burden for patients and researchers associated with repeated administration of a full psychiatric interview.

In our sample we found that 78 (57.8%) of the non-remitted patients still suffered from a depressive disorder, 15 (11.1%) still suffered from an anxiety disorder, and 42 (31.1%) suffered from both a depressive and an anxiety at 2-year follow-up. Interestingly, the remission rate was significantly lower in the subgroup with a comorbid anxiety disorder at baseline compared to those with a pure depression (37.0% vs 58.1%). Other independent predictors of complete remission were baseline depression and anxiety severity levels and the somatic disease burden, which are in line with a systematic review and meta-analysis of predictors of remission in 67 depression treatment studies⁽²⁾ as well as community samples⁴¹. When we additionally applied the stricter remission criteria, using also the scores on a symptom severity scale, seven predictors were identified in three or more treatment studies, i.e. baseline depression severity, baseline anxiety symptoms, executive dysfunction, physical illness, current episode duration, early improvement, and age of which only the first three remained significant applying meta- analysis². A systematic review of community samples by Sami⁴² showed strong evidence for an association of baseline depression level, older age, external locus of control, somatic comorbidity and functional limitations with persistent depression⁴¹. Of the two studies identified by this review, one study found that the somatic disease burden was associated with the persistence of both depressive and anxiety disorders during a 12-month period,⁴³ whereas the other study showed that neuroticism was associated with persistent anxiety disorders even after controlling for baseline anxiety symptom severity⁴⁴.

In contrast to our hypothesis, NLEburden and childhood trauma did not predict complete remission independent of baseline severity parameters. Neuroticism had an overall main effect on complete remission, replicating many previous studies on the predictive value of neuroticism^{45,46}. Nonetheless, the impact of mastery was conditional upon the presence of childhood trauma. A lower sense of mastery predicted non-remission in the presence of childhood trauma. A relatively low sense of mastery is common in patients suffering from a depressive or anxiety disorder^{47,48,49}. Having a lower sense of control seems to be especially hindering recovery when this feeling activates an 'old' feeling of loss of control during any kind of childhood trauma²¹. Interventions (e.g.

Cognitive Behavioral Therapy) that promote more adaptive perceptions of control are associated with recovery from anxiety⁴⁹ and depression⁵⁰.

Course of anxiety symptoms

Among the 267 patients with BAI data at follow-up, 72 (26.7%) of our patients still suffered from clinically relevant comorbid anxiety symptoms at the end of this period. This is clinically relevant as even subthreshold anxiety among currently depressed patients is associated with greater psychosocial morbidity^{51,52}. Thus, residual anxiety symptoms have a significant impact on remitted patients' well-being.

Neuroticism and stressors are not necessarily inert until they interact. Instead, stressors and neuroticism have predicted depression and anxiety directly (as statistical main effects), as well as via their interactions^{17,53,54}. Persons with high neuroticism may also produce or worsen stressors in their lives (e.g. through avoidance behavior or ineffective social interactions^{55,56}).

Our results showed that older patients with high neuroticism or low mastery at baseline who suffer a high NLE-burden during the two-year follow up tend to have a less favorable course of anxiety. Stressors, including negative life events often^{17,57,58} but not always^{18,59} interact with high neuroticism to predict depression and anxiety. Interestingly, de Beurs⁵⁹ studied these interactions in an elderly sample. They did find an association between low mastery, high neuroticism, and an increase in negative affect, lack of positive affect, and anxiety. Furthermore, high mastery protected against the negative impact of loss events, but neuroticism did not augment the negative impact of threat events on emotional health.

Strengths and weaknesses

The main strength of this study is the large sample of clinically depressed patients followed in a naturalistic setting with repeated measures of NLE, depression and anxiety during follow-up. The sample is representative for routine mental health care. On the other hand, it should be noted that our findings cannot be generalized to community dwelling older persons. The study design, with repeated diagnostic measurements in addition to symptom severity scales, made it possible to evaluate complete diagnostic remission rates.

The present study focused on complete remission. In other words, the comparison group of non-remitted patients is rather heterogenous including both treatment responders as well as those without any treatment response. Patient numbers, however, were too small to make a meaning differentiation between both types of non-remission.

Since our sample size was relatively small, the effect-sizes of significant effects were at least moderate indicating clinically relevant findings²³. Nonetheless, our sample size is too small to detect small but theoretically interesting results.

Moreover, we also cannot discern between patients who achieved a full remission but relapsed within the two-years, which may be important as comorbid anxiety symptoms have not only been associated with unfavorable treatment response, but also with relapse after a full remission⁶⁰.

Being a clinical cohort study with fixed measurements over time, we did not have detailed information on treatment received, like psychotherapy or timing and reasons for

medication switches. Therefore, we only adjusted all analyses for the use of antidepressants and benzodiazepines at baseline and we cannot exclude confounding due to differential treatment between patients by the level of neuroticism, sense of mastery, NLEburden, or childhood trauma.

In general, studies show that neuroticism remains rather stable in middle and older adulthood, with some apparent increase in late life⁶¹. The measurement of personality traits may be partly biased due to a depressed state. Although, personality traits are considered to be stable, the presence of depression is known to amplify the personality profile of people prone to depression. After recovery of depression, however, the overall shape of the profile does not change⁶². Nonetheless, the relationship between change in personality and change in depressive symptoms is at most moderate^{63–65}.

Clinical implications

In clinical practice, depression and anxiety are strongly entangled and residual symptoms increase the risk of relapse. When evaluating remission rates, it is important that depressive and anxiety disorders are absent at follow-up. Because the pathology of depression with concurrent anxiety is believed to be more complex, case conceptualization is needed to unravel this ‘Gordian knot’ and some have suggested it requires specialized interventions^{66–68}. Interventions to reduce depression and anxiety symptomology need to incorporate techniques that enhance aspect of psychological well-being, like the sense of mastery⁶⁹ for daily life-stress continues to be a risk factor among non- or partly remitted⁷⁰.

REFERENCES

- 1 Lenze, E. J. et al. Comorbidity of depression and anxiety disorders in later life. *Depression and Anxiety* vol. 14 86–93 (2001).
- 2 Tunvirachaisakul, C. et al. Predictors of treatment outcome in depression in later life: A systematic review and meta-analysis. *J. Affect. Disord.* 227, 164–182 (2018).
- 3 Ionescu, D. F., Niciu, M. J., Henter, I. D. & Zarate, C. A. Defining anxious depression: A review of the literature. *CNS Spectrums* vol. 18 252–260 (2013).
- 4 Ionescu, D. F., Niciu, M. J., Mathews, D. C., Richards, E. M. & Zarate, C. A. Neurobiology of anxious depression: A review. *Depression and Anxiety* vol. 30 374–385 (2013).
- 5 Van Der Veen, D. C., Comijs, H. C., Van Zelst, W. H., Schoevers, R. A. & Oude Voshaar, R. C. Defining anxious depression in later life: A scaring heterogeneity in results. *Am. J. Geriatr. Psychiatry* 22, 1375–1378 (2014).
- 6 Andreescu, C., Chang, C. C., Mulsant, B. H. & Ganguli, M. Twelve-year depressive symptom trajectories and their predictors in a community sample of older adults. *Int. psychogeriatrics* 20, 221–236 (2008).
- 7 Byers, A. L. et al. Twenty-year depressive trajectories among older women. *Arch. Gen. Psychiatry* 69, 1073–1079 (2012).
- 8 de Beurs, E., Beekman, A. T., Deeg, D. J., Dyck, R. Van & van Tilburg, W. Predictors of change in anxiety symptoms of older persons: results from the Longitudinal Aging Study Amsterdam. *Psychol. Med.* 30, 515–527 (2000).
- 9 Schuurmans, J. et al. Long-term effectiveness and prediction of treatment outcome in cognitive behavioral therapy and sertraline for late-life anxiety disorders. *Int. psychogeriatrics* 21, 1148–1159 (2009).
- 10 Spinhoven, P., Spinhoven, P., van der Veen, D. C. C., Comijs, H. C. & Voshaar, R. C. O. Worry and cognitive control predict course trajectories of anxiety in older adults with late-life depression. *Eur. Psychiatry* 44, 134–140 (2017).
- 11 Kraaij, V., Arensman, E. & Spinhoven, P. Negative life events and depression in elderly persons: a meta-analysis. *The Journals Gerontol. B, Psychol. Sci. Soc.* 57, P87-94 (2002).
- 12 Gibb, B. E., Chelminski, I. & Zimmerman, M. Childhood emotional, physical, and sexual abuse, and diagnoses of depressive and anxiety disorders in adult psychiatric outpatients. *Depress. Anxiety* 24, 256–263 (2007).
- 13 Paykel, E. S. Life events, social support and depression. *Acta Psychiatr. Scand.* 377, 50–58 (1994).
- 14 de Beurs, E. et al. Treatment results for severe psychiatric illness: which method is best suited to denote the outcome of mental health care? *BMC Psychiatry* 18, 224–225 (2018).
- 15 Clark, L. A., Watson, D. & Mineka, S. Temperament, personality, and the mood and anxiety disorders. *J. Abnorm. Psychol.* 103, 103–116 (1994).
- 16 Ormel, J., Stewart, R. & Sanderman, R. Personality as modifier of the life change-distress relationship. A longitudinal modelling approach. *Soc. Psychiatry Psychiatr. Epidemiol.* 24, 187–195 (1989).
- 17 Kendler, K. S., Kuhn, J. & Prescott, C. A. The Interrelationship of Neuroticism, Sex, and Stressful Life Events in the Prediction of Episodes of Major Depression. *Am. J. Psychiatry* 161, 631–636 (2004).
- 18 Spinhoven, P. et al. Positive and negative life events and personality traits in predicting course of depression and anxiety. *Acta Psychiatr. Scand.* 124, 462–473 (2011).
- 19 Vasunilashorn, S., Lynch, S. M., Gleib, D. A., Weinstein, M. & Goldman, N. Exposure to stressors and trajectories of perceived stress among older adults. *journals Gerontol. B, Psychol. Sci. Soc. Sci.* 70, 329–337 (2015).
- 20 Kotov, R., Gamez, W., Schmidt, F. & Watson, D. Linking ‘big’ personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychol. Bull.* 136, 768–821 (2010).
- 21 Chorpita, B. F. & Barlow, D. H. The development of anxiety: the role of control in the early environment. *Psychol. Bull.* 124, 3–21 (1998).

- 22 Mirowsky, J., & Ross, C. E. Well-being across the life course. In A. V. Horwitz & T. L. Scheid (Eds.) *A handbook for the study of mental health: Social contexts, theories, and systems* (p. 328–347). Cambridge University Press. (1999).
- 23 Comijs, H. & Dekker, J. The Netherlands Study of Depression in Older persons (NESDO). *Int. Psychogeriatrics* 23, S70–S71 (2011).
- 24 Comijs, H. C. et al. The two-year course of late-life depression; results from the Netherlands study of depression in older persons. *BMC Psychiatry* 15, 20–25 (2015).
- 25 Wittchen, H. U. Reliability and validity studies of the WHO–Composite International Diagnostic Interview (CIDI): a critical review. *J. Psychiatr. Res.* 28, 57–84 (1994).
- 26 Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. An inventory for measuring clinical anxiety: Psychometric properties. *J. Consult. Clin. Psychol.* 56, 893–897 (1988).
- 27 Rush, A. J., Gullion, C. M., Basco, M. R., Jarrett, R. B. & Trivedi, M. H. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol. Med.* 26, 477–486 (1996).
- 28 De Graaf, R., Bijl, R. V., Ten Have, M., Beekman, A. T. F. & Vollebergh, W. A. M. Pathways to comorbidity: The transition of pure mood, anxiety and substance use disorders into comorbid conditions in a longitudinal population-based study. *J. Affect. Disord.* 82, 461–467 (2004).
- 29 Penninx, B. W. J. H. et al. The Netherlands Study of Depression and Anxiety (NESDA): Rationale, objectives and methods. *Int. J. Methods Psychiatr. Res.* 17, 121–140 (2008).
- 30 Hovens, J. G. et al. Childhood life events and childhood trauma in adult patients with depressive, anxiety and comorbid disorders vs. controls. *Acta Psychiatr. Scand.* 122, 66–74 (2010).
- 31 Brugha, T., Bebbington, P., Tennant, C. & Hurry, J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol. Med.* 15, 189–194 (1985).
- 32 Shields, G. S. & Slavich, G. M. Lifetime Stress Exposure and Health: A Review of Contemporary Assessment Methods and Biological Mechanisms. *Soc. Personal. Psychol. Compass* 11, 10.1111/spc3.12335. Epub 2017 Aug 3 (2017).
- 33 Sonia J. Lupien Bruce S. McEwen, M. R. G. & Heim, C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* vol. 10 (6) 434 (2009).
- 34 Costa P. T. Jr & McCrae, R. R. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. *J. Pers. Assess.* 64, 21–50 (1995).
- 35 Pearlin, L. I. & Schooler, C. The structure of coping. *J. Health Soc. Behav.* 19, 2–21 (1978).
- 36 Maaren, Y. W. S. et al. Reference values for major depression questionnaires: the Leiden Routine Outcome Monitoring Study. *J. Affect. Disord.* 149, 342–349 (2013).
- 37 Aiken, L., West, S. & Reno, R. *Multiple regression: Testing and interpreting interactions*. Sage Publication Inc (1991).
- 38 West, B. T. Analyzing longitudinal data with the linear mixed models procedure in SPSS. *Eval. Health Prof.* 32, 207–228 (2009).
- 39 Shek, D. T. & Ma, C. M. Longitudinal data analyses using linear mixed models in SPSS: concepts, procedures and illustrations. *TheScientificWorldJournal*. 11, 42–76 (2011).
- 40 Johnston, R., Jones, K. & Manley, D. Confounding and collinearity in regression analysis: a cautionary tale and an alternative procedure, illustrated by studies of British voting behaviour. *Qual. Quant.* 52, 1957–1976 (2018).
- 41 Licht-Strunk, E., van der Windt, D. A., van Marwijk, H. W., de Haan, M. & Beekman, A. T. The prognosis of depression in older patients in general practice and the community. A systematic review. *Fam. Pract.* 24, 168–180 (2007).
- 42 Sami, M. B. & Nilforooshan, R. The natural course of anxiety disorders in the elderly: a systematic review of longitudinal trials. *Int. psychogeriatrics* 27, 1061–1069 (2015).

- 43 Preville, M. et al. Persistence and remission of psychiatric disorders in the quebec older adult population. *Can. J. psychiatry.Revue Can. Psychiatr.* 55, 514–522 (2010).
- 44 Schuurmans, J. et al. The outcome of anxiety disorders in older people at 6-year follow-up: Results from the Longitudinal Aging Study Amsterdam. *Acta Psychiatr. Scand.* 111, 420–428 (2005).
- 45 Vittengl, J. R. Who pays the price for high neuroticism? Moderators of longitudinal risks for depression and anxiety. *Psychol. Med.* 47, 1794–1805 (2017).
- 46 Jeronimus, B. F., Kotov, R., Riese, H. & Ormel, J. Neuroticism's prospective association with mental disorders halves after adjustment for baseline symptoms and psychiatric history, but the adjusted association hardly decays with time: a meta-analysis on 59 longitudinal/prospective studies with 443 313 pa. *Psychol. Med.* 46, 2883–2906 (2016).
- 47 Abramson, L. Y., Metalsky, G. I. & Alloy, L. B. Hopelessness depression: A theory-based subtype of depression. *Psychol. Rev.* 96, 358–372 (1989).
- 48 Gallagher, M. W., Naragon-Gainey, K. & Brown, T. A. Perceived Control is a Transdiagnostic Predictor of Cognitive-Behavior Therapy Outcome for Anxiety Disorders. *Cognit. Ther. Res.* 38, 10–22 (2014).
- 49 Gallagher, M. W., Bentley, K. H. & Barlow, D. H. Perceived Control and Vulnerability to Anxiety Disorders: A Meta-analytic Review. *Cognit. Ther. Res.* 38, 571–584 (2014).
- 50 Craske, M. G. et al. Cognitive behavioral therapy for panic disorder and comorbidity: more of the same or less of more? *Behav. Res. Ther.* 45, 1095–1109 (2007).
- 51 Mendlowicz, M. V & Stein, M. B. Quality of life in individuals with anxiety disorders. *Am. J. Psychiatry* 157, 669–682 (2000).
- 52 Grenier, S. et al. The epidemiology of specific phobia and subthreshold fear subtypes in a community based sample of older adults. *Depress. Anxiety* 28, 456–463 (2011).
- 53 Oddone, C. G., Hybels, C. F., McQuoid, D. R. & Steffens, D. C. Social support modifies the relationship between personality and depressive symptoms in older adults. *Am. J. Geriatr. Psychiatry* 19, 123–131 (2011).
- 54 Caska, C. M. & Renshaw, K. D. Personality traits as moderators of the associations between deployment experiences and PTSD symptoms in OEF/OIF service members. *Anxiety. Stress. Coping* 26, 36–51 (2013).
- 55 Lahey, B. B. Public health significance of neuroticism. *Am. Psychol.* 64, 241–256 (2009).
- 56 Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R. & Ellard, K. K. The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clin. Psychol. Sci.* 2, 344–365 (2014).
- 57 Cox, B. J., Taylor, S., Clara, I. P., Roberts, L. & Enns, M. W. Anxiety sensitivity and panic-related symptomatology in a representative community-based sample: A 1-year longitudinal analysis. *J. Cogn. Psychother.* 22, 48–56 (2008).
- 58 Brown, T. A. & Rosellini, A. J. The direct and interactive effects of neuroticism and life stress on the severity and longitudinal course of depressive symptoms. *J. Abnorm. Psychol.* 120, 844–856 (2011).
- 59 de Beurs, E. et al. Stability and change of emotional functioning in late life: modelling of vulnerability profiles. *J. Affect. Disord.* 84, 53–62 (2005).
- 60 Andreescu, C. et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: Controlled study. *Br. J. Psychiatry* 190, 344–349 (2007).
- 61 Steunenberg, B., Twisk, J. W., Beekman, A. T., Deeg, D. J. & Kerkhof, A. J. Stability and change of neuroticism in aging. *The Journals Gerontol. B, Psychol. Sci. Soc.* 60, P27–33 (2005).
- 62 Santor, D. A., Bagby, R. M. & Joffe, R. T. Evaluating stability and change in personality and depression. *J. Pers. Soc. Psychol.* 73, 1354–1362 (1997).
- 63 Costa, P. T., Bagby, R. M., Herbst, J. H. & McCrae, R. R. Personality self-reports are concurrently reliable and valid during acute depressive episodes. *J. Affect. Disord.* 89, 45–55 (2005).

- 64 Ormel, J., Oldehinkel, A. J. & Vollebergh, W. Vulnerability before, during, and after a major depressive episode: A 3-wave population-based study. *Archives of General Psychiatry* vol. 61 990–996 (2004).
- 65 Spinhoven, P., Penelo, E., De Rooij, M., Penninx, B. W. & Ormel, J. Reciprocal effects of stable and temporary components of neuroticism and affective disorders: Results of a longitudinal cohort study. *Psychol. Med.* 44, 337–348 (2014).
- 66 Petersen, T., Andreotti, C. F., Chelminski, I., Young, D. & Zimmerman, M. Do comorbid anxiety disorders impact treatment planning for outpatients with major depressive disorder? *Psychiatry Res.* 169, 7–11 (2009).
- 67 Kush, F. R. An Operationalized Cognitive Therapy Approach With Mixed Anxiety and Depression. *Psychother. Theory, Res. Pract. Train.* 41, 266–275 (2004).
- 68 Papakostas, G. I. et al. Fluoxetine-clonazepam cotherapy for anxious depression: an exploratory, post-hoc analysis of a randomized, double blind study. *Int. Clin. Psychopharmacol.* 25, 17–21 (2010).
- 69 Burns, R. A., Anstey, K. J. & Windsor, T. D. Subjective well-being mediates the effects of resilience and mastery on depression and anxiety in a large community sample of young and middle-aged adults. *Aust. N. Z. J. Psychiatry* 45, 240–248 (2011).
- 70 van Winkel, M. et al. Daily life stress reactivity in remitted versus non-remitted depressed individuals. *Eur. Psychiatry* 30, 441–447 (2015).

CHAPTER 7

WORRY AND COGNITIVE CONTROL PREDICT COURSE TRAJECTORIES OF ANXIETY IN OLDER ADULTS WITH LATE-LIFE DEPRESSION

Based on:

Spinhoven, P., **van der Veen, D. C.**, Comijs, H. C., & Oude Voshaar, R. C. (2017). Worry and cognitive control predict course trajectories of anxiety in older adults with late-life depression. *European Psychiatry*, 44, 134–140.

ABSTRACT

Background

Many older adults with depressive disorder manifest anxious distress. This longitudinal study examines the predictive value of worry as a maladaptive cognitive emotion regulation strategy, and resources necessary for successful emotion regulation (i.e., cognitive control and resting heart rate variability (HRV)) for the course of anxiety symptoms in depressed older adults. Moreover, it examines whether these emotion regulation variables moderate the impact of negative life events of severity of anxiety symptoms.

Methods

Data of 378 depressed older adults (CIDI) between 60-93 years (of whom 144 (41%) had a comorbid anxiety disorder) from the Netherlands Study of Depression in Older Adults (NESDO) were used. Latent Growth Mixture Modeling was used to identify different course trajectories of six-months BAI scores. Univariable and multivariable longitudinal associations of worry, cognitive control and HRV with symptom course trajectories were assessed.

Results

We identified a course trajectory with low and improving symptoms (57.9%), a course trajectory with moderate and persistent symptoms (33.5%), and a course trajectory with severe and persistent anxiety symptoms (8.6%). Higher levels of worry and lower levels of cognitive control predicted persistent and severe levels of anxiety symptoms independent of presence of anxiety disorder. However, worry, cognitive control and HRV did not moderate the impact of negative life events on anxiety severity.

Conclusions

Worry may be an important and malleable risk factor for persistence of anxiety symptoms in depressed older adults. Given the high prevalence of anxious depression in older adults modifying worry may constitute a viable venue for alleviating anxiety levels.

INTRODUCTION

Anxiety is among the most prevalent and debilitating mental health problems in older adults¹ and often co-occurs with depression². Few studies have traced course trajectories of anxiety disorder and anxiety symptoms and its prognostic course determinants in a cohort of community-dwelling older adults^{3,4}. A rather unfavorable long-term outcome of anxiety after 6 years has been observed, predicted by female gender and higher levels of neuroticism at baseline.

Cognitive emotion regulation strategies have never been studied as determinants of the course of anxiety in older adults. Cognitive emotion regulation strategies are cognitive responses to emotion-eliciting events that consciously or unconsciously attempt to modify the magnitude and/or type of individuals' emotional experience or the event itself⁵. Maladaptive strategies (such as rumination and suppression) are strongly associated with various forms of psychopathology, such as anxiety and depression⁶. In younger adults it has been repeatedly shown that worry is a dysfunctional cognitive emotion regulation strategy implicated in onset, maintenance and relapse of anxiety (and depressive) disorders⁷.

Inhibitory control is a key mechanism for successful emotion regulation as persons are required to inhibit prepotent emotional responses in service of more desirable and appropriate ones. As cognitive control impairs by aging, it can be assumed that older adults will have more difficulty to regulate their emotions⁸. Moreover, research in late life anxiety has shown that anxiety disorders result in cognitive control deficits arising from disturbances in goal maintenance due to disruption of the ability to inhibit task irrelevant information⁹. Reduced cognitive functioning through aging coupled with late life anxiety suggest that anxiety and aging pose a double jeopardy for impaired cognitive control of emotion.

Ageing also causes a decrease in parasympathetic tone at rest what is manifested by a decrease in heart rate variability (HRV)¹⁰. HRV is a readily available index and measure of inhibitory control, and more specifically, emotion regulation capacity¹¹. Individuals with better emotion regulation skills manifest higher levels of resting HRV, and HRV appears to be increased during successful performance on emotion regulation tasks¹². Moreover, decreases in HRV in response to complex negative situations that affected multiple life domains have been found to be more pronounced in older people than in younger adults¹³.

The aim of the present study is to examine whether depressed older adults with higher levels of worry and lower levels of cognitive control and HRV will be more likely to show an unfavorable course of anxiety symptoms. Moreover, we studied whether exposure to negative life events possibly overtaxing emotion regulation capacities will result in more severe anxiety symptoms in depressed older adults with higher levels of worry and lower levels of cognitive control and HRV.

METHODS

Participants

Data from the Netherlands Study of Depression in Older persons (NESDO)¹⁴ were used. NESDO is a multi-site prospective cohort study, including 378 depressed and 132 non-depressed older persons (60–93 years). Depressed persons were included when they fulfilled the DSM-IV-TR criteria for major depression (95.0%), dysthymia (26.5%) in the previous 6 months or current

minor depression (5.0%). Of the depressed older persons, 144 (41.0 %) also displayed a comorbid anxiety disorder. The population and methods of the NESDO study have been described in detail elsewhere¹⁴. The study was approved by the ethical boards of the participating institutes and written informed consent was obtained from all participants. In the present study, only depressed persons with and without comorbid anxiety were included (n = 378) of whom 285 (75.4%) completed the two-year follow-up assessments¹⁵.

Measurements

Psychiatric diagnoses

Diagnoses of depression and anxiety at baseline and two-year follow-up were assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization (WHO) version 2.1) according to DSM-IV-TR criteria¹⁶.

Symptom severity

The severity of anxiety symptoms was assessed with the Beck Anxiety Inventory (BAI)¹⁷ at baseline and 6-, 12-, 18-, and 24-months follow-up. Severity of depressive symptoms at baseline was assessed with the self-report version of the Inventory of Depressive Symptomatology (IDS- SR)¹⁸.

Negative life events

The occurrence of recent negative life-events (NLE), such as experiencing serious illness or major financial loss, was assessed using the Brugha questionnaire^{19,20}. These events reflect the presence of life stressors during the last 12 months before baseline or last six months before the 6-, 12-, 18-, and 24-months follow-up.

Worry

Symptoms of worrying at baseline were assessed with a revised version of the Worry Scale²¹. This questionnaire is especially developed for use with older adults with subscales that reflect severity of worry about financial, health, and social concerns. Based on factor loadings, skewness of mean scores on each item, 15 items were selected for the shortened version²².

Cognitive control

Cognitive control was measured with the abbreviated version of the Stroop color-word test²³. This test consisted of three subtasks; the first card (I) had color words (red, blue, green, yellow) printed in black, the second card (II) had colored patches of the same colors, and the last card (III) had color words printed in incongruent colored ink. During the third task the participants were shown cards displaying names of colors in a non-matching color and asked to name the color of the ink as fast and as accurate as possible. Cognitive control was assessed with the interference score calculated by the following formula: $(t_{III} - 0.5 \times (t_I + t_{II})) / (0.5 \times (t_I + t_{II}))$ (t = time in seconds)²⁴.

Heart Rate Variability

Physiological measurements were performed with the "Vrije Universiteit Ambulatory Monitoring System" recording the electrocardiogram (ECG) and changes in thorax impedance (dZ) from six

electrodes placed on the chest and back of the participants²⁵. NESDO participants wore the Vrije Universiteit Ambulatory Monitoring System device during around 116 minutes of the NESDO baseline assessment. The assessment procedure has been described in more detail elsewhere²⁶. The interbeat interval (IBI) time series was extracted from the ECG signal to obtain HR. Respiratory sinus arrhythmia (RSA) is a reliable index of cardiac parasympathetic control²⁷ and was used as a measure of HRV. RSA was obtained by combining the IBI time series with the filtered (0.1–0.4 Hz) dZ signal, which corresponds to the respiration signal. RSA was obtained by subtracting the shortest IBI during HR acceleration in the inspirational phase from the longest IBI during deceleration in the expirational phase for all breaths, as described in detail elsewhere²⁵. As several studies have suggested that research investigating RSA should take RR into account as a confounder²⁸, all RSA analyses were adjusted for RR.

Statistical analyses

The Stroop interference scores were log-transformed to obtain a near-normal distribution. Moreover, we categorized the number of life-events measurements as none, one or two or more life events. The other measures showed a normal distribution. In the moderation analyses, scores for worry, cognitive control and HRV were transformed to z-scores.

As it is unlikely that a single growth trajectory of anxiety symptoms will adequately describe the course of anxiety symptoms among depressed older adults, we first tried to identify different course trajectories of anxiety symptoms, based on repeated BAI scores during 2-year follow-up using Latent Growth Mixture Modeling (LGMM). LGMM assesses whether multiple unobserved latent trajectories are available within an observed overarching group of individuals allowing for different groups of individual growth trajectories to vary around different means. In LGMM each subgroup trajectory is defined by two latent variables: intercept and slope²⁹. To determine the number of underlying latent trajectories successive models of one to more subgroups are specified and estimated to find the model that best approximates the subgroups within the data. We first fitted standard models with intercept and linear effects of time. Next, we successively added a quadratic slope factor to allow for curved trajectories. As parameter estimates we used maximum likelihood with robust standard errors (MLR) that are robust to non-normality and non-independence of observations.

To determine which model best fitted the data, we combined Maximum Likelihood, Bayesian Information Criterion (BIC), sample size adjusted BIC (ssaBIC), Lo-Mendell-Rubin likelihood ratio test (LMR), and bootstrapped likelihood ratio test (BLRT). Both the BLRT and LMR provide a p-value, which indicates whether the $k-1$ class model is rejected in favor of the k class model³⁰. After the identification of the number of classes, persons were assigned to their most likely class based on model probabilities. Classification quality of the final LGMM model was evaluated based on entropy and average posterior probabilities for latent class membership.

Next, we examined to what extent emotion regulation variables (worry, cognitive control, HRV) were predictive of course trajectories using univariate and multivariate, multinomial logistic regression analyses with the low anxiety group as reference category. In addition to unadjusted analyses, we controlled our multinomial logistic regression analyses for demographic variables (age, gender, education), as well presence of anxiety disorder and use of antidepressant and

anxiolytic medication as we were interested in whether the predictive value of emotion regulation variables is independent of presence of anxiety disorder and medication use is known to affect cognitive control and HRV in particular³¹.

Finally, we assessed whether emotion regulation variables modified the effect of exposure to negative life events on severity of anxiety symptoms. Because anxiety severity and exposure to negative life events were measured repeatedly, we used linear mixed models (LMM). This approach allowed us to model the effects of NLEs as time varying variables as well as of time invariant emotion regulation factors on anxiety severity (BAI). In these moderation analyses, the possible additional effect of the interaction of emotion regulation variables with exposure to NLE on severity of anxiety symptoms on top of the direct effect of emotion regulation variables and NLEs could be analyzed.

Statistical analyses were run using SPSS version 23³² except the LGMM analyses, which were performed using *MPlus* v. 7.1³³. A p -value $< .05$ was considered statistically significant.

RESULTS

Descriptives

The overall sample of 378 participants had a mean age of 70.7 years ($SD = 7.4$) and consisted of 250 (66.1%) women and 138 (33.9%) men. The mean number of years of education was 10.9 ($SD = 3.6$). Of the depressed persons, 274 (73.1%) used antidepressant medication and 123 (32.5%) used anxiolytic medication. Among the subgroup of depressed persons with comorbid anxiety disorder, 25.7% fulfilled the diagnostic criteria for Generalized Anxiety Disorder, 18.1% for Panic disorder with or without Agoraphobia, 25.0% for Agoraphobia, and 45.8% for Social Anxiety Disorder.

Course trajectories and the external validation of these trajectories

A linear model with an additional quadratic slope factor provided the best representation of the various course trajectories (see Table 1). Although the LMR-test failed to reach significance from the 5-class model onwards, we chose the 3-class model as providing the best fit for the observed data, because the addition of a fourth class served only to split one of the classes into two parallel trajectories with no substantive distinction in symptom levels and the fourth class in this model also consisted of 5 persons (1.3%) only precluding meaningful prediction analyses of class membership.

The level of entropy of the 3-class model was high (.87). Moreover, posterior probabilities for class membership were high (Class 1: .91; Class 2: .97; and Class 3: .90), while posterior probabilities for membership to another class were low (ranging from .00 to .10). Figure 1 shows the course trajectories of the three identified latent classes. As the first class, consisting of 33.5% of our sample ($n=125$), showed a moderate level of anxiety and no significant decline in anxiety during follow-up (intercept = 23.4, $p < .001$; linear slope = -1.50 , $p = .12$; quadratic slope = 0.208 , $p = .345$), we labeled this subgroup as the moderate anxiety group. As the second class, consisting of 57.9% of our sample ($n = 216$), had low anxiety score which significantly decreased over time (intercept = 10.334, $p < .001$; linear slope = -2.502 , $p < .001$; quadratic slope = 0.446 , $p < 0.001$), we labeled this group as the low anxiety group.

Table 1. |Parameters of fit of Latent Growth Mixture Modelling based on BAI scores at T1 to T5 (n = 375)^a

Linear model	Classes	Maximum Likelihood	BIC	ssaBIC	Entropy	Lo-Mendell-Rubin test		BLRT p	Proportion of individuals in class				
						2LL	p		1	2	3	4	5
1.1	1	-5703.836	11460.966	11432.412	(-)	(-)	(-)	(-)	1.00				
1.2	2	-5442.517	10962.014	10920.768	0.843	501.468	0.0018	<.001	0.66	0.34			
1.3	3	-5349.727	10800.121	10746.185	0.875	178.062	0.0187	<.001	0.34	0.58	0.08		
1.4	4	-5323.642	10771.636	10705.010	0.887	50.057	0.0118	<.001	0.32	0.10	0.01	0.57	
1.5	5	-5307.166	10762.373	10683.054	0.839	31.616	0.2791	<.001	0.04	0.04	0.23	0.14	0.55

Note. ^a 375 participants because of missing baseline BAI scores in three persons; BIC=Bayesian Information Criterion; ssaBIC= sample size adjusted BIC; BLRT= bootstrapped likelihood ratio test; 2LL= 2 log likelihood

Figure 1. | Identified course trajectories of late-life depression based on anxiety symptoms (n = 375)

Note. BAI = Beck Anxiety Inventory; Follow-up: 0= baseline; 1 = 6, 2 = 12, 3 = 18 and 4 = 24-month follow-up; Low anxiety group (n=216; 57.9%); Moderate anxiety group (n=125; 33.5%); Severe anxiety group (n = 32; 8.6%)

As symptoms in the third group, consisting of 8.6% of our sample (n= 32), were severe and persistent (mean intercept = 35.740, p <.001; slope = 1.813, p =0.388; quadratic slope = -0.427, p = 0.436), we labeled this group as the severe anxiety group. Participants from both the moderate and severe anxiety group manifested a significantly higher proportion of anxiety disorders and significantly higher levels of anxiety symptomatology at T1 and T5 compared to participants from the low anxiety group (see Table 2).

Table 2. | *Distribution of putative risk factors at baseline across the identified three course trajectories (n = 375)*

	LA		MA		SA		MA vs LA		SA vs LA	
	(n=216)		(n = 125)		(n = 32)					
	M	Sd	M	Sd	M	Sd	OR	95%CI	OR	95%CI
<i>Demographics</i>										
Age	70.98	(7.27)	70.21	(7.70)	71.63	(7.32)	.99	(.96 - 1.02)	1.01	(.96 - 1.06)
Gender (female)	134	(62.0%)	88	(70.4%)	25	(78.1%)	1.45	(.91 - 2.33)	2.19	(.90 - 5.28)
Education (years)	10.68	(3.34)	10.39	(3.72)	8.88	(2.79)	.98	(.92 - 1.04)	.84 (.74 - .95)	
<i>Clinical variables</i>										
Anxiety disorder T1	67	(31.0%)	58	(46.4%)	17	(53.1%)	1.92 (1.22 - 3.03)		2.52 (1.19 - 5.34)	
Anxiety disorder T5 ^a	14	(8.4%)	37	(37.4%)	7	(36.8%)	6.52 (3.30 - 12.90)		6.37 (2.16 - 18.79)	
BAI T1	11.06	(7.31)	24.35	(8.20)	34.94	(11.30)	1.21 (1.16 - 1.27)		1.38 (1.29 - 1.48)	
BAI T5 ^a	7.22	(5.15)	20.56	(8.11)	35.74	(11.27)	1.34 (1.25 - 1.44)		1.60 (1.44 - 1.78)	
IDS	24.44	(11.09)	36.81	(10.87)	41.84	(12.82)	1.10 (1.07 - 1.12)		1.14 (1.10 - 1.89)	
ADM use (yes)	157	(73.0%)	95	(77.2%)	18	(56.3%)	1.25	(.75 - 2.10)	.47	(.22 - 1.02)
Anxiolytica use (yes)	57	(26.4%)	47	(37.6%)	16	(50.0%)	1.68 (1.05 - 2.69)		2.79 (1.31 - 5.94)	
<i>Emotion regulation</i>										
Worry	5.20	(6.58)	8.90	(7.98)	11.00	(8.53)	1.07 (1.04 - 1.11)		1.10 (1.05 - 1.55)	
Cognitive control ^b	1.42	(.79)	1.36	(.90)	1.81	(.97)	.69	(.44 - 1.08)	2.27 (1.10 - 4.65)	
HRV ^c	18.01	(11.51)	19.62	(14.12)	24.24	(27.76)	1.01	(.99 - 1.03)	1.02 (1.01 - 1.05)	

Note. LA = Low Anxiety Group (reference category); MA = Moderate Anxiety Group; SA = Severe Anxiety Group; OR = Odds Ratio; 95%CI = 95% Confidence Interval; BAI = Beck Anxiety Inventory; IDS = Inventory of Depressive Symptomatology; ADM = Anti-Depressive Medication; ^a Only available for 285 study completers; ^b Non-transformed Stroop interference scores; ^c Heart Rate Variability (HRV) analyses controlled for respiratory rate (RR); # NLEs = Number of Negative Life Events (NLE) before baseline

Emotion regulation variables as predictors of the course of anxiety severity

Univariate multinomial logistic regression analyses showed that worry, cognitive control and HRV predicted course trajectories (see Table 2). The level of worry of both the moderate and severe anxiety group was significantly higher than of the low anxiety group. Moreover, the severe anxiety group obtained significantly lower scores for cognitive control and higher scores for HRV than the low anxiety group. Repeating the analyses of the emotion regulation variables while controlling for demographic variables, presence of anxiety disorder and use of antidepressant

and anxiolytic medication showed that the significant effect of worry (OR = 1.07; 95% CI = 1.03 – 1.11, respectively OR = 1.09; 95% CI = 1.04 – 1.15), and cognitive control (OR = 2.22; 95% CI = 1.02 – 4.85) remained. However, the predictive value of HRV for course trajectories was no longer significant (OR = 1.02; 95% CI = .99 - 1.05).

Emotion regulation variables as moderators of the relationship of negative life events with anxiety severity

Participants with or without anxiety disorder reported on average exposure to 1.0 negative life event during each 6-month period. Two negative life events were mentioned on at least three of the five measurements by more than 10% of the respondents: 'being seriously ill, wounded or victim of violence of family member' and 'a friend or family member died'. LMM analyses with a random intercept showed that exposure to 1 (estimate = .62; 95% CI = -.25 – 1.49) or 2 or more negative life events (estimate = .89; 95% CI = -.08 – 1.86) in comparison to no exposure did not predict severity of anxiety symptoms. Moreover, worry, cognitive control and HRV did not moderate the impact of NLE on course of anxiety severity in unadjusted (see Table 3), as well as adjusted analyses (data not shown).

Table 3. | *Parameter estimates from the linear mixed models predicting the intercept and slope of baseline, 6-, 12-, 18- and 24-months BAI scores by exposure to negative life events and emotion regulation variables (n = 373)^a*

Parameter	Worry		Cognitive control		HRV ^a	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Intercept	14.99	13.90 – 16.07	14.78	13.63 – 15.92	14.73	13.52-15.94
Predictor	3.90	2.75 – 5.05	1.25	.13 – 2.36	1.05	-.16 – 2.26
NLE(1)	.60	-.29 – 1.49	.60	-.27 – 1.47	.67	-.26 – 1.60
NLE(>1)	.62	-.36 – 1.60	.88	-.09 – 1.85	.99	-.02 – 2.01
Predictor*NLE(1)	-.48	-1.49 - .52	.10	-.81 – 1.00	.29	-.59 – 1.18
Predictor*NLE(>1)	.28	-.68 – 1.24	-.52	-1.46 - .42	-.61	-1.60 - .38

Note. ^a 373 participants because of missing baseline BAI and NLE scores in five persons; BAI = Beck Anxiety Inventory; NLE = Negative Life Events; No NLEs is reference category; a RSA analyses controlled for RR, and RR * NLE

DISCUSSION

We identified a group of participants with moderate symptoms of anxiety, which improved during the 2-year follow-up period, a group with moderate and persistent anxiety symptom, and a group with severe and persistent anxiety symptoms. These results concur with those of previous studies on the course of anxiety symptoms in older adults^{3,34} and younger adults^{35,36} with anxiety disorder in that they challenge the idea that a 'chronic' clinical course is characteristics for all patients with anxiety disorders in general. Also, in depressed older adults, those with moderate anxiety symptoms (of whom around 30% had an anxiety disorder) tended to improve, while anxiety symptoms were more persistent in those with moderate or severe anxiety symptoms (of whom around 50% had an anxiety disorder).

As hypothesized emotion regulation variables were predictive of course trajectories with higher levels of worry predicting both persistent moderate and severe levels of anxiety symptoms across the 2-year follow-up period. Worry in depressed older adults may predict more persistent levels of anxiety symptoms irrespective of the presence of an anxiety disorder, as worry may function as a cognitive avoidance response attenuating somatic responses to fear related stimuli³⁷. Moreover, although we did not measure rumination, the predictive value of worry may reflect the effect of repetitive negative thinking traversing a number of different psychiatric phenomena^{7,38}. There are more similarities than differences across the processes of worry and rumination, including the fact that they are repetitive, difficult to control, negative in content, predominantly verbal, and relatively abstract³⁹ and RNT may constitute a common dimension underpinning rumination and worry^{40,41}.

These results may have implications for the definition of anxious depression. Anxious depression in late life can be defined based on a syndromal and dimensional approach⁴². In an elderly sample, a syndromal approach seems to identify a completely different group of older adults than using a dimensional approach²². Consistent with this worry predicted moderate and severe symptom levels of anxiety over and above the presence of anxiety disorder. Worry refers to the new specifier of depression 'with anxious distress' in the DSM 5⁴³, as it relates to symptoms as difficulty concentrating due to worry and fear that something awful may happen. These results suggest that high levels of worry in late life depression may be of importance for a dimensional approach to anxious depression in late life.

Lower levels of cognitive control (as measured with a higher interference score on the Stroop test) were also predictive of persistent and severe levels of anxiety. This result extends previous research in late life anxiety by showing that anxiety disorders are not only associated with problems in inhibiting task irrelevant information⁹, but also that this diminished cognitive control is predictive of the course of anxiety in depressed older adults with high levels of anxiety.

Contrary to expectations, we found that higher levels of HRV were predictive of high and persistent symptom levels. The predictive value of HRV for course trajectories of anxiety however was no longer significant after taking use of antidepressant medication into account. This result concurs with recent studies showing that depressive and anxiety disorder per se are not associated with cardiac autonomic control, but antidepressants and specifically tricyclic antidepressants are^{26,31}. As depressed participants from the high anxious group tended to use less

antidepressant medication (56.3%) than from the other two groups (73.0 and 77.2%), it is likely that their high baseline HRV levels primarily expressed their relative non-use of medication and not their symptom severity.

Exposure to negative life events did not systematically impact upon the severity of anxiety symptomatology. This finding concurs with those of a previous study showing that although negative life events were one of the best predictors of becoming anxious in community dwelling older adults, negative life events proved to be unrelated to chronicity of anxiety symptoms after three³ and six years of follow-up³⁴. Critically, we found no evidence supporting our hypothesis that the resource demands of negative events may overtax individual cognitive capacities resulting in impaired cognitive control of emotions and enhanced psychological and physiological responding.

There are several explanations for these unexpected findings. The relatively low prevalence of negative life events in the current study (on average one life event per six months) as well as the relatively poor fit of the type of concerns as measured by the Worry questionnaire with the specific life events covered by the Brugha questionnaire, may have precluded meaningful analyses of the question whether worry might modulate the impact of those negative life events or daily hassles that are the primary focus of habitual worry.

Regards cognitive control, we assessed whether depressed older adults with high levels of persistent anxiety were less able to inhibit prepotent responses using the classical Stroop test, but we did not measure the extent to which these persons also exhibit enhanced attention to threat-related stimuli as would have been possible with an emotional Stroop test⁴⁴. So, it remains undecided whether 'hot' cognitive control, which involves emotionally valenced information, could have made persons more susceptible to the detrimental effects of exposure to negatively valenced life events. Moreover, according to the selection, optimization, and compensation with emotion regulation (SOC-ER) framework⁴⁵, the social-emotional selectivity theory (SST)⁴⁶, and strength and vulnerability integration (SAVI) model⁴⁷, older adults report high levels of well-being among others because they adapt their use of emotion regulation strategies with aging. To compensate for their age-related decline in cognitive control, they are more prone to avoid or limit exposure to negative situations to preserve a sense of well-being. And it is conceivable that in particular anxious-depressed older adults are likely to show this type of avoidance behavior.

Finally, resting state HRV measurements may not be optimal to examine the effect of HRV on emotional responding, as an ecological momentary assessment study showed that when dealing with complex unpleasant events that affected multiple life domains, psychological and HRV responding to unpleasant events was more pronounced the older the participants were¹³. To overcome the study limitations mentioned above, clinical studies using experiencing sampling methods (ESM) to measure emotion regulation in real life seem warranted, and also feasible in aging research^{48,49}. Such studies would allow a finer grained analysis of the impact of e.g. state worry, cognitive control and HRV when exposed to negative life events on anxiety.

CONCLUSION

The present study also bears clinical relevance. Depressed persons with higher levels of worry may be at risk for an unfavorable course of their anxiety. As worry constitutes a malleable risk factor, worry has been shown to constitute a viable venue for alleviating anxiety using interventions such as mindfulness⁵⁰ or cognitive-behavioral therapies targeting perseverative thinking patterns⁵¹. Given the high prevalence of anxious depression in late life, future studies into the malleability of worry in anxious older persons and its therapeutic effects are urgently called for.

REFERENCES

- 1 Bryant, C., Jackson, H. & Ames, D. The prevalence of anxiety in older adults: Methodological issues and a review of the literature. *J Affect Disord* vol. 109 233–250 (2008).
- 2 Lenze, E. J. et al. Comorbidity of depression and anxiety disorders in later life. *Depress Anxiety* vol. 14 86–93 (2001).
- 3 de Beurs, E., Beekman, A. T., Deeg, D. J., Dyck, R. Van & van Tilburg, W. Predictors of change in anxiety symptoms of older persons: results from the Longitudinal Aging Study Amsterdam. *Psychol. Med.* 30, 515–527 (2000).
- 4 Schuurmans, J. et al. Long-term effectiveness and prediction of treatment outcome in cognitive behavioral therapy and sertraline for late-life anxiety disorders. *Int. psychogeriatrics* 21, 1148–1159 (2009).
- 5 Thompson, R. A. Emotion Regulation: A Theme In Search Of Definition. *Monogr. Soc. Res. Child Dev.* 59, 25–52 (1994).
- 6 Aldao, A., Nolen-Hoeksema, S. & Schweizer, S. Emotion-regulation strategies across psychopathology: A meta-analytic review. *Clin Psychol Rev* vol. 30, 217–237 (2010).
- 7 Olatunji, B. et al. Worry and the anxiety disorders: A meta-analytic synthesis of specificity to GAD. *Appl Prev Psychol* 14, 1–24 (2010).
- 8 Braver, T. S. & Barch, D. M. A theory of cognitive control, aging cognition, and neuromodulation. *Neurosci. Biobehav. Rev.* 26, 809–817 (2002).
- 9 Beaudreau, S. A., MacKay-Brandt, A. & Reynolds, J. Application of a cognitive neuroscience perspective of cognitive control to late-life anxiety. *J. Anxiety Disord.* 27, 559–566 (2013).
- 10 Levy, W. C. et al. Effect of endurance exercise training on heart rate variability at rest in healthy young and older men. *Am. J. Cardiol.* 82, 1236–1241 (1998).
- 11 Thayer, J. F. & Lane, R. D. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord* 61, 201–216 (2000).
- 12 Appelhans, B. M. & Luecken, L. J. Heart Rate Variability as an Index of Regulated Emotional Responding. *Rev. Gen. Psychol.* 10, 229–240 (2006).
- 13 Wrzus, C., Müller, V., Wagner, G. G., Lindenberger, U. & Riediger, M. Affective and cardiovascular responding to unpleasant events from adolescence to old age: complexity of events matters. *Dev. Psychol.* 49, 384–397 (2013).
- 14 Comijs, H. & Dekker, J. The Netherlands Study of Depression in Older persons (NESDO). *Int. Psychogeriatrics* 23, S70–S71 (2011).
- 15 Comijs, H. C. et al. The two-year course of late-life depression; results from the Netherlands study of depression in older persons. *BMC Psychiatry* 15, 20–25 (2015).
- 16 Wittchen, H. U. Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J. Psychiatr. Res.* 28, 57–84 (1994).
- 17 Beck, A. T., Epstein, N., Brown, G. & Steer, R. A. An inventory for measuring clinical anxiety: Psychometric properties. *J. Consult. Clin. Psychol.* 56, 893–897 (1988).
- 18 John Rush, A. et al. The inventory for depressive symptomatology (IDS): Preliminary findings. *Psychiatry Res.* 18, 65–87 (1986).
- 19 Brugha, T., Bebbington, P., Tennant, C. & Hurry, J. The List of Threatening Experiences: a subset of 12 life event categories with considerable long-term contextual threat. *Psychol. Med.* 15, 189–194 (1985).
- 20 Brugha, T. S. & Cragg, D. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatr. Scand.* 82, 77–81 (1990).
- 21 Wisocki, P. A., Handen, B. & Morse, C. K. The Worry Scale as a measure of anxiety among homebound and community active elderly. *Behav. Ther.* 9, 91–95 (1986).

- 22 Van Der Veen, D. C., Comijs, H. C., Van Zelst, W. H., Schoevers, R. A. & Oude Voshaar, R. C. Defining anxious depression in later life: A scaring heterogeneity in results. *Am. J. Geriatr. Psychiatry* 22, 1375–1378 (2014).
- 23 Stroop, J. R. Studies of interference in serial verbal reactions. *J Exp Psychol* 18, 643–662 (1935).
- 24 Klein, M., Ponds, R. W. H. M., Houx, P. J. & Jolles, J. Effect of test duration on age-related differences in Stroop interference. *J. Clin. Exp. Neuropsychol.* 19, 77–82 (1997).
- 25 de Geus, E. J. C., Willemsen, G. H. M., Klaver, C. H. A. M. & van Doornen, L. J. P. Ambulatory measurement of respiratory sinus arrhythmia and respiration rate. *Biol. Psychol.* 41, 205–227 (1995).
- 26 Licht, C. M. M. et al. The association between depressive disorder and cardiac autonomic control in adults 60 years and older. *Psychosom. Med.* 77, 279–291 (2015).
- 27 Bernston, G. G. et al. Autonomic cardiac control. III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockades. *Psychophysiology* 31, 599–608 (1994).
- 28 Grossman, P., Karemaker, J. & Wieling, W. Prediction of Tonic Parasympathetic Cardiac Control Using Respiratory Sinus Arrhythmia: The Need for Respiratory Control. *Psychophysiology* 28, 201–216 (1991).
- 29 Jung, T. & Wickrama, K. A. S. An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. *Soc. Personal. Psychol. Compass* 2, 302–317 (2008).
- 30 Nylund, K. L., Asparouhov, T. & Muthén, B. O. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Struct. Equ. Model.* 14, 535–569 (2007).
- 31 Licht, C. M. M., de Geus, E. J. C., van Dyck, R. & Penninx, B. W. J. H. Association between Anxiety Disorders and Heart Rate Variability in The Netherlands Study of Depression and Anxiety (NESDA). *Psychosom. Med.* 71, 508–518 (2009).
- 32 IBM Corp. IBM SPSS Statistics for Windows, Version 23.0. (2013).
- 33 Muthén, L. K. & Muthén, B. O., *Mplus User's Guide*, 7th ed. Los Angeles, CA: Muthen & Muthen (1998–2012).
- 34 Schuurmans, J. et al. The outcome of anxiety disorders in older people at 6-year follow-up: Results from the Longitudinal Aging Study Amsterdam. *Acta Psychiatr. Scand.* 111, 420–428 (2005).
- 35 Batelaan, N. M., Rhebergen, D., Spinhoven, P., Van Balkom, A. J. & Penninx, B. W. J. H. Two-Year course trajectories of anxiety disorders: Do DSM classifications matter? *J. Clin. Psychiatry* 75, 985–993 (2014).
- 36 Spinhoven, P. et al. Prediction of 6-yr symptom course trajectories of anxiety disorders by diagnostic, clinical and psychological variables. *J. Anxiety Disord.* 44, 92–101 (2016).
- 37 Borkovec, T. D. The nature, functions, and origins of worry. In: Davey, G. C. L. & Tallis, F. (Eds.) *Worrying: Perspectives on theory, assessment and treatment* 5–34. New York: Wiley (1994).
- 38 Olatunji, B. O., Naragon-Gainey, K. & Wolitzky-Taylor, K. B. Specificity of rumination in anxiety and depression: A multimodal meta-analysis. *Clin. Psychol. Sci. Pract.* 20, 225–257 (2013).
- 39 Ehling, T. & Watkins, E. R. Repetitive Negative Thinking as a Transdiagnostic Process Does working memory training reduce rumination? View project RuMeChange: Mechanisms of Rumination Change in Adolescents with remitted MDD View project. *Artic. Int. J. Cogn. Ther.* 1, 192–205 (2008).
- 40 Brosschot, J. F., Gerin, W. & Thayer, J. F. The perseverative cognition hypothesis: A review of worry, prolonged stress-related physiological activation, and health. *J Psychosom Res.* 60, 113–124 (2006).
- 41 Spinhoven, P. et al. Common rather than unique aspects of repetitive negative thinking are related to depressive and anxiety disorders and symptoms. *J Anxiety Disord.* 33, 45–52 (2015).
- 42 Ionescu, D. F., Niciu, M. J., Mathews, D. C., Richards, E. M. & Zarate, C. A. Neurobiology of anxious depression: A review. *Depress Anxiety* 30, 374–385 (2013).
- 43 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders* (5th ed.) American Psychiatric Association. Washington, DC: APA (2013).
- 44 Williams, J. M. G., Mathews, A. & MacLeod, C. The Emotional Stroop Task and Psychopathology. *Psychol. Bull.* 122, 3–24 (1996).

- 45 Urry, H. L. & Gross, J. J. Emotion Regulation in Older Age. *Curr Dir Psychol Sci.* 19, 352–357 (2010).
- 46 Charles, S. T. Strength and vulnerability integration: a model of emotional well-being across adulthood. *Psychol Bull.* 136, 1068–1091 (2010).
- 47 Carstensen, L. L., Isaacowitz, D. M. & Charles, S. T. Taking time seriously: A theory of socioemotional selectivity. *Am. Psychol.* 54, 165–181 (1999).
- 48 Cain, A., Depp, C. & Jeste, D. V. Ecological momentary assessment in aging research: a critical review. *J Psychiat Res.* 43, 987–996 (2009).
- 49 Kroeze, R. et al. Personalized Feedback on Symptom Dynamics of Psychopathology: A Proof-of-Principle Study. *J. Pers. Res.* 3, 1–10 (2017).
- 50 Hoge, E. A. et al. Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: Effects on anxiety and stress reactivity. *J. Clin. Psychiatry* 74, 786–792 (2013).
- 51 Topper, M., Emmelkamp, P. M. G., Watkins, E. & Ehring, T. Prevention of anxiety disorders and depression by targeting excessive worry and rumination in adolescents and young adults: A randomized controlled trial. *Behav. Res. Ther.* 90, 123–136 (2017).

CHAPTER 8

PERSONALIZED FEEDBACK ON SYMPTOM DYNAMICS OF PSYCHOPATHOLOGY: A PROOF-OF-PRINCIPLE STUDY

Based on:

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ABSTRACT

Background

In the proposed symptom network approach to psychopathology, psychiatric disorders are assumed to result from the (causal) interplay between symptoms. By implementing this approach, we explored whether individual feedback on symptom dynamics complements current categorical classification and treatment. The aim of this proof-of-principle case-study was to explore the feasibility, acceptability and usability of this transdiagnostic approach.

Methods

A female patient, aged 67, suffering from treatment resistant anxious and depressive symptoms was treated in our tertiary outpatient clinic for old age psychiatry. She participated in ecological momentary assessments (EMA), which involved intensive repeated measurements of mood and context-related items during two weeks. Visualizations of the interplay between the items were provided by network graphs and were discussed with the patient.

Results

Network graphs were explained as that feeling relaxed increased physical activity, causing physical discomfort in the following hours. Physical discomfort caused stress as its symptoms resembled her feared somatic anxiety symptoms. This increased the patient's insight that stress, expressed as somatic symptoms, played a central role in her panic disorder. This started a dialogue on how to cope with stress caused by somatic (anxiety) symptoms and provided a rationale for the patient to start an interoceptive exposure intervention she had repeatedly refused before.

Conclusions

Personalized diagnosis of psychopathology incorporating complex symptom dynamics is feasible and a promising addition to current categorical diagnostic systems and could guide intervention selection. This merits further exploration. An important limitation is that the observed symptom dynamics may not be generalizable to a random other two weeks.

INTRODUCTION

Pathology of individual patients is often not adequately captured by the diagnostic categories of the Diagnostic and Statistical Manual of Mental Disorders-5¹ as there is high co-morbidity of mental disorders² and high heterogeneity within mental disorder classifications³. This heterogeneity increases with age^{4,5}. For instance, it is assumed that late-life depression, compared to depression in younger patients, is more often accompanied by severe anxiety symptoms, psychotic symptoms, somatic morbidity, apathy and neurocognitive decline⁴⁻⁶. Increased diagnostic heterogeneity could explain the lower treatment effectiveness of affective disorders in geriatric patients⁷⁻⁹, as different subtypes may need different treatment strategies⁷. Personalized diagnostic procedures are thus especially relevant for geriatric patients with affective disorders.

To obtain a better understanding of the complex symptom dynamics in a geriatric patient, we investigated the usefulness and feasibility of a new and innovative transdiagnostic approach. The ecological momentary assessment (EMA) method was combined with the network approach to psychopathology in generating personalized feedback of complex symptom dynamics. With the EMA method, an individual is asked to fill out questions about their thoughts, feelings, and appraisal of their context multiple times a day during normal daily life¹⁰. Despite concerns about patient burden, this method has already shown promising first results concerning feasibility and usefulness in aging research¹¹, although it has not been implemented as a personalized clinical tool yet. These data can be used to gain insight into the interplay between cognitions, emotions, behavior, and environment in the daily life of individuals by the network approach. The network approach to psychopathology assumes that complex interactions between symptoms produce a disordered state of the 'system' that can be labeled as for example, depressed, anxious or psychotic¹². This line of reasoning is in contrast to the classic disease approach in which a latent construct (psychiatric disorder) is assumed to produce a specific set of symptoms¹³.

Recently, the EMA method and the network approach have been combined into a new idiographic approach to diagnosis, which is based on daily-life fluctuations in affective, cognitive, and physical symptoms and environmental factors^{14,15}. These individual network diagnoses entail a visual display of (causal) relationships between symptoms and environment and could be used as personalized feedback as well as guidance to personalized interventions¹⁶. To our knowledge, only one study implemented EMA-derived personalized feedback in addition to pharmacological interventions for adult patients with a major depressive disorder¹⁷. This addition of person-tailored daily life information to existing approaches seemed feasible and usable and showed promising enhancements to standard treatment. However, the possibilities of adding the network approach to the descriptive information of EMA-derived personalized feedback are not explored yet.

The primary aim of this study was therefore to explore the added value of this new approach in a geriatric patient with complex symptom dynamics. The network approach of psychopathology was added to the care as usual for the patient in our clinic. The specific aims were to test the feasibility, acceptability and usability of personalized symptom network feedback generated out of symptom data assessed during real-life.

METHODS

Participant

A 67-year-old female patient was referred to our tertiary outpatient clinic for old age psychiatry in 2011. She suffered from treatment-resistant mixed symptoms of anxiety and depression since 2008. She was initially diagnosed with a panic disorder with agoraphobia, complicated by a comorbid major depressive disorder with melancholic features.

Additional cognitive screening revealed a maximum Mini Mental State Examination (MMSE)18 score of 30 indicating the absence of cognitive deficits. At the time of referral, she used Lorazepam 3 mg and Mirtazapine 30 mg per day. From 2011 onwards, she was treated for her depressive and anxiety symptoms according to a guideline-based pharmacological treatment algorithm as well as with individual cognitive behavioral therapy focusing on the panic disorder. The first intervention of choice in cognitive behavioral therapy for panic disorders, interoceptive exposure (triggering symptoms of somatic arousal through e.g. hyperventilation provocation) was repeatedly suggested and refused by the patient. Exposure in vivo (e.g. entering a place that is associated with arousal and a previous panic attack) was acceptable for her and applied. Nevertheless, the treatment was only partly successful. She remained anxious of symptoms of somatic arousal. Her insight in symptoms and behavior remained poor; she strongly believed that her symptoms would initiate a panic attack and she continued to cope with this anxiety through avoidance behavior or safety behavior (e.g. staying in the company of her husband). In May 2014, the residual complaints were high levels of fear for somatic stress symptoms (anxiety sensitivity) and depression combined with feelings of derealization and depersonalization upon early morning wakening. Most symptoms generally resolved around mid-afternoon. The core symptoms that bothered her most and which she wanted to resolve first were symptoms of physical discomfort experienced such as heart pondering, sweating and trembling.

Procedure

The protocol was submitted to the ethical review board of the University Medical Center Groningen, who confirmed that formal assessment was not required. Prior to participation, the patient was fully informed about the study after which she gave written informed consent.

Moreover, the patient and her partner received an extensive briefing plus written user instructions for the EMA measurements. Direct support was available 24/7.

Patient's data were gathered with our secured server system (RoQua)¹⁹. With this system, text messages with links to online questionnaires were sent to the patient's smartphone.

Measurements were scheduled five times a day every three hours from 10 a.m. onwards for two weeks and took three to five minutes to complete. The timing of the measurements was adjusted to her daily rhythm with the last measurement timed 30 minutes before going to bed. The patient was instructed to fill out the questionnaires as soon as possible after receiving the text message (beep), but preferably within 15 minutes. The patient received a reminder after 30 minutes, and after 60 minutes the link was closed. Of a maximum of 70 possible assessments, only 4 (5.71%) were missed and deleted pairwise. After the two-week measurement period, the patient was prompted to fill out a questionnaire to evaluate the EMA procedure.

Results on mood fluctuations, somatic status, physical activity level, social context, and the relationships between these variables were drafted in a personalized feedback report and extensively discussed with the patient and her husband by both the researcher and her therapist. Finally, the patient and therapist's view on the guidance of the research team, the feasibility and impact of the daily measurements on the patient and the feedback reports were assessed and evaluated with a semi-structured interview.

Ecological momentary assessments

A pilot version of an EMA protocol of an ongoing prospective cohort study, The Netherlands Study of Depression and Anxiety (www.nesda.nl; the full list of items is available upon request) was used. In short, to assess daily fluctuations, items address non-overlapping aspects of current affect, energy level, physical activity level, social context, and daily experiences. The EMA questionnaire was supplemented with a printed manual which provided explanations and examples of the items. Prior statistical analysis, the researchers, in close collaboration with the patient's therapist, selected 21 items (shown in table 1) based on relevance for this particular individual patient, as well as variability in items and feasibility of interpretation of the network. To present the patient and therapist with an interpretable network (e.g. number of nodes and minimalizing overlap between nodes) and in order to create meaningful nodes, the 21 items of the EMA questionnaire were used to compose 10 nodes; four for mood, three for physical sensations and activity, and three for social context and daily experiences. The rationale and methods how these nodes were aggregated, are described below.

Table 1. | The 21 selected items from the ecological monitoring assessments (EMA) and the 10 numbered nodes (bold face) based on these items (see the method section for further details).

	N	Mean	(SD)
Mood			
1 Excited (high arousal high pleasure)			
I feel enthusiastic	66	1.65	(1.03)
I feel energetic	66	2.55	(1.28)
I feel cheerful	66	2.03	(1.12)
2 Relaxed (low arousal high pleasure)			
I feel satisfied	66	2.94	(1.33)
I feel relaxed	66	2.79	(1.32)
I feel calm	66	3.24	(1.30)
3 Stressed (high arousal low pleasure)			
I feel nervous	66	3.97	(1.24)
I feel irritated	66	1.58	(0.95)
I feel upset	66	2.73	(1.58)
4 Depressed (low arousal low pleasure)			
I feel bored	66	1.02	(0.12)
I feel down	66	3.68	(1.30)
I feel listless/apathic	66	3.45	(1.24)
Psychical sensations & activity			
5 I feel tired	66	4.00	(1.16)
6 Physical discomfort	66	3.03	(1.70)
7 Physical activity?	66	3.89	(0.88)
Social context & daily experiences			
8 Pleasant company	66	5.82	(1.34)
I would have preferred to be in company	7	2.57	(0.53)
I experienced the company as	59	6.20	(0.74)
9 Pleasant experience	66	3.40	(1.57)
How pleasant was the experience?	66	1.96	(1.75)
How important was the experience?	66	4.85	(2.01)
10 Unpleasant experience	66	5.24	(1.86)
How unpleasant was the experience?	66	5.74	(1.50)
How important was the experience?	66	4.73	(2.53)

Momentary mood

Mood was assessed at each beep with 12 affect items. Examples of items are: 'I feel down' or 'I feel enthusiastic'. All items could be answered on a 7-point Likert scale varying from '1=not at all' to '7=very much'. In order to improve on interpretability of the planned network graphs, the 12 affect items were aggregated into four mood variables following the affect grid²⁰. The grid (Figure 1) consists of two axis, valence and arousal, which are considered to be the fundamental building blocks of affect. Where valence indicates the pleasantness of an affect, arousal indicates the degree of psychological activation. When affective states are rated in a valence-arousal two-dimensional space or grid^{20,21} four quadrants (or mood states) are created: stress, excitement, depression or relaxation. In figure 1 in each quadrant, three words indicate the items used to assess affect in the current study. These items were developed recently in the Uncovering the Positive Potential of Emotional Reactivity (UPPER) study²² and were, for the above described reason preselected by

the researchers. Within each quadrant, data of three of the 12 affect items, were used to specify its mood state. The score on an aggregated mood variable consisted of the mean score of the three corresponding affect items.

Figure 1 | The Affect Grid

The affective states are rated along the valence (unpleasant, pleasant) and arousal (low, high) axis, in capital letters, in Russell's two axes circumplex model²¹. The two axes combined result in four quadrants in Russell's affect grid²⁰ to assess what an individual feels right now: stress, excitement, depression, or relaxation.

Physical sensation & activity

To assess experienced momentary physical sensation, after each beep the patient filled out the item "I experience physical discomfort". For our patient, her somatic anxiety symptoms (heart pondering, sweating, and trembling) were reflected in this physical discomfort item. Energy level was measured with the item "I feel tired". Physical activity was measured with the item:

"How physically active have you been since the last measurement?". These items were scored on a 7-point Likert scale varying from '1=not at all' to '7=very much'. In the manual examples were given that represented for example low physical activities (e.g. lying on the couch), medium physical activities (e.g. going for a walk) and high physical activities (e.g. exercising sports).

Momentary social context & daily experiences

Ratings of momentary social context were assessed with items on whether the patient was alone or with others, and subsequent ratings the appreciation of being alone or in the presence of company of others. The experienced *pleasantness of company* was hypothesized to be of importance for the patient. When being depressed the company of others is often regarded as aversive (e.g. 'I have nothing to say. I'm not interesting'). When anxious of panic attacks being alone is frightening and the company of others is often comforting ('They will help me when something goes wrong') and considered as *safety behavior*.

In order to use all the available data provided by the ESM, the variable "pleasant company" needed to be composed out of both experiences of being alone and of being in the company of others. Following a beep the patient was first asked whether she was *alone* or *in the company of others*. When she was in company of others she was asked to rate the pleasantness of her company. This was scored on a 7-point Likert scale varying from 1=very unpleasant to 7=pleasant. When the patient was alone, she was asked whether she would have preferred to be in the company of others. This was scored on a 7-point Likert scale varying from 1=not at all to 7=very much. Prior to the analyses these scores were inversely recoded and used to compose the variable "pleasant company".

The definition of daily (un-)pleasant experiences was extensively explained to the patient in the manual and assessed by the item "Think of the most pleasant experience since the previous beep". The patient was then asked to rate the degree of pleasantness and how important this experience was for her, both on a 7-point Likert scale varying from '1=not at all' to '7=very much'. Next the patient was asked which experience she had in mind and to type her answer in the electronic diary. These notes were taken into account when discussing her personalized feedback report. Analogue to this procedure daily unpleasant experiences were assessed. A daily (un-)pleasant-experience-variable was computed by taking the mean of the degree of (un-)pleasure and of importance of the experience, and used in network modeling.

Visualization of the networks

To improve on the readability of the network graphs we summarized variables in 10 aggregated variables (see table 1), which were visualized in differently colored 'nodes' in the networks according to three main categories: i) orange for mood (I feel excited, stressed, relaxed, depressed), ii) yellow for physical activity & activity (I feel tired, I experienced physical discomfort, I have been physically active), and iii) blue for social context daily experiences (pleasant company, pleasant experiences, unpleasant experiences). The colors of the lines represent either a positive (green) or negative (red) connection between nodes. The thickness of the lines represents the weight of the connection: the thicker the line, the stronger the association.

Statistical analysis

With EMA the patient was assessed repeatedly within short time intervals (i.e. three hour time windows) during daily life to obtain time series data of the variables of interest. For descriptive purposes the daily fluctuations of EMA items were plotted in line graphs. In these graphs all individual ratings as well as mean ratings per time point aggregated over a single day were depicted. Two network graphs were obtained: a undirected contemporaneous and a temporal

The ratings on, for example, the item “I feel good” were depicted over the course of one day, which the earlier reported circadian pattern of the patient’s complaints (Figure 2). This figure was discussed with the patient to show that her initial low mood at the beginning of the day generally improves, which helped to undermine her belief ‘that things would never get better’. Other data were discussed as well. For example, that the patient had indicated that during the two weeks of monitoring she had been alone for only 25% of the time and with others for 75% of the time, although she reported a slightly better mood when being alone. Moreover, relevant details of the described daily (un)pleasant experiences were discussed. For example, how her daughter in law reacted distant during dinner in a restaurant. Or eating fries in front of the television and receiving a loving text message from my daughter.

Contemporaneous network

Visualized correlations resulted in an undirected contemporaneous network (Figure 3a). The contemporaneous network clearly depicts two clusters of nodes that are correlated with each other. The first cluster is a positive affect cluster formed by connections between the nodes of feeling relaxed, feeling excited, and having pleasant daily experiences. This co-occurring of daily symptoms was recognized by the patient. When she, for example, performed her exposure in vivo exercises (e.g. a family visit), this resulted in excitement about having achieved a goal and resulted in a pleasant experience. The other cluster concerns correlations of negative affect nodes and is formed by connections between the nodes of feeling stressed, relaxed (negative correlation) and physical discomfort, and to a lesser extent feeling depressed and having unpleasant daily experiences. This co-occurring of daily symptoms was also recognized by the patient and her husband. For example, when her mood was low in the (early) morning she also experienced more symptoms of stress, caused by the unpleasant physical experience of derealization. Finally, the nodes ‘physical activity’ and ‘pleasant company’ were not meaningfully associated with nodes of the positive affect cluster.

Figure 3a | Network graphs from personalized feedback report

Network of contemporaneous associations of nodes. The color of the nodes represents variable categories: orange for affect (exc: excited, rlx: relaxed, str: stressed, dpr: depressed), yellow for somatic (trd: tired, phd: physical discomfort, act: physically active), and blue for context (cmp: pleasant company, pls: pleasant experience, unp: unpleasant experience). The colors of the lines represent either a positive (green) or negative (red) connection between two nodes. The thickness of the lines represent the weight of the connection: the thicker the line, the stronger the association.

Temporal network

Visualized lag-1 correlations resulted in a directed network, given in figure 3b, which depicts the temporal associations between the variables. This means that an arrow from one node to another should be interpreted as the effect of fluctuations in one node over a three-hour time lag on the fluctuations of the other node to which the head of the arrow is pointing. The emerging arrow pointing to the same node, shown for example at the node 'excited', indicates that this node has a large autocorrelation effect and means that if the patient reported to feel excited she most likely would feel even more excited three hours later as well. Feeling excited related to more pleasant experiences and becoming more tired three hours later. The other cluster includes the 'physical discomfort' node, which was the core symptom of the patient. It was hypothesized and discussed with the patient that feeling relaxed seemed to relate to increased physical activity, followed by more physical discomfort (heart pondering, sweating, and trembling) and more stress about these somatic symptoms in the next three hours. These stress feelings were explained by the patient as caused by her fear for the somatic anxiety symptoms. Moreover, subsequent negative feedback loops to counter these effects were described and recognized. For instance, experiencing more physical discomfort and feeling stressed decreased physical activity in the next three hours, and being less physically active decreased feeling relaxed in the next three hours. This chain of events related to more depressed feelings, and rating of her company (social context) as more pleasant.

This latter relationship was hypothesized as an expression of safety behavior: being in company decreased her fear for symptoms of physical discomfort, through the assumption that when something is wrong, people will help her.

Effects of feedback

The patient and her husband recognized the shown graphical associations. This initiated a dialogue in which the patient and her husband began to reason in terms of causal and dynamic processes. They formulated the hypothesis that tension, expressed as (feared) somatic anxiety symptoms, played a central role. Together with the ‘physical discomfort’-node being the node in the network with the most influential causal arrows (Figure 3b), this opened up a dialogue on how to cope with stress related to the physical discomfort itself.

As mentioned earlier, up until that point, the patient had been reluctant to do interoceptive exposure (inducing physical discomfort through e.g. hyperventilation provocation), the first intervention of choice in cognitive behavioral therapy for panic disorders. Discussing the patterns found in the networks motivated her to try this intervention for the first time.

Evaluation of feedback

Information from the semi-structured interview conducted with the therapist and patient separately indicated that the EMA measurements were found to be both feasible and acceptable. The network graphs provided new insights in symptom dynamics and a change in treatment direction. Both patient and therapist therefore positively evaluated the process. Moreover, not only did the feedback bring about new insights and treatment directions, but the approach was also evaluated as compatible with and an addition to outpatient treatment.

Figure 3b | Temporal network graphs from personalized feedback report
Network of temporal associations of nodes (i.e. across three-hour time lags)

DISCUSSION

We explored the implementation of the symptom network approach of psychopathology in an individual patient in addition to care-as-usual. We found that EMA assessments were feasible for, and well accepted by, our geriatric patient. The personalized feedback based on EMA data and network graphs were evaluated as useful by the patient and the therapist as it initiated a dialogue about the causes and consequences of symptoms in our treatment resistant patient. The dialogue resulted in increased insight in the patient's symptom dynamics beyond descriptive diagnosis as well as motivation for a new direction in treatment.

Although this proof-of-principle was successful, the following limitations need to be discussed. First, not all potentially relevant variables (e.g., medication use) may have been assessed using the standardized questionnaire. However, the selection of the items used for the network analyses was done in close collaboration with the therapist. Moreover, the patient and her husband recognized the items included in the feedback report as highly relevant ones. Using the items of a standardized questionnaire, we optimally personalized the feedback report. In the case of some items, e.g. "pleasant company", this meant we had to inversely recode and compose certain items in order to avoid missing values. This could result in unclear and ambiguous reports as one deviates from the original questions asked during EMA. This serves as an argument to completely personalize a questionnaire in EMA research to enhance clinical usefulness, but is a time-consuming process.

Second, in this proof-of-principle study we used the currently available statistical tools. The statistical methods for analyzing intensive time-series data is currently evolving rapidly. Further studies are needed to examine whether other techniques, such as Vector Autoregressive modeling, and sparser network estimation based on partial correlations and LASSO methods²⁶ will generate different networks. Simulation studies are needed to establish the stability of networks with increasing numbers of missing values in the time series. Finally, the patient was monitored intensively during two weeks to obtain ecologically valid data on current mood states. Although these data may be more representative compared to a single retrospective questionnaire assessment, it remains unclear whether the observed symptom dynamics will be generalizable to any other random two weeks in the patient's life. Earlier or later monitoring might result in different network graphs due to changes in the symptom dynamics, which needs to be investigated.

Indeed, there is still work to be done before EMA and network based personalized feedback can routinely be implemented in clinical practice. However, our results showed that personalized diagnosis of psychopathology incorporating complex symptom dynamics is feasible and desirable. Our personalized feedback approach gave insight in the dynamic interplay between affect and context variables in an individual geriatric patient with complex and persistent symptomatology. It facilitated the process of jointly generating hypotheses and selecting interventions. In particular, in such patients our approach may reduce certain limitations of current diagnostic classification systems²⁷. We therefore conclude that the network approach of psychopathology is a promising addition to the current diagnostic systems that definitely merits further exploration.

REFERENCES

- 1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). (American Psychiatric Association, 2013).
- 2 Widiger, T. A. & Samuel, D. B. Diagnostic categories or dimensions? A question for the Diagnostic and statistical manual of mental disorders - fifth edition. *J. Abnorm. Psychol.* 114, 494–504 (2005).
- 3 Wardenaar, K. J. & de Jonge, P. Diagnostic heterogeneity in psychiatry: Towards an empirical solution. *BMC Medicine* vol. 11 (2013).
- 4 Fiske, A., Wetherell, J. L. & Gatz, M. Depression in older adults. *Annu. Rev. Clin. Psychol.* 5, 363–389 (2009).
- 5 Wolitzky-Taylor, K. B., Castriotta, N., Lenze, E. J., Stanley, M. A. & Craske, M. G. Anxiety disorders in older adults: a comprehensive review. *Depress. Anxiety* 27, 190–211 (2010).
- 6 Hegeman, A. J. M., Kok, R. M., Van Der Mast, R. C. & Giltay, E. J. Phenomenology of depression in older compared with younger adults: Meta-analysis. *Br. J. Psychiatry* 200, 275–281 (2012).
- 7 Calati, R. et al. Antidepressants in elderly: Metaregression of double-blind, randomized clinical trials. *J. Affect. Disord.* 147, 1–8 (2013).
- 8 Gould, R. L., Coulson, M. C. & Howard, R. J. Efficacy of cognitive behavioral therapy for anxiety disorders in older people: A meta-analysis and meta-regression of randomized controlled trials. *J. Am. Geriatr. Soc.* 60, 218–229 (2012).
- 9 Gould, R. L., Coulson, M. C. & Howard, R. J. Cognitive behavioral therapy for depression in older people: A meta-analysis and meta-regression of randomized controlled trials. *J. Am. Geriatr. Soc.* 60, 1817–1830 (2012).
- 10 Myin-Germeys, I. et al. Experience sampling research in psychopathology: Opening the black box of daily life. *Psychol. Med.* 39, 1533–1547 (2009).
- 11 Cain, A., Depp, C. & Jeste, D. V. Ecological momentary assessment in aging research: a critical review. *J. Psychiatr. Res.* 43, 987–996 (2009).
- 12 Bringmann, L. F. et al. A network approach to psychopathology: new insights into clinical longitudinal data. *PLoS One* 8, e60188 (2013).
- 13 Fried, E. I. et al. Mental disorders as networks of problems: a review of recent insights. *Soc. Psychiatry Psychiatr. Epidemiol.* 52, 1–10 (2017).
- 14 Van Os, J., Delespaul, P., Wigman, J., Myin-Germeys, I. & Wichers, M. Psychiatry beyond labels: Introducing contextual precision diagnosis across stages of psychopathology. *Psychol. Med.* 43, 1563–1567 (2013).
- 15 Van Os, J., Delespaul, P., Wigman, J., Myin-Germeys, I. & Wichers, M. Beyond DSM and ICD: Introducing ‘precision diagnosis’ for psychiatry using momentary assessment technology. *World Psychiatry* vol. 12 113–117 (2013).
- 16 Wigman, J. T. W. et al. Psychiatric Diagnosis Revisited: Towards a System of Staging and Profiling Combining Nomothetic and Idiographic Parameters of Momentary Mental States. *PLoS One* 8, e59559 (2013).
- 17 Kramer, I. et al. A therapeutic application of the experience sampling method in the treatment of depression: a randomized controlled trial. *World Psychiatry* 13, 68–77 (2014).
- 18 Cockrell, J. R. & Folstein, M. F. Mini-Mental State Examination (MMSE). *Psychopharmacol. Bull.* 24, 689–692 (1988).
- 19 Sytema, S., van der Krieke, L. Routine outcome monitoring: A tool to improve the quality of mental health care? In Thornicroft, G., Ruggeri, M., Goldberg, D. (Eds.), *Improving mental health care: The global challenge* (pp. 246–263). Chichester, England: John Wiley. (2013).
- 20 Russell, J. A., Weiss, A. & Mendelsohn, G. A. Affect Grid: A Single-Item Scale of Pleasure and Arousal. *J. Pers. Soc. Psychol.* 57, 493–502 (1989).
- 21 Russell, J. A. A circumplex model of affect. *J. Pers. Soc. Psychol.* 39, 1161–1178 (1980).

- 22 Bennis, E. Every dark cloud has a colored lining: the relation between positive and negative affect and reactivity to positive and negative events. University of Groningen (2015).
- 23 Epskamp, S., Cramer, A. O. J., Waldorp, L. J., Schmittmann, V. D. & Borsboom, D. Qgraph: Network visualizations of relationships in psychometric data. *J. Stat. Softw.* 48, 1–18 (2012).
- 24 Borsboom, D. & Cramer, A. O. J. Network analysis: An integrative approach to the structure of psychopathology. *Ann. Rev. Clin. Psychol.* 9 91–121 (2013).
- 25 Opsahl, T., Agneessens, F. & Skvoretz, J. Node centrality in weighted networks: Generalizing degree and shortest paths. *Soc. Networks* 32, 245–251 (2010).
- 26 Costantini, G. et al. State of the aRt personality research: A tutorial on network analysis of personality data in R. *J. Res. Pers.* 54, 13–29 (2015).
- 27 Rapoport, M. J. Geriatric psychiatry: What's in a name, and five concerns about DSM-5. *Can. Geriatr. J.* 17 115–117 (2014).

CHAPTER 9

SUMMARY AND FINAL DISCUSSION

SUMMARY

Our work showed that anxiety in late-life depression is common and may complicate clinical practice. As an overarching theme, this thesis shows that it may be prudent to distinguish between comorbid anxious arousal and anxiety disorders in late-life depression (chapter 2) as both yields different determinants (chapter 3-7). Moreover, differentiating between specific comorbid anxiety disorders results in even more specific determinants. In this chapter we will discuss these findings (see box 1) in the broader perspective of the research field. After having summarized the results we have found, we will describe a method to illustrate how these nomothetic results may be used and translated to clinical practice (partly based on chapter 8).

Box 1. | Determinants of anxious arousal and comorbid anxiety disorders in late-life depression

Study design		Determinants
<i>Explorative studies</i>		
• Any anxiety disorder	Cross-sectional	Lower age ³ , female sex ³ , higher depressive symptom severity ³ , early childhood traumatization ³ , shorter duration of illness ⁴ , more psychotropic drugs use (other than antidepressants) ⁴ , living alone ⁴ , lower <i>estimated</i> suicide risk ⁴
• Specific anxiety disorders	Cross-sectional	Lower age ³ , female sex ³ , lower educational level ³ , higher depressive symptom severity ³ , early traumatization ³ , neuroticism ³ , extraversion ³ , conscientiousness ³
• Remission (DSM-IV)	Longitudinal	Higher depressive symptom severity ⁶ , higher severity of anxiety symptoms ⁶ , comorbid anxiety disorder ⁶ , poorer physical health ⁶ , higher neuroticism ⁶ , lower mastery in the presence of childhood trauma ⁶
• Anxious arousal (severity)	Cross-sectional	Life-events in the presence high neuroticism ⁵ , life-events in the presence of high openness ⁵ , life-events in the presence of low conscientiousness ⁵ , life-events in the presence of low mastery ⁵
<i>Hypothesis driven studies</i>		
• Anxious arousal (course)	Longitudinal	Life-events in the presence of high neuroticism ⁶ , life-events in the presence of low mastery ⁶ , higher worrying ⁷ , lower cognitive control ⁷

* Footnote refer to the corresponding chapters in the thesis

Anxious depression in later life: one or two disorder

Chapter 2, we examined the levels of agreement between the proposed dimensional and syndromal approach of anxious depression by Ionescu et al. (2013) using the baseline data of the Netherlands Study of Depression in Older persons (NESDO). Among the 378 depressed older patients, both definitions yield comparable high prevalence rates of anxiety with 41.9% of the patient suffering from high levels of anxious arousal and, fully in line with previous studies, 39.4% suffering from a comorbid anxiety disorder¹⁻⁴. However, when we compare both patient groups using the proposed definitions the agreement was extremely poor, indicated kappa's between 0.06 and 0.23^{5,6}. This indicates that depressed older adults who report high levels of somatic anxious arousal and/or high levels of worrying suffer from a subtype of depression, one could classify as an anxious depression, while the other depressed older adults are suffering from a depressive and anxiety disorder at the same time. The recently introduced specifier of "anxious distress" in the DSM-5 classification to further subtype depressive disorder has been based on this kind of findings (as will be discussed below).

Determinants (Chapter 3,4,5,6,7)

Previous studies in (older) adult populations show the presence of comorbid anxiety, defined as either as a disorder or as anxious distress, increases the chronicity, slows recovery, and increases the likelihood of a recurrence once the patient has recovered⁷⁻¹⁰. This is in line with the results described in chapter 6 that show anxious distress and the presence of a comorbid anxiety disorder both independently predict non-remission after two years. These results will be addressed in more detail below.

However, existing literature on determinants of 'anxiety in depression' is difficult to interpret as studies on depressed patients with a high level of anxiety symptoms and depressed patients with concurrent anxiety disorders are often grouped together. Building on our findings in chapter 2, showing that both definitions of 'comorbid anxiety' in late-life depression refers to different subgroups, we explored determinants for each type of 'comorbid anxiety' separately. The findings described in the chapters 3-5 are based on cross-sectional studies. The chapters 6 and 7 are longitudinal studies covering a follow-up period of two years. The overall attrition rate in the NESDO study is one out of five participants. The most important reason for attrition was death (28.0%) and mental problems (37.6%). Attrition was significantly associated with less education, more severe psychopathology, and lower cognitive functioning (all $p < 0.05$)¹¹. In the Longitudinal Aging Study Amsterdam, a population-based cohort study among older persons age 55 years and older, three-year attrition rates were around 19% and was mainly due to death¹². We may therefore conclude that the attrition rate in our study is not extremely high, when taking age and disease status of our sample into account, although it may still limit the generalizability of our findings.

Determinants of the state of comorbid anxiety (Chapter 3,4,5)

In chapter 3, we broadly explored determinants of comorbid anxiety disorders among the 378 depressed older patients participating in NESDO. Cross-sectional, we found that determinants included age, sex, educational level, depressive symptom severity, three of the BIG-five personality traits and early childhood traumatization. However, determinants differ across the individual comorbid anxiety disorders and some determinants are even masked by lumping all anxiety disorders together, like the level of education (agoraphobia) and the personality traits neuroticism, extraversion and conscientiousness (social phobia).

The exploration of determinants of the presence of anxious distress in depressed older adults was examined hypothesis driven. Cross-sectional (chapter 5), we found that having gone through a negative life-event in the past year was not associated with the severity of either anxiety or depression. However, past-year life-events were associated with higher levels anxiety in the presence of high levels of neuroticism and openness as well as in the presence of low levels of conscientiousness or mastery. These results were specific for the level of anxiety and were not found for depressive symptom severity.

Also interesting was that cross-sectional, recent life-events did not interact with neuroticism when any comorbid anxiety disorder was present at baseline, but did so when we looked at levels of anxious distress. One explanation might be that this finding shows the robustness of a comorbid anxiety disorder, in contrast to the reactivity of anxious distress to recent life-events in high neurotic depressed older adults.

In chapter 4 we explored the characteristics of depressed older patients with and without comorbid anxiety disorders who died by suicide. Data of 1909 cases that were 60 years or older came from the NCISH¹³, a nation-wide suicide monitoring system in the United Kingdom. Depressed patients who died by suicide with comorbid anxiety disorders had a longer illness duration, they more often lived alone, and reported more emotional distress during their last contact with the mental health team. They were prescribed more psychotropic drugs other than antidepressants (mainly benzodiazepines) and the short- and long-term suicide risk of depressed patients with comorbid anxiety disorders was estimated significantly more often as low during their last appointment by their treating clinicians compared to those without.

Determinants of course (Chapter 6,7)

In the chapters 6 and 7 we explored determinants of complete remission after two years, defined as remission of both the depressive disorder as well as comorbid anxiety disorder, as well as the course of anxiety distress over two years in the NESDO cohort. We found depressed patients with a comorbid anxiety disorder at baseline less often achieved complete remission within two years compared to those without a comorbid anxiety disorder (37% vs 58%). The course of anxious distress in older depressed adults over two years was less favorable over two years when more negative life-events occurred in this period. However, this only held true for patients with a high level of neuroticism or a low level of mastery. Separately, we explored and described in chapter 7 that higher levels of worry and lower levels of cognitive control predicted more persistent and severe levels of anxiety symptoms over time. However, worry, cognitive control as well as heart rate variability (as marker for autonomic distress) did not moderate the impact of negative life events on the course of anxious distress. These findings indicate that worry may be an important and malleable risk factor for persistence of anxious distress in depressed older adults. Unlike the above-mentioned maladaptive personality traits, it does not moderate the impact of negative life-events.

EMA-case report

Regarding the many determinants, often with a small effect, we explored the feasibility, acceptability and usability of an idiographic diagnostic approach to Hereto, we described a case-report of a 67-year-old female patient in chapter 8. We propose a possible solution for the above-mentioned challenges by introducing personalized Ecological Momentary Assessments as a method to collect valid patient data, and the statistical network approach to psychopathology as a descriptive model for case conceptualization (CC). This methodology, and the way the patient and clinician closely collaborate, was described in chapter 8. Our findings showed that the intensive assessment was feasible and acceptable for our patient. The dynamics between the different symptoms and situations were visualized by network graphs. These person-specific networks (PSN) were discussed with the patient and proved useful to both the clinician and the patient. It provided clarity on the core symptom dynamics and gave direction for intervention selection. Besides that, reasoning in symptom dynamics, visualized by the PSN motivated the patient for the intervention by creating a clear rationale for it.

DISCUSSION

Classification of anxious depression by the DSM

The NESDO study started recruiting in 2007 and used the criteria of the fourth edition of the Diagnostic and Statistical manual of Mental disorders (DSM-IV of the American Psychiatric Association¹⁴ to categorize the depressive and anxiety disorders. The NCISH study, starting in 1997 used the 10th or previous versions of International Classification of Diseases as published by the World Health Organisation¹⁵. Both classification systems contain criteria that can be called a "hierarchy rule". For example, a person who meets the diagnostic criteria of a generalized anxiety disorder (GAD) only during a mood disorder, this person is not diagnosed with (comorbid) GAD. Hierarchy rules are based on ideas about the hierarchical nature of psychiatric disorders. On the one hand, these rules prevent overreporting of psychiatric comorbidity, but on the other hand they may mask clinically and scientifically relevant comorbidity. Therefore, application of these rules, either in clinical practice or research, should explicitly be made. In the NESDO study hierarchical rules, concerning the depressive and anxiety disorders were not followed to make meaningful comparison possible. Furthermore, both classification systems lack anxiety symptoms in their diagnostic criteria for depression. The exclusion of anxiety as a criterion for depressive disorders as well as applying hierarchy rules have been introduced to reduce overlap between both disorders. Nonetheless, in reality comorbidity is rather the rule than the exception^{16–18} and diagnostic stability of depressive and anxiety disorder over time is limited¹⁹.

The DSM-5 taskforce acknowledged the importance of anxiety in depressed patients by introducing criteria for an anxious distress specifier of major depression. This DSM-5 specifier consists of five symptoms: 1. Feeling keyed up or tense; 2. Feeling unusually restless; 3. Difficulty concentrating because of worry; 4. Fear that something awful may happen; 5. Feeling that the individual might lose control of him/herself. When a patient meets two or more out of these five criteria, the qualitative label 'with anxious distress' should be added to the diagnosis major depressive disorder. The severity of the anxious distress can be labelled as mild (2 symptoms), moderate (3 symptoms), moderate-severe (4 or 5 symptoms), or severe (4 or 5 symptoms with motor agitation). Studies using the formal DSM-5 specifier shows that even more than 70% of depressed adults met the criteria for anxious distress^{20–22}. This is almost twice the rate we found. An explanation for this difference might be the ways anxious distress was defined. Higher percentages (>70%) are attained when patients 'only' have to meet two of the DSM-5 criteria. Our study used the DSM-IV-R criteria for depression and the anxious distress specifiers were not available at that time. We defined anxious distress based on predefined cut-off scores of either the Beck Anxiety Inventory (BAI) or Worry Scale (WS) in chapter 2, and on the Beck Anxiety Inventory in chapter 5–7 that represent clinically relevant levels of anxiety (see table 1).

Table 1. | Items of the BAI and the WS corresponding with the formal DSM-5 criteria of anxious distress

DSM-5 criteria Anxious Distress	Beck Anxiety Inventory and The Worry Scale
Feeling keyed up or tense	Unable to relax ¹ ; Terrified or afraid ¹
Feeling unusually restless	Heart pounding / racing ¹ ; Nervous ¹
Difficulty concentrating because of worry	Fear of worst happening ¹ ; The Worry Scale specifies worries, but does not relate worrying to concentration
Fear that something awful may happen	Fear of worst happening ¹
Feeling that the individual might lose control of him/herself	Fear of losing control ¹

¹Items from the BAI

With respect to the criteria of the DSM-5 specifier, it remains unknown whether each combination of meeting two criteria results in clinically relevant levels of anxiety, nor whether one of these criteria would even better perform for diagnosing depression than the formal nine criteria of a depressive episode.

To our knowledge there are no studies available that validate the BAI or WS in relation to the DSM-5 anxious distress specifiers, let alone how they perform in an older adult sample.

In controlled studies of antidepressant treatment, the anxiety/somatization factor of the Hamilton Depression Scale²³ has been most often applied to classify patients into anxious and non-anxious subgroups²⁴. Zimmermann and colleagues examined the level of agreement between the DSM-5 anxious distress specifier and six other approaches (including the syndromal approach) to define anxious depression in a sample aged between 18 and 80 years. The level of agreement between all definitions was significant, albeit modest (median kappa = .28). The modest association between the different definitions of anxious depression suggests, in line with our results in chapter 2, that results based on previously applied approaches towards subtyping may not generalize to the DSM-5 anxious distress specifier²².

Complete remission

Examining the course of anxiety in late-life depression, we defined remission as having no depressive nor anxiety disorder at two-year follow-up. We refer to this state with the term *complete remission* in order to avoid confusion, where the term *remission* is often used in relation to the diagnosis of primary interest. Beside this semantical issue, complete remission in studies on anxiety in depression is important because untreated comorbid anxiety disorders or residual anxiety symptoms have a high impact on the quality of life²⁵ and increase the risk of relapse²⁶. Anxiety disorders often precede a depressive disorder. The Netherlands Study of Depression and Anxiety (NESDA) showed that, in an adult sample (aged 18-65), in 57% of comorbid cases, anxiety preceded depression¹⁶. Similar results were found in an older adult sample (aged

65-84) of The Amsterdam Study of the Elderly (AMSTEL)¹⁸. Dealing with an older population, having lived in a time where there was more of a taboo on seeking help for mental problems, many were not treated adequately for the anxiety disorder. Additionally, most of the effective (psychotherapeutic) treatment protocols were developed for (younger) adults in the sixties of the twentieth century²⁷. When now presenting a depressive disorder, the (primary, underlying and/or comorbid) anxiety disorder is often underrecognized^{28,29} and both disorders are diagnostically insufficiently differentiated³⁰.

In the NESDO study, the Composite International Diagnostic Interview (CIDI; WHO version 2.1; life-time version) was used to assess the diagnoses of interest. The CIDI is a structured clinical interview that is designed for use in research settings and has high validity for depressive and anxiety disorders³¹. The determinants were either assessed with self-report measures (e.g. severity of psychopathology, BIG-five personality traits) or structured interviews (early childhood traumatization). These measures have been selected for their psychometric qualities in a population of older adults³². Studies, however, show that self-report measurements in general and the CIDI specifically are not unbiased when it comes to age. Age-related changes in cognitive and communicative functioning have specific influences on the question answering process (e.g. dependent on the order of the questions or the response alternatives)³³. Older respondents may deny symptoms when subjected to complex batteries of questions concerning severity, time frame, attribution and consequences³⁴. More research needs to be done to develop methods to assess psychopathology and psychological concepts more reliable and valid in older adults. Until then, clinical judgment will be essential.

Unfortunately, it was not possible to explore the pathogenesis of the comorbid disorders. The age of onset of the depression concurrent anxiety disorder were assessed, but no information was available on the history of prior anxiety disorders. It is unclear whether patients had been suffering from a chronic anxiety disorder and eventually developed a comorbid depressive disorder or if the depressive disorder came first. Although it goes beyond the scope of the studies described here, clinically it could influence the treatment strategy when the sequence of disorders is clear. Here again, clinical judgment remains essential for case conceptualization and intervention selection. In the NESDO study 378 patients with a primary diagnosis of major depression, dysthymia or minor depression according to the DSM -IV criteria were included. Forty-one percent of these depressed participants also had an anxiety disorder during or six months prior to the baseline assessment. Depressed patients with a concurrent diagnosis of an anxiety disorder that needed primary treatment like severe obsessive-compulsive disorder (OCD) or posttraumatic stress disorder (PTSD) were excluded from the study. This may have resulted in a sparse selection bias, but because the primary focus of this study was depression with comorbid anxiety disorders or anxious distress this was not of any influence on the results. Moreover, in DSM-5, OCD and PTSD are no longer classified as anxiety disorders.

Suicide in late-life depression with and without comorbid anxiety disorders

Researchers, theorists, and clinicians have evidenced a longstanding interest in the role of anxiety and its disorders in suicide³⁵⁻³⁷. Different studies show that concurrent anxiety disorders add to the burden of depression, reflecting in a higher level of suicidality^{1,38,39}. Our study in the

NCISH sample showed that among the depressed suicide cases, a comorbid anxiety disorder was identified in one out of six cases and associated with a higher prevalence of several suicide risk factors. However, the short- and long-term suicide risk of depressed patients with comorbid anxiety disorders was estimated as significantly less during their last appointment by their treating clinicians compared to depressed patients without comorbid anxiety disorders. In other words, the presence of comorbid anxiety disorders in depressed older adults did not trigger clinicians to recognize suicide risk. One explanation might be that clinicians simply address anxious distress during a consultation, but fail to realize that this effect is only temporarily and anxious distress may easily return and increase suicidal risk. This is relevant, since the comorbidity rate of 17% found in the NCISH sample is rather low compared to the NESDO sample (39%) and other samples (48%)⁴ and suggests under detection of comorbid anxiety disorders.

In 2016, after our study was published, a meta-analysis was published by Bentley and colleagues⁴⁰. They included studies on all age groups above 18 years and challenged the idea that anxiety is an independent risk factor for completed suicide. Studies were included that measured clinically relevant anxiety symptoms, anxiety disorders, or their combination at baseline. As outcome, this meta-analysis addressed suicidal thoughts, suicidal behavior and completed suicide. A total of 65 prospective studies were identified, including 852,159 participants. Their main result showed that all measures of anxiety predicted both the onset of suicidal ideation as well as suicide attempts, but not suicide death. If true, this may explain the low prevalence of comorbid anxiety disorder we found in our study. Nonetheless, when we look at the results in more detail, we see that the main finding of this paper has been based on the pooled odds ratios. Some studies did not provide enough data to convert their estimates into an odds ratio. Meta-analyses of the 10 studies that did not provide enough data for converting the hazard ratio into an odd ratio, revealed that in these 10 studies, anxiety did predict death by suicide. So maybe anxiety has more impact in the short-term risk, as the hazard ratio takes time- to-suicide into account. Secondly, the impact of individual anxiety disorders is difficult to estimate from this meta-analysis. Most studies, including our study, lumped all anxiety disorders together. Studies providing disorder specific data showed that both, adjustment disorders and obsessive-compulsive disorders had a protective effect for completed suicide. These data may have masked the predictive effect of specific anxiety disorders for suicide death in other studies⁴¹. Since the samples consisted mainly of adults below the age of 60 years these results cannot be generalized to the older adults. Therefore, at this end we have to conclude that it remains equivocal whether comorbid anxiety in late-life depression is an independent risk factor for suicide or not.

Dealing with complexity

As we showed in chapter 2 it seems prudent to distinct anxious arousal in late-life depression from comorbid anxiety disorders in late-life depression. Therefore, determinants should be explored separately. The results of our explorative study in chapter 3 also stress the need to examine determinants of comorbid anxiety disorders for specific anxiety disorders separately.

Unfortunately, explorative studies testing many determinants may easily results false-positive findings due to multiple testing. Even when ignoring potentially false positive findings, the diversity of these findings links poorly to the usability in clinical practice for we still do not

know what aspects makes a specific patient vulnerable and what focus is needed in treatment. Confronted with complex psychiatric presentations a case conceptualization is often made. Case conceptualization is a process of using theoretical frameworks to organize interview, observational, and assessment data to formulate hypotheses that may explain the underlying dynamics of the presenting problems in order to formulate an appropriate treatment plan⁴². In other words, a case conceptualization builds on nomothetic research and theoretical knowledge and is personalized with patient specifics (e.g. personality traits and other aspects of the learning history (e.g. life-events), and specific maladaptive behavior (e.g. depressive and anxious avoidance) that is related to specific depressive and anxiety disorders⁴³. In this respect, knowledge on determinants will inform clinicians to make patient-specific treatment plans, but as described above this knowledge will not be sufficient to map comorbid anxiety and its phenomenology at the individual level.

In chapter 8 we describe a proof-of-principle case study of the above outlined process of cases conceptualization. It was feasible for the participating older patient to collect data on affect, cognition, activities, etc. with a frequency of five times a day during two weeks, so-called Experience Sampling Methods (ESM). This is in line with other studies that show commitment of adult patients participating in ESM-studies with an average response rate of 78%⁴⁴. Response rates however depend several demographic, clinical, and sampling factors^{45,46}.

Besides the feasibility, it also proved useful for the participating patient and therapist to formulate working hypotheses and a treatment plan, which motivated the patient. Other proof-of-principle studies also showed that feedback reports on collected ESM-data are experienced as useful as a starting point for a dialog between the patient and clinician during regular consults⁴⁷⁻⁵⁰. Up-until now, there are two Randomized Controlled Trials (RCT) published on the effectiveness of ESM-based feedback as a therapeutic tool. A pioneer RCT showed the that efficacy of traditional passive pharmacological approach to treatment of major depression in an adult sample can be enhanced by using person-tailored daily life information regarding positive affect⁵¹. However, less than 10% of the patients received psychological treatment. This means that the addition of ESM as a therapeutic tool was tested mainly in the absence of psychological treatment, which makes the study less generalizable to standard clinical practice. In a recent pragmatic RCT, the effectiveness of ESM-based feedback prior to a pharmacological and/or psychological TAU was not established in depressed patients⁵². In this study, patients monitored their momentary positive and negative affect for 4 weeks during a waiting-list period for their psychological treatment. Weekly feedback was emailed to the patient. Though ESM-feedback was highly appreciated by both patient and clinician in this study, no impact on momentary affect was found.

Both RCT's^{51,52} have in common that ESM was neither personalized nor fully integrated in the psychological treatment. This implies that there was no close collaboration between the patient and clinician on either choosing which items would be relevant for the patient to measure with an ESM items or discussing the feedback.

Interestingly, first evidence is reported on insights in patients and clinicians that ESM is only perceived as effective in psychiatric care when it is personalized, and includes gathered information on affect, activities, and (social) context⁵³. Bos and colleagues also outlined that successful implementation of ESM is only feasible for an interdisciplinary team of patients, clinicians, researchers, and information technology specialists.

Personality and negative life-events

Dealing with the complex psychiatric state of anxiety in late-life depression give rise to the presumption that going through a life event in certain cases affects the level of comorbid anxious arousal. In the chapters 5, 6, and 7, we focused on vulnerable personality traits (e.g. neuroticism), negative life-events, and related coping mechanisms (e.g. worry and cognitive control).

Neuroticism is perceived as the single most important risk factor in behavioral public health^{54,55}. Neuroticism refers to the tendency to perceive the world as threatening and to be prone experience unpleasant and disturbing emotions. There are many mechanisms to cope with threats and negative emotions, which can all result in a sense of mastery. A methodological issue of our studies is that personality traits e.g. neuroticism, were measured during a depressed state. Although, personality traits are relative stable, individuals often rate themselves as more neurotic during depressive or anxious episodes^{56–58}. Prior research distinguishes three possible sources of variance for neuroticism: an allegedly stable set-point neuroticism component representing the general trait level of neuroticism, a transient state-deviation component that changes in response to life-events and current psychopathology, and an error component^{57,59–61}. Our findings showed no direct association of negative life-events with anxiety in late-life depression, only in interaction with a higher level of neuroticism. Given the fact that all participants suffered from depression, the overall level of neuroticism is expected to be elevated. It is, therefore not to be expected that these results are distorted.

Cognitive reappraisal is seen as an adaptive coping strategy. In a maladaptive form, such as rumination or worry, it is associated with anxiety and depression^{62,63}. Especially in an older adult population worry is an important driving force for the development of mental disorders⁶⁴.

Depressive and anxiety symptoms negatively influence executive functioning, like working memory and inhibitory control, which are associated with increased worrying^{64,65}.

All determinants of interest were measured in a depressed state and associated with anxious arousal. Facing a negative life-event stronger impacts those who are vulnerable to negative emotions (high neuroticism), like anxiety. One could argue that loss of (cognitive) control and worrying are not moderators but merely manifestations of anxiety. This is consistent with the DSM 5 specifier of depression ‘with anxious distress’⁶⁶, as it relates to symptoms as difficulty concentrating due to worry and fear that something awful may happen. To gain more insight in the above-described intricate dynamics, future clinical studies could use experience sampling methods (ESM) to get a finer grained analyses of the mutual interaction of anxious distress, life-events and the determinants of interest.

Interpretation of cross-sectional findings

Four of the seven studies described in this thesis are based on cross-sectional findings. This limits causal interpretation, as it cannot be determined which factor occurred first. The findings that concern, in any way the role of life events is not pure cross-sectional, because the occurrence of a life event was retrospectively assessed over a period of 6-12 months preceding the baseline assessment. In our studies negative life-events (NLE) in the past 6-12 months have been assessed and as a sum-score used in the analyses. Two aspects are relevant in this respect. First of all, regarding chapter 5, it can be reasoned that personality traits are persistent over years and

present even before the onset of the depressive disorder and occurrence of life-events. The life-events have been assessed retrospectively and have occurred in the year before baseline. The severity of anxiety, the primary outcome, highly fluctuates. So, interpretation of personality traits and life-events on the actual level of anxious distress may be considered as a prospective study. In this respect the longitudinal results trying to replicate this 'cross-sectional' finding, as presented in chapter 6, may even be considered as more biased as in this study the life-events occurred after baseline. The specific state of the mental disorder may make older adults more or less prone to new life-events to mutual independence of these data may be less guaranteed.

Secondly, previous studies indicate that stressful life-events may trigger an anxious/depressive episode typically within maximal 3 months⁶⁷⁻⁷⁰. The effect of some NLE on neuroticism have showed to be long-lasting (at least one year) and seem to have a stronger mediating effect on the severity of depressive symptoms than on anxiety symptoms⁷¹. Concerning the assessment of NLE during the past 6-12 months, the following limitations should be taken into account: retrospective self-reports of NLEs inherently incorporate response components such as cognition, appraisal, interpretation and recall, which may be influenced by current mental state⁷²⁻⁷⁴. Furthermore, the focus on the number of life-events rather than their ecological context is a simplification. The stress and impact of various events depend on a variety of non- assessed factors regarding resources, age, skills, social support, unpredictability, magnitude of change/disruption produced, or potential to exhaust the individual physically⁷¹. Our results show that even with the above-described factors that cause variance, the found associations are robust.

Clinical implications and future directions

A meaningful comparison between the efficacy of any treatment of depressed patients with either a comorbid anxiety disorder or anxious distress cannot be made based on observational studies as we did. A study by Ionescu and colleagues⁷⁵ in an adult sample shows that, despite achieving response with SSRIs, SNRIs, and TCAs, patients with an anxious depression do not maintain response or remission. They often report a larger burden of side effects compared to non-anxious depressive patients, suggesting that it is a harder-to-treat subtype of major depressive disorder. Anxious depression in this study was defined as a current DSM-IV diagnosis of MDD and score of 7 or higher on anxiety somatization subscale of the Hamilton Depression Rating Scale. A review by Pollack⁷⁶ shows the presence of comorbid anxiety and depression adversely affects clinical and treatment outcomes. SSRIs are usually considered first-line treatment for patients with these disorders, although alternative antidepressants or additional therapies are often necessary. Pollack explicitly states that cognitive-behavioral therapy may also be an effective treatment for patients with anxious depression.

In the research field of late-life depression the main emphasis is on different levels of senescence in relation to depression. Physical frailty and cognitive decline are both levels of clinical senescence and are related to late-life depression. A study by Lugtenburg and colleagues however, showed that in the same NESDO cohort 45% of the of the depressed could be subtyped by specific combinations of age-related clinical features. The other 55% was suffering from pure depression⁷⁷. Therefore, we emphasize here that research in late-life depression should not solely focus on senescence factors, but also on factors that have been identified as having clinical relevance in

studies on younger depressed adults. Factors like comorbid anxiety⁷⁸, negative life-events⁷⁹, and personality traits^{58,80} or personality disorders⁸¹ should take a more prominent role in this research field.

High levels of anxiety are present in depression with anxious distress as well as in depression with comorbid anxiety disorders. As described in the case of Jane (see General Introduction) anxiety easily exceeds the frame of tolerance and triggers a strong fight-flight reaction, which may lessen the patient's ability to learn. We hypothesize that older patients with anxious distress are less receptive to the process of inhibitory learning⁸². In contrast, as described in the case of Frank, patients with a (comorbid) anxiety disorder only suffer from elevated levels of anxiety when confronted with the feared stimuli. Exposure to the feared stimulus can be done in a graded manner. In CBT these exposure exercises are well prepared and evaluated to enhance the inhibitory learning.

Systematic reviews and meta-analyses have shown that CBT is effective for late-life depression and late-life anxiety^{83–85}. Effectiveness may be improved with some adjustments e.g. including learning and memory aids to standard CBT, but to our knowledge, this is tested once empirically by in a comparative study between standard CBT and Enhanced CBT⁸⁶. Nonetheless, several directions have been outlined for the further development of CBT for older adults (e.g. wisdom enhancement in CBT or a qualitative change of focus to themes that are relevant for older people)⁸⁷.

A treatment strategy for the depressed patient with anxious distress could be to reduce fear by medication (beyond the use of SSRIs as first-line agents as anxious distress often point to more severe type of depression). When the depressive and anxious symptoms decrease, the patient may become more receptive for psychotherapy (e.g. CBT or Interpersonal Psychotherapy (IPT)). The treatment strategy for the depressed patient with a comorbid anxiety disorder could be to start with either with an antidepressant, CBT or preferred the combination to beat the depression⁸⁸. In these patients, however, it is important to also indicate CBT for the anxiety disorder and thus to adapt the traditional CBT-protocol for depression. Irrespective of the type of anxious depression, a clear case-conceptualization which explains the *Gordian knot* of comorbid anxiety and depression could be helpful to motivate the patient to do exposure exercises combined with behavioral activation.

REFERENCES

- 1 Lenze, E. J. et al. Comorbid anxiety disorders in depressed elderly patients. *Am. J. Psychiatry* 157, 722–728 (2000).
- 2 Ritchie, K. et al. Prevalence of DSM-IV psychiatric disorder in the French elderly population. *Br. J. Psychiatry* 184, 147–152 (2004).
- 3 Cairney, J., Corna, L. M., Veldhuizen, S., Herrmann, N. & Streiner, D. L. Comorbid depression and anxiety in later life: Patterns of association, subjective well-being, and impairment. *Am. J. Geriatr. Psychiatry* 16, 201–208 (2008).
- 4 Beekman, A. T. et al. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am. J. Psychiatry* 157, 89–95 (2000).
- 5 Landis, J. R. & Koch, G. G. The Measurement of Observer Agreement for Categorical Data. *Biometrics* 33, 159 (1977).
- 6 Fleiss, J. L., Levin, B. & Paik, M. C. Statistical Methods for Rates and Proportions. Statistical Methods for Rates and Proportions. John Wiley & Sons, Inc. (2003).
- 7 Brown, C., Schulberg, H. C., Madonia, M. J., Shear, M. K. & Houck, P. R. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. *Am. J. Psychiatry* 153, 1293–1300 (1996).
- 8 Tunvirachaisakul, C. et al. Predictors of treatment outcome in depression in later life: A systematic review and meta-analysis. *J. Affect. Disord.* 227, 164–182 (2018).
- 9 Andreescu, C. et al. Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: Controlled study. *Br. J. Psychiatry* 190, 344–349 (2007).
- 10 Greenlee, A. et al. Anxiety impairs depression remission in partial responders during extended treatment in late-life. *Depress. Anxiety* 27, 451–456 (2010).
- 11 Comijs, H. C. et al. The two-year course of late-life depression; results from the Netherlands study of depression in older persons. *BMC Psychiatry* 15, 20–25 (2015).
- 12 Huisman, M. et al. Cohort Profile: The Longitudinal Aging Study Amsterdam. *Int. J. Epidemiol.* 40, 868–876 (2011).
- 13 Appleby, L. et al. Safety First: Report of the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness. (2001).
- 14 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed., Text Revision). (2000).
- 15 WHO. The ICD-10: The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. (1992).
- 16 Lamers, F. et al. Comorbidity patterns of anxiety and depressive disorders in a large cohort study: The Netherlands Study of Depression and Anxiety (NESDA). *J. Clin. Psychiatry* 72, 342–348 (2011).
- 17 Kessler, R. C. et al. Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiol. Psychiatr. Sci.* 24, 210–226 (2015).
- 18 Schoevers, R. A. Depression and Generalized Anxiety Disorder: Co-Occurrence and Longitudinal Patterns in Elderly Patients. *Am. J. Geriatr. Psychiatry* 13, 31–39 (2005).
- 19 Scholten, W. D. et al. Diagnostic instability of recurrence and the impact on recurrence rates in depressive and anxiety disorders. *J. Affect. Disord.* 195, 185–190 (2016).
- 20 Hasin, D. S. et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry* 75, 336–346 (2018).
- 21 Rosellini, A. J. et al. Anxious distress in depressed outpatients: Prevalence, comorbidity, and incremental validity. *J. Psychiatr. Res.* 103, 54–60 (2018).
- 22 Zimmerman, M. et al. Validity of the DSM-5 anxious distress specifier for major depressive disorder. *Depress. Anxiety* 36, 31–38 (2019).

- 23 Hamilton, M. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62 (1960).
- 24 Ionescu, D. F., Niciu, M. J., Henter, I. D. & Zarate, C. A. Defining anxious depression: A review of the literature. *CNS Spectrums* vol. 18 252–260 (2013).
- 25 Mendlowicz, M. V & Stein, M. B. Quality of life in individuals with anxiety disorders. *Am. J. Psychiatry* 157, 669–682 (2000).
- 26 Fava, G. A., Rafanelli, C., Grandi, S., Conti, S. & Belluardo, P. Prevention of recurrent depression with cognitive behavioral therapy: Preliminary findings. *Arch. Gen. Psychiatry* 55, 816–820 (1998).
- 27 Kaczurkin, A. N. & Foa, E. B. Cognitive-behavioral therapy for anxiety disorders: An update on the empirical evidence. *Dialogues Clin. Neurosci.* 17, 337–346 (2015).
- 28 Katz, I. R. What should we do about undertreatment of late life psychiatric disorders in primary care? *Journal of the American Geriatrics Society* vol. 46 1573–1575 (1998).
- 29 Sareen, J. et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: A population-based longitudinal study of adults. *Arch. Gen. Psychiatry* 62, 1249–1257 (2005).
- 30 Palmer, B. W., Jeste, D. V & Sheikh, J. I. Anxiety disorders in the elderly: DSM-IV and other barriers to diagnosis and treatment. *J. Affect. Disord.* 46, 183–190 (1997).
- 31 Wittchen, H. U. et al. Cross-cultural feasibility, reliability and sources of variance of the composite international diagnostic interview (CIDI). *Br. J. Psychiatry* 159, 645–653 (1991).
- 32 Comijs, H. & Dekker, J. The Netherlands Study of Depression in Older persons (NESDO). *Int. Psychogeriatrics* 23, S70–S71 (2011).
- 33 Knäuper, B. et al. How aging affects self-reports. *European Journal of Ageing* vol. 13 185–193 (2016).
- 34 O'Connor, D. W. & Parslow, R. A. Mental health scales and psychiatric diagnoses: Responses to GHQ-12, K-10 and CIDI across the lifespan. *J. Affect. Disord.* 121, 263–267 (2010).
- 35 Nock, M. K. et al. Cross-national analysis of the associations among mental disorders and suicidal behavior: Findings from the WHO World Mental Health Surveys. *PLoS Med.* 6, (2009).
- 36 Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R. & Ellard, K. K. The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clin. Psychol. Sci.* 2, 344–365 (2014).
- 37 Rudd, M. D. et al. Warning Signs for Suicide: Theory, Research, and Clinical Applications. *Suicide Life-Threatening Behav.* 36, 255–262 (2006).
- 38 Allgulander, C. & Lavori, P. W. Causes of death among 936 elderly patients with 'pure' anxiety neurosis in Stockholm County, Sweden, and in patients with depressive neurosis or both diagnoses. *Compr. Psychiatry* 34, 299–302 (1993).
- 39 Bartels, S. J. et al. Suicidal and death ideation in older primary care patients with depression, anxiety, and at-risk alcohol use. *Am. J. Geriatr. Psychiatry* 10, 417–427 (2002).
- 40 Bentley, K. H. et al. Anxiety and its disorders as risk factors for suicidal thoughts and behaviors: A meta-analytic review. *Clin. Psychol. Rev.* 43, 30–46 (2016).
- 41 Kanwar, A. et al. The association between anxiety disorders and suicidal behaviors: A systematic review and meta-analysis. *Depress. Anxiety* 30, 917–929 (2013).
- 42 Ridley, C. R. & Jeffrey, C. E. The Conceptual Framework of Thematic Mapping in Case Conceptualization. *J. Clin. Psychol.* 73, 376–392 (2017).
- 43 Hallam, R. Individual case formulation. Oxford: Academic Press (2013).
- 44 Rintala, A., Wampers, M., Myin-Germeys, I. & Viechtbauer, W. Response compliance and predictors thereof in studies using the experience sampling method. *Psychol. Assess.* 31, 226–235 (2019).
- 45 Vachon, H., Viechtbauer, W., Rintala, A. & Myin-Germeys, I. Compliance and retention with the experience sampling method over the continuum of severe mental disorders: Meta-analysis and recommendations. *J. Med. Internet Res.* 21, (2019).

- 46 Eisele, G. et al. The Effects of Sampling Frequency and Questionnaire Length on Perceived Burden, Compliance, and Careless Responding in Experience Sampling Data in a Student Population. *Assessment* (2020)
- 47 Wichers, M., Smit, A. C. & Snippe, E. Early warning signals based on momentary affect dynamics can expose nearby transitions in depression: A confirmatory single-subject time-series study. *J. Pers. Res.* 6, 1–15 (2020).
- 48 Bak, M., Drukker, M., Hasmi, L. & Van Jim, O. S. An n=1 Clinical network analysis of symptoms and treatment in psychosis. *PLoS One* 11, e0165762 (2016).
- 49 Groot, P. C. Patients can diagnose too: How continuous self-assessment aids diagnosis of, and recovery from, depression. *J. Ment. Heal.* 19, 352–362 (2010).
- 50 Kroeze, R. et al. Personalized Feedback on Symptom Dynamics of Psychopathology: A Proof-of-Principle Study. *J. Pers. Res.* 3, 1–10 (2017).
- 51 Kramer, I. et al. A therapeutic application of the experience sampling method in the treatment of depression: a randomized controlled trial. *World Psychiatry* 13, 68–77 (2014).
- 52 Ornée, D. A., Bastiaansen, J. & Oldehinkel, A. Comparison of Two Ecological Momentary Intervention Modules for Treatment of Depression on Momentary Positive and Negative Affect. *Collabra: Psychology* 7, 18910 (2020)
- 53 Bos, F. M., Snippe, E., Bruggeman, R., Wichers, M. & van der Krieke, L. Insights of patients and clinicians on the promise of the experience sampling method for psychiatric care. *Psychiatr. Serv.* 70, 983–991 (2019).
- 54 Lahey, B. B. Public health significance of neuroticism. *Am. Psychol.* 64, 241–256 (2009).
- 55 Ormel, J. et al. Neuroticism and common mental disorders: Meaning and utility of a complex relationship. *Clin. Psychol. Rev.* 33, 686–697 (2013).
- 56 Ormel, J., Oldehinkel, A. J. & Vollebergh, W. Vulnerability before, during, and after a major depressive episode: A 3-wave population-based study. *Arch. Gen. Psychiatry* 61, 990–996 (2004).
- 57 Jr, P. T. C., Bagby, R. M., Herbst, J. H. & McCrae, R. R. Personality self-reports are concurrently reliable and valid during acute depressive episodes. *J. Affect. Disord.* 89, 45–55 (2005).
- 58 Kotov, R., Gamez, W., Schmidt, F. & Watson, D. Linking ‘big’ personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychol. Bull.* 136, 768–821 (2010).
- 59 Fleeson, W. Toward a structure- and process-integrated view of personality: Traits as density distributions of states. *J. Pers. Soc. Psychol.* 80, 1011–1027 (2001).
- 60 Clark, L. A., Vittengl, J., Kraft, D. & Jarrett, R. B. Separate personality traits from states to predict depression. *J. Pers. Disord.* 17, 152–172 (2003).
- 61 Courvoisier, D. S., Nussbeck, F. W., Eid, M., Geiser, C. & Cole, D. A. Analyzing the Convergent and Discriminant Validity of States and Traits: Development and Applications of Multimethod Latent State-Trait Models. *Psychol. Assess.* 20, 270–280 (2008).
- 62 Andrews, V. H. & Borkovec, T. D. The differential effects of inductions of worry, somatic anxiety, and depression on emotional experience. *J. Behav. Ther. Exp. Psychiatry* 19, 21–26 (1988).
- 63 Ruscio, A. M., Seitchik, A. E., Gentes, E. L., Jones, J. D. & Hallion, L. S. Perseverative thought: A robust predictor of response to emotional challenge in generalized anxiety disorder and major depressive disorder. *Behav. Res. Ther.* 49, 867–874 (2011).
- 64 Beaudreau, S. A. et al. Unlocking neurocognitive substrates of late-life affective symptoms using the research domain criteria: Worry is an essential dimension. *Front. Aging Neurosci.* 9, 380 (2017).
- 65 Davey, G. C. L. & Meeten, F. The perseverative worry bout: A review of cognitive, affective and motivational factors that contribute to worry perseveration. *Biol. Psychol.* 121, 233–243 (2016).
- 66 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). American Psychiatric Association (2013).

- 67 Suh, E., Diener, E. & Fujita, F. Events and subjective well-being: Only recent events matter. *J. Pers. Soc. Psychol.* 70, 1091–1102 (1996).
- 68 Kendler, K. S., Karkowski, L. M. & Prescott, C. A. Causal relationship between stressful life events and the onset of major depression. *Am. J. Psychiatry* 156, 837–841 (1999).
- 69 Brilman, E. I. & Ormel, J. Life events, difficulties and onset of depressive episodes in later life. *Psychol. Med.* 31, 859–869 (2001).
- 70 Faravelli, C., Catena, M., Scarpato, A. & Ricca, V. Epidemiology of life events: Life events and psychiatric disorders in the Sesto Fiorentino study. *Psychother. Psychosom.* 76, 361–368 (2007).
- 71 Jeronimus, B. F., Ormel, J., Aleman, A., Penninx, B. W. & Riese, H. Negative and positive life events are associated with small but lasting change in neuroticism. *Psychol. Med.* 43, 2403–2415 (2013).
- 72 Dohrenwend, B. P. Inventorying stressful life events as risk factors for psychopathology: Toward resolution of the problem of intracategory variability. *Psychol. Bull.* 132, 477–495 (2006).
- 73 Schwartz, N. Retrospective and Concurrent Self-Reports: The Rationale for Real-Time Data Capture. In *The science of real-time data capture: Self-reports in health research* (eds. Stone, A., Shiffman, S. S., Atienza, A. & Nebeling, L.) 11–26. Oxford University Press (2007).
- 74 Monroe, S. M. Modern Approaches to Conceptualizing and Measuring Human Life Stress. *Annu. Rev. Clin. Psychol.* 4, 33–52 (2008).
- 75 Ionescu, D. F., Niciu, M. J., Richards, E. M. & Zarate, C. A. Pharmacologic treatment of dimensional anxious depression: A review. *Prim. Care Companion CSN Disord.* 16, PCC. 13r01621 (2014).
- 76 Pollack, M. H. Comorbid anxiety and depression. *J. Clin. Psychiatry* 66, 22–29 (2005).
- 77 Lugtenburg, A. et al. Subtypes of Late-Life Depression: A Data-Driven Approach on Cognitive Domains and Physical Frailty. *J. Gerontol. A Biol. Sci. Med. Sci.* 76, 141–150 (2021).
- 78 Dold, M. et al. Clinical characteristics and treatment outcomes of patients with major depressive disorder and comorbid anxiety disorders - results from a European multicenter study. *J. Psychiatr. Res.* 91, 1–13 (2017).
- 79 Kessler, R. C. The effects of stressful life events on depression. *Annu. Rev. Psychol.* 48, 191–214 (1997).
- 80 Malouff, J. M., Thorsteinsson, E. B. & Schutte, N. S. The relationship between the five-factor model of personality and symptoms of clinical disorders: A meta-analysis. *J. Psychopathol. Behav. Assess.* 27, 101–114 (2005).
- 81 Asp, M. et al. Recognition of personality disorder and anxiety disorder comorbidity in patients treated for depression in secondary psychiatric care. *PLoS One* 15, e0227364 (2020).
- 82 Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T. & Vervliet, B. Maximizing exposure therapy: An inhibitory learning approach. *Behav. Res. Ther.* 58, 10–23 (2014).
- 83 Ayers, C. R., Sorrell, J. T., Thorp, S. R. & Wetherell, J. L. Evidence-based psychological treatments for late-life anxiety. *Psychol. Aging* 22, 8–17 (2007).
- 84 Jayasekara, R. et al. Cognitive behavioural therapy for older adults with depression: A review. *J. Ment. Health* 24, 168–171 (2015).
- 85 Raue, P. J., McGovern, A. R., Kiosses, D. N. & Sirey, J. A. Advances in Psychotherapy for Depressed Older Adults. *Curr. Psychiatry Rep.* 19, 57 (2017).
- 86 Mohlman, J. et al. Standard and enhanced cognitive-behavior therapy for late-life generalized anxiety disorder: Two pilot investigations. *Am. J. Geriatr. Psychiatry* 11, 24–32 (2003).
- 87 Kishita, N. & Laidlaw, K. Cognitive behaviour therapy for generalized anxiety disorder: Is CBT equally efficacious in adults of working age and older adults? *Clin. Psychol. Rev.* 52, 124–136 (2017).
- 88 Kok, R. M. & Reynolds, C. F. Management of depression in older adults: A review. *JAMA.* 317, 2114–2122 (2017).

SAMENVATTING IN HET NEDERLANDS

PUBLICATIELIJST

NAWOORD

CURRICULUM VITAE

SAMENVATTING IN HET NEDERLANDS

Relatief veel ouderen lijden aan een depressie. In verschillende studies in de algemene bevolking kunnen de percentages oplopen tot ruim 7%. De gevolgen van een depressie op latere leeftijd zijn groot. Mensen zijn daarbij vaker lichamelijk ziek en het herstel hiervan verloopt moeizamer. De beperkingen in het dagelijkse leven zijn groter en daarmee verminderd de kwaliteit van leven aanzienlijk. Ook de kans op sterfte is hoger.

In het diagnostische handboek van de psychiatrie dat we ten tijde van deze studies hanteerden (de DSM-IV-TR), worden verschillende soorten depressie onderscheiden op basis van het klinische beeld. Angst staat echter in geen van deze subtypen depressie centraal. Dit was opmerkelijk omdat angst bij depressie in de klinische praktijk wordt herkend als een veelvoorkomende en 'lastige' combinatie. Daarnaast was er inmiddels aanzienlijk veel onderzoek gedaan naar deze *angstige depressie*, zoals dit in de literatuur wel gedifferentieerd werd aangeduid. De onderzoeken naar kenmerken van patiënten met een angstige depressie en het beloop van de behandelingen lieten uiteenlopende resultaten zien. In grote lijnen komt het erop neer dat angst in bijna de helft van de gevallen voorkomt bij een depressie op latere leeftijd. Als dit het geval is, hangt het samen met een (nog) lagere kwaliteit van leven en meer suïcidale gedachten en pogingen om het leven te beëindigen. Het beloop van de depressie met angst is ernstiger en chronischer, het effect van een behandeling heeft meer tijd nodig en de kans op terugval is groter.

Zoals hierboven beschreven heeft angst net als depressie verschillende gezichten. We kunnen angst kenmerken als een lichamelijke en mentale uiting, zoals bijvoorbeeld trillen en hartkloppingen of piekeren. We kunnen angst met al zijn bijkomende problemen ook classificeren als een angststoornis, zoals de paniekstoornis of de gegeneraliseerde angststoornis. In beide vormen komen ze voor samen met een depressie. In veel studies naar de angstige depressie werd geen onderscheid gemaakt tussen depressie met angstige kenmerken of een depressie en angststoornis die gelijktijdig optreden.

Depressie met angst – twee voorbeelden

We leiden dit proefschrift in met een beschrijving van twee patiënten met een depressie met angst om te laten zien dat het mogelijk om twee verschillende toestandsbeelden gaat.

Voorbeeld A

Frank is 83 jaar oud en weduwnaar. Als jongen was hij verlegen en groeide op ten tijde van de Tweede Wereldoorlog. Zijn ouders waren lid van de Nationaal-Socialistische Beweging. Dit bracht bepaalde privileges met zich mee, maar voor Frank betekende dit ook dat hij werd buitengesloten, gepest en regelmatig moest vechten om zich te verdedigen. Hij trok zich zoveel mogelijk terug en deed niet mee aan de sociale activiteiten die bij zijn ontwikkeling hoorden. Na de oorlog ging hij studeren en vond een baan als boekhouder. Hij ontmoette een levendige, sociale vrouw. Zij trouwden en kregen drie kinderen. Zijn vrouw bleek de drijvende kracht achter Frank zijn sociale leven, al bleef hij altijd bang om geconfronteerd te worden met zijn jeugd in de oorlog. In contacten was hij terughoudend en angstig. Na zijn pensioen overlijdt zijn vrouw en Frank ontwikkelt een depressie. Hij worstelt met somberheid, gebrek aan plezier bij activiteiten en een

negatief zelfbeeld. Hij trekt zich terug en vermijdt voorheen betekenisvolle activiteiten en sociale contacten. De vraag die we ons als klinici stellen is: lijdt Frank onder enkel een ernstige depressie of wordt dit beeld gecompliceerd door een reeds lang aanwezige sociale angststoornis?

Voorbeeld B

Jannie is 71 jaar oud en weduwe. Na het overlijden van haar echtgenoot ontwikkelt zij een ernstige depressie en wordt hiervoor opgenomen in onze kliniek. Haar toestandsbeeld kenmerkt zich naast haar sombere stemming ook met veel angstige symptomen. Zij beschrijft hartkloppingen en we zien dat ze trilt, een versnelde ademhaling heeft en veel onrustig heen en weer loopt. Hierbij komt ze regelmatig bij de verpleging, zonder duidelijke vraag, maar lijkt dan te zoeken naar geruststelling. Hoewel bij Jannie niet eerder een psychiatrisch toestandsbeeld is vastgesteld, beschrijft haar dochter haar als nerveuze, angstige vrouw. Als zij niet herstelt na start met een SSRI en later een SNRI en een tricyclisch antidepressivum, wordt overgestapt op een MAO-remmer. Hier herstelt ze grotendeels op, maar na ontslag verloopt de poliklinische traject moeizaam met goede en slechtere perioden. Jannie krijgt veel ondersteuning van haar dochter en als die om eigen gezondheidsredenen hierin een stap terug moet zetten, verslechtert haar toestand weer. Jannie wordt opnieuw opgenomen, maar knapt dan ook spoedig weer op. Patiënten als Jannie zien we regelmatig in onze kliniek en roepen de vraag op: lijdt Jannie aan een terugkerende angstige depressie? Spelen persoonlijkheidstrekken een bepalende rol, waarbij het toestandsbeeld met poliklinische zorg verslechterd?

Angstige depressie

Op basis van de voorgestelde differentiatie door Ionescu en collega's, maken we in dit proefschrift onderscheid tussen een depressie die gelijktijdig optreedt met een angststoornis en een depressie met angstige kenmerken.

Als het gaat om een depressie en een angststoornis die gelijktijdig optreden, wordt de angststoornis bij ouderen vaak niet als dusdanig herkend. Zo wordt veelvuldig piekeren, passend bij een gegeneraliseerde angststoornis, geduid als rumineren, passend bij een depressie. Agorafobische vermijding kan worden opgevat als verlies aan plezier of interesse en paniekaanvallen worden gezien als uiting van de ernst van het depressieve toestandsbeeld. Daarnaast lijkt het feit dat angststoornissen vaak al voor het 21ste levensjaar ontstaan een rol te spelen in het niet onderkennen van de angststoornis. Lang bestaande angstklachten en angstig vermijdingsgedrag worden onderdeel van het zelfnarratief en door patiënt en clinicus vaak onterecht toegeschreven aan persoonlijkheidsfactoren.

Bij een depressie met angstige kenmerken lijken patiënten door het hoge angstniveau minder toegankelijk te zijn voor een psychotherapeutische benadering. Bij het starten met serotonerge antidepressiva reageren ze in eerste instantie ook met een toename van angst, mede als het gevolg van de somatische bijwerkingen bij de opbouw. Het hoge angstniveau van deze patiënten roept veel zorg op bij omstanders en betrokken hulpverleners. Dit leidt vaak tot een opname en daarmee tot het overnemen van de autonomie van de patiënt.

Behandelrichtlijnen voor depressie en angststoornissen bij ouderen zijn afzonderlijk beschikbaar. Indien er sprake is van het gezamenlijk optreden van depressie en angst geldt een gouden standaard om, conform de hiërarchische regels van de DSM-IV, de depressie eerst te behandelen. Uitgangspunt is dat de angstklachten ook zullen afnemen. Indien er sprake is van een gelijktijdige angststoornis leidt dit echter vaak tot onder-behandeling omdat, opgeleide van de depressieve klachten, de behandeling wordt beëindigd zonder dat de angststoornis is behandeld. Als er sprake is van twee gelijktijdige stoornissen kan *casus conceptualisatie* helpen om geschikte aanknopingspunten te vinden voor de farmacologische en psychologische behandeling. In een casus conceptualisatie komen de persoonlijke kenmerken van de patiënt over zijn of haar symptoomprofiel, gedragsrepertoire en leergeschiedenis samen met de beschikbare theoretische en wetenschappelijke kennis. Dit leidt tot werkhypothesen die de behandelaar en patiënt samen opstellen.

Samenvatting van de bevindingen

Ook onze studie laat zien dat angst bij depressieve ouderen veel voorkomt. Onze algemene boodschap is, dat het belangrijk is om onderscheid te maken tussen een depressie met angstklachten en een depressie met een gelijktijdig aanwezige angststoornis. Beide toestandsbeelden hebben verschillende kenmerkende factoren en het is van belang om ten aanzien van deze kenmerken, verder te differentiëren tussen de verschillende angststoornissen. De combinatie van angst en depressie laat een ongunstiger beloop zien over de duur van 2 jaren.

In **hoofdstuk 2** beschrijven we onze resultaten die laten zien dat een angststoornis bij een depressie in 39% van de gevallen voorkomt. Angstige kenmerken bij een depressie komen bij 42% van de depressieve ouderen voor. Deze percentages liggen dicht bij elkaar, maar toch is de overlap tussen de twee vormen waarop angst bij depressie kan voorkomen opvallend laag. Zoals Ionescu veronderstelde, zou dit wijzen op twee verschillende toestandsbeelden. Voor verder onderzoek is het dan van belang om dit onderscheid te maken en separaat verder te onderzoeken.

In **hoofdstuk 3** onderzoeken we de samenhang tussen de kenmerken van depressieve ouderen en de aanwezigheid van een angststoornis bij de beginmeting. Hieruit komt naar voren dat ze jonger zijn, dat het vaker vrouwen betreft en het opleidingsniveau lager is. Ze rapporteren meer depressieve klachten en geven aan dat er in hun jeugd ingrijpende dingen zijn gebeurd. Drie persoonlijkheidstrekken komen sterker naar voren; neuroticisme, extraversie en zorgvuldigheid. Specifieke kenmerken, die samenhangen met specifieke angststoornissen, worden gemist als je de angststoornissen 'op een hoop gooit'.

In **hoofdstuk 4** onderzoeken we de kenmerken van depressieve ouderen die stierven door suïcide. Bij een op de zes gevallen werd ook een angststoornis vastgesteld. We vergelijken een groep die enkel depressief was met de groep die naast een depressie ook een angststoornis had. Uit de resultaten komt naar voren dat deze laatste groep vaker al langer ziek was en de behandeling vaker bestond uit kalmerende medicatie. Bij het laatste consult met hun arts maakten zij een meer ontredderde indruk. Hierbij werd echter het suïciderisico juist lager ingeschat.

In **hoofdstuk 5** onderzoeken we de hypothese dat het meemaken van een recente ingrijpende gebeurtenis in combinatie met bepaalde persoonlijkheidstrekken samenhangt met de mate van angst bij een depressie. Dit wordt bevestigd. Een ingrijpende gebeurtenis in het voorafgaande jaar hangt samen met meer angst bij depressie, echter alleen in die gevallen waarbij ook sprake is van meer neuroticisme of openheid, en minder zorgvuldigheid of ervaren controle (mastery). Deze interactie is specifiek voor de mate van angst (en niet voor de mate van depressie).

Hoofdstuk 6 beschrijft de resultaten van de studie waarbij we onderzoeken wat de voorspellers zijn van volledig herstel na 2 jaar (geen depressie- en geen angstdiagnose). Allereerst vonden we dat minder mensen volledig herstelden als zij bij het begin een depressie en een angststoornis hebben. Daarnaast zijn de ernst van de depressieve- en angstklachten, een slechtere somatische gezondheid en een hogere mate van neuroticisme onafhankelijke voorspellers voor het uitblijven van volledig herstel. De impact van mastery (ervaren controle) op volledig herstel verschilt tussen ouderen met en zonder jeugdtrauma. Ouderen met een jeugdtrauma en een lage mate van mastery herstellen minder vaak. In dit hoofdstuk hebben we ook gekeken naar het beloop van de angstige kenmerken bij een depressie. Dit beloop is minder gunstig bij ouderen met een hoge mate van neuroticisme of een lage mate van mastery en die gedurende de twee jaren meer ingrijpende gebeurtenissen meemaken.

In **hoofdstuk 7** onderzochten we de vraag of het beloop van angst ongunstiger is bij depressieve ouderen die meer piekeren, minder cognitieve controle en een minder regelmatige hartslagvariantie hebben. Daarbij keken we ook of deze factoren bepalen wat de impact van een ingrijpende gebeurtenis is op het beloop van de angst bij een depressie. Het minst gunstige beloop met ernstige en blijvende angstklachten werd voorspeld door een hogere mate van piekeren en een mindere mate van cognitieve controle. Er was geen interactie met ingrijpende gebeurtenissen ten aanzien van het beloop van de angst bij depressie.

In **hoofdstuk 8** beschrijven we de toepasbaarheid van het intensief meten van depressieve en angstige kenmerken bij een patiënte van 67 jaar. De informatie die dit meten oplevert over de samenhang tussen de angstige en depressieve kenmerken werd met de patiënte besproken. Dit leidde tot meer inzicht en motivatie tot specifieke interventies bij patiënte.

Hoofdstuk 9 vat de hoofdbevindingen van de studies samen. Deze bevindingen worden tegen het licht van het huidige onderzoeksveld en klinische praktijk gehouden.

PUBLICATIELIJST

van der Veen D. C., Comijs H. C., van Zelst W. H., Schoevers R. A., Oude Voshaar R. C. (2014). Defining anxious depression in later life: a scaring heterogeneity in results. *Am J Geriatr Psychiatry*. 22(11), 1375-1378.

van der Veen D. C., van Zelst W. H., Schoevers R. A., Comijs H. C., Voshaar R. C. (2015). Comorbid anxiety disorders in late-life depression: results of a cohort study. *Int Psychogeriatr*. 27(7), 1157-1165.

Oude Voshaar R. C., **van der Veen D. C.**, Hunt I., Kapur N. (2015). Suicide in late-life depression with and without comorbid anxiety disorders. *Int J Geriatr Psychiatry*. 31(2), 146-152.

Hovenkamp-Hermelink J. H., Riese H., **van der Veen D. C.**, Batelaan N. M., Penninx B. W., Schoevers R. A. (2016). Low stability of diagnostic classifications of anxiety disorders over time: A six-year follow-up of the NESDA study. *J Affect Disord*. 15(190), 310-315.

van der Veen D. C., van Dijk S. D. M., Comijs H. C., van Zelst W. H., Schoevers R. A., Oude Voshaar R. C. (2016). The importance of personality and life-events in anxious depression: from trait to state anxiety. *Aging Ment Health*. 21(11), 1177-1183.

Spinhoven P., **van der Veen D. C.**, Oude Voshaar R. C., Comijs H. C. (2017). Worry and cognitive control predict course trajectories of anxiety in older adults with late-life depression. *Eur Psychiatry*. 44, 134-140.

Kroeze R., **van der Veen D. C.**, Servaas M. N., Bastiaansen J. A., Oude Voshaar R. C., Borsboom D., Ruhe H. G., Schoevers R. A., Riese H. (2017). Personalized Feedback on Symptom Dynamics of Psychopathology: A Proof-of-Principle Study. *J Pers Oriented Res*. 3(1), 1-10.

Voshaar R. C., **van der Veen D. C.**, Kapur N., Hunt I., Williams A., Pachana N. A. (2015). Suicide in patients suffering from late-life anxiety disorders; a comparison with younger patients. *Int Psychogeriatr*. 27(7), 1197-1205.

Epskamp S., van Borkulo C. D., **van der Veen D. C.**, Servaas M. N., Isvoranu A. M., Riese H., Cramer A. O. J. (2018). Personalized Network Modeling in Psychopathology: The Importance of Contemporaneous and Temporal Connections. *Clin Psychol Sci*. 6(3), 416-427.

Hovenkamp-Hermelink J. H. M., **van der Veen D. C.**, Oude Voshaar R. C., Batelaan N. M., Penninx B. W. J. H., Jeronimus B. F., Schoevers R. A., Riese H. (2019). Anxiety sensitivity, its stability and longitudinal association with severity of anxiety symptoms. *Sci Rep*. 13(1), 4314.

Hovenkamp-Hermelink J. H. M., Jeronimus B. F., **van der Veen D. C.**, Spinhoven P., Penninx B. W. J. H., Schoevers R. A., Riese H. (2019). Differential associations of locus of control with anxiety, depression and life-events: A five-wave, nine-year study to test stability and change. *J Affect Disord.* 15, 26-34.

van der Flier F. E., Kwee C. M. B., Cath D. C., Batelaan N. M., Groenink L., Duits P., **van der Veen D. C.**, van Balkom A. J. L. M., Baas J. M. P. (2019). Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias: study protocol of a randomized controlled trial. *BMC Psychiatry.* 13, 19(1), 69.

Burger J., **van der Veen D. C.**, Robinaugh D. J., Quax R., Riese H., Schoevers R. A., Epskamp S. (2020). Bridging the gap between complexity science and clinical practice by formalizing idiographic theories: a computational model of functional analysis. *BMC Med.* 8, 18(1), 99.

von Klipstein L., Riese H., **van der Veen D. C.**, Servaas M. N. , Schoevers R. A. (2020). Using person-specific networks in psychotherapy: challenges, limitations, and how we could use them anyway. *BMC Med.* 23, 18(1), 345.

Bringmann L. F., **van der Veen D. C.**, Wichers M., Riese H., Stulp G. (2020). ESMvis: a tool for visualizing individual Experience Sampling Method (ESM) data. *Qual Life Res.* 22.

Bastiaansen J. A., Kunkels Y. K., Blaauw F. J., Boker S. M., Ceulemans E., Chen M., Chow S. M., de Jonge P., Emerencia A. C., Epskamp S., Fisher A. J., Hamaker E. L., Kuppens P., Lutz W., Meyer M. J., Moulder R., Oravecz Z., Riese H., Rubel J., Ryan O., Servaas M. N., Sjobeck G., Snippe E., Trull T. J., Tschacher W., **van der Veen D. C.**, Wichers M., Wood P. K., Woods W. C., Wright A. G. C., Albers C. J., Bringmann L. F. (2020). Time to get personal? The impact of researchers choices on the selection of treatment targets using the experience sampling methodology. *J Psychosom Res.* 5, 137, 110211.

Riese H., von Klipstein L., Schoevers R. A., **van der Veen D. C.**, Servaas M. N. (2021). Personalized ESM monitoring and feedback to support psychological treatment for depression: a pragmatic randomized controlled trial (Therap-i). *BMC Psychiatry.* 10, 21(1), 143.

van der Veen D. C., Gulpers B., van Zelst W., Köhler S., Comijs H. C., Schoevers R. A., Oude Voshaar R. C. (2021). Anxiety in Late-Life Depression: Determinants of the Course of Anxiety and Complete Remission. *Am J Geriatr Psychiatry.* 29(4), 336-347.

Burger, J., Epskamp, S., **van der Veen, D. C.**, Dablander, F., Schoevers, R. A., Fried, E. I., Riese, H. (submitted). A clinical PREMISE for personalized models: Towards a formal integration of case formulations and statistical networks.

Kwee C. M. B., Baas J. M. P., Flier F. E., Groenink L., Duits P., Eikelenboom M., **van der Veen D. C.**, Moerbeek, M., Batelaan N. M., van Balkom A. J. L. M., Cath D. C. (submitted). Effect of cannabidiol enhancement of exposure therapy in treatment refractory patients with anxiety disorders: A randomised controlled trail.

NAWOORD

Het tot stand brengen van dit proefschrift heb ik ervaren als een proces van vallen en opstaan, hollen en stilstaan. In dit proces zijn veel mensen meer of minder betrokken geweest. Ik ga hier niet iedereen noemen, omdat ik hoop dat iedereen weet hoe dankbaar ik ze ben.

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CURRICULUM VITAE

Date van der Veen is geboren op 2 oktober 1975 te Elburg. Daar slaagde hij in 1994 voor zijn vwo-examen en ging studeren in Groningen. Oorspronkelijk was het plan om Geneeskunde te studeren. Na uitgeloot te zijn, besloot hij Psychologie te gaan studeren. In het eerste jaar raakte hij al snel geïnteresseerd in de psychiatrie en besloot de richting klinische psychologie te volgen. Hij liep zijn klinische stage op een gesloten afdeling van Groot Bronswijk te Wagenborgen. Zijn afstudeerscript ging over de samenhang tussen alexithymie en somatisatie bij mensen die een poliklinische behandeling volgden bij de toenmalige GGz Groningen aan de Hereweg.

Na zijn afstuderen begon hij als onderzoeker bij het RinG, de onderzoeksafdeling van de GGz Groningen. Hier verrichte hij onderzoekswerkzaamheden in het kader van een gecontroleerde studie naar het effect van een rehabilitatiemethode voor patiënten met persisterende psychiatrische klachten. Na 3½ jaar begon hij in 2003 aan de GZ-opleiding in een poliklinisch team van de GGz Groningen. Na de opleiding werkte hij hier nog enige tijd als GZ-psycholoog. In 2006 stapte hij over naar het Universitair Centrum Psychiatrie (UCP) van het UMCG en werkte daar bij de polikliniek Angst en Dwang. In 2009 begon hij aan de specialistische opleiding tot klinisch psycholoog. Gedurende de opleiding rouleerde hij door het UCP en tijdens zijn stage bij de afdeling Ouderenpsychiatrie pakte hij samen met Richard Oude Voshaar de onderzoekswerkzaamheden weer op. Dit was de start van zijn promotietraject, wat resulteerde in het onderhavige proefschrift. Zijn klinische werk zette hij voort als klinisch psycholoog waarbij hij o.a. een deeltijdbehandeling opzette voor patiënten met persisterende depressieve klachten. Hierbij implementeerde hij de CBASP-methode in een groepstherapie. In 2012 droeg hij deze deeltijdbehandeling over en werd behandelcoördinator van de afdeling Angst en Dwang in het UCP. Daarnaast was hij geruime tijd voorzitter van de werkgroep eHealth van het UCP. In deze tijd raakte hij betrokken bij dagboekstudies in de kliniek en ontstond er een samenwerking met Harriette Riese van het iLab. In 2019 startte hij met zijn werkzaamheden als P-opleider in het UMCG en zette hij zijn klinische werkzaamheden voort op de opnameafdeling Depressie van het UCP. Zijn onderzoeksdag wordt nu o.a. gevuld met taken binnen het Therap-i onderzoeksteam en andere dagboekstudies van het iLab.